K. L. Ameta
Anshu Dandia *Editors*

Green Chemistry: Synthesis of Bioactive Heterocycles

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Preface

Since many decades, research on bioactive heterocycles is one of the main topics of interest for the medicinal chemists because of a number of pharmacological activities of this class of compounds. Nitrogen, sulphur and oxygen containing five- and six-membered heterocyclic compounds, but even smaller or larger cyclic structures, have occupied enormous significance in the field of medicinal chemistry. The majority of pharmaceuticals and biologically active agrochemicals are heterocycles while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural feature inherent to heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substituent's around a core scaffold in defined three-dimensional representations. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.

In the recent years a renewed sensitivity to the environmental problems connected with the organic syntheses was the driving force that moves the chemists to introduce novel techniques and particularly eco-friendly procedures. Atom-economy and minimization of side products formation, solvent less conditions, use of unconventional techniques to run reactions (microwave, ultrasound, ball-milling, ionic liquids, etc) were introduced and play a relevant role in today chemistry labs and will be probably more intensively and massively used in the synthetic labs in the next future.

Green chemistry uses highly efficient and environmental benign synthetic procedures to synthesize various bioactive heterocyclic frameworks which are the useful synthons for the synthesis of medicines, plastics, petrochemicals, agrochemicals, cosmetics and many more. Green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials [1, 2]. Green chemistry offers enhanced chemical process economics concomitant with a reduced environmental burden. Green sustainable chemistry (GSC) is defined as the chemistry and chemical technology for eco-friendly products and processes.

Thus, the purpose behind writing this book is to provide a succinct summary of various green chemistry approaches for the synthesis and biological activities of different bioactive heterocycles.

[1] Anastas PT, Warner JC (1998) Green chemistry, theory and practice. Oxford University Press, New York
[2] Clark JH (1999) Forum. Green Chem 1(1):G1–G2

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Dr. K. L. Ameta received his doctorate degree in Organic Chemistry from M. L. Sukhadia University, Udaipur, India in the year 2002. Presently, he is working as Assistant Professor of Chemistry, Faculty of Arts, Science and Commerce, Mody Institute of Technology and Science (Deemed University) Lakshmangarh, Rajasthan, India. He has vast experience of teaching both graduate and postgraduate level students. His research area involves synthesis, characterization and biological evaluation of different sized bioactive heterocyclic systems. In addition to this, he has keen interests in heterogeneous catalyzed organic synthesis and photocatalysis. He has published a number of research articles in various journals of national and international repute.

Chapter 1
Synthesis of Heterocycles Through Multicomponent Reactions in Water

Pethaiah Gunasekaran, J. Carlos Menéndez and Subbu Perumal

Contents

Abstract Heterocyclic chemistry is one of the most important and fascinating branches of organic chemistry. It involves the study of compounds endowed with very high structural complexity and diversity and plays a pivotal role in any developed society as evident from the fact that pharmaceuticals, agrochemicals, dyes and

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many other kinds of products are mostly heterocyclic in nature. Consequently, the preparation of heterocycles in an environmentally benign and synthetically efficient way is one of the main goals of modern organic synthesis. In this context, this chapter focuses on the combination of two green strategies, namely multicomponent reactions (MCRs) and the use of aqueous reaction media, for the construction of a wide variety of heterocyclic systems. These processes are of much current interest because they intertwine eco-friendliness with synthetic efficiency.

Keywords Green solvents · Multicomponent reactions · Heterocycles · Reactions in water

1 Introduction

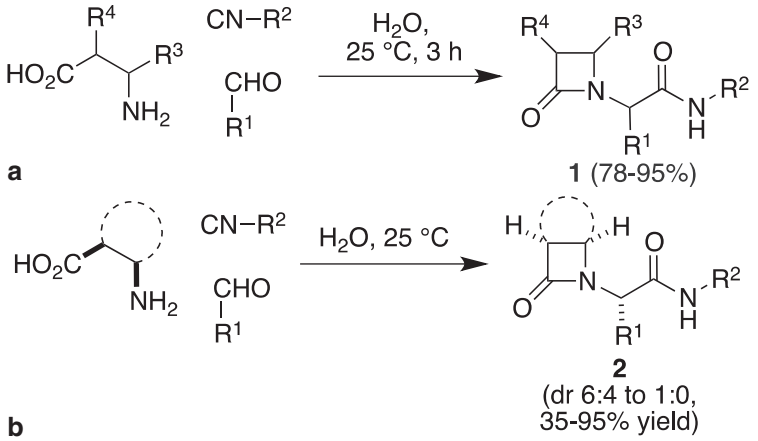
Multicomponent reactions (MCRs) involve the combination of more than two reactants in a one-pot operation affording a final product that incorporates in its structure significant structural fragments of each of these inputs. These reactions provide expedient and fast access to structural complexity and diversity as they (i) proceed through two or more steps via the formation of several bonds in a single operation and hence are characterized by a high bond-forming index, enabling them to approach the features of the ideal synthesis and (ii) allow a high intrinsic structural variability, achievable by structural modifications in each component. These reactions conform to the principles of green chemistry because their intermediates are not purified, resulting in large savings in terms of solvent, chromatographic adsorbent, energy and operator time. Understandably, these processes, being convergent, furnish higher product yields and hence higher synthetic efficiencies than equivalent multistep processes. MCRs have become an increasingly favoured and useful tool for the assembly of libraries of chemically and biologically important compounds in an eco-friendly manner.

When performed in water, MCRs illustrate another important facet of green chemistry, as volatile, flammable, and often toxic organic solvents are replaced by water. From the viewpoint of environmental impact and economy of operations, synthetic chemists increasingly prefer the use of water as the reaction medium. Thus water, the solvent in which all biochemical reactions occur, emerges as the one that is most environmentally friendly and safe, besides being the most abundant. Furthermore, the use of water enables the ready segregation and facile workup of products of a lipophilic nature. Many organic reactions are greatly facilitated when water is employed as the solvent with respect to organic solvents. Insight into these processes led to their characterization as occurring ‘on water’ with the reactants initially emulsionated in water and the transition states solvated more efficiently by hydrogen bonds with the unsymmetrically solvated water molecules than the reactants, resulting often in enhancements of rate and product yield. Finally, the use of water as solvent facilitates unique solvation modes and assembly processes enabling selectivities and reactivities that are often difficult to achieve in organic solvents. Consequently, the development of synthetically useful transformations in aqueous media has emerged as a topic of great interest.

In this chapter, we focus on the utility of MCRs in water in the construction of heterocycles, since they play a vital role in any developed society. This is easily discerned from the fact that about 60 % of all drug substances are heterocycles and they also play a vital role as agrochemicals, dyes and new materials, as well as synthons for the construction of more complex entities. The subject matter of this chapter has been normally arranged in increasing order of ring size of the heterocycle generated by the multicomponent process, the rings with heteroatoms of lower atomic numbers and highest degree of unsaturation given precedence. For each ring size, compounds have been ordered in increasing number of heteroatoms. These criteria are not completely rigid, especially when several rings of different sizes were generated in the same multicomponent process. Although the arrangement of the reactions on the basis of mechanistic consideration was an attractive option, we believe that the criterion employed will enable the reader to access more easily the information pertinent to any particular heterocyclic ring system. Finally, we will mention that in this chapter we have discussed reactions taking place in water as the sole solvent, generally excluding those carried out in water–organic solvent mixtures.

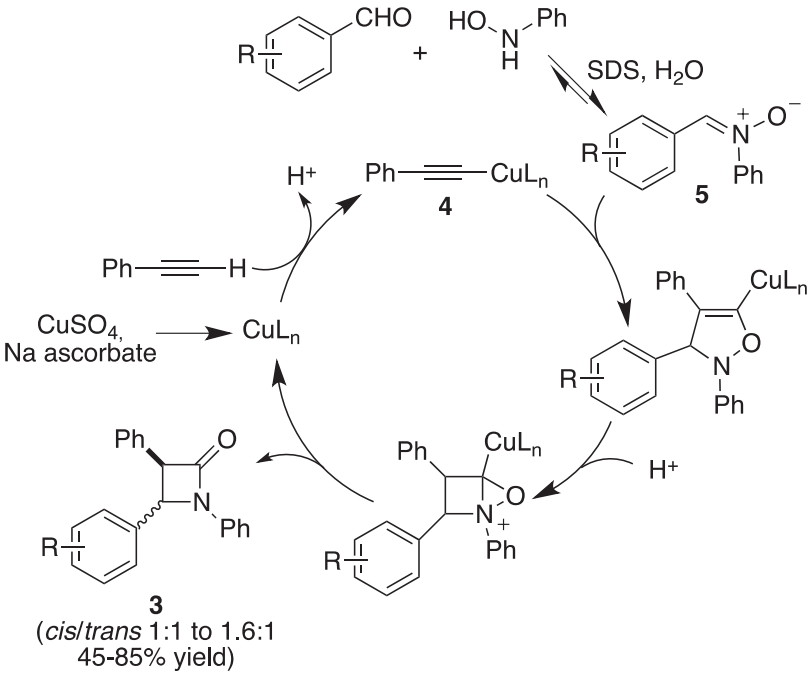
2 Four-Membered Heterocycles: β-Lactams

As part of an investigation into the feasibility of accelerating MCRs in water, Pirrung reported a three-component protocol for the synthesis of strained four-membered β-lactam ring systems **1** based on the Ugi reaction between β-amino acids, aldehydes and isocyanides in water (Scheme 1.1a). Interestingly, the creation of these strained rings was not possible in organic solvents, as shown by the failure of a model reaction in tetrahydrofuran, methanol and dichloromethane [1]. In related work, Fülöp described a diastereoselective synthesis of bi- and tricyclic β-lactam derivatives **2** in good yields from the reaction of cyclic β-amino acids, isocyanides and aldehydes in water at room temperature, as shown in Scheme 1.1b [2, 3].



Scheme 1.1

Peczaki has described a three-component Kinugasa reaction wherein phenylhydroxylamine, phenylacetylene and benzaldehyde derivatives led to the formation of β-lactams **3**. The reaction was performed in water, in the presence of sodium dodecyl sulphate (SDS) to generate micellar conditions, and using a Cu(I) catalyst generated from copper(II) sulphate and sodium ascorbate. This transformation has as the key step a 1,3-dipolar cycloaddition between the in situ-generated copper acetylide intermediate **4** and nitrone **5** and proceeds via the catalytic cycle summarized in Scheme 1.2. In this case, the diastereoselection was modest and favoured only slightly the cis β-lactam derivatives [4].



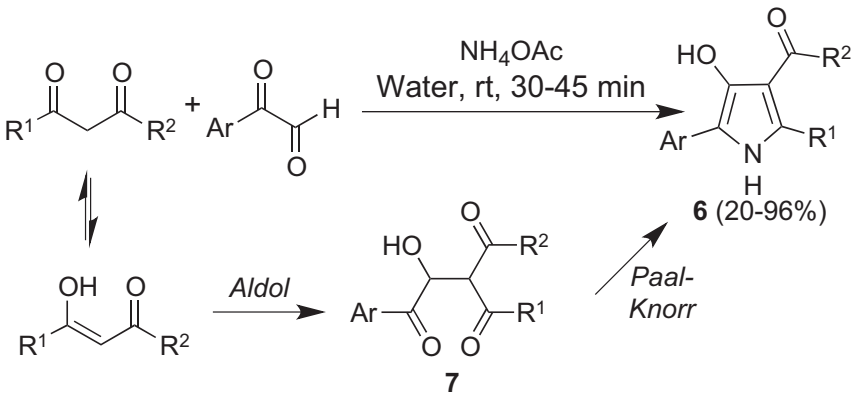
Scheme 1.2

3 Five-Membered Nitrogen-Only Heterocycles and their Fused Derivatives

In view of the great relevance of MCRs for the synthesis of pyrroles [5], we start this section by discussing some syntheses of pyrroles in aqueous media. Pyrazoles and imidazoles are treated next, followed by a final discussion of triazole and tetrazole derivatives.

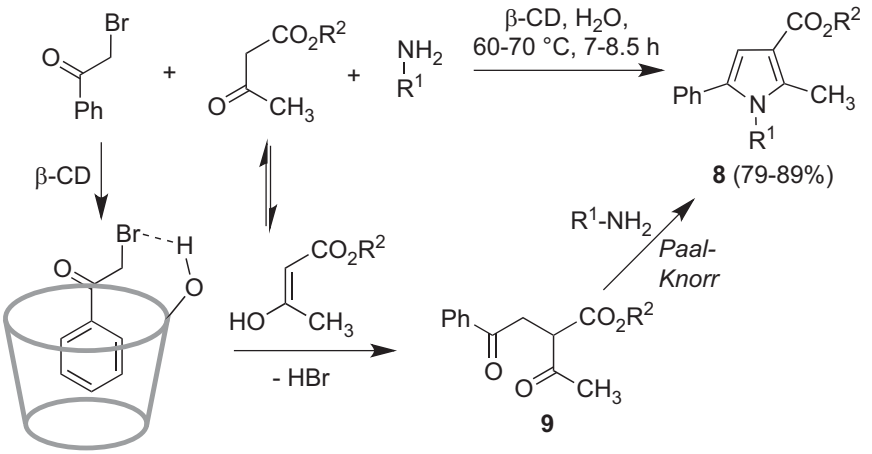
3.1 Pyrroles

Hashemi has described a three-component protocol for the synthesis of 2-alkyl-5-aryl-(1*H*)-pyrrole-4-ols **6** from the reaction of β-dicarbonyl compounds (β-ketoesters or symmetrical β-diketones) with arylglyoxals in the presence of ammonium acetate in water at room temperature (Scheme 1.3). This transformation proceeds through the attack of the enol tautomer of the starting β-ketoester onto the phenylglyoxal aldehyde group, affording a hydroxydiketo ester **7**, which upon reaction with ammonia, furnishes the final tetrasubstituted pyrrole products via a standard Paal–Knorr mechanism [6]. The final pyrroles precipitated from the reaction medium, underscoring the usefulness of aqueous media to direct complex processes, involving a large number of equilibria, towards a specific final product.



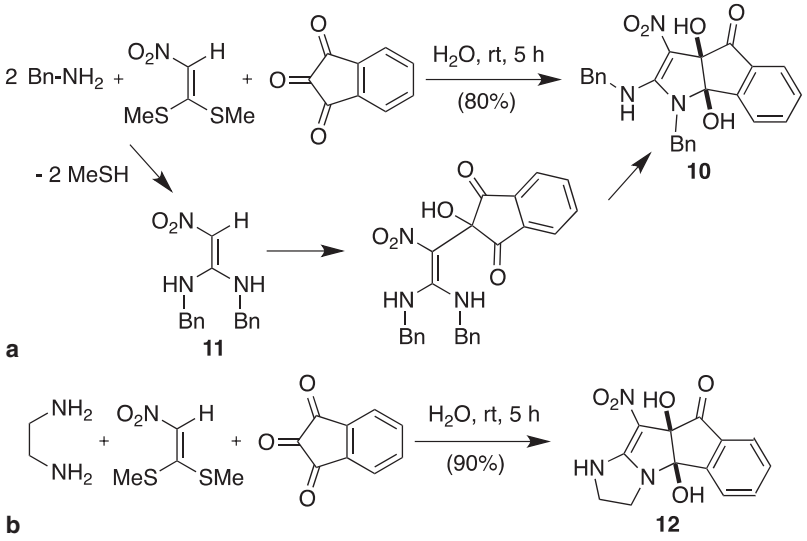
Scheme 1.3

The reaction between phenacyl bromide, acetylacetone and ammonium acetate or primary amines, mostly aromatic, afforded 1,5-diarylpyrroles **8** in good to excellent yields. The starting materials are identical to those employed in the classical Hantzsch pyrrole synthesis, but in this case the transformation did not follow the standard Hantzsch mechanism, which is initiated by the generation of a β-enaminone from the dicarbonyl and amine components. Instead, the order of reagent addition was adjusted so that β-cyclodextrin formed initially an inclusion complex with phenacyl bromide, leading to activation of the latter via hydrogen bonding of its Br atom with hydroxyl groups in the cyclodextrin rim. This complex would then react with the enol form of ethyl acetoacetate to give a 1,4-diketone **9**, which would finally yield the observed pyrroles via a standard Paal–Knorr reaction (Scheme 1.4). Supramolecular catalysis by β-cyclodextrin turned out to be crucial for the success of this protocol, since control experiments showed no reaction in its absence, both in water and in polyethyleneglycol [7].



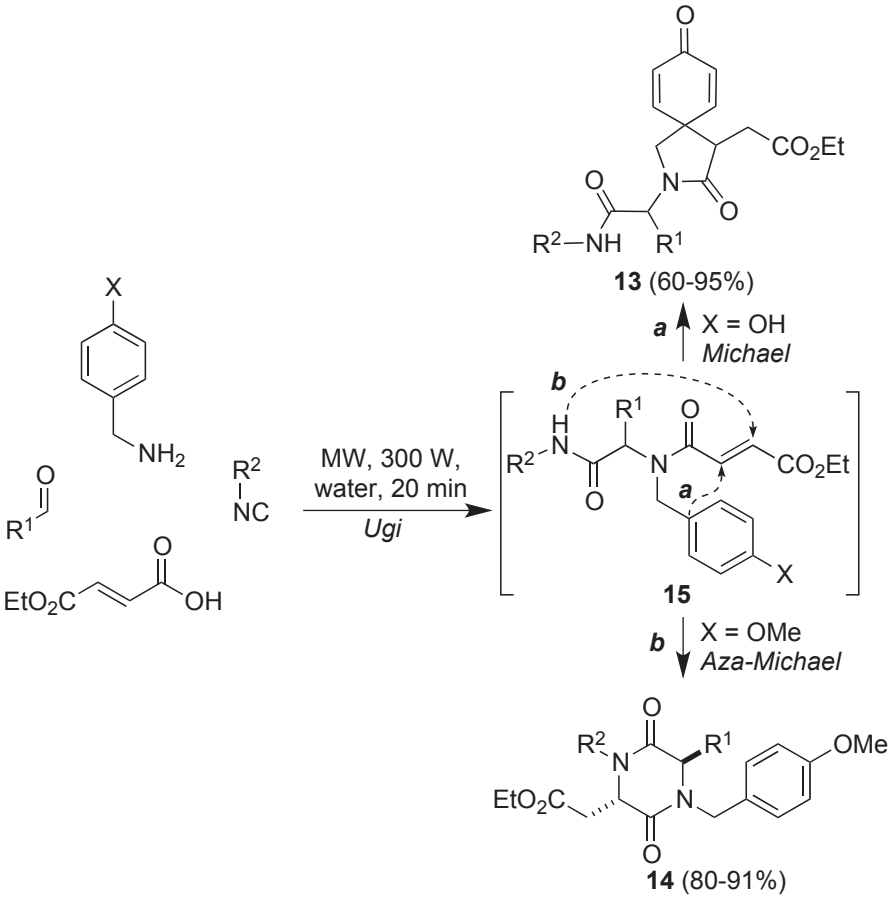
Scheme 1.4

MCRs in water can also be employed to access complex, polycyclic systems containing pyrrole rings. Thus, Alizadeh investigated the three-component reaction between primary amines, 1,1-bis(methylthio)-2-nitroethene, a ketene dithioacetal [8] and ninhydrin under aqueous conditions, which provides a wide range of dihydroindeno[1,2-*b*] pyrroles, out of which **10** is a representative example. This transformation presumably takes place by a mechanism involving an initial Gould–Jacobs-type displacement of two molecules of methanethiol from the ketene dithiocetal by attack of two molecules of the starting amine to give intermediate **11**. The addition of its enamine fragment to the more reactive C-2 carbonyl of ninhydrin, followed by a final addition, furnishes the hemiacetal moiety, presumably stabilized by intramolecular hydrogen bonding (Scheme 1.5a). The use of ethylenediamine as the amine component led to the formation of an additional ring and afforded tetracyclic indeno[2′,1′:4,5]pyrrolo[1,2-*a*]imidazole derivatives **12** in excellent yields, as shown in Scheme 1.5b [9].



Scheme 1.5

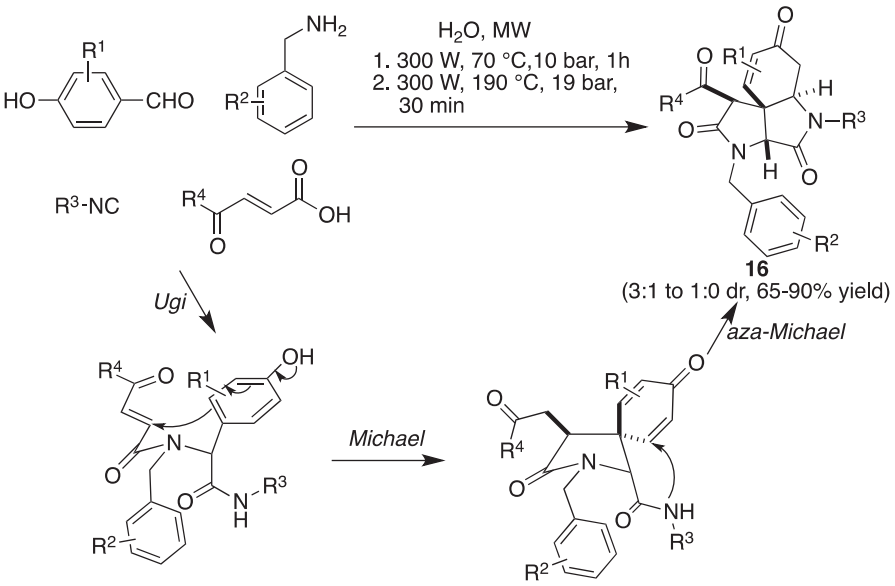
Santra reported a microwave-promoted, chemodivergent four-component reaction that afforded either spiro pyrrolidines **13** or 2,5-diketopiperazines **14** from the reaction of ethyl hydrogen fumarate, aldehydes, benzylamine derivatives and isonitriles. The product selectivity of this reaction depends mainly on the substituent on the amine component, since it affords compounds **13** for the case X = OH and **14** for X = OMe [10]. Its mechanism involves an initial Ugi four-component reaction that gives intermediate **15**, which undergoes either an intramolecular Michael reaction to give **13** (pathway *a*) or, for less reactive aromatic rings, an intramolecular aza-Michael reaction that affords **14** (pathway *b*; Scheme 1.6).



Scheme 1.6

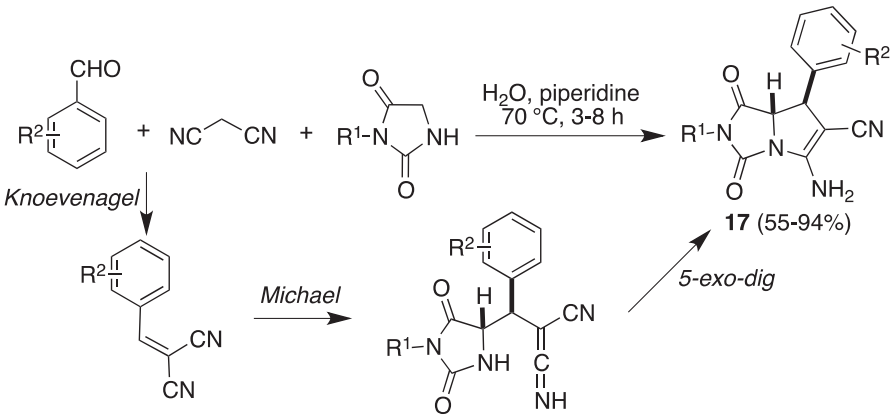
Building on this chemistry, the same authors developed a novel four-component reaction of *p*-hydroxybenzaldehyde derivatives, benzylamine derivatives, fumaric acid monoethyl ester and isonitriles in water under microwave irradiation to give natural product-like 5,5,6-fused azaspiro tricycle systems **16** as the main products [11]. This transformation can be assumed to proceed through addition of a final aza-Michael step to the previously developed Ugi/Michael domino sequence, and generates six contiguous bonds and four stereogenic centres, including one

quaternary carbon (Scheme 1.7). This one-pot process serves as a good illustration of the expedient creation of molecular complexity by multicomponent domino reactions in water.



Scheme 1.7

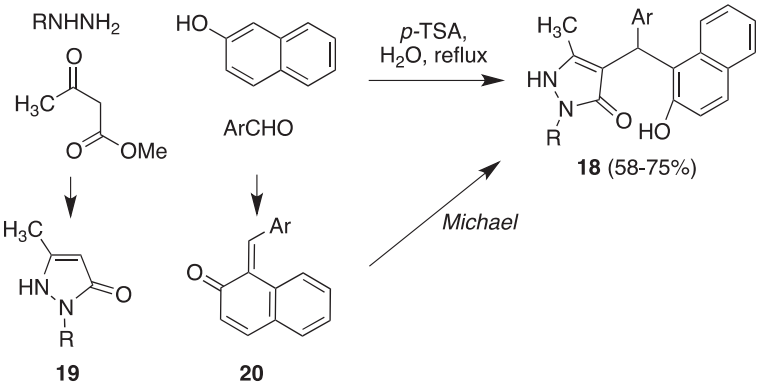
Another MCR that generates a pyrrole ring contained in a fused heterocycle allows the regio-, chemo- and stereoselective synthesis of azapyrrolizidines **17** from the three-component reaction of 3-substituted hydantoins, aromatic aldehydes and malononitrile in water [12]. These compounds, which can be viewed as natural product heteroanalogues, contain two contiguous stereocentres and can be proposed to arise from an initial Knoevenagel condensation between malononitrile and the aldehyde component, followed by an intermolecular Michael addition of the hydantoin and a final 5-*exo-dig* cyclization (Scheme 1.8).



Scheme 1.8

3.2 Pyrazoles

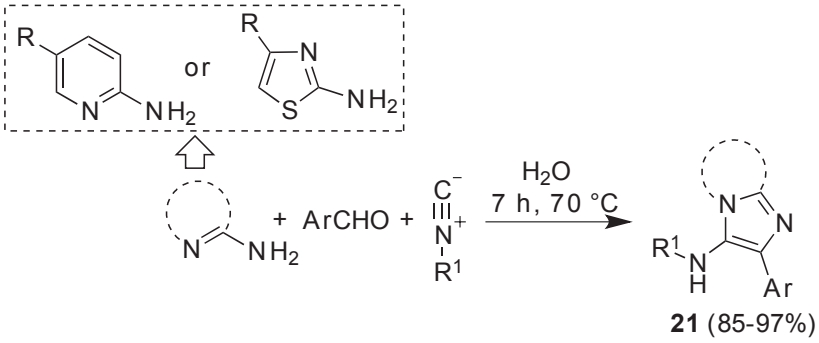
Perumal has described a four-component sequential protocol that allows the synthesis in good yields of antitubercular 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **18** from arylhydrazines, methyl acetoacetate, aromatic aldehydes and β-naphthol in the presence of *p*-TSA in water under reflux conditions [13]. The reaction proceeds by an initial acid-catalyzed cyclocondensation of the hydrazine and dicarbonyl components to give pyrazolinone **19**. A parallel acid-catalyzed condensation between β-naphthol and the aromatic aldehyde affords the intermediate quinone methide **20**, and Michael addition of the enol form of **19** onto the exocyclic double bond of **20** furnishes the final product (Scheme 1.9).



Scheme 1.9

3.3 Imidazoles

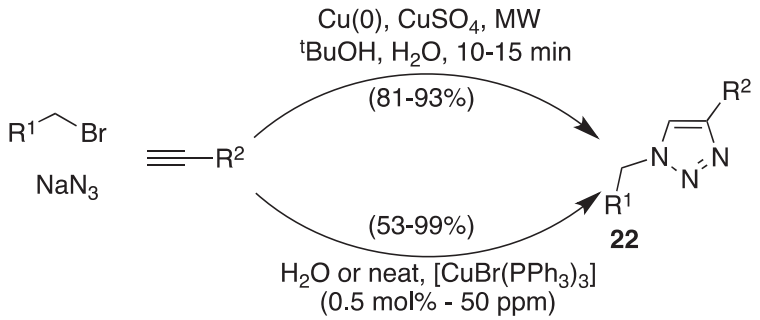
A catalyst-free protocol has been described by Adib for the synthesis in good to excellent yields of 3-aminoimidazo[1,2-*a*]pyridines and 5-aminoimidazo[2,1-*b*][1,3]thiazoles via three-component reactions between 2-aminopyridines or 2-aminothiazoles, aldehydes and isocyanides in water (Scheme 1.10) [14]. Presumably, this process involves the initial formation of an imine, which then reacts with the isonitrile in a formal [4+2] cycloaddition.



Scheme 1.10

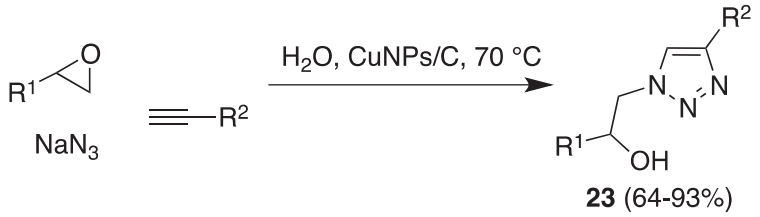
3.4 Triazoles

A huge amount of work has been carried out on the Sharpless variation of the azide-alkyne Huisgen cycloaddition, also known as the 'click' reaction, which has found widespread application in medicinal chemistry and chemical biology [15]. Some authors have studied three-component versions of this reaction in aqueous media (Scheme 1.11), and thus Van der Eycken reported a copper-promoted, microwave-assisted three-component synthesis of a series of 1,4-disubstituted 1,2,3-triazoles from the reaction of alkyl halides, sodium azide and alkynes in *tert*-butyl alcohol–water, in which organic azides are generated in situ [16]. Further developments of this reaction have allowed the use of catalytic amounts of copper and fully aqueous media. For instance, Díez-González effected the synthesis of triazoles from two- and three-component reactions of alkynes with either alkyl azides or alkyl bromide and sodium azide, respectively, in the presence of $[CuBr(PPh_3)_3]$ catalyst at room temperature, with loadings of the [Cu] catalyst as low as 50 ppm, in the absence of any additive. This protocol has the additional advantage of requiring no further purification of the products [17].



Scheme 1.11

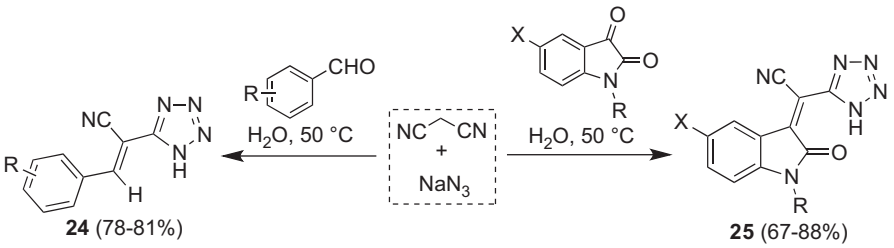
In a different approach, Alonso and Yus [18] reported a three-component synthesis of β-hydroxyalkyl-1,2,3-triazoles from the three-component reaction of sodium azide, a series of epoxides and alkynes in water, in the presence of copper nanoparticles (CuNPs) on activated carbon as the catalyst (Scheme 1.12).



Scheme 1.12

3.5 Tetrazoles

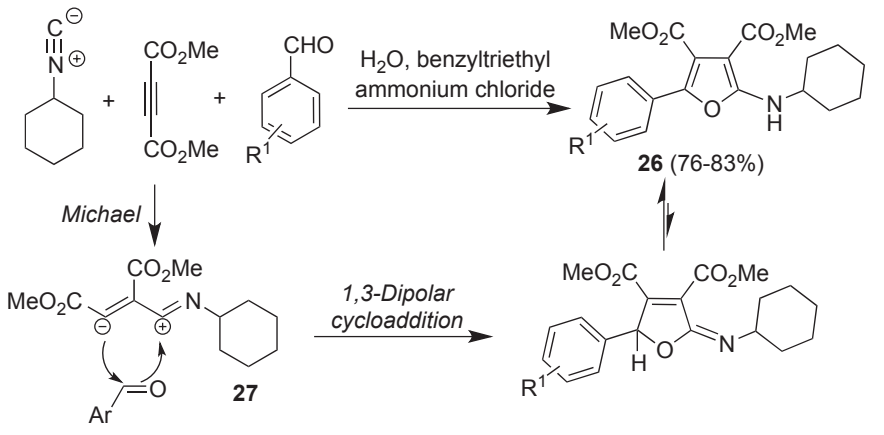
Dabiri has developed a catalyst-free three-component synthesis of a series of structurally diverse 5-substituted tetrazoles **24** and **25** in good yields under mild conditions from carbonyl compounds (including benzaldehydes, isatin and ninhydrin), malononitrile and sodium azide in water [19]. This process can be assumed to proceed through a domino Knoevenagel condensation/1,3-dipolar cycloaddition sequence (Scheme 1.13).



Scheme 1.13

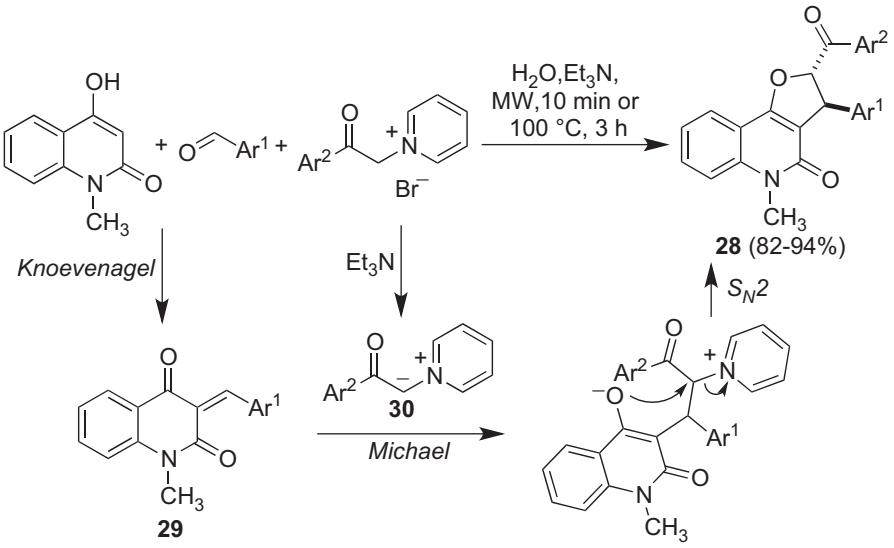
4 Oxygen and Sulphur-Containing Five-Membered Heterocycles and their Fused Derivatives

Some interesting multicomponent syntheses of simple furan derivatives in water have been disclosed. For instance, Yadav reported the preparation of highly functionalized 2-aminofuran derivatives **26** in water via the coupling of aldehydes with dimethyl acetylenedicarboxylate and cyclohexyl isocyanide [20]. This transformation presumably starts by the initial Michael addition of the isocyanide onto the acetylenedicarboxylate diester, generating the 1,3-dipole **27**, whose subsequent [3+2] cycloaddition to the aldehyde carbonyl followed by tautomerization leads to the observed product (Scheme 1.14).



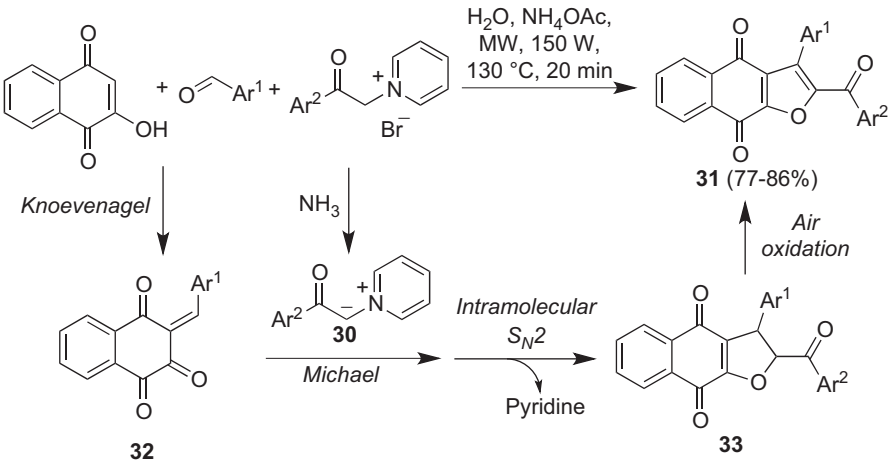
Scheme 1.14

Fused dihydrofuran systems have been prepared via MCRs in water by Perumal, whose group developed a protocol for the synthesis of novel *trans*-2-aroyl-5-methyl-3-aryl-3,5-dihydrofuro[3,2-*c*]quinolin-4(2*H*)-ones **28** in good yields from the three-component reaction of 4-hydroxy-1-methylcarbostyryl, aromatic aldehydes and pyridinium salts obtained from phenacyl bromides and pyridine [21]. This green domino transformation was performed in the presence of a catalytic amount of triethylamine in water under microwave irradiation, presumably via the generation of an α,β-βunsaturated diketone **29** by Knoevenagel reaction between the carbostyryl and aldehyde components and ylide **30**, arising from deprotonation of the pyridinium salt. A Michael addition between **29** and **30** followed by intramolecular cyclization via S_N2 displacement of a molecule of pyridine completes the formation of the final products **28** (Scheme 1.15).



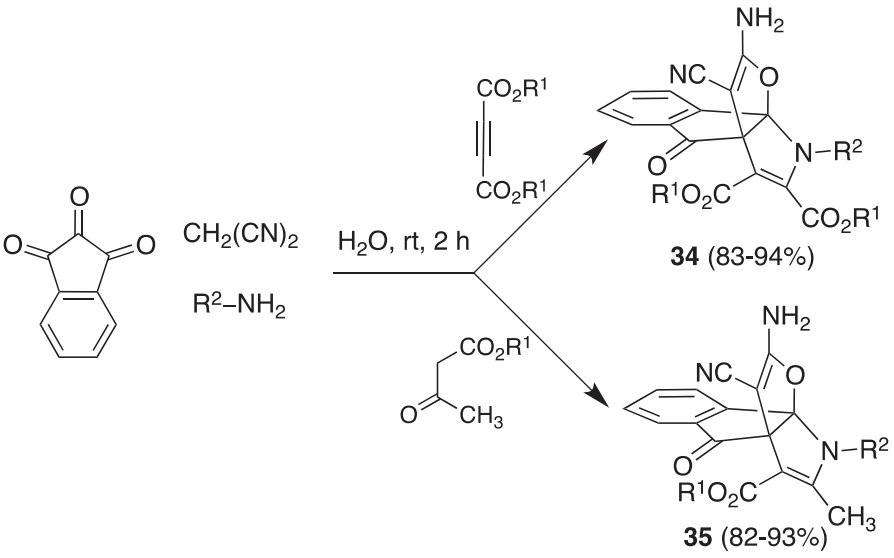
Scheme 1.15

In a related transformation, the same group described a three-component domino reaction of 2-hydroxy-1,4-naphthoquinone, acting as a β-dicarbonyl surrogate, aromatic aldehydes and 1-(2-oxo-2-phenylethyl)pyridinium bromides in the presence of ammonium acetate, in water under microwave irradiation, that affords naphtho[2,3-*b*]furan-4,9-diones **31** [22]. Mechanistically, this domino reaction probably follows the same Knoevenagel–Michael intramolecular S_N2 pathway described for the preparation of compounds **28**, with ammonium acetate acting in this case as the base, to give intermediates **33**. These compounds, which can be considered as tautomers of a hydroquinone species, would be finally transformed into the observed quinones by air-promoted oxidation, yielding the final products **31** (Scheme 1.16).



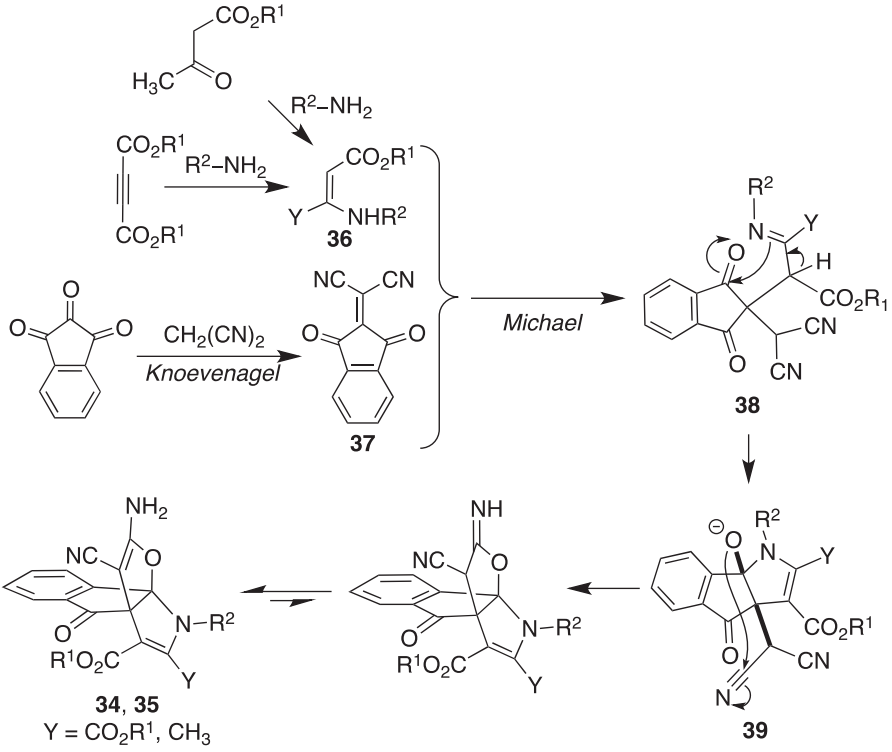
Scheme 1.16

Alizadeh has disclosed a highly chemoselective heteroannulation protocol for the synthesis of polysubstituted heterocyclic[3.3.3]propellane systems comprising dihydropyrrole and dihydrofuran rings (compounds **34** and **35**) from the sequential four-component reaction in water at room temperature between ninhydrin, malononitrile, primary amines and a fourth component chosen between dialkyl acetylenedicarboxylates or β-ketoesters [23] (Scheme 1.17).



Scheme 1.17

This complex transformation proceeds through the initial generation of enamine **36**, either from addition of the starting amine to the acetylene dicarboxylate component or by its condensation with the β-dicarbonyl compound. Simultaneously, the Knoevenagel condensation between ninhydrin and malononitrile affords the Michael acceptor **37**, and combination of both intermediates furnishes an open-chain zwitterion intermediate that equilibrates to neutral species **38** by intramolecular proton migration. Imine–enamine tautomerism followed by a nucleophilic addition of the amino group to either of the remaining ninhydrin carbonyl groups leads to **39**, which undergoes a final 5-*exo-dig* cyclization by nucleophilic attack of the former carbonyl oxygen onto one of the nitrile groups, followed by imine–enamine tautomerization, leading to the observed final products (Scheme 1.18).



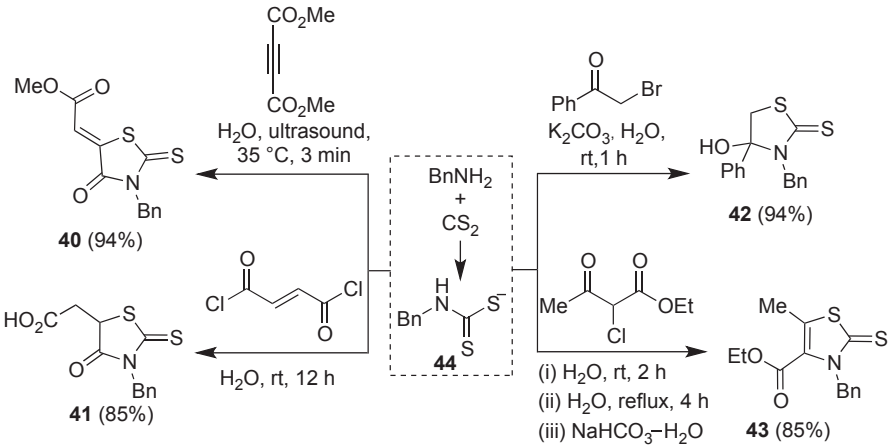
Scheme 1.18

Several authors have exploited MCRs in water starting from carbon disulfide, primary amines and carbon dielectrophiles for the construction of 1,3-thiazole derivatives. Representative examples are summarized in Scheme 1.19 and include:

1. The three-component reaction of dimethyl acetylenedicarboxylate, carbon disulfide and benzylamine in water under ultrasonic irradiation or high-speed (1500 rpm) stirring to give rhodanine derivative **40** in excellent yield [24].

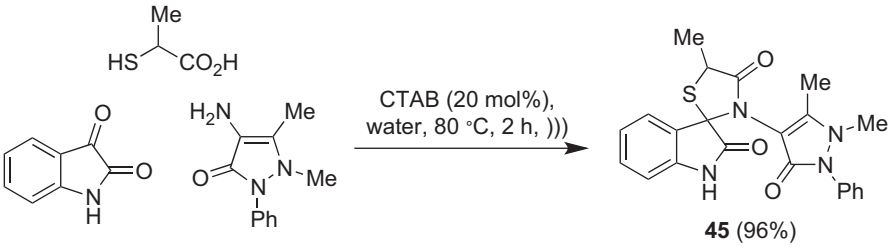
2. The catalyst-free three-component reaction between fumaryl chloride, carbon disulfide and benzylamine in water at room temperature to give 2-(3-alkyl-4-oxo-2-thioxo-1,3-thiazolan-5-yl)acetic acid derivatives **41** [25].
3. The synthesis of multisubstituted thiazolidine-2-thione derivatives **42** in good to excellent yields via a three-component reaction of amines, carbon disulfide and α-bromoketones in water in the presence of K_2CO_3 as base [26].
4. When 2-chloro-1,3-dicarbonyl compounds were used instead of α-bromoketones, N-alkylthiazoline-2-thiones **43** were obtained in good to excellent yields [27].

All these reactions start by the addition of the starting amine to carbon disulfide to yield intermediate **44**, which then adds in various fashions to the organic electrophiles.



Scheme 1.19

Recently, an ultrasound-promoted synthesis of a series of medicinally relevant derivatives of the spiro[indole-thiazolidinone] ring system (compound **45**) has been carried out from the three-component reaction of isatin, a 4-aminopyrazolin-3-one derivative and 2-mercaptopropionic acid in water, using cetyltrimethylammonium bromide (CTAB) as a phase-transfer catalyst (Scheme 1.20). This protocol avoided the need for either azeotropic removal of water or the use of a dehydrating agent, as required by conventional methods [28].

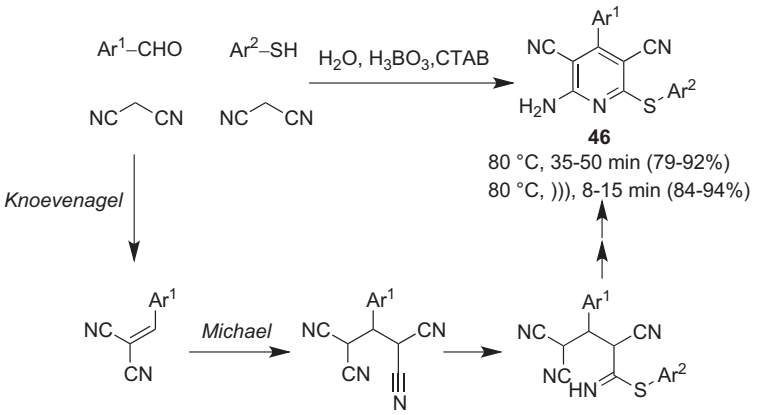


Scheme 1.20

5 Six-Membered Nitrogen-Only Heterocycles and their Fused Derivatives

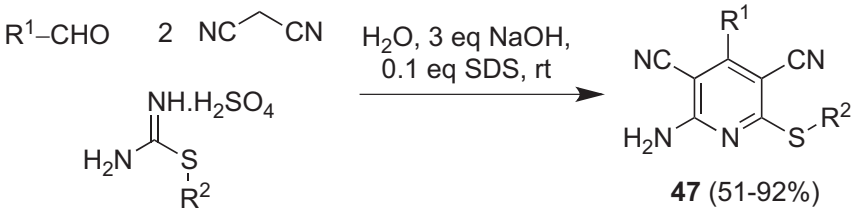
5.1 Pyridines

Because of the huge importance of pyridine derivatives, a considerable amount of effort has been directed to the development of multicomponent routes for their synthesis, including reactions performed in water. For instance, a one-pot four-component condensation of aldehydes, malononitrile and thiophenols in the presence of boric acid as catalyst in aqueous medium afforded high yields of 2-amino-3,5-dicarbonitrile-6-thiopyridines **46** [29], either by conventional heating or under ultrasound-aided conditions (Scheme 1.21). This reaction can also be performed in an aqueous suspension of basic alumina [30] or in water with microporous molecular sieves as catalysts [31]. Mechanistically, this transformation involves an initial Knoevenagel condensation of the aldehyde with a molecule of malononitrile, followed by the Michael addition of the second molecule of malononitrile, reaction of one of the nitrile groups with the thiol, cyclization and a final air oxidation step.



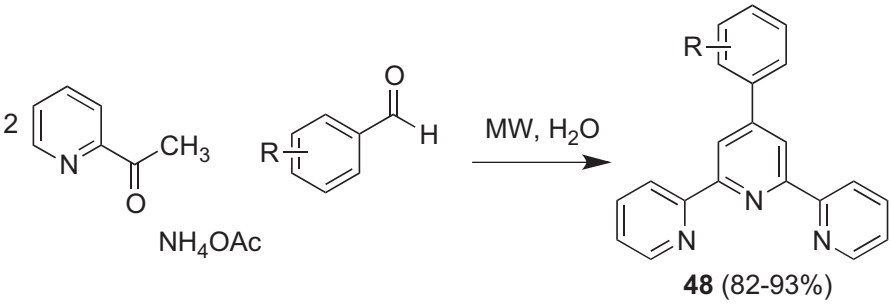
Scheme 1.21

In an analogous strategy, a one-pot, three-component reaction of aldehydes with a S-alkylisothiouronium salt and malononitrile in water in the presence of an inorganic base and SDS as a phase-transfer catalyst provided a method for synthesizing 2-amino-4-aryl(alkyl)-6-alkylsulphanyl pyridine-3,5-dicarbonitriles **47** [32] (Scheme 1.22).



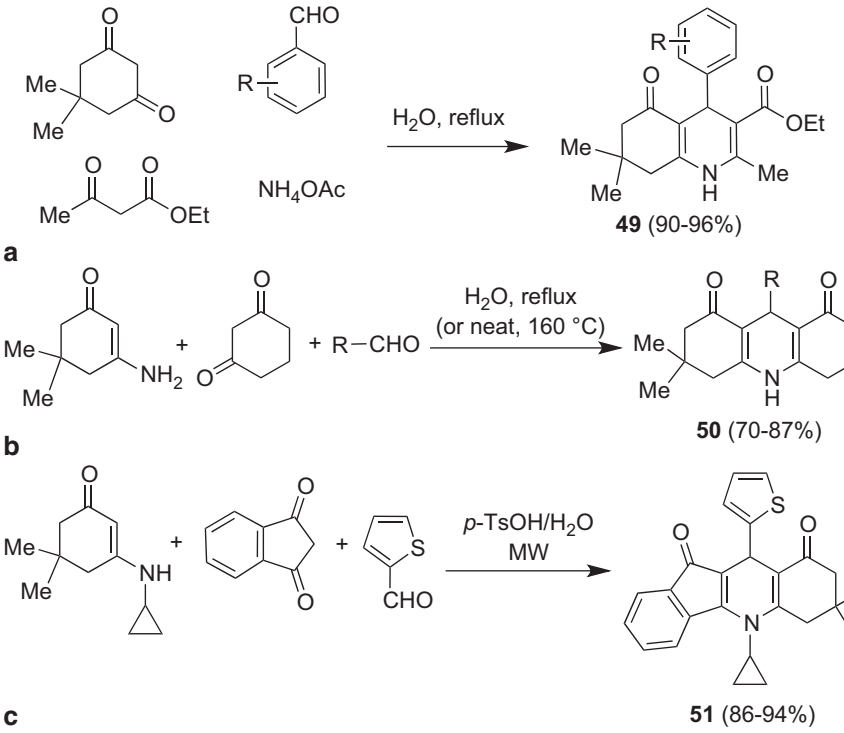
Scheme 1.22

2,4,6-triarylpyridines were synthesized in water by an application of the Krönke pyridine synthesis, i.e. a pseudo four-component reaction between aromatic ketones and aromatic aldehydes in a 2:1 molar ratio in the presence of ammonium acetate as the nitrogen source, under microwave irradiation [33]. In this specific case, the authors focused their attention on reactions starting from 2-acetylpyridine, which led to a method for the preparation of 4′-aryl-2,2′:6′,2″-terpyridines **48**, potentially useful as ligands in coordination chemistry (Scheme 1.23).



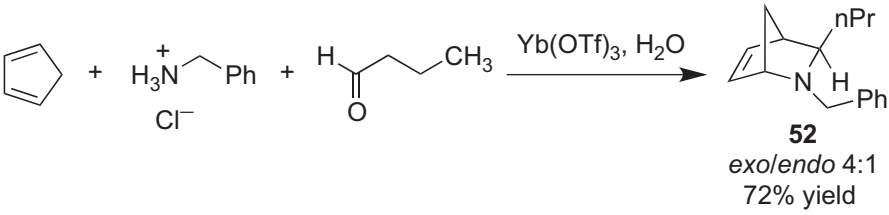
Scheme 1.23

The Hantzsch reaction is the most widely employed method for the preparation of dihydropyridines. Khadilkar reported the possibility to perform the Hantzsch dihydropyridine synthesis in water under microwave irradiation in an unmodified domestic microwave oven. In this reaction, aqueous sodium butylmonoglycolsulphate was used as an additive (hydrotrope) to enhance the aqueous solubility of the reactants [34]. Following this early precedent, other authors have investigated Hantzsch or Hantzsch-like reactions in water, and thus Bandgar developed a four-component synthesis of 1,4,5,6,7,8-hexahydroquinoline-3-caboxylates **49** from the reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in water, wherein the products could be isolated by simple filtration [35]. Similarly, unsymmetrical acridinediones **50** were synthesised by Wang from the three-component reaction of cyclic enaminone with aldehyde and 1,3-cyclohexanedione in water under reflux [36]. Tu performed a related transformation allowing the synthesis of indenoquinoline derivatives 51 from aldehydes, 1,3-indanedione and enaminones in aqueous medium in the presence of *p*-TsOH under microwave irradiation [37]. These reactions are summarized in Scheme 1.24.



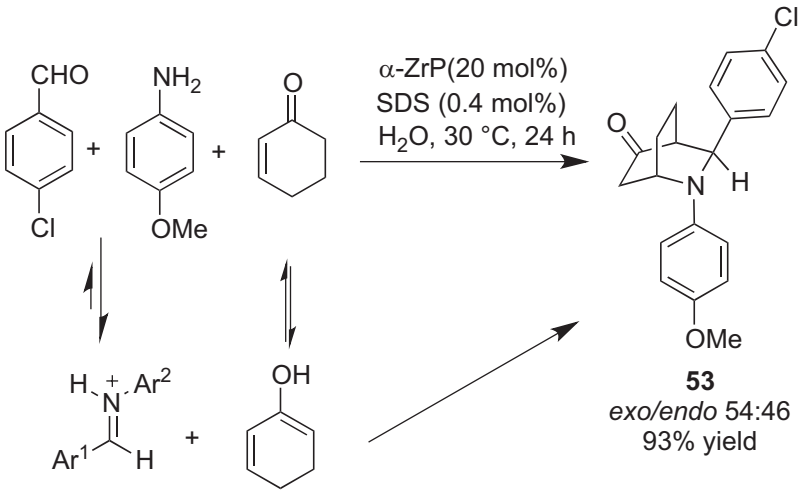
Scheme 1.24

Wang discovered that the imino Diels–Alder reaction of simple aldehydes, amine hydrochlorides and dienes, initially reported by Grieco, could be performed in water in the pH range of 5–7 in the presence of lanthanide triflates as Lewis acid catalysts to obtain 2-benzyl-3-ethyl-2-azabicyclo[2.2.1]hept-5-ene derivatives **52** [38] (Scheme 1.25).



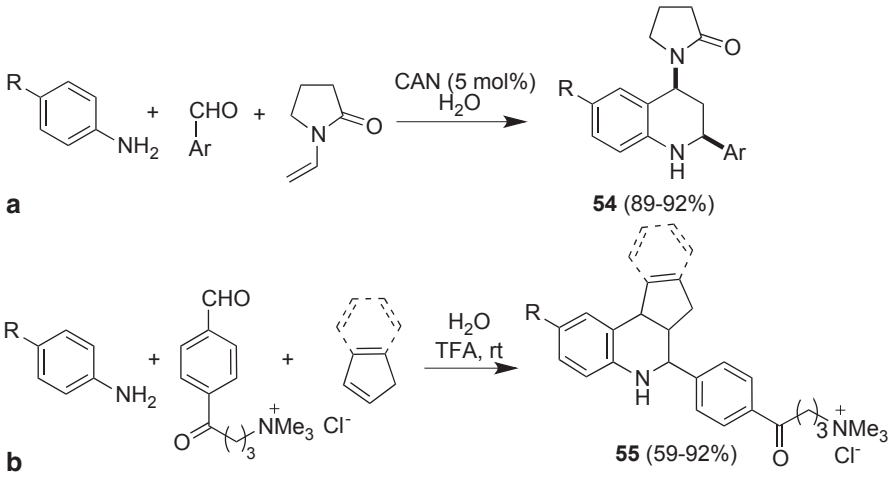
Scheme 1.25

In a different approach to performing hetero Diels–Alder reactions in water, Piermatti reported three-component aza Diels–Alder reaction of 2-cyclohexen-1-one, aniline and aldehyde in water in the presence of α-zirconium hydrogenphosphate (α-ZrP) and SDS for the synthesis of diaryl-2-azabicyclo[2.2.2]octan-5-ones **53** [39]. The reactions performed in water at room temperature had higher *exo* selectivities than in organic solvents (Scheme 1.26).



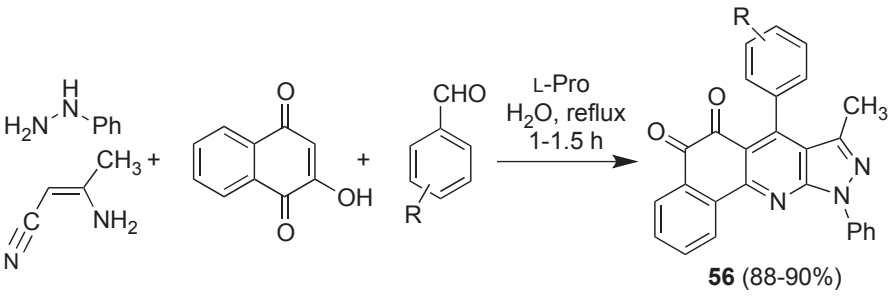
Scheme 1.26

The Povarov reaction is related to the previous examples in that it can be defined as the formal imino Diels–Alder reaction between aromatic imines and electron-rich olefins. It is one of the most popular methods for the synthesis of tetrahydroquinolines [40], and two examples of Povarov reactions in water are summarized in Scheme 1.27. In an early example of the use of ceric ammonium nitrate as a catalyst in synthesis [41], Perumal reported a few examples of a CAN-catalyzed Povarov reaction of aldehydes, amines and N-vinylpyrrolidin-2-ones as the olefin component in water for the synthesis of heteroaryl-substituted tetrahydroquinolines **54** [42]. Using a different approach, Vaultier later described an onium salt-supported Povarov three-component reaction in water at room temperature affording tricyclic compounds **55**. In this study, either the aldehyde or the amine components were linked to a side chain containing an onium salt, which confers solubility to the reactant [43].



Scheme 1.27

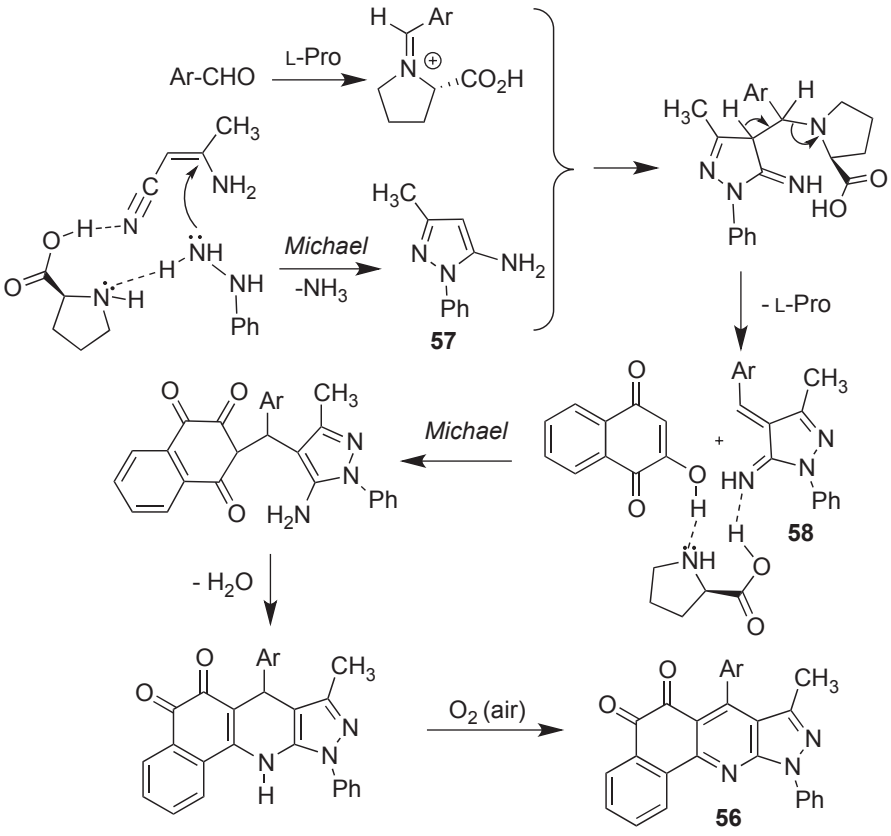
In a more complex process leading to the formation of pyrazole and pyridine rings in the same synthetic operation, Perumal and Menéndez reported a four-component sequential reaction in water of phenylhydrazine, 3-aminocrotononitrile, 2-hydroxynaphthoquinone and substituted benzaldehydes, employing L-proline as an organocatalyst [44]. This reaction provided a green, highly convergent protocol for the synthesis of 7-aryl-8-methyl-10-phenyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6-diones **56**, containing a biologically relevant tetracyclic *ortho*-quinone core, as shown in Scheme 1.28.



Scheme 1.28

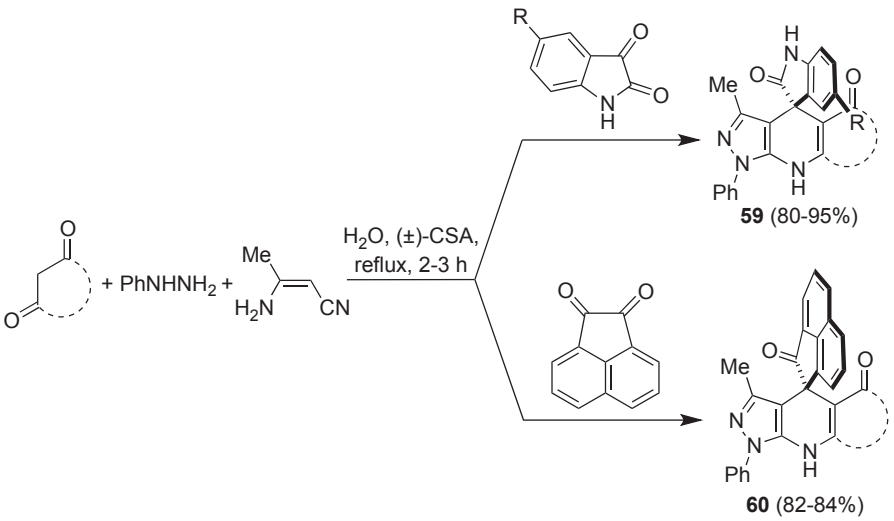
This transformation presumably involves the initial formation of pyrazolamine **57** and its L-proline-promoted conversion to azadiene **58**. This intermediate gives a Michael addition with 2-hydroxy-1,4-naphthoquinone affording a naphthotrione

intermediate, which undergoes an intramolecular annulation followed by air oxidation, furnishing **56** (Scheme 1.29).



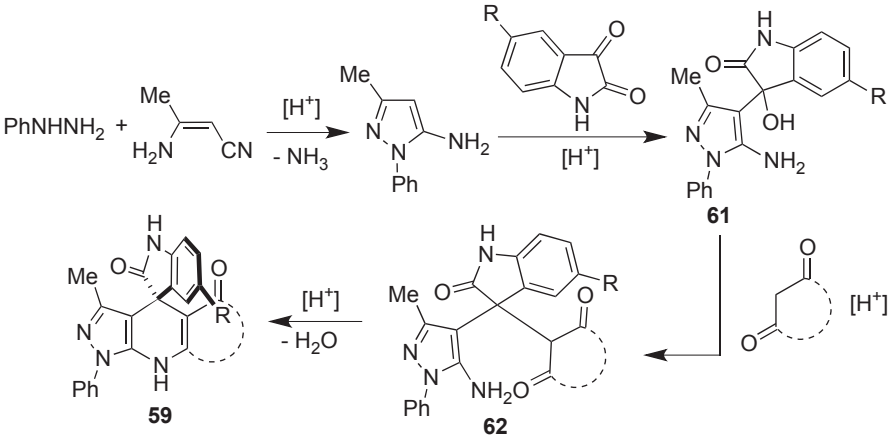
Scheme 1.29

In related work, the same researchers described a four-component domino reaction that allows the one-pot synthesis of highly complex spiro systems, i.e. spiro[indoline/acenaphthylene-3,4-pyrazolo[3,4-*b*]pyridine derivatives **59** and **60** from phenylhydrazine, 3-aminocrotononitrile, isatin or acenaphthylene-1,2-dione and cyclic 1,3-dicarbonyl compounds, including cyclohexane-1,3-diones and barbituric or thiobarbituric acid, in the presence of (±)-camphor-10-sulphonic acid (CSA) as catalyst (Scheme 1.30).



Scheme 1.30

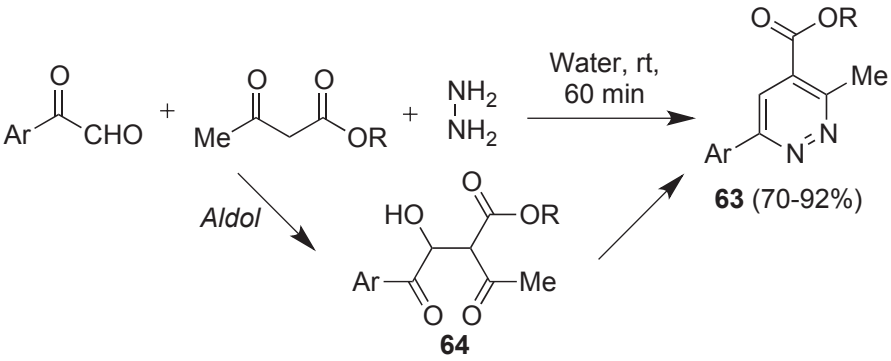
The mechanism proposed to explain this domino sequence of reactions is summarized in Scheme 1.31 for the case of the reactions with isatin, and was proposed to be initiated by the formation of 5-amino-3-methyl-1-phenylpyrazole from phenylhydrazine and 3-aminocrotononitrile. Its acid-catalyzed reaction with isatin leads to **61**, which was proved to be an intermediate of the reaction by its isolation by reducing the reaction time and its transformation in the final products under the standard reaction conditions. The combination of **61** with the starting cyclic 1,3-dicarbonyl compounds, again under acidic catalysis, would then afford intermediate **62**, and then the observed product **59** after a final cyclocondensation step with loss of a molecule of water [45].



Scheme 1.31

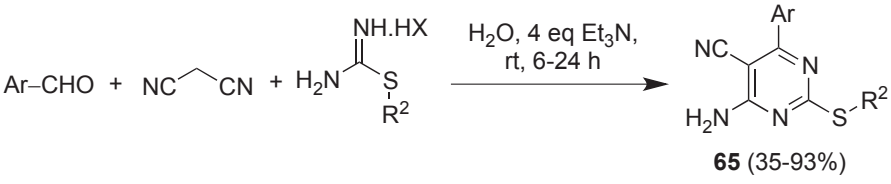
6 Diazines

A method for preparing alkyl 6-aryl-3-methylpyridazine-4-carboxylates **63** from β-ketoesters, arylglyoxal derivatives and hydrazine in water was developed by Khalafy (Scheme 1.32). The key step of this three-component transformation was proposed to be the generation of a 3-hydroxy-1,4-dicarbonyl intermediate **64** from the aldol reaction between the ketoester and arylglyoxal components [46], although the same group subsequently proposed an initial Knoevenagel condensation for a very similar transformation starting from ethyl butyrylacetate [47]. This intermediate then undergoes a double condensation with hydrazine to form the cyclized product. The use of 1,3-cyclohexanedione and dimedone under the same conditions afforded cinnoline derivatives [48].



Scheme 1.32

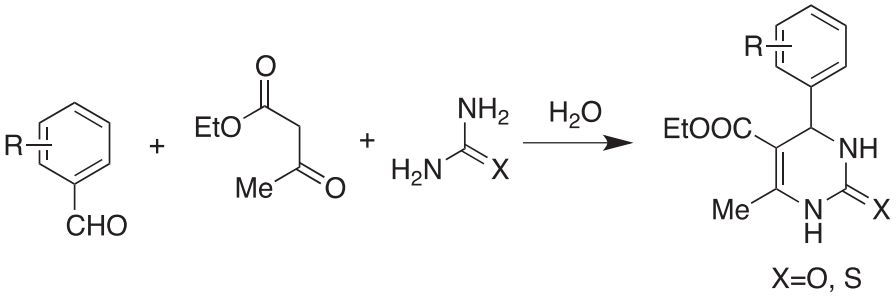
In the course of the work summarized in Scheme 1.22, involving the three-component reaction of aldehydes, malononitrile and S-alkylisothiouronium salts in water, the authors noticed the formation of small amounts of pyrimidine derivatives **65**. After some optimization work, they discovered that by removing SDS and replacing sodium hydroxide by triethylamine, the pyrimidine became the sole product in moderate to good yields [49] (Scheme 1.33).



Scheme 1.33

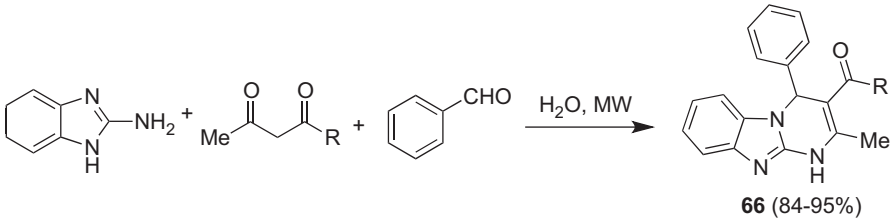
The Biginelli reaction between β-ketoesters, aromatic aldehydes and urea is one of the best-studied approaches to 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 1.34). This reaction was found to proceed expediently in water, with easy workup and

the ability to tolerate a wide variety of substitutions in all three components. A variety of catalysts have been reported for this transformation, including KSF clay [50], metal triflimides [51], cerium (III) chloride [52] and polystyrenesulphonic acid (PSSA) [53]. Using a water-based biphasic Biginelli reaction, Bose developed a method for the large-scale manufacturing of dihydropyrimidones in high yield and purity [54].



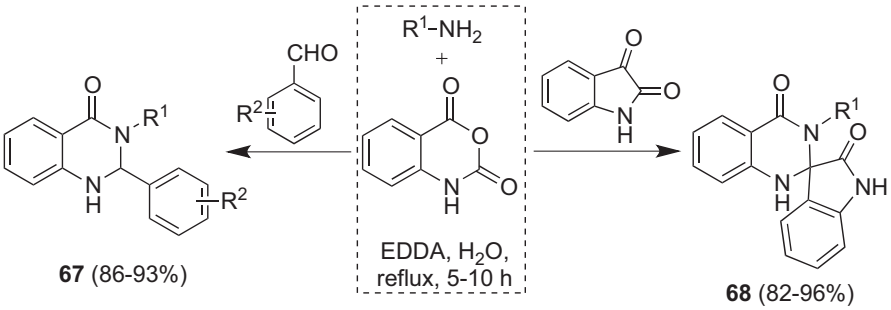
Scheme 1.34

In a reaction leading to fused pyrimidine derivatives, the group led by Tu reported a catalyst-free, three-component reaction of aldehydes, β-dicarbonyl compounds and 2-aminobenzimidazole under microwave irradiation in water affording functionalized imidazopyrimidine derivatives **66** via a Hantzsch-like mechanism [55], as shown in Scheme 1.35.



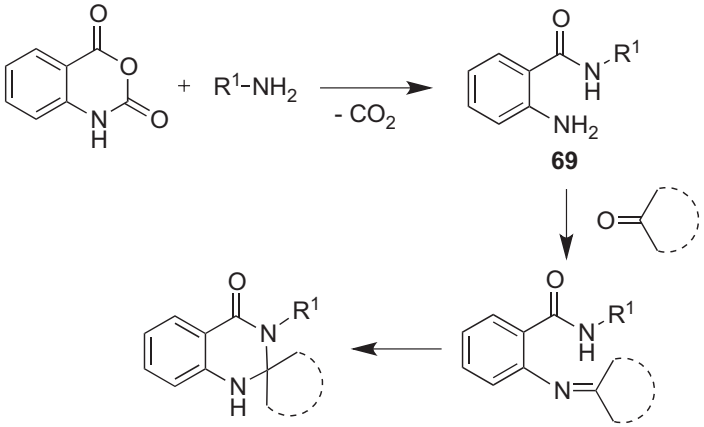
Scheme 1.35

Quinazolines and their spiro derivatives are also available via MCRs in water. The three-component condensation of isatoic anhydride, primary amines and aromatic aldehydes or isatin to give 2,3-dihydroquinazolin-4(1*H*)-ones **67** or spirooxindole derivatives **68** (Scheme 1.36) was performed in water using ethylenediamine diacetate (EDDA) as catalyst [56].



Scheme 1.36

Mechanistically, this transformation is probably initiated by the reaction between the primary amine and isatoic anhydride to give a carbamic acid derivative that spontaneously decarboxylates to afford anthranylamide derivative **69**. The reaction of the latter with the carbonyl component affords the corresponding imine, which undergoes a final intramolecular 6-*endo*-*trig* cyclization to give the final product, as summarized in Scheme 1.37 [57].

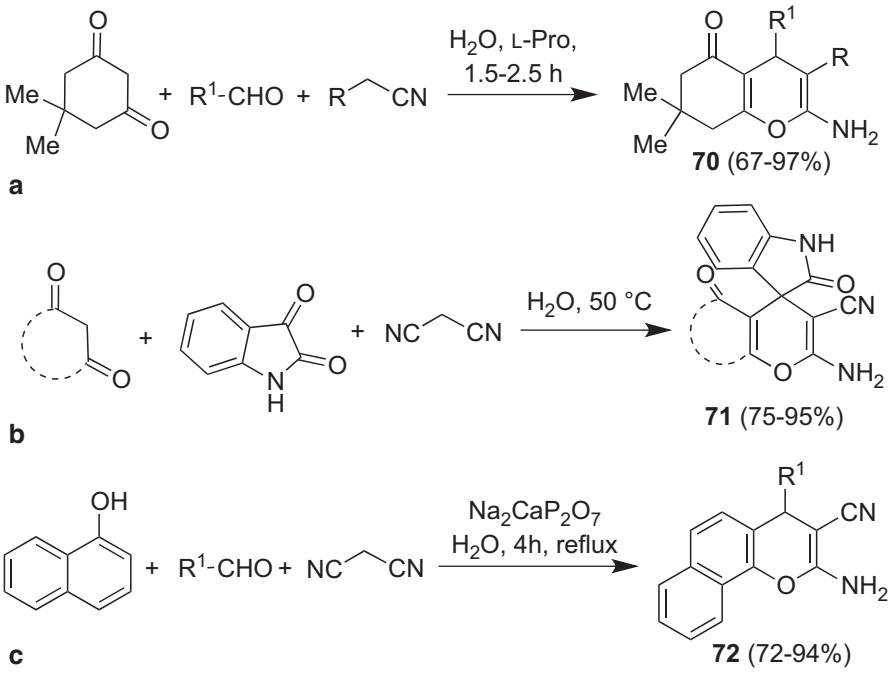


Scheme 1.37

7 Six-Membered Oxygen-Only Heterocycles and their Fused Derivatives

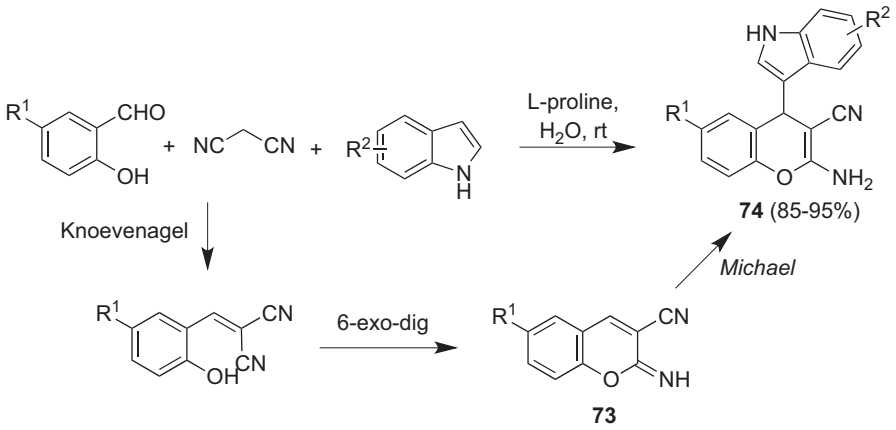
A number of groups have reported MCRs in water involving the construction of pyran rings (Scheme 1.38). One example is the (*S*)-proline-catalyzed three-component reaction in water between aromatic aldehydes, a nitrile acting as an active methylene

compound and dimedone to afford fused pyran derivatives **70** [58]. Similarly, Zhao reported a catalyst-free three-component reaction in water between isatins, malononitrile and a variety of cyclic β-dicarbonyl substrates for the fast synthesis of a range of structurally diverse spirooxindole derivatives **71** [59]. Finally, we will mention the work of Zahouily, who showed the possibility of using naphthol derivatives as surrogates for the β-dicarbonyl component, leading to the synthesis of fused 2-aminochromenes **72** from the three-component reaction of 1-naphthol, malononitrile and aldehyde in water in the presence of nanostructured diphosphate $Na_2CaP_2O_7$ as catalyst [60].



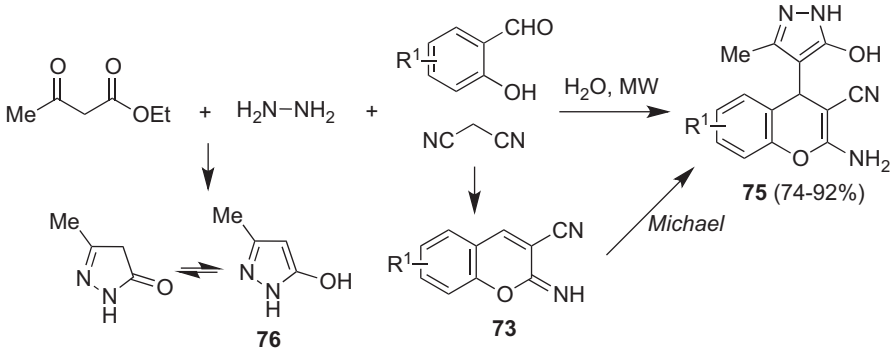
Scheme 1.38

In a different approach to the synthesis of chromane derivatives, Perumal developed a three-component reaction between salicylaldehyde, malononitrile and indole in water using L-proline as the catalyst (Scheme 1.39). In the mechanism of this transformation, indole reacts readily via a Michael addition with a 2-imino-3-chromene-3-carbonitrile intermediate **73**, generated from salicylaldehyde and malononitrile in water, to furnish compounds **74** [61].



Scheme 1.39

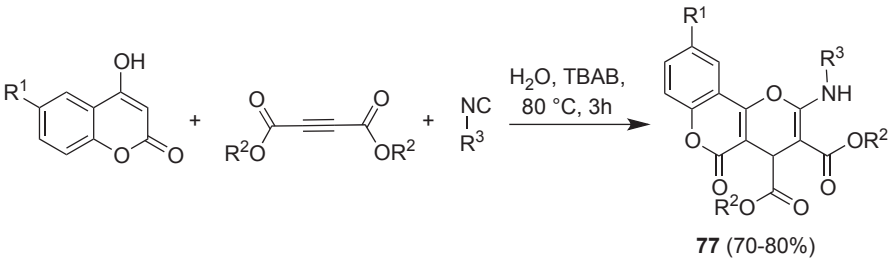
Vasuki and her group investigated a related, catalyst-free synthesis of 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitriles **75** (Scheme 1.40). Their method involved a four-component reaction between hydrazine hydrate, ethyl acetoacetate, 2-hydroxybenzaldehydes and malononitrile in water at room temperature, which must take place via the parallel generation of 3-methyl-5-hydroxypyrazol **76** from the first two components and intermediate **73** from the third and fourth ones, followed by their final combination by a Michael addition [62].



Scheme 1.40

In the presence of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst, a three-component reaction of an isocyanide, dialkyl acetylenedicarboxylate and 4-hydroxycoumarin or its 6-Me derivative in water at 80 °C, which generated

pyrano[3,2-*c*]-coumarin derivatives **77** in good yields (Scheme 1.41). The formal [3 + 3] cycloaddition may proceed through the addition of the 4-hydroxycoumarin derivative to the dialkyl acetylenedicarboxylate to form an anionic intermediate that would then add to the isonitrile carbon, finally generating the tricyclic product by formation of a carbon–oxygen bond [63].



Scheme 1.41

8 Other Six-Membered Heterocycles

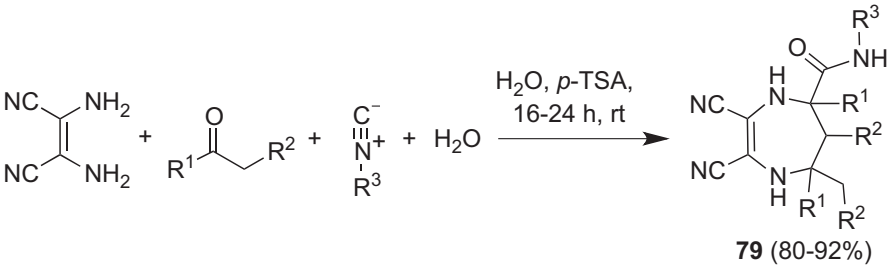
Fused 1,3-oxazines containing a bridgehead nitrogen atom (compounds **78**) are readily available by the three-component reactions between isoquinoline, phenacyl bromides and epoxides in a basic aqueous micellar system (Scheme 1.42). In many other solvents, such as hexane, THF, acetonitrile and toluene, the yield of the product decreased, indicating that water plays an indispensable role in accelerating this reaction [64].

Scheme 1.42

9 Seven-Membered Heterocycles

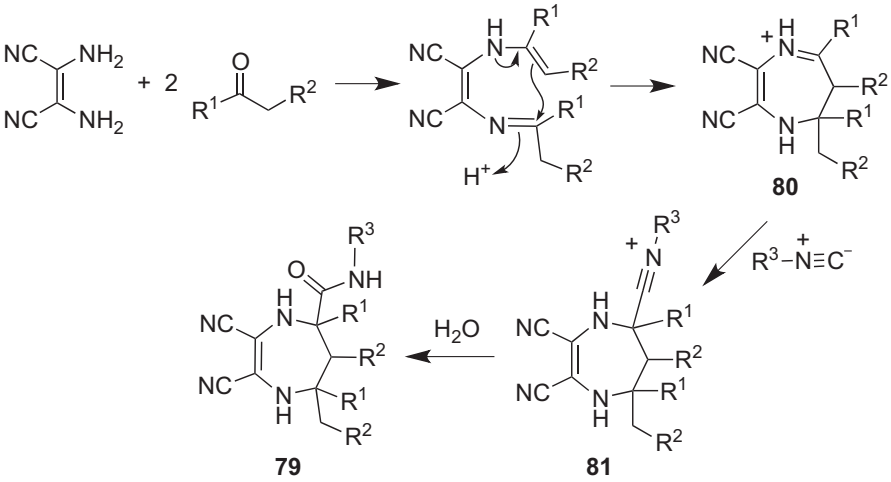
Shaabani reported a pseudo-five-component synthesis of 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives **79** from 2,3-diaminomaleonitrile, a cyclic or acyclic ketone, an isocyanide and a molecule of water in the presence of a catalytic

amount of *p*-toluenesulphonic acid in water as solvent at ambient temperature (Scheme 1.43). It is interesting to underscore the double role of water, which serves both as a reactant and as the reaction medium.



Scheme 1.43

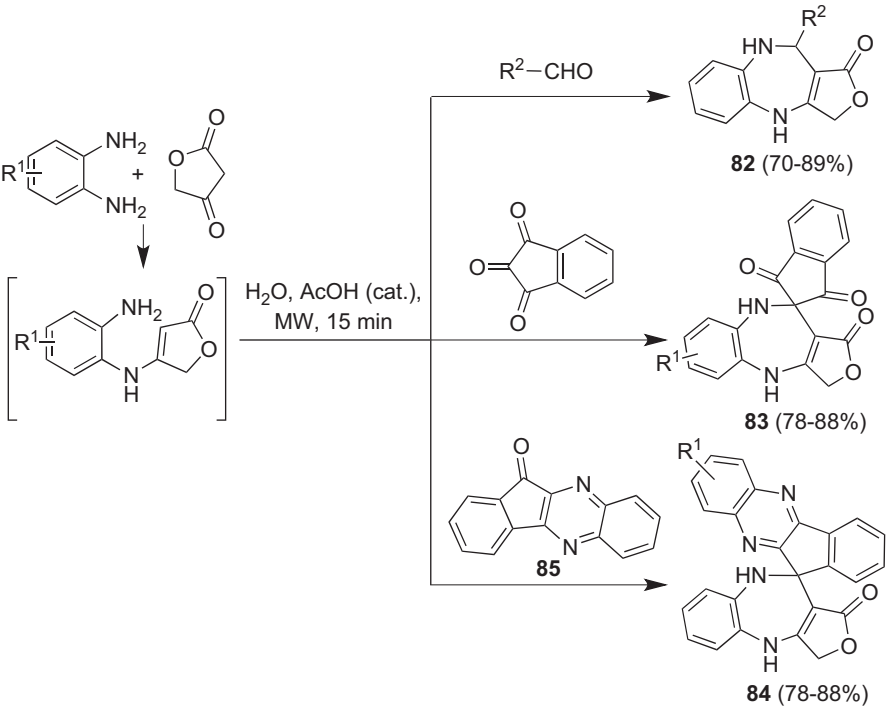
The mechanism proposed for this complex transformation is summarized in Scheme 1.44. It involves the initial reaction between 2,3-diaminomaleonitrile and two molecules of the carbonyl compound, yielding a double imine. The monoamine tautomer of this intermediate undergoes an intramolecular cyclization that affords iminium derivative **80**, which reacts with the isonitrile to give **81**. A hydrolysis step affords the final product **79** [65].



Scheme 1.44

Li has described a three-component reaction of benzene-1,2-diamines, tetronic acid and aldehydes in water containing a catalytic amount of acetic acid under microwave irradiation, provides a broad range of type benzo[*f*]azulen-1-ones **82** [66],

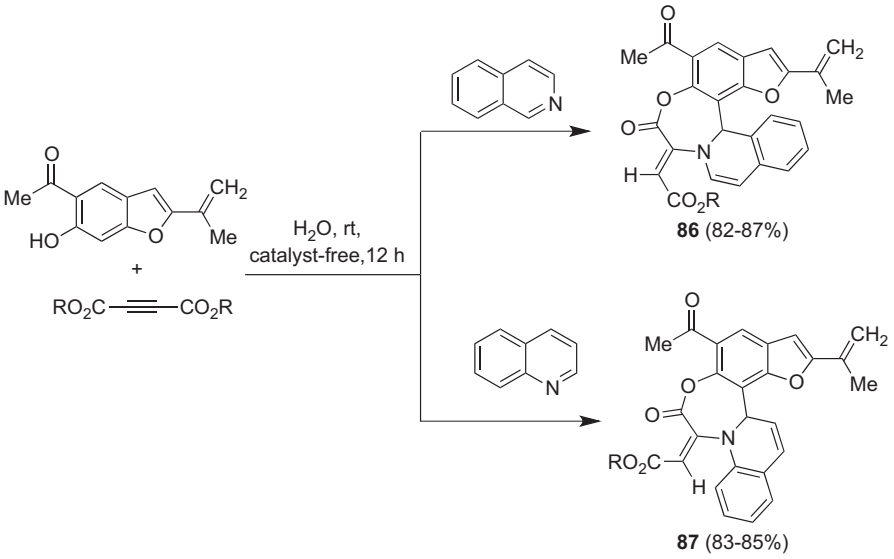
generating three new bonds and presumably via the formation of an intermediate β-enaminone (Scheme 1.45). Almost simultaneously, the same group published the extension of this chemistry for the preparation of spiro benzo[*b*]furo[3,4-*e*][1,4]diazepines like **83** and **84** in good to excellent yields using ketones such as ninhydrin or the indenoquinoxaline derivative **85**, respectively [67]. These reactions have the advantage of providing materials that do not require purification via chromatography and recrystallization could also be avoided, since the pure products were obtained simply by washing with 95% EtOH. Therefore, Li ascribes these reactions to the *Group-Assisted Purification* (GAP) concept that he had defined in the context of previous work.



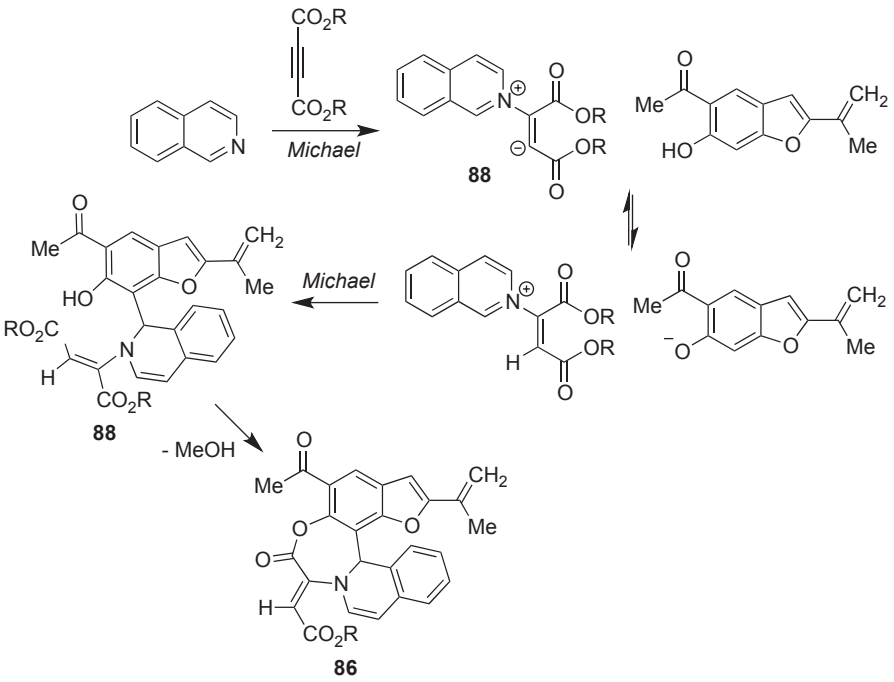
Scheme 1.45

As shown in Scheme 1.46, a simple synthesis of complex fused 1,4-benzoxazepin-2-one derivatives **86** and **87** was achieved via a three-component reaction of quinoline or isoquinoline, acetylene dicarboxylic esters and 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone in water, in the absence of any catalyst [68]. Presumably, this transformation proceeds via the initial formation of a 1:1 zwitterionic intermediate **88** from the Michael addition of isoquinoline (or quinolone) to the activated ester. A proton transfer reaction takes then place in which this species is protonated by the phenol group in the 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone substrate, and this is followed by a second Michael addition of the resulting phenoxide anion to the isoquinolinium ion to afford intermediate **88**, containing benzofuryl and isoquinoline ring systems. This intermediate then undergoes

a lactonization that creates the final pentacyclic ring system via transesterification with concomitant elimination of methanol to furnish the final product (Scheme 1.47).



Scheme 1.46



Scheme 1.47

10 Conclusions

We trust that this chapter sufficiently illustrates the utility of MCRs in aqueous media in the efficient assembly of heterocycles of varied structural complexity and diversity. Water has proved to be a useful solvent for a variety of transformations leading to the efficient construction of ring systems. In some reactions, it was found that the reaction occurs only in water and in many others higher yields were obtained in water than in organic solvents. In appropriate cases, water plays multiple roles including those of a reactant, a solvent and even a catalyst in the case of 'on water' processes. We hope that the information contained here encourages the readers to make use of these green protocols for the efficient and eco-friendly construction of novel heterocyclic frameworks.

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Chapter 2
Sustainable Approaches Towards the Synthesis of Quinoxalines

Pradeep S. Jadhavar, Dinesh Kumar, Priyank Purohit, Bhavin V. Pipaliya, Asim Kumar, Srikant Bhagat and Asit K. Chakraborti

Contents

Abstract The quinoxaline (Qx) nucleus is present in various bioactive molecules. Thus, synthesis of Qxs continues to draw the attention of synthetic organic/medicinal chemists. The contemporary interest in search for newer synthetic methods for this privileged class of compounds remains unabated and a vast number of publications continue to appear. The focus of this chapter is on the research works published in this area after the year 2000 with the inherent objective to attain sustainability towards the synthesis. The attention will be on the key sustainable approaches of pharmaceutical industries like the solvent-free reactions, use of alternate reaction media (e.g., water, fluorous alcohols, polyethylene glycols, and ionic liquids), and alternate modes of synthesis such as microwave-assisted synthesis and flow reactions.

Keywords Quinoxaline · Bioactivity · Sustainable synthesis

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1 Introduction

Heterocyclic compounds, especially the N-heterocycles, are the most important class of compounds in the pharmaceutical and agrochemical industries. There is a strong preponderance (~60%) of N-containing heterocycles among the drug candidate molecules [1]. The 6-membered aromatic rings containing two nitrogen atoms, such as phthalazine, quinazoline, pyrimidines, and quinoxalines (Qxs), possess a broad spectrum of biological activities and are therefore of interest as target compounds in pharmaceutical and medicinal chemistry. Qx, the diazine derivative, is a heterocyclic compound comprising of a benzene ring fused with pyrazine ring. Qx and its derivatives are important nitrogen-containing heterocycles due to their broad spectrum of biological activities [2] and applications in material science [3].

2 Biological Importance of Quinoxalines (Qxs)

The Qx-based compounds exhibit versatile biological activities that include anticancer [4], antimicrobial/antitubercular [5], antiprotozoal [6], antiviral [7], inhibition of the enzyme phosphodiesterase [8], anti-inflammatory [9], etc.

The Qx derivatives are known for their cancer chemopreventive effect [4a]. The compounds **1–4** have been recently identified as potent and selective inhibitors of human tyrosine kinase (TRK) in liver cancer HepG2 and breast cancer MCF-7 cell lines similar to the known anticancer drug doxorubicin [4a]. The transglutaminase 2 (TGase 2) inhibitory activity has been exhibited by **5** [4b]. The TGase 2 is a cross-linking enzyme which plays an important role in oncogenesis by inducing NF-κB activation through I-κBα polymerization which leads to the increase of pro-survival factors and suppression of apoptosis. The Qx urea analog **6** acts on IKKβ and thereby inhibits the mTOR (mammalian target of rapamycin) and NF-κB pathways in pancreatic cancer and has shown good oral bioavailability along with *in vivo* efficacy, and being devoid of toxicities it becomes a viable cancer therapeutic [4c]. The structure–activity relationship (SAR) of these Qx ureas has been further elaborated through evaluation of a library of quinoxalin-6-amine derivatives against a panel of cancer cell lines [4e] (Fig. 2.1).

The Qx derivatives have shown interesting antimicrobial properties (antibacterial, antiviral, antifungal, antiprotozoal, etc.) and assessment of their therapeutic potential is still an active area of research in medicinal chemistry. Through the biological evaluation of a series of fluoro/trifluoromethyl quinoxalinones bearing various substituents (alkyl, haloalkyl, arylmethyl, and aryl groups) at C-3, the compounds **7** and **8** were found to have promising inhibitory activity against various strains of *Candida* [5a]. The 2,3-bis(bromomethyl)quinoxaline **9** has shown antifungal activity and the compounds **10** and **11** exhibited antibacterial activity [5b]. Substitution at the sixth position is very crucial and highest antibacterial activity was observed with CF_3 group at this position, whereas the presence of the fluoro group at this position imparted maximum antifungal activity to these compounds. Recently, 4′-acetoxybenzyl-2-quinoxalinecarboxylate **13** has been found to have antitubercular

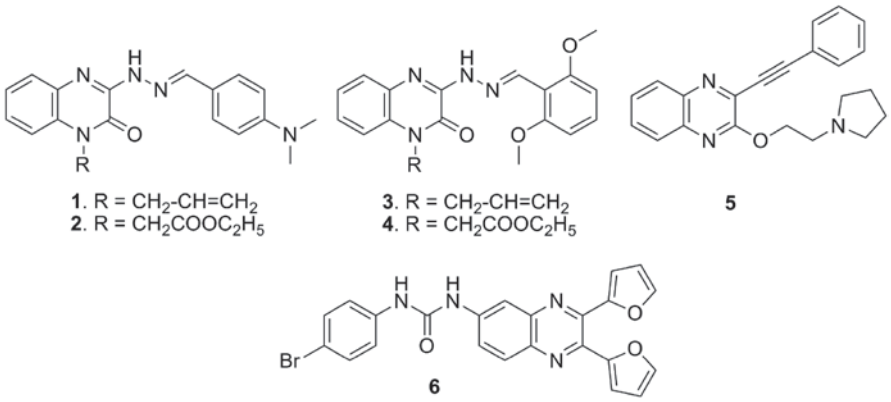


Fig. 2.1 Quinoxaline (*Qx*) derivatives with anticancer activity

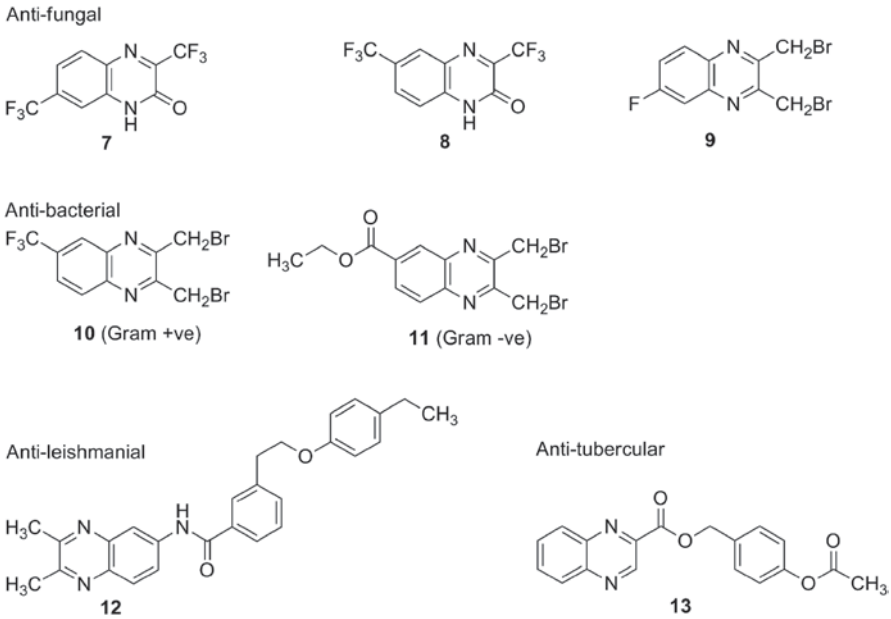


Fig. 2.2 Quinoxaline (*Qx*) derivatives with antimicrobial activity

activity against *M. tuberculosis* (Mtb) and *M. avium* (MAC) with minimal inhibitory concentrations (MIC) of < 1–6.25 μg/mL [5d]. Qx derivatives have been also evaluated for *in vitro* antiprotozoal (*Leishmania donovani, Trypanosoma brucei,* and *Trichomonas vaginalis*) activity among which the quinoxaline amide **12** has shown potent *in vitro* anti-leishmanial properties with IC_{50} of 8.2 comparable to that of miltesfosine (IC_{50} 7.3) [6] (Fig. 2.2).

Fusion of the Qx moiety with another ring system and covalent attachment to other bioactive fragments led to compounds with antiviral activity. The compounds **14** and **15** with 6-(2-aminoethyl)-6*H*-indolo[2,3-b]quinoxaline scaffold containing

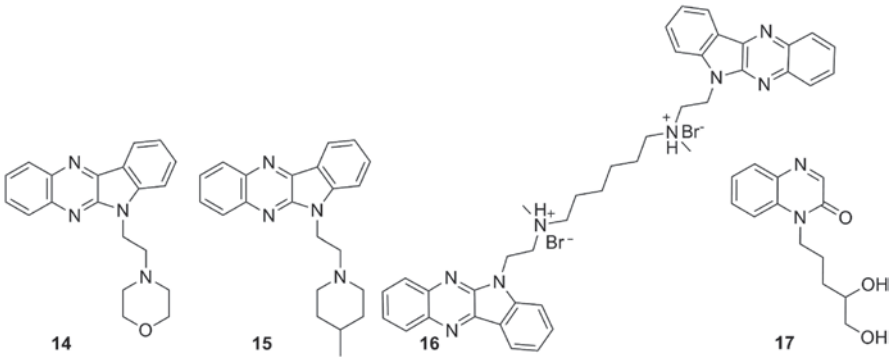


Fig. 2.3 Quinoxaline (*Qx*) derivatives with antiviral activity

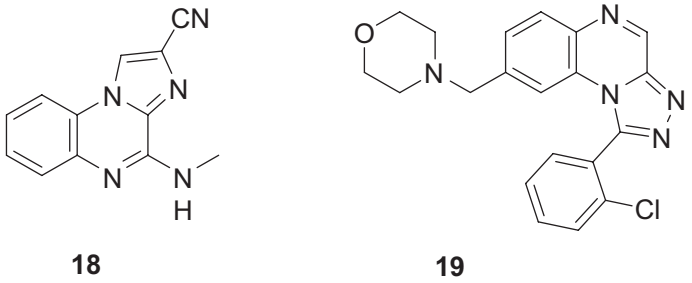


Fig. 2.4 Quinoxaline (*Qx*) derivatives with phosphodiesterase (*PDE*) inhibitory activity

morpholine and 4-methyl-piperidine moieties are potent antiviral compounds [7a]. The 2,3-dimethyl-6(2-dimethylaminoethyl)-6*H*-indolo-(2,3-b)quinoxaline also has shown excellent antiviral activity against human cytomegalovirus (CMV), herpes simplex virus type 1 (HSV-1), and varicella-zoster virus (VZV) [7b]. These observations led to the indoloquinoxaline derivative **16** with DNA-binding constants of ($\sim 10^9$). These findings led to the understanding of the antiviral effect of these derivatives and provided invaluable information for the future lead optimization for these kinds of compounds [7c]. The 1-(4,5-dihydroxypentyloxy)quinoxaline **17** has shown promising anti-HIV activity with EC_{50} value of 0.15 ± 0.1 μg/ml and therapeutic index (SI) of 73.2 for HIV-1 of [7c] (Fig. 2.3).

The imidazo[1,2-*a*]quinoxaline derivatives are cyclic nucleotide phosphodiesterase type III (PDE-III) and type IV (PDE-IV) inhibitors with promising activity in case of 4-(methylamino)imidazo[1,2-*a*]quinoxaline-2-carbonitrile **18** [8a]. 1-Aryl-4-methyl[1,2,4]triazolo[4,3-*a*]quinoxaline **19** acts as dual phosphodiesterase II/phosphodiesterase X (PDE-II/PDE-X) inhibitor with acceptable brain uptake and high selectivity for both PDE-II and PDE-X enzymes [8b] (Fig. 2.4).

Qxs and quinoxaline-1,4-di-*N*-oxide derivatives also have anti-inflammatory and antioxidant potential [9] and provide important scavenging activities and promising *in vitro* inhibition of lipoxygenase (LOX), an enzyme which plays an important role

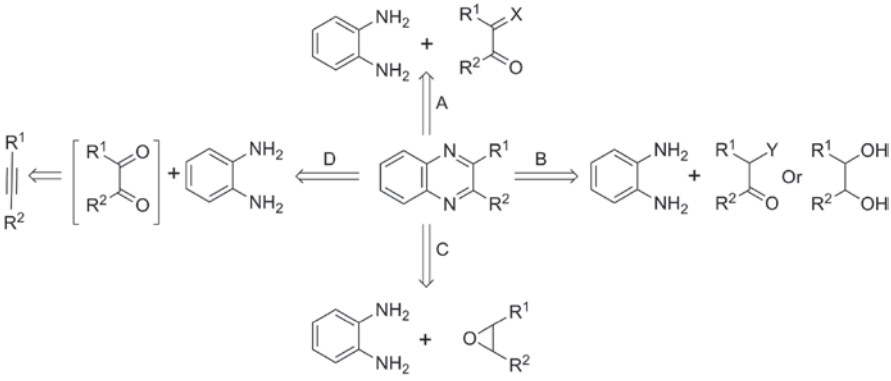
in inflammation and inflammatory process. The *in vivo* anti-inflammatory activity (41%; carrageenin-induced edema model) was comparable with that of indomethacin (47%) used as the reference drug.

3 Synthesis of Quinoxalines (Qxs)

The broad spectrum of biological activities of Qx-based compounds and their applications as useful materials [1–9] have inspired synthetic organic/medicinal chemists to develop new and more efficient synthetic methodologies for the preparation of Qx derivatives. Thus, search for newer and more effective synthetic methodologies for this privileged class of compounds continues to be an inspirational area of research and various reviews have been published describing the synthesis of Qxs [10, 11]. This chapter focuses on the research works involving the development of methodologies for the synthesis of aromatic Qxs (and not their reduced or polycyclic derivatives) published after the year 2000 with the inherent objective of attaining sustainability.

3.1 Sustainable Methods For Synthesis of Qxs

The various approaches (Scheme 2.1) for the synthesis of Qxs involve the Lewis/Brönsted acid or Lewis-base-promoted reaction of *o*-phenylenediamine (commercially available or prepared in situ through the reduction of the corresponding *o*-nitroaniline) with (1) 1,2-diketone/1,2-ketomonoxime (Route A) [12]; (2) α-hydroxyketone/α-haloketone/1,2-diol or α-methyleno ketone (Route B) [13]; (3) appropriately substituted epoxide (Route C) [14]; and (4) substituted alkynes (Route D) [15] under heating or microwave irradiation.



Scheme 2.1 Synthetic strategies for the construction of the Qx scaffold

The development of eco-friendly/green approaches (sustainable development) is an ongoing demand and subject of current interest due to the adverse effects of the manufacturing processes of drugs and pharmaceuticals on the environment [16]. There is considerable influence of green chemistry tools on medicinal chemistry and chemistry research-based organizations [17]. These urge for the requirement to enrich the medicinal chemist's tool box through improvement of existing transformations for more general application to make them amenable to parallel chemistry and potentially broaden the diversity of compounds for medicinal chemistry purposes [18]. There are twelve principles of green chemistry [19]; however, "It isn't expected that new chemical processes should always satisfy all 12 principles, but the check-list does provide a rough idea of whether one process is greener than the other" [16]. On a similar note, "Whether a reaction is green is highly subjective based upon the specific synthetic situation in a global context of a synthesis" [20]. The attainment of sustainability in chemical synthesis is subjected to the fulfillment of the "triple bottom-line philosophy" of green chemistry [21]. In the pharmaceutical industry, the sustainability of a chemical process is assessed by its "Green Index" determined by the following criteria:

1. Consumption of resources
2. Consumption of energy
3. Undesirable effects on human beings
4. Undesirable effects on ecosystem
5. Safety (physical, chemical, and biological)

These guidelines drive the pharmaceutical research to prioritize the R & D targets in the following aspects:

1. Stoichiometric to catalytic reactions
2. Multi- to fewer-step routes
3. Liquid acid/base to solid acid/base catalysts
4. Safer processes: avoidance of dangerous/toxic reagents and by-products
5. Improvements of reaction media: solvent free, solid state, water, supercritical media, ionic liquid (IL), etc.
6. Routes of higher atom utilization/economy

The highlight of the literature reports on Qx synthesis will be on these directives of green chemistry.

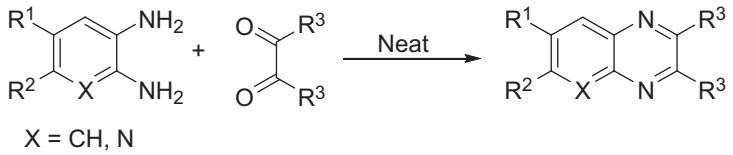
3.1.1 Solvent-Free Synthesis

The uses of volatile organic solvents (VOSs) are the major contributory factors towards environmental pollution due to their abundant use (solvents constitute more than 85% of the total mass utilization of a chemical process) and incomplete recovery efficiency (50–80%) [22]. Therefore, the major drive towards the initiative of sustainable development in chemical synthesis is focused on the replacement of the VOSs by solvent-free conditions [23] to reduce the waste, time period, and total

cost associated with the organic reactions. Thus, "the best solvent is no solvent" is often vouched as a good campaign for sustainability development [24]. Many reactions are known to proceed efficiently in the solid state as, in the solid-state, organic reaction occurs more efficiently and more selectively than in the solution phase [25]. This has witnessed increasing efforts for heterocyclic synthesis under solvent-free condition in the recent years [26].

However, the use and understanding of solvent-free conditions has remained underdeveloped in comparison to the solvent-based methods [27].

Synthesis using 1,2-diketones



Scheme 2.2 Synthesis of Qx from 1,2-diketone and 1,2-diamine without solvent

The Qx synthesis involves the condensation of 1,2-diamines with 1,2-diketones and require either an electrophilic activation of the diketone-coupling partner or nucleophilic activation of the diamine-reacting partner that necessitate the use of an acid and base catalyst, respectively. To achieve sustainability, the R & D priority of the pharma industry directs the use of solid acid/base catalysts to reduce waste generation as solid acid/base catalysts can be recovered and recycled. Reactions catalyzed by solid acids are by far the most important contribution of catalysis towards green chemistry [28]. Various solid acid catalysts are clay-based materials [29], silica [30], and mineral dust [31]. Although the heteropolymetallic salts are good contenders as solid acids, the solid-supported protic acids are better options for the "electrophilic activation" strategy due to their ease of preparation and cost effectiveness. Similarly, solid-supported base would also provide a better option for nucleophilic activation process. Among the solid-supported protic acids, such as H_2SO_4-SiO_2 [32a], HBF_4-SiO_2 [32b], and $HClO_4$-SiO_2 [32c], the silica-supported perchloric/fluoboric acid catalyst systems developed in this laboratory [32b–32d] have attracted the attention of synthetic chemists worldwide and appeared to be the most effective [33]. On the other hand, KF–alumina [34] has been considered as the most effective solid base as the interaction of the KF with the oxyanionic site of alumina generates the naked F^- species as a strong base which otherwise require the use of aprotic polar solvents for catalytic uses as has been demonstrated through the "demand-based thiolate anion generation" protocols [35].

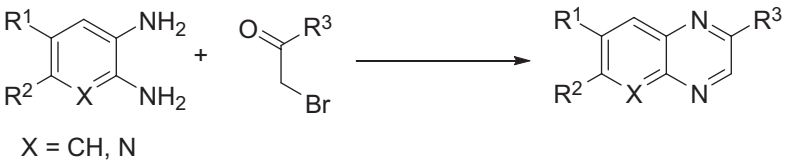
Several reports have appeared for the synthesis of Qxs using different electrophilic components like 1,2-diketones (Scheme 2.2, Table 2.1). Most of these methods [36–44] are high yielding and use different heterogeneous catalysts. The reactions can be performed at room temperature (rt) or under heating at 80 °C. The isolation/purification of the product is simple (largely nonchromatographic). The catalyst

Table 2.1 Synthesis of Qxs using 1,2-diketones

Sr. No.	Catalyst	Key features	Reference
1.	$PW_{12}ZrO_2$	80 °C, simple workup, reusable catalyst, high yield (65–99 %), 5–300 min	36
2.	TBBDA/PBBS	80 °C, excellent yield (85–98 %), 3–120 min	37
3.	TSA	rt, 20–180 min and high yield, reusable catalyst	38
4.	KF/Alumina	rt, 60–150 min, 78–92 %, reusable catalyst	39
5.	Acidic alumina	80 °C, good to excellent yield (45–96 %), 2–90 min, reusable catalyst	40
6.	Silica gel	100 °C, 20–70 min, excellent yield, easy non-chromatographic purification	41
7.	Basic Al_2O_3	rt, grinding, 10–25 min and high yield (87–99 %), reusable catalyst	42
8.	Silica sulfuric acid	rt, excellent yield, reusable catalyst	43
9.	*p*-TsOH	rt, fast reaction (5–10 min), and high yield (88–99 %)	44

can be easily recycled and reused. The solid-supported inorganic heterogeneous catalysts such as tungstophosphoric acid supported on zirconia ($PW_{12}ZrO_2$), tungstate sulfuric acid (TSA), KF/alumina, acidic alumina, silica gel, basic alumina, and silica sulfuric acid (entry 1 and 3–8, Table 2.1) are used which offer ease of handling, high reactivity and selectivity, easy separation of the product, recyclability and reusability, and economic advantage. The major drawbacks with the heterogeneous catalyst are the higher amount required than the homogenous conditions and the blocking of the pores of the catalyst during the reaction progress. However, the reusability and the other benefits offered by the heterogeneous conditions outweigh these drawbacks. The $PW_{12}ZrO_2$ is a heteropolyacid (HPA) modified with zirconia and has acidic strength comparable to the protic acids. Zirconia is a thermally stable material with acidic properties. KF/alumina is one of the most important basic heterogeneous catalysts having wider applications in organic synthesis. Acidic catalysts like PBBS/TBBDA and *p*-TsOH (entry 2 and 9, Table 2.1) have also been used.

Synthesis using α-bromoketones



Scheme 2.3 Solvent-free synthesis of Qxs from α-bromoketones and 1,2-diamine

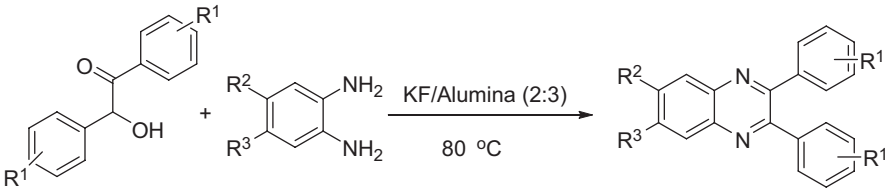
This is another strategy for the synthesis of Qxs (Scheme 2.3, Table 2.2) apart from diketones with diamine nucleophile and is based on the initial imine formation through the condensation of one of the amino groups of the diamine with the carbonyl group of the α-bromoketone. This would be followed by intramolecular

Table 2.2 Synthesis of Qxs using α-bromoketones

Sr. No.	Catalyst	Key features	Reference
1.	Cellulose sulfuric acid	rt, 20–30 min, recyclable and reusable catalyst, 89–96%	45
2.	γ-Maghemite-silica nanocomposite	65 °C, good to excellent yield (72–93%), recyclable catalyst, 8–30 min	46
3.	$Ga(ClO_4)$	rt, grinding, good to excellent yield (60–88%), 20–60 min	47
4.	KF/alumina	rt, simple, mild condition, (1.5–5 h), 82–94%	39
5.	$HClO_4$-SiO_2	rt, fast reaction (15–60 min) and high yield (70–94%), reusable catalyst	48

nucleophilic substitution of the bromine atom by the other amine group and dehydrogenation/aromatization to form the Qx. The solid/heterogeneous catalysts (e.g., cellulose sulfuric acid, γ-maghemite-silica nanocomposite, KF/Alumina, and $HClO_4/SiO_2$) or Lewis such as $Ga(ClO_4)_3$ are used to promote the imine formation (Table 2.2) and finally leading to the Qxs as the synthetic target [45–48]. However, the commercial availability of the α-bromoketone as the electrophilic partner limits the general applicability. Further, the formation of regio-isomeric Qxs would also pose problems with unsymmetrically substituted 1,2-diamine as the nucleophilic coupling partner.

Synthesis using α-hydroxy ketone

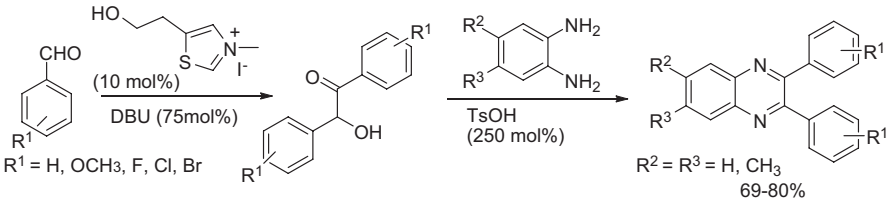


Scheme 2.4

The most commonly used electrophilic coupling partner for the synthesis of Qxs is the 1,2-diketones that are usually obtained by oxidation of the precursor α-hydroxyketones, readily obtained through benzoin condensation. Thus, the direct use of benzoin would constitute a newer approach for the synthesis of Qxs as the initial reaction between the benzoin and the 1,2-diamine would form the imine which would undergo intramolecular nucleophilic substitution of the hydroxyl group by the other amine and finally would form the Qxs through dehydrogenation/aromatization. The heterogeneous solid-supported catalyst KF/alumina has been used (Scheme 2.4) for the synthesis of Qxes directly from α-hydroxyl ketenes at 80°C [39].

Synthesis using aldehyde

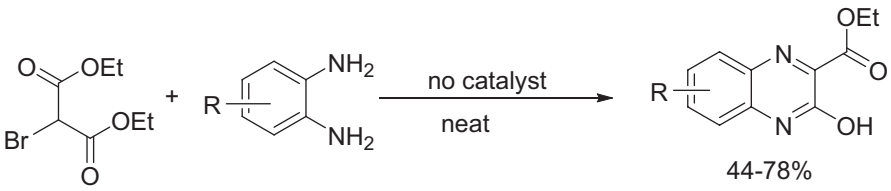
Although the need to use 1,2-diketone may be replaced by the use of benzoin, the requirement of toxic KCN to catalyze the benzoin condensation becomes detrimental in the context of sustainable/green synthesis. However, the use of N-heterocyclic carbene (NHC), generally formed in situ, would avoid the use of KCN for benzoin condensation. Thus, Qxs have been synthesized from aldehydes directly using a cascade reaction catalyzed by NHC, generated in situ from a thiazolium-based IL and diazabicycloundecene (DBU) as the base, forming an intermediate α-hydroxy ketone via the NHC-mediated benzoin condensation, which subsequently undergoes cyclocondensation with the 1,2-diamine in the presence of TsOH as the catalyst (Scheme 2.5) [49]. The inherent restriction of the use of aromatic aldehydes is the limitation of this strategy.



Scheme 2.5

Synthesis using α-bromomalonate ester

The Qx synthesis can also be performed by the reaction of 1,2-diamines with α-bromo-malonates (Scheme 2.6) [50]. The presence of the bromo group adjacent to the two ester groups makes it highly susceptible for nucleophilic substitution by the amine group of the 1,2-diamine to form the intermediate N-alkylated derivative which undergoes intramolecular cyclocondensation involving the reaction of the other amine group with one of the ester carbonyl and finally forms the Qxs via amide–imine tautomerism and dehydrogenation. Thus, the Qx formation following this procedure does not require any catalyst.



Scheme 2.6

3.1.2 Synthesis Using Innocuous Alternate Reaction Media

Although the solvent-free reaction condition offer means to avoid the detrimental VOSs, the scalability would pose problems due to lack of heat transfer. The uses of

alternative reaction media for replacing the VOSs thus become an essential feature to maintain sustainability in chemical processes. The major contenders as alternate reaction media are: water, supercritical fluids, ILs, and fluorous solvents [16, 17, 51].

Water as the Reaction Medium

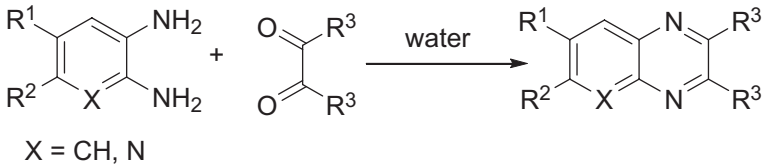
The use of water as the reaction medium dates back to the earliest discovery of organic reaction in Wholer's synthesis of urea from ammonium cyanate. However, the first report on organic reaction in water involving organic reactants was made by Diels and Alder [52]. Woodward and Baer repeated the Diels–Alder reaction in water in 1948 and noticed a change in the endo-to-exo ratio compared to organic solvent. The beneficial effect in rate enhancement of organic reaction by water was first reported by Eggelte, de Koning, and Huisman in 1973. However, the common knowledge of water as the reaction medium was inducted by Breslow in 1980, although in relation to the Diels–Alder reaction [53]. Since then, the use of water as a nonclassical medium for organic reactions has been increasingly receiving popularity [54].

The potential of water as a medium for organic transformations has been recognized as a significant advancement of sustainable development as water is the cheapest, most abundant, noninflammable, nontoxic solvent and provides ease of product isolation. The beneficial influence for rate acceleration and modulating selectivity indicates that water is not merely an environmentally friendly alternative reaction medium. The exact role of water in promoting organic reactions remained inadequately addressed. Several views such as "on water [55]," "in water or in the presence of water [56]," and "on water and in water both" [57] have been put forth. Although rate acceleration and selectivity control of water-mediated reactions were ascribed primarily to hydrophobic effects [58], it was realized that the role of hydrogen bonding (HB) is also important [59] and may even be predominant [59c–59e]. Other factors responsible for the rate acceleration may be the single or combined effect of the small size and high polarity of a water molecule, hydrogen-bonded networking of bulk water which provides some exclusive properties such as large cohesive energy density (about 550 cal/cm^3), large surface tension (72 dyne/cm), and large heat capacity [60]. The mechanistic model of "electrophile–nucleophile dual activation" through a cooperative hydrogen-bond network has been proposed from this laboratory [61] that finds support from subsequent suggestion "even single water molecules can act as catalysts" during the gas-phase radical reaction [61]. The proposal on "electrophile–nucleophile dual activation" by water dimer forms the basis of the selective formation of the tetrahydropyran core of the natural brevetoxin B in the marine water through epoxide-opening cascades [63] for which the additional beneficial role of water has been realized through its ability to reorganize the substrate into a reactive conformation [63b]. In the oil–water interface, the water molecules have a free OH group that protrudes into the organic phase enabling catalysis via HB [55b]. The cooperative HB-assisted ambiphilic (electrophile–nucleophile) activation by water has been the key feature in the

synthesis of heterocyclic compounds of biological importance and constitutes the key feature of some novel "all-water" synthetic methods [64].

The insolubility or very poor solubility of most of the organic compounds in water often makes an adverse impact on the campaign of water-mediated organic synthesis and this has brought to light the use of surfactants [65] or surfactant-combined metal Lewis acid [66] in aquatic organic reaction. However, the role of a surfactant in promoting organic reaction may not be solely to act as the solubility enhancer and new chemistries such as non-heme model of dioxygen activation may be invoked that would lead to greener oxidation protocol [67].

Synthesis using 1,2-diones



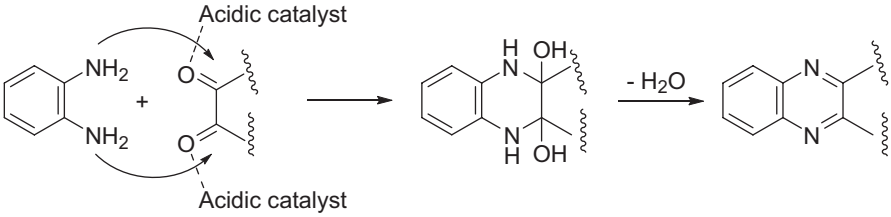
Scheme 2.7

The direct cyclocondensation involving 1,2-diones with 1,2-diamines has been the most common strategy for Qx synthesis in aqueous medium and has been successfully employed by various groups [68–82] (Scheme 2.7, Table 2.3). The product yields are generally low with electron-withdrawing substituents on the amine, and such substrates require longer reaction time. The reaction can be carried out in water using one electron oxidant like CAN. Various catalysts used in the aqueous medium are: $InCl_3$, which is well accepted because of its low toxicity and very good stability; $CuSO_4 \cdot 5H_2O$; $Bi(OTf)_3$; $ZrOCl_2 \cdot 8H_2O$; Montmorillonite K-10; Amberlyst-15 and sulfated titania (TiO_2–SO_4^{2-}) as heterogeneous catalysts which can be easily recycled and reused; Lewis acid surfactant [$Zr(DS)_4$]; Brönsted acid IL [$(CH_2)_4SO_3HMIM][HSO_4$]; and *p*-dodecylbenzenesulphonic acid (DBSA) as a Brönsted acid surfactant-combined catalyst. Recently, a catalyst-free synthesis of Qxs has been reported in water using different diketones and aromatic 1,2-diamines. The ability of the surfactants to act as microreactors can be used to synthesize a wide variety of Qxs using different 1,2-diamines in excellent yields. The superior catalytic efficiency of the surfactant (Tween 40) over water-tolerant acidic catalysts for Qx formation is observed during Qx formation in water [81]. The efficiency of Tween 40 for Qx formation has been found to be better in water than in an organic solvent. This study revealed that acidic catalysts known for Qx formation performed better/equally in organic solvents (particularly MeOH and MeCN) than in water, hence indicating that surfactants are better suited for carrying out the reaction in water while the Lewis/Brönsted acids are better suited for their use in organic solvents.

Table 2.3 Synthesis of Qxs using 1,2-diketones in water

Sr. No.	Catalyst	Key features	Reference
1.	Cerium (IV) ammonium nitrate	rt, excellent yield, simple filtration to isolate product	68
2.	$InCl_3$ (10 mol%)	80 °C, excellent yield, aliphatic as well as aromatic diketones used	69
3.	$CuSO_4 \cdot 5H_2O$ (10 mol%)	rt, excellent yield, few examples, recyclable catalyst, both electron-withdrawing and electron-donating substitutions are effective	70
4.	$Bi(OTf)_3$	rt, high yield, various diamines and diketones studied, fast reaction (5–10 min)	71
5.	Montmorillonite K-10	rt, high yield, cheap and reusable catalyst (2–4 h), less yield with electron-withdrawing substitution on diamine	72
6.	$[Zr(DS)_4]$ (2.5 mol%)	rt, high yield, short reaction time (30–110 min), reusable catalyst	73
7.	Amberlyst-15 (24 mol%)	70 °C, excellent yield, varied examples (aliphatic/aromatic/heterocyclic ketones and diamines)	74
8.	$[(CH_2)_4SO_3HMIM][HSO_4]$,	rt, short reaction time(10–55 min)	75
9.	Sulfated titania	rt, excellent yield, recyclable catalyst, fast reaction (5–120 min)	76
10.	PEG-600	rt, excellent yield, various aromatic and aliphatic amines as well as ketones used, 5–10 min	77
11.	Brönsted acid hydrotrope combined catalyst	rt, excellent yield, recyclable catalyst, few examples, 7–25 min	78
12.	DBSA (10 mol%)	rt, excellent yield, no reaction with aliphatic amine, 2–24 h	79
13.	Catalyst free	rt, good to excellent yield, mother liquor can be recycled, various diketones with three aromatic diamines	80
14.	Tween 40	rt, good to excellent yield, varied examples (aliphatic/aromatic/heterocyclic ketones)	81
15.	$ZrOCl_2 \cdot 8H_2O$ (25 mol%)	rt, good to excellent yield	82

The Qx formation in the presence of acidic catalyst is expected to take place as depicted in Scheme 2.8.

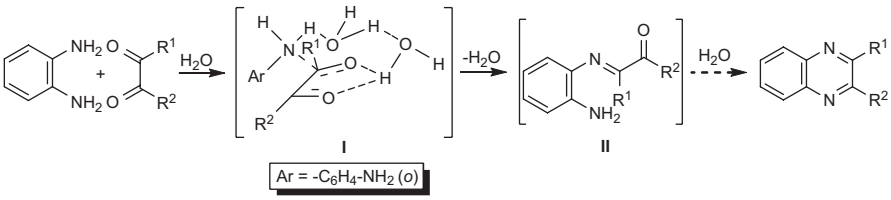


Scheme 2.8 Plausible mechanism for Qx formation using acidic catalyst from 1,2-diketone

Table 2.4 Synthesis of Qxs using α-bromoketones in water

Sr. No.	Catalyst	Key features	Reference
1.	β-CD	70 °C, good to excellent yield, only variations on ketone part, 2–2.5 h	83
2.	TMSCl (1 equiv)	rt, good yield, few examples, only variations on ketone part, 8 h	84
3.	Sodium hexafluorophosphate bound Amberlite resin	rt, water and methanol (1:1), good to excellent yield, 5–8 h	85
4.	SDS	rt, good to excellent yield, varied examples, 6–7 h	86

However, in aqueous medium, water serves as the catalyst through HB formation and the role of water in accelerating this reaction has been proposed [81] through the formation of hydrogen-bonded species **I** (Scheme 2.9).



Scheme 2.9 Role of water during Qx formation in aqueous media

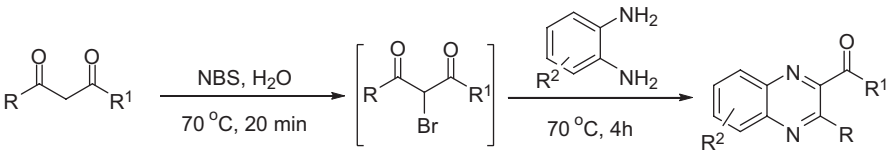
Synthesis using α-bromoketones

Scheme 2.10

This strategy has been also employed [83–86] to a limited extent (Scheme 2.10) with diamine nucleophile. A biomimetic approach can be used to synthesize Qxs (entry 1, Table 2.4) using β-CD as a catalyst. The use of trimethylsilyl chloride (TMSCl) as a catalyst has also been reported; however, this method requires longer time and is applicable for only limited substrates (entry 2, Table 2.4). Other methods used the solid-supported catalyst sodium hexafluorophosphate bound Amberlite resin and micellar sodium dodecylsulfate (SDS; entries 3 and 4, Table 2.4).

Synthesis using 1,3-diketones/esters/ketoesters

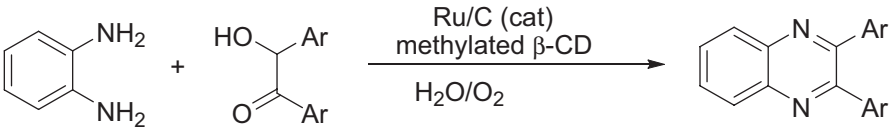
Water has been used as the medium for the synthesis of Qxs in good yields from 1,3-diketones/esters/ketoesters via tandem one-pot procedure (Scheme 2.11). The synthesis proceeds through in situ formation of intermediate α-halo-β-keto esters using N-bromosuccinimide (NBS), which undergo tandem *N*-alkylation-condensation-dehydrogenation with the 1,2-diamines to form the Qx [87].



Scheme 2.11

Synthesis from α-hydroxy ketones

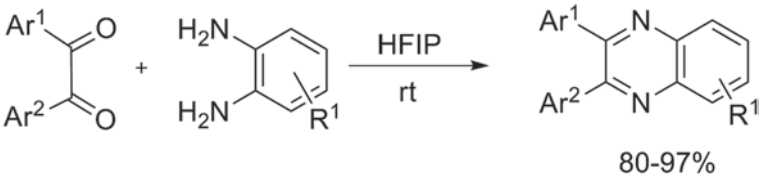
Ruthenium on charcoal and randomly methylated β-cyclodextrin has been used as a recyclable catalyst system to form Qxs in water from benzoin and 1,2-diamines (Scheme 2.12) [88]. Molecular oxygen has been used perhaps to facilitate in situ formation of the 1,2-diketone from the benzoin and the final dehydrogenation.



Scheme 2.12

Fluorous Alcohols as the Reaction Media

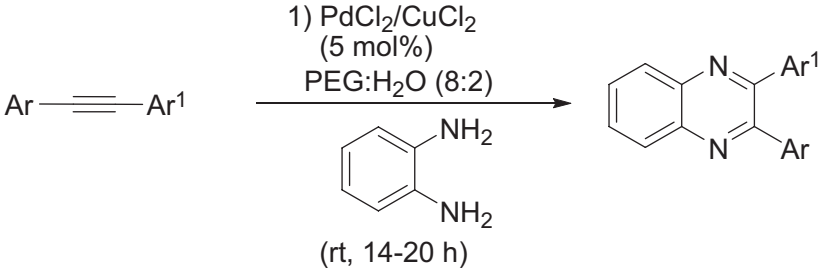
Fluorinated alcohols such as trifluoro ethanol (TEF) and hexafluoro isopropanol (HFIP) have emerged as alternative reaction media for clean synthesis [89]. The presence of the CF_3 group(s) in TFE and HFIP impart the TFE and HFIP good HB donor ability due to which these solvents can activate the electrophile through HB and thus promote organic reactions. The ability of TFE/HFIP in promoting organic reactions through HB-mediated electrophilic activation has been exploited for the synthesis of bioactive heterocycles [90]. Fluorinated alcohol HFIP can be used as a solvent for making Qxs from 1,2-diketones and 1,2-phenylenediamines (Scheme 2.13) in excellent yield (80–97%), in short time (1 h) [91].



Scheme 2.13

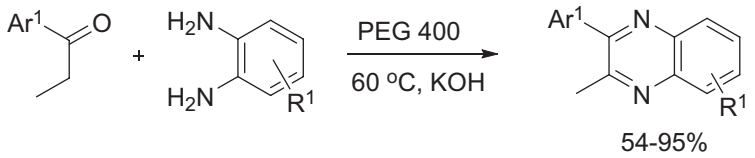
Polyethylene Glycols as the Reaction Media

Polyethylene glycol (PEG) has drawn considerable attention as a green reaction medium for organic synthesis [92]. Alkynes are successfully employed for the synthesis of Qxs using $PdCl_2/CuCl_2$ as the catalyst system in PEG-400 and water (8:2; Scheme 2.14) [93]. The solvent system assists the oxidation of the alkyne to form the 1,2-dione as the intermediate species that undergo PEG-assisted cyclocondensation with the 1,2-diamine to form the Qx.



Scheme 2.14

PEG-400 has been used as the reaction media for oxidative cyclocondensation of α-methyleno ketones with 1,2-phenylenediamines in the presence of KOH to form Qxs requiring a longer period of time (40 h; Scheme 2.15) [94].



Scheme 2.15

Table 2.5 Synthesis of Qxs using 1,2-diketones in ILs

Sr. No.	Catalyst (ILs)	Key features	Reference
1.	1-Butylimidazolium Tetrafluoroborate ([Hbim]BF_4)	rt, good to excellent yield, aromatic and aliphatic diketones, 10–96 min, excellent yield with electron deficient aromatic diamines	104
2.	Heteropolyanion-based ILs	rt, high yields, short reaction times, and easy workup	105
3.	1-Butyl-3-methylimmidazolium tetrafluoroborate ([bmim]BF_4)	rt, fast (10–60 min), under grinding condition, excellent yield with electron-withdrawing substituents on diamine	106
4.	N, N, N-Trimethyl-N-propanesulfic acid ammonium hydrogen sulfate [TMPSA] • HSO_4	mild conditions, catalyst can be recycled	107
5.	1-Butyl-3-methylimidazolium bromide([bmim]Br)	130 °C, Excellent yields and short reaction time and microwave irradiation conditions (30–35 min)	108

ILs as the Reaction Media

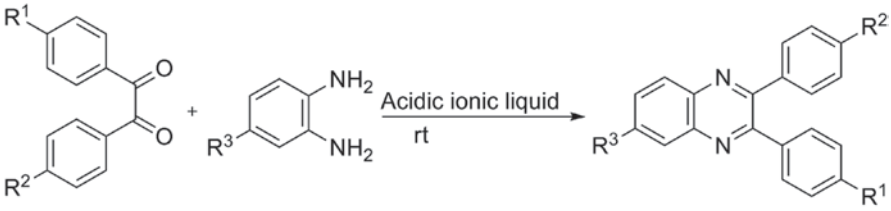
ILs are salts formed by the association of organic nitrogen or sulfur or phosphorus cations and organic or inorganic anions which generally exist in liquid state at ambient temperature [95]. The negligible vapor pressure, non-flammability, and outstanding solvation potential are the basis for their uses for clean technology and consideration as green solvents of the future [96]. The ILs have been recognized for their versatile uses in designing safer chemicals [97] and find applications in chemical industries [98] including the synthesis of heterocycles [99]. The ILs often dramatically change the course of a chemical reaction that is unmatched by the classical solvents. These unique properties of the ILs have triggered curiosity to understand the reaction mechanism in these solvents [100]. Although the role of ILs in promoting Diels–Alder reaction has been attributed to their HB donor ability [101], the molecular-level interaction of the ILs with the reactants that would form the basis of their selection in performing organic reactions remained inadequately understood. The role of the imidazolium-based ILs in promoting organic reactions has been revealed from this laboratory as "electrophile–nucleophile dual activation" to form supramolecular assembly of the ILs and the reacting partners as the active species through a network of HB and the charge–charge interaction [102]. The formation of such supramolecular assemblies has been demonstrated through spectroscopic aids (infrared, IR, and nuclear magnetic resonance, NMR) and even through the identification of the active species using various mass-spectrometric tools [102c–102e]. The generality of the mechanistic role of the ILs has been demonstrated through different organic reactions as well as the synthesis of heterocyclic compounds [103]. These studies form the basis of selection of ILs in promoting organic reactions.

The Qx synthesis involves the cyclocondensation reaction, where reaction between two nucleophilic centers and two carbon electrophilic centers takes place

to form a six-membered ring. Such reactions could be performed by utilizing ILs through their ability to activate the electrophile/nucleophile.

Synthesis using 1,2-diketones

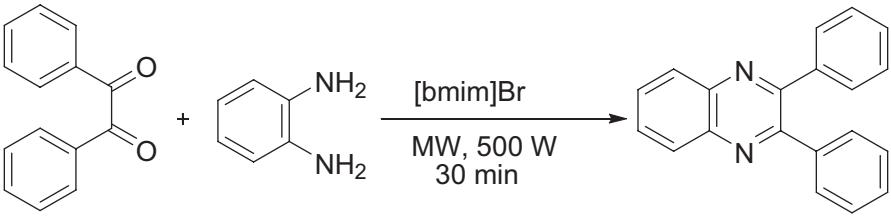
Several reports have been published for the synthesis of Qx from 1,2-diones (Scheme 2.16, Table 2.5) using different ILs under different reaction conditions: using room temperature Bronsted acid ILs like 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) [104], Heteropolyanion-based ILs [105], 1-butyl-3-methylimmidazolium tetrafluoroborate ([bmim]BF_4) [106] and *N*, *N*, *N*-trimethyl-*N*-propanesulfic acid ammonium hydrogen sulfate [TMPSA]•HSO_4 [107].



Scheme 2.16

The use of the neutral IL 1-butyl-3-methylimidazolium bromide ([bmim]Br; Scheme 2.17) under microwave irradiation in the absence of any metal catalyst afforded Qxs in excellent yield [108].

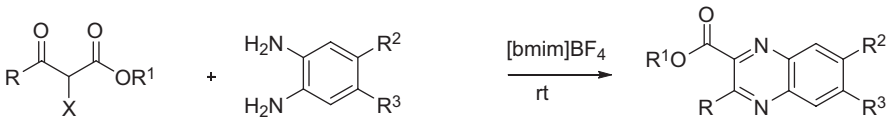
The use of environmentally benign ILs with high atom economy and high yield of products are the important aspects of these protocols.



Scheme 2.17

Synthesis using α-halo-β-ketoesters

The synthesis of Qxs is achieved by using 1-butyl-3-methylimmidazolium tetrafluoroborate ([bmim]BF_4) as a room-temperature acidic IL (Scheme 2.18) in high yields (82–94%) [109].



R = CH_3, CF_3, Ph, ^{i}Pr; R^2 = H, CH_3, COOMe, NO_2;
R^1 = Me, Et, Bn; R^3 = H, CH_3
X = Cl, Br

Scheme 2.18

3.1.3 Alternate Modes of Synthesis

Use of alternate modes to carry out the synthesis that would minimize the energy consumption is one of the main objectives in attaining sustainable chemical processes. Some of the popular techniques such as use of microwaves, sonication, flow reactors, and photoreactors can be used effectively [110].

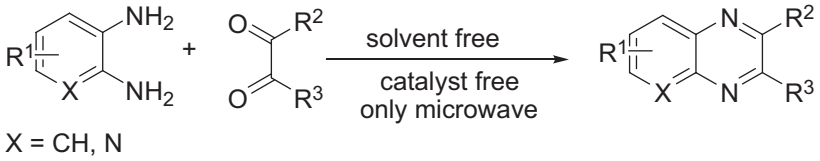
Microwave-Assisted Synthesis

Gedye and Giguere/Majetich reported the first microwave-assisted reaction in 1986. The basis behind microwave heating is the dielectric heating effect, in which specific material (solvent or reagent) absorbs microwave energy and converts it to heat, which helps to accelerate the reaction rate by many folds. This technique has emerged as a successful tool for chemists. Higher yield (because the probability of unwanted side reaction is less) and shorter time is the main advantage of microwave heating compared to the conventional heating [111]. Thus, microwave-assisted organic synthesis could be successfully implemented to promote various organic reactions such as aromatic nucleophilic substitution, cyclocondensation involving poor leaving group and elimination reactions [112], and for the synthesis of heterocycles [113].

The Qx synthesis involving the cyclocondensation of 1,2-diketones with 1,2-diamines has been performed under microwave irradiation.

Synthesis using 1,2-diketones
Several reports have been published for the synthesis of Qxs using dielectrophilic components like 1,2-diones (Table 2.6) under microwave heating with diamine nucleophile.

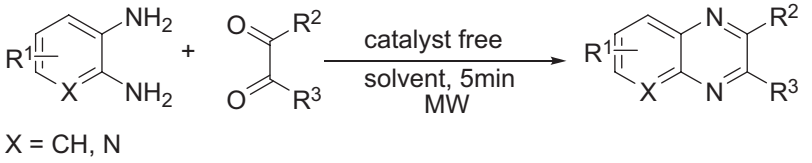
Catalyst-free, solvent-free conditions
The Qx synthesis (Scheme 2.19) has been performed under microwave irradiation in the absence of solvent and catalyst [114–116] affording high yields in a short reaction time (1–6 min; Table 2.6, entries 1–3).



Scheme 2.19

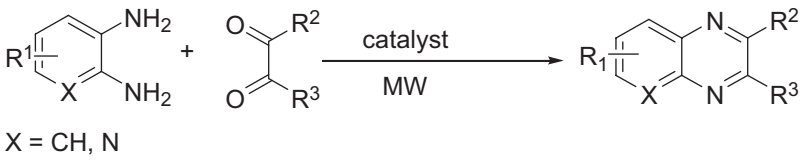
Catalyst-free conditions

The Qx synthesis (Scheme 2.20) has been carried out under microwave irradiation in the absence of any catalyst in MeOH and HOAc (9:1) at a high temperature of 160 °C affording excellent yield (69–99%; Table 2.6, entry 4). The reaction is cleaner than the conventional synthesis and suppresses the polymerization of the starting material which is observed when the same reaction is carried out under conventional heating [117]. The use of a small quantity of solvent to make a polar paste of the reactants and irradiation with microwaves forms Qxs in excellent yields [118].



Scheme 2.20

Using catalyst with or without solvent



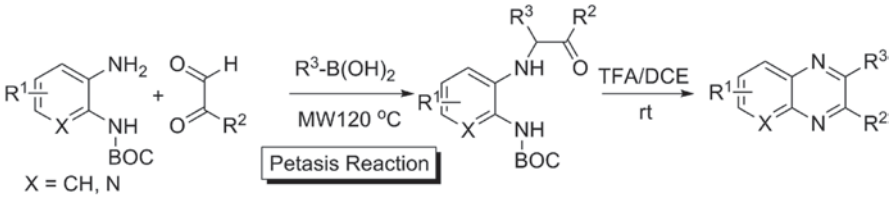
Scheme 2.21

The use of PEG-400 [119], I_2 in EtOH and water (1:1) [120] or solid-supported recyclable catalyst like sulfated titania [121], $MgBr_2.OEt_2$ [122], and PEG-4500 [123] under microwave irradiation affords the Qxs in high yields and in a short reaction time (Scheme 2.21).

A Petasis reaction (Scheme 2.22) under microwave irradiation is used to prepare Qxs in two steps [121]. The microwave-assisted Petasis reaction is followed by the acid-mediated unmasking of the amino group followed by cyclocondensation to give the Qxs in good to excellent yields.

Table 2.6 Microwave-assisted Qx synthesis using 1,2-diketones

Sr. No.	Condition	Key features	Reference
1.	Solvent and catalyst free 100–120 °C	Good to excellent yield, short reaction time (2–6 min), good yield with electron-deficient amines	114
2.	Solvent and catalyst free MW (400 Watts)	Good to excellent yield, shorter reaction time (1–5 min)	115
3.	Solvent and catalyst free 100–130 °C	84–98 % yield, 3–6 min, excellent yield with electron-deficient amines	116
4.	MeOH and HOAc (9:1) MW 160 °C	Rapid, high-yielding process and suppression of polymeric species, 5 min	117
5.	Polar paste (0.2 ml DMSO/ diglyme) 900 W	Excellent product yield and simple washing with water and filtration in the absence of organic solvent, 3 min, few examples	118
6.	MW120 °C, PEG-400 (15 mol%)	Mild reaction conditions, and excellent product yield, short reaction time (3–5 min)	119
7.	I_2 in EtOH and water (1:1)	Excellent yield, shorter reaction time (3–5 min)	120
8.	TiO_2/ SO_4^{2-} catalyst	Efficient, ecofriendly, and easily recyclability of catalyst	121
9.	$MgBr_2 \cdot OEt_2$	rt, 160 W, excellent yield, short reaction time 1–2.5 min (MeCN)	122
10.	PEG-4000 polymer support	130 °C, 150 w, 8 min, short reaction time, elimination of chromatographic purification step. MeOH/ AcOH (9:1)	123
11.	MW 120°C, TFA/DCE	Petasis methodology in two synthetic operations	124

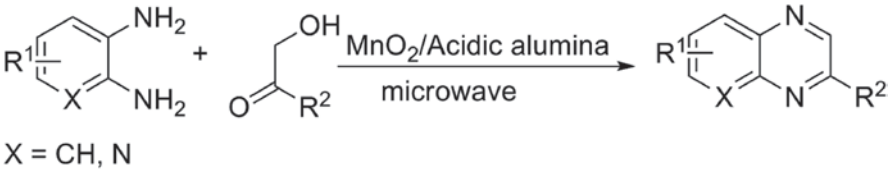


Scheme 2.22

Most of these microwave-assisted reaction protocols are efficient and high yielding. Different protocols have their own advantages which have been enlisted in Table 2.6.

Syntheis using α-hydroxy ketone

A few reports had been published using α-hydroxyketone for in situ generation of the 1,2-diones by an oxidizing agent like MnO_2 on acidic alumina [125] under microwave heating (Scheme 2.23).

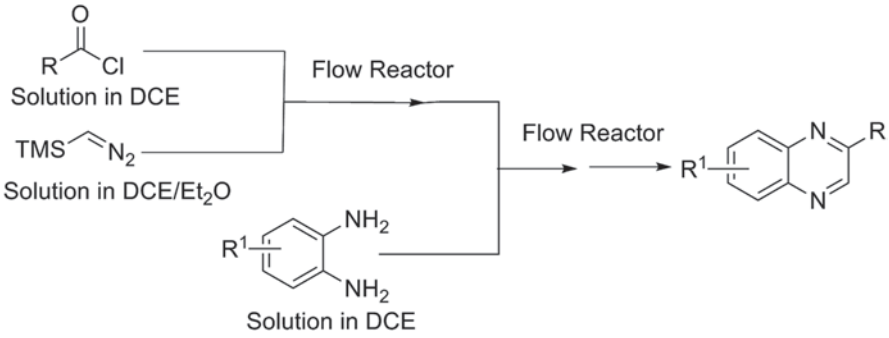


Scheme 2.23

Flow Chemistry

Flow chemistry allows the reaction to be carried out safely with high selectivity and reduced energy consumption contributing to green and sustainable chemical synthesis and has become the emerging technology for organic synthesis in the drug discovery program [126] including the construction of the heterocycle through multicomponent reaction [127].

Flow reactors can be used effectively for synthesizing Qxs in good to excellent yield. The explosive diazoketones were synthesized from the aliphatic and aromatic acyl chlorides in a flow reactor and are used without further purification in a continuous operation and treated with *o*-phenylenediamines to obtain the Qxs (Scheme 2.24). The major advantage of this synthesis is avoidance of a separate purification step, less solvent consumption, and elimination of the exposure of solvents and toxic/explosive chemicals [128].



Scheme 2.24

4 Conclusion

The Qxs are one of the most desired organic framework to build and explore therapeutic potential. Various strategies are used to make these molecules. The growth in the environmentally benign approaches to construct these molecules has spurred further interest in this scaffold. The availability of solvent-free methods which provide the ultimate benefits of low waste and address the environmental and personal toxicity concerns has been of immense value. The use of innocuous media like water, ionic liquid, etc., has decreased the environmental burden of VOSs. Alternate modes of synthesis using microwave has decreased the energy consumption and made the process more safe, selective, fast, and economic. Mostly, the synthesized Qxs are isolated by filtration, washed, and recrystallized with organic solvents. Ethanol is the most frequently used solvent for recrystallization, otherwise the product is extracted in an organic solvent and dried or sometimes purified through column chromatography. These developments will prove as landmarks in the ready supply and further exploration around this scaffold and will help in the exploration of Qxs as new therapeutic agents.

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Chapter 3
Eco-Friendly Synthesis of Bioactive Heterocycles

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Contents

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Abstract Green chemistry also offers enhanced chemical process economics concomitant with a reduced environmental burden. Green sustainable chemistry (GSC) is, in a word, chemistry and chemical technology for environmentally friendly products and processes. Heteropolyacids (HPAs) have several advantages as catalysts which make them economically and environmentally attractive. Basic characteristics of HPAs as green catalysts are overviewed, focusing on the various reaction fields in which the HPA catalysts function as acid. Herein, we present the very latest developments from synthesis to structure and function of polyoxometalates (POMs) and the synthesis of heterocyclic and organic chemistry compounds by using POMs and HPAs.

Keywords Nanocatalyst · Heterocyclic · Heteropolyacid (HPA) · Synthesis · Green

1 Introduction

Green chemistry uses highly efficient and environmental benign synthetic procedures to deliver life-saving medicines, accelerating guide optimization processes in drug discovery, with reduced needless environmental impact. Green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials [1, 2].

If one compares the technology with medical care, green and sustainable chemistry (GSC) focuses on precaution (or prevention) rather than diagnosis and cure. When the GSC Network, Japan was launched, a new organization for the promotion of GSC activities, "green and sustainable chemistry" was defined in a slightly broader sense, that is, innovative chemical technologies for sustainable society, including waste treatment and reuse. The chemical technologies are expected to realize such important objectives as "human and environmental health and safety," and "efficient utilization of resources and energies," by minimizing the undesirable environmental influences of chemical products and processes through all the steps of the product life cycle, that is, selection of feed stocks, manufacture, uses, waste treatments, etc.

In general, GSC is a concept developed by integrating preceding ideas and activities such as environmentally benign (or friendly) products and processes, clean (or zero-waste) production, ecochemistry, etc. Another important aspect of GSC is that it is a movement involving various disciplines, sectors, and industries and aims at the shift of the present paradigm of the chemical industry (an entire system of materials flow) to a new paradigm. The most important goals of sustainable development are reducing the adverse consequences of the substances that we use and generate. The role of chemistry is essential in ensuring that our next generation of chemicals, materials, and energy is more sustainable than the current generation. Worldwide demand for environmentally friendly chemical processes and products requires the development of novel and cost-effective approaches to pollution prevention. One of the most attractive concepts in chemistry for sustainability is green chemistry, which is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products [1]. It should be noted that the rapid development of green chemistry is due to the recognition that environmentally friendly products and processes will be economical on a long term. Catalysis remains one of the most important fields of green chemistry by providing atom-economical, selective, and energy-efficient solutions to many industrially important problems. The utilization of inorganic [3, 4] solid-supported reagents has attracted attention because of enhanced selectivity, milder reaction conditions and associated ease of manipulation. Microwave (MW) heating has attracted the attention of investigators in that it makes it possible to shorten the length of reactions significantly, to increase their selectivity, and to increase the product yields, which is particularly important in the case of high-temperature processes that take a long time. In the last decade, microwave radiation (MWR) [5–7] has been used more and more often in organic synthesis.

In most cases, the investigations are carried out in domestic-type MW ovens or in equipment for the preparation of samples and analysis (digests). MW equipment specially designed for carrying out organic reactions has also been created [8, 9]. The synthetic chemical community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of substances required by society in short periods of time, and the best option to accelerate these synthetic processes is to use MW technology. The time saved by using the MW heating approach is potentially important in traditional organic synthesis and assembly of heterocyclic systems [10].

2 Assessment of Greenness in the Synthesis of Heterocyclic and/or Organic Compounds

Anastas and Warner proposed 12 principles for green chemistry [1]. As for green catalysts or catalysts for clean production, various targets of R&D [11, 12], such as solid acid catalysts, improvement of reaction media, synthetic routes of high atom economy, and catalysts for selective oxidation, can be listed. However, it is difficult for any new technology to satisfy all of these principles or targets simultaneously and there are usually trade-off relationships between these principles and targets. Here, a couple of remarks may be made. First, although most of the principles and targets mentioned earlier are concerned with green processes, we should pay equal attention to green products. Second, in order to evaluate the greenness of a new technology, it is necessary to assess quantitatively or semiquantitatively the environmental impacts brought about by the new technology and the impacts thus estimated must be compared with those of the existing or other possible technologies. The assessment is also necessary to give priority to an R&D project over other projects.

The life-cycle assessment (LCA) would be a basic approach for this purpose. But, reliable LCA is not an easy task even for the simplest items such as energy consumption. Moreover, in the case of chemical processes and materials, we need to seriously consider their toxicity and safety. Economy is another factor which cannot be neglected. Uneconomical processes cannot be utilized widely and are possibly inefficient from the standpoint of green chemistry. Assessment integrating all of these items will be far more difficult. Sometimes, bio-processes are conceived as if they were always green. But bio-processes can be green or black:red, depending on the situation. The same applies to the other targets of green catalysts, e.g., solid acids and alternative solvents. Water is probably a green solvent in several cases, but it may need more energy in the separation step and the major source of volatile organic compounds (VOCs) in the atmosphere is not the organic solvents used for reaction.

As for solid acids, it should be noted that there are already very green processes using acid catalysts in solution (not solid) as exemplified later. It is also noted in these examples that the greenness very much depends on the selectivity of the reaction and the separation of products and catalysts. Therefore, we must consider carefully for each case the trade-off relationships between risk and benefit and between one risk and other risks. Several methods at different levels may be necessary for the evaluation. For ordinary chemists and chemical engineers involved in R&D, an easily applicable method is desirable.

3 Heteropolyacids as Green Catalysts

The heteropolyacid (HPA) catalysts will be introduced as promising candidates for green catalysts in the following order: an overview, latest experimental result, and then examples of industrial application. As described later, several successful examples have already demonstrated that HPAs can be used as green catalysts. Furthermore, since they can be active solid acid catalysts and can provide unique reaction fields such as pseudoliquid, that is, "catalytically active solid solvent," HPA catalysts will find more green/sustainable applications in future. HPAs as solid acid catalysts are green catalysts with respect to their noncorrosive nature, safety, low quantity of waste, and easy separation. One of the unique features that make solid HPAs economically and environmentally attractive is their stability and high acidity. HPA catalysts are useful acid and oxidation catalysts that can be used in various reaction media, e.g., as solid catalysts (one surface and two bulk-type catalysis in both gas–solid and liquid–solid systems) and in homogeneous solution (organic and aqueous) and in bi-phase solution systems [13].

Here, several green and sustainable aspects of HPA catalysts are described. The application of HPAs as catalytic materials is growing continuously in the catalytic field. These compounds possess unique properties, such as well-defined structure, Brønsted acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, etc. [14]. In view of green chemistry, the substitution of harmful liquid acids by solid reusable HPAs as a catalyst in organic synthesis is the most promising application of these acids.

Various methods have been reported for the synthesis of fused heterocyclic compounds using mineral acids such as H_2SO_4 and polyphosphoric acid. These catalysts have their own disadvantages and drawbacks. They generate many problems such as pollution, care of handling, safety, corrosion, and tedious workup procedures. Strong solid acids and solid acids based on supported transition metal oxides are suitable for replacement of liquid acids to decrease these disadvantages [15, 16]. The catalytic function of HPAs and related polyoxometalate (POM) compounds has attracted much attention particularly in the past two decades [17–19]. POMs are a class of molecularly defined organic metal-oxide clusters, possessing intriguing structure and diverse properties [20, 21].

These compounds exhibit high activity in acid–base type of catalytic reactions; hence, they are used in many catalytic areas as homogeneous and heterogeneous catalysts [22]. The application of Preyssler catalyst is mostly limited and only a few demonstrations of catalytic activity have been reported [23]. The structure of this catalyst is shown in Fig. 3.1 [24].

On the other hand, Keggin HPAs are other catalysts in the green method of the synthesis of heterocyclic, drugs, and organic compounds in chemistry. Recently, we have explored the application of Preyssler and Keggin catalysts in various organic reactions [25, 26]. Green chemistry has been defined as a set of principles which reduce or eliminate the use of hazardous substances or catalysts [1, 2]. Introducing clean processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions have been under permanent attention and demands.

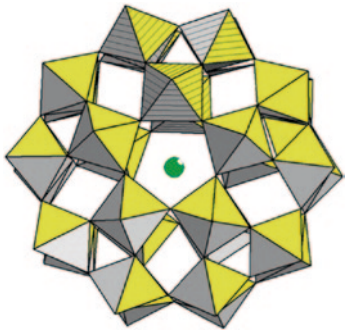


Fig. 3.1 Preyssler structure

Recently, HPAs which are low in toxicity and they being recyclable have attracted special attention [27–29]. Many reactions catalyzed by Bronsted and Lewis acids now, in the presence of HPAs, proceed more effectively under milder conditions with greater selectivity, better yields, and shorter reaction times. Among HPAs, the application of Keggin and Wells–Dawson structures have been extensively studied [30–37]. One of the intriguing heteropoly compounds is Preyssler's anion. The catalytic applicability of Preyssler's anion, $[NaP_5W_{30}O_{110}]^{14-}$ with high thermal and hydrolytic stability throughout a wide pH range has been largely overlooked and only a few reports for catalytic performance of this catalyst have been cited [38]. This HPA is remarkable because of the following advantages: (1) strong Brønsted acidity with 14 titrable acidic protons, (2) high thermal stability, (3) high hydrolytic stability (pH 0–12), (4) reusability, (5) more safety, (6) lower waste quantity, (7) better separability, (8) less corrosiveness, (9) high oxidation potential, and (10) greenness [39–42]. We are interested in catalytic reactions [43] and catalytic applicability of heteropoly compounds [42, 43]. Recently, we have been exploring the application of the Preyssler catalyst for many reactions [43]. The green catalysts can be easily recovered and recycled with retention of their initial structure and activity. Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds. Because of the drug-like character and considerable range of structural diversity, large collections or libraries of diverse heterocycles are routinely employed in high-throughput screening at early stages of drug discovery programs. The remarkable ability of heterocyclic nuclei to serve as both biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs [44]. In both lead identification and lead optimization processes, there is an acute need for new small organic molecules. Conventional methods of organic synthesis are orders of magnitude too slow to satisfy the demand for generation of such compounds. The fields of combinatorial and automated medicinal chemistry have emerged to meet the increasing requirement of new compounds for drug discovery, where speed is of the essence. Also, in the context of green chemistry, there are several issues which influence the

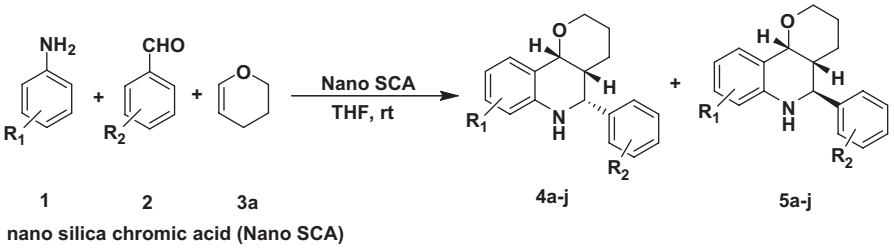
choice of solvent. It should be relatively nontoxic and relatively nonhazardous (e.g., not flammable or corrosive).

The solvent should also be contained, that is, it should not be released to the environment. All these traits are ideally fulfilled by water, which is nontoxic, nonflammable, abundantly available, and inexpensive [10, 45]. Moreover, owing to its highly polar character, one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, this provides an opportunity to overcome a serious shortcoming of homogeneous catalysts, namely, the cumbersome recovery and recycling of the catalysts. To illustrate the advantages of greener alternatives in the synthesis of bioactive heterocyclic compounds, we have developed various environmentally benign protocols.

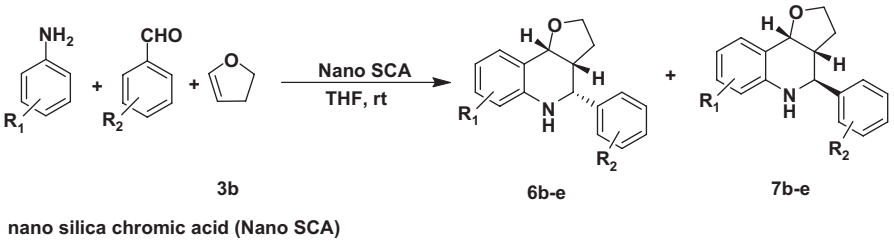
4 Catalytic Synthesis of Pyrano- and Furoquinolines Using Nano-Silica Chromic Acid at Room Temperature

In this protocol, nano-silica chromic acid (nano-SCA) is found to catalyze efficiently the three-component coupling reactions of aldehydes, amines, and cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran under mild conditions to afford the corresponding pyrano- and furanoquinolines in excellent yields with high endo-selectivity.

Interestingly, 2,3-dihydrofuran afforded selectively endo-products under the similar reaction conditions. Heterogeneous reaction conditions, easy procedure, short reaction time, and high yields are some important advantages of this method (Schemes 3.1 and 3.2) [46].



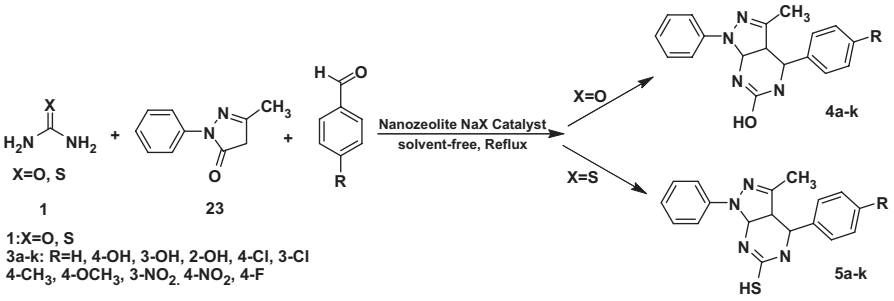
Scheme 3.1 Synthesis of pyrano[3,2-*c*]quinolines using nano silica chromic acid (nano silica chromic acid) catalyst



Scheme 3.2 Synthesis of furo[3,2-*c*]quinolines using nano silica chromic acid (nano silica chromic acid) catalyst

5 Catalytic Synthesis of Pyrazolo[3,4-*d*]pyrimidin-6-ol and Pyrazolo[3,4-*d*]pyrimidine-6-thiol Derivatives Using Nanoparticles of NaX Zeolite as Green Catalyst

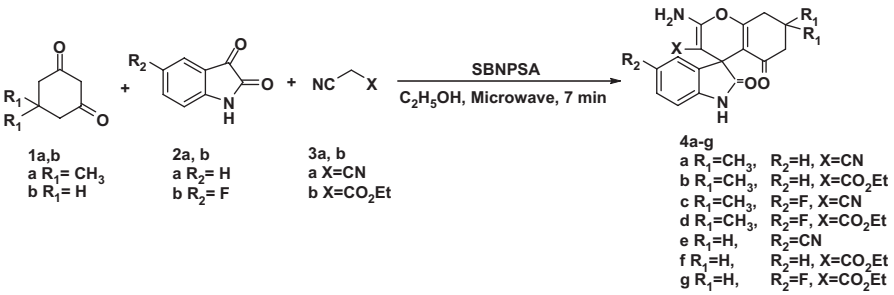
An efficient and environmental benign method is reported for the synthesis of some pyrazolopyrimidine derivatives using 3-methyl-1-phenyl-5-pyrazolone with carbonyl compounds in the presence of nano zeolite NaX catalysts, solvent free and at reflux conditions. It is noteworthy to mention that this method of the synthesis requires less time, less temperature, and better yield (Scheme 3.3) [47].



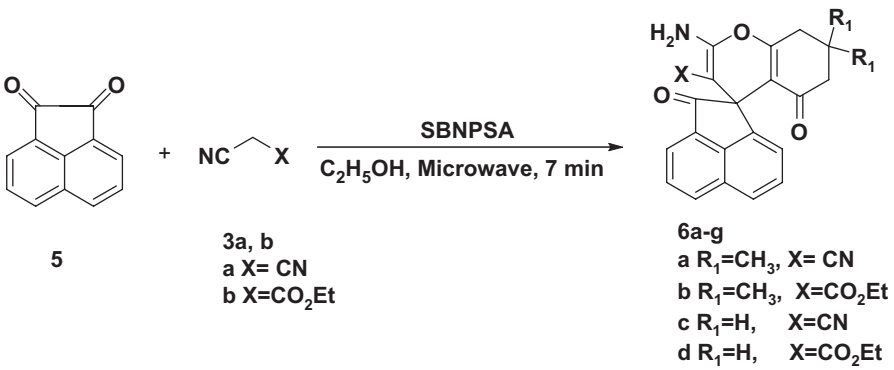
Scheme 3.3 Synthesis of pyrazolone-pyrimidine derivatives by using nanoparticles of NaX Zeolite catalysts

6 Silica-Bonded *N*-Propyl Sulfamic Acid: a Recyclable Catalyst for Microwave-Assisted Synthesis of Spirooxindoles via Three-Component Reaction

Silica-bonded *N*-propyl sulfamic acid (*SBNPSA*) is employed as a solid acid catalyst for the synthesis of spirooxindoles via three-component reaction in good yields and short reaction times in ethanol under irradiation MW conditions. Irradiation of the combination of isatin or acenaphthoquinone, an activated methylene reagent, and 1,3-dicarbonyl compounds in the presence of catalytic *SBNPSA* was found to be a suitable and efficient method for the synthesis of the biologically important spirooxindoles (Schemes 3.4 and 3.5) [48].



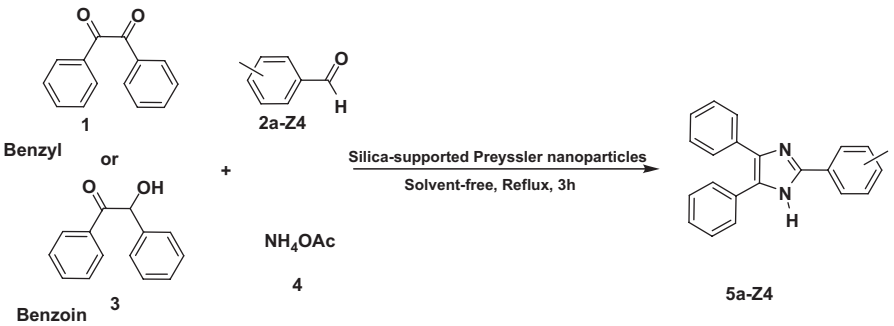
Scheme 3.4 Synthesis of spirooxindoles (*4a–g*) via three-component reaction with isatin (*2*) in the presence of silica-bonded *N*-propyl sulfamic acid (*SBNPSA*) as catalyst under irradiation microwave conditions



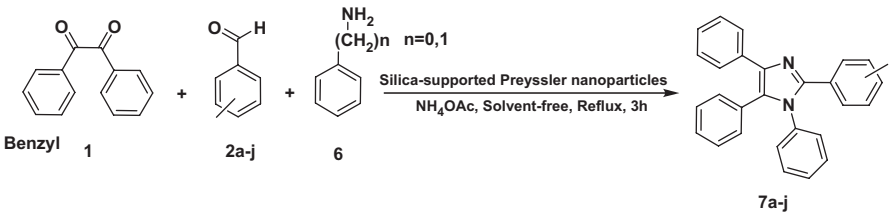
Scheme 3.5 Synthesis of spirooxindoles (*6a–g*) via three-component reaction with acenaphthoquinone (*5*) in the presence of silica-bonded *N*-propyl sulfamic acid (*SBNPSA*) as catalyst under irradiation microwave conditions

7 Synthesis of 2,4,5-Trisubstituted and 1,2,4,5-Tetrasubstituted-1*H*-Imidazole Derivatives and/or 2,4,5-Triaryloxazoles Using of Silica-Supported Preyssler Nanoparticles

One-pot multicomponent condensation of benzyl and/or benzoin, aldehydes, ammonium acetate, and primary amines were used for synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives under reflux conditions using silica-supported Preyssler nanoparticles HPA as a catalysts. This catalyst has several advantages (simple workup, inexpensive, and reusability). These catalysts were also successfully employed in the synthesis of triaryloxazoles (Schemes 3.6 and 3.7) [49].



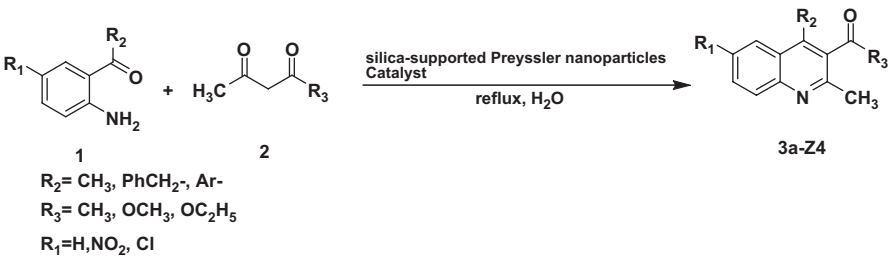
Scheme 3.6 Synthesis of 2,4,5-trisubstituted-1*H*-imidazole derivatives (*5a–Z4*) in the presence of silica-supported Preyssler nanoparticles under solvent-free conditions at reflux conditions and in proper times



Scheme 3.7 Synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives (*7a–j*) in the presence of silica-supported Preyssler nanoparticles under solvent-free conditions at reflux conditions and in proper times

8 Preyssler Heteropolyacid Supported on Nano-SiO_2, $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$: a Green and Reusable Catalyst in the Synthesis of Polysubstituted Quinolines

The synthesis of polysubstituted quinolines in the presence of silica-supported Preyssler nanoparticles (*SPNP*), $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$, Preyssler $H_{14}[NaP_5W_{30}O_{110}]$, and Keggin HPAs, $H_3PW_{12}O_{40}$, $H_7[PMo_8V_4O_{40}]$, $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, and $H_3[PMo_{12}O_{40}]$ as catalyst under aqueous conditions is described. The best conditions were observed using Preyssler and silica-supported Preyssler nanoparticles as catalysts. The catalyst is recyclable and reusable (Scheme 3.8) [50].



Scheme 3.8 The reaction of 2-aminobenzophenone (*1*), and ethyl acetoacetate (*2*) under solvent-free condition at reflux conditions in the presence of silica-supported Preyssler nanoparticles catalyst, $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$

The efficiency of Preyssler nanoparticles, $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$, is attributed to the nanoporous structure of this solid acid catalyst, which could act as a nanoreactor (Fig. 3.2).

The HPA $H_{14}[NaP_5W_{30}O_{110}]$ in the SiO_2 nanoparticle was confirmed by infrared spectroscopy as shown in Fig. 3.2. The asymmetric stretching frequency of the ter-

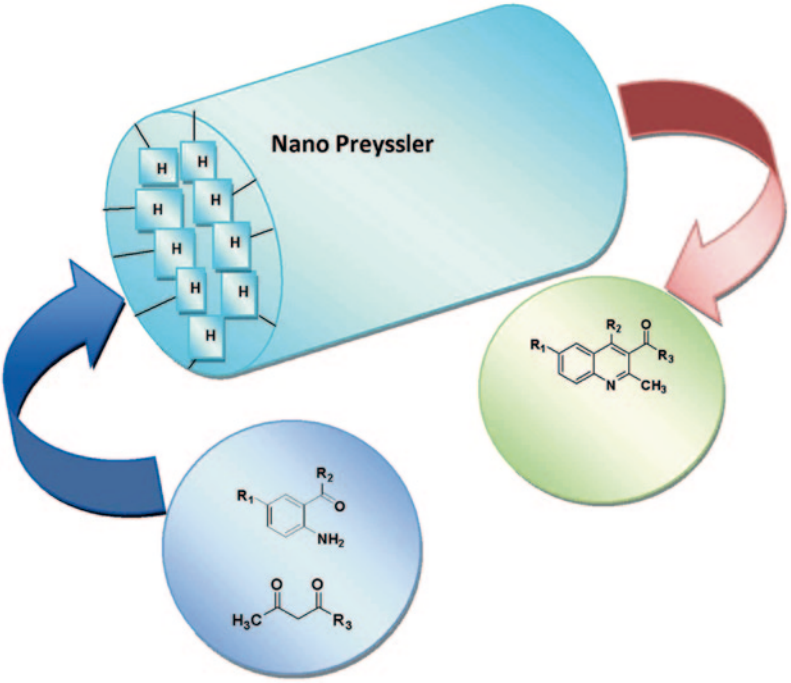


Fig. 3.2 Preyssler nanoparticles, $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$, act as a nano-reactor

minal oxygen is observed at 960 cm^{-1} and the P–O asymmetric stretching frequency is noted at 1,080 and 1,165 cm^{-1}. The prominent P–O bands at 960, 1,080, and 1,165 cm^{-1} are consistent with a C_{5V} symmetry anion. These bands demonstrate that $H_{14}[NaP_5W_{30}O_{110}]$ is preserved in the HPA/SiO_2 nanoparticles. In addition, the protonated water of $H_{14}[NaP_5W_{30}O_{110}]$ also remained in the nanoparticles at 1,730 cm^{-1}. It could be confirmed that the HPA $H_{14}[NaP_5W_{30}O_{110}]$ was successfully immobilized into the SiO_2 nanoparticles since the HPA does not react with SiO_2 or with water, but it can remain in the silica nanoparticles without appreciable change of the structures (Fig. 3.3).

9 Novel Catalytic Method in Synthesis of Calix[4] pyrroles Using Preyssler and Wells–Dawson HPAs

A catalytic synthesis of calix[4]pyrroles and *N*-confused calix[4]pyrroles by reaction of dialkyl or cycloalkyl ketones with pyrrole was performed using Preyssler, sodium 30-tungsto pentaphosphate, $[NaP_5W_{30}O_{110}]^{14-}$, and Wells–Dawson HPAs as acidic catalysts. The process occurred under mild, eco-friendly, and environmentally friendly conditions and as a reusable, green catalyst at room temperature for 6 h. The results showed that the yield for this synthesis is excellent with the

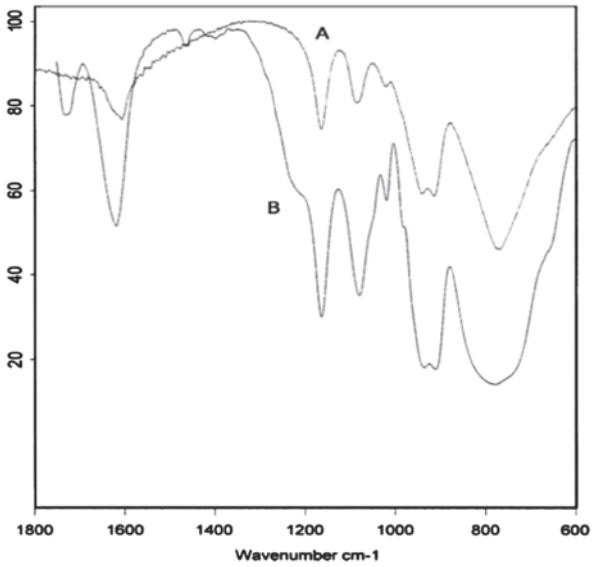
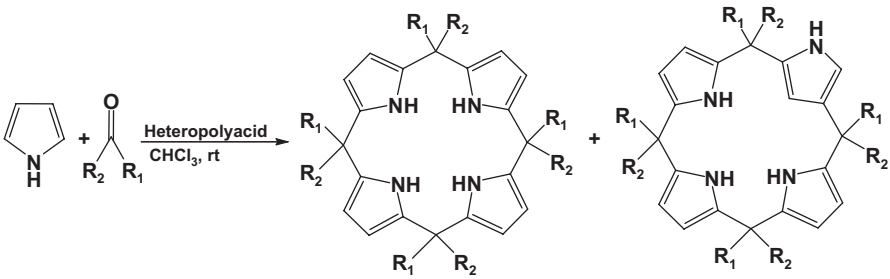


Fig. 3.3 Infrared spectroscopy of Preyssler heteropolyacid in bulk form (*B*) and nano form (*A*)

use of Preyssler and Wells–Dawson-type tungstophosphoric HPA, $H_6[P_2W_{18}O_{62}]$, catalysts. The synthesis of calix[4]pyrroles and *N*-confused calix[4]pyrroles was developed using different solvents and the best yields were obtained in chloroform (Scheme 3.9) [51].

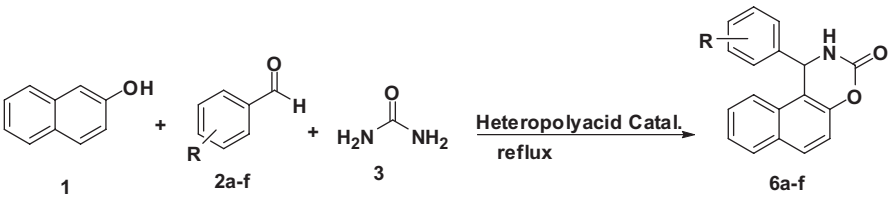


Scheme 3.9 Synthesis of calix[4]pyrroles derivatives using green catalysts

10 An Efficient and Convenient Method for Synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one Derivatives Using Silica-Supported Preyssler HPAs, $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$, as a Heterogeneous Catalyst

Preyssler-type HPA is found to be an efficient catalyst for the synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives in good yields in a convenient, efficient, and green reaction by condensation of naphthol, aromatic

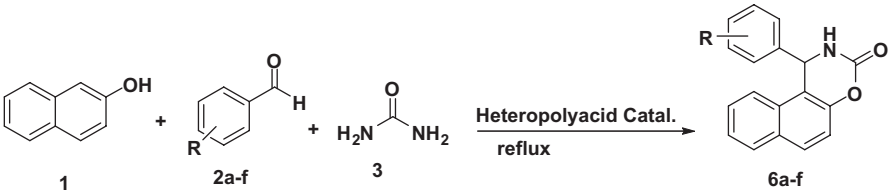
aldehydes, urea, ethanol, and silica-supported Preyssler HPA catalysts under reflux conditions. The catalyst is recycled and reused several times (Scheme 3.10) [52].



Scheme 3.10 Synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives using green catalysts

11 An Efficient Catalytic Synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one Derivatives Using Silica-Supported Preyssler HPA, $H_{14}[NaP_5W_{30}O_{110}]$/$SiO_2$ (50 %) as a Heterogeneous Catalyst

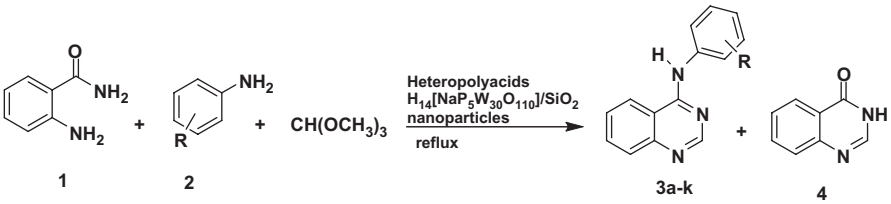
Silica-supported Preyssler-type HPAs are found to be efficient catalysts for the synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2-*e*][1,3]oxazin-3-one derivatives in a convenient, efficient, good yield, and green reaction by condensation of β-naphthol, aromatic aldehydes, urea, and ethanol under reflux conditions. The catalyst is recycled and reused several times (Scheme 3.11) [52].



Scheme 3.11 Synthesis of 1,2-dihydro-1-aryl-3*H*-naphth[1,2–*e*][1,3]oxazin-3-ones using $H_{14}[NaP_5W_{30}O_{110}]$/$SiO_2$ catalyst (50 % catalyst loading)

12 Heteroplyacids Accelerated Multicomponent Synthesis of *N*-phenylquinazolin-4-amines by Using Silica-Supported Preyssler Nanoparticles in Green Solvent

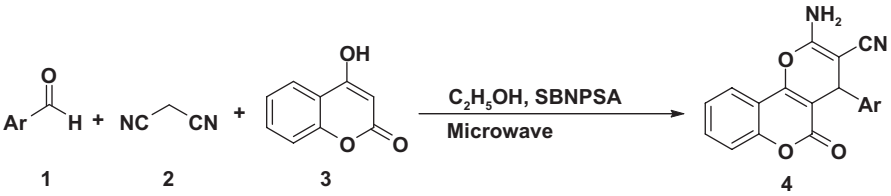
N-phenylquinazolin-4-amines derivatives were obtained in high yields with excellent purity from the reaction of 2-aminobenzamide, orthoesters, and substituted anilines in the presence of silica-supported Preyssler nanoparticles and various HPAs (Scheme 3.12) [53].



Scheme 3.12 Synthesis of *N*-phenylquinazolin-4-amine derivatives using Preyssler nanoparticles, $H_{14}[NaP_5W_{30}O_{110}]/SiO_2$

13 Silica-Bonded *N*-propyl Sulfamic Acid: a Recyclable Catalyst for Microwave-Assisted Synthesis of Various Dihydropyrano[3,2-*c*]chromenes

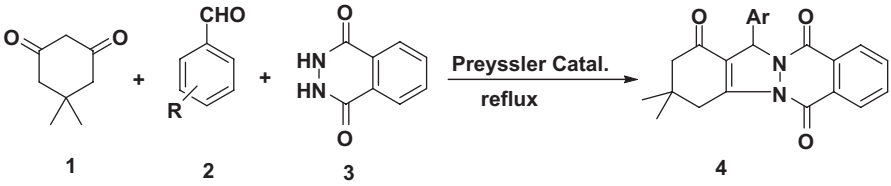
A novel and simple method for the synthesis of various dihydropyrano[3,2-*c*] chromenes is reported and obtained in good to excellent yields by a simple, mild, and efficient procedure using silica-bonded *N*-propyl sulfamic acid (SBNPSA) as catalyst under irradiation MW conditions (Scheme 3.13) [54].



Scheme 3.13 Synthesis of various dihydropyrano[3,2-*c*]chromenes in the presence of silica-bonded *N*-propyl sulfamic acid (SBNPSA) as catalyst under irradiation microwave conditions

14 Efficient and Convenient Synthesis of 2*H*-indazolo[2,1-*b*] phthalazine-triones by Using Reusable Silica-Supported Preyssler Heteropolyacid

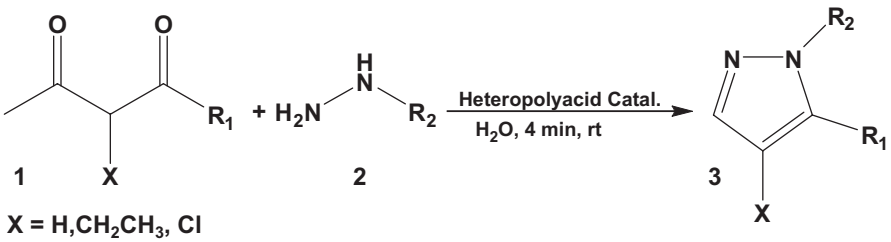
An efficient synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives has been achieved in one-pot reaction at room temperature from the three-component condensation reaction of phthalhydrazide, dimedone, and aromatic aldehydes under solvent-free conditions in good to excellent yields and short reaction times using reusable silica-supported Preyssler HPAs as a heterogeneous acid catalyst has been investigated (Scheme 3.14) [55].



Scheme 3.14 Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones using green conditions

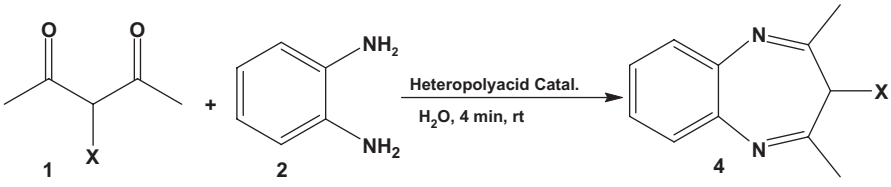
15 Catalytic Synthesis of Pyrazoles and Diazepines Under Green Conditions and Room Temperature Using Heteropolyacids Catalysts

Catalytic performance of Preyssler, $H_{14}[NaP_5W_{30}O_{110}]$, Wells–Dawson, $H_6P_2W_{18}O_{62}$ and Keggin, $H_3[PW_{12}O_{40}]$ and $H_4PMo_{11}VO_{40}$, HPAs as pure have been studied synthesis of pyrazoles and diazepines in condensation of hydrazines, hydrazides and diamines with various 1,3-diketones. In all cases, the best yields were obtained using $H_{14}[NaP_5W_{30}O_{110}]$ (Schemes 3.15 and 3.16) [56].



X = H,CH_2CH_3, Cl
R_1 = CH_3, OCH_2CH_3
R_2 = CO-thirnyl, CO-furyl, C_6H_5, 4-ClC_6H_5, COC_6H_5

Scheme 3.15 Synthesis of pyrazoles using green conditions

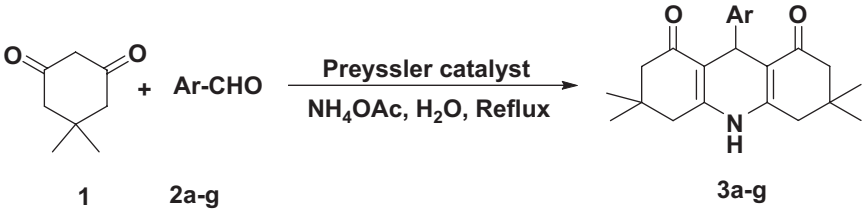


X = H, CH_3, CH_2CH_3, Cl

Scheme 3.16 Synthesis of diazepines using green conditions

16 Catalytic Synthesis of Fused 1,4-dihydropyridines and 1,4-dihydropyridine Derivatives Using Preyssler Heteropolyacids Catalyst

An efficient and convenient method for the synthesis of 1,4-dihydropyridines (1,4-DHPs) from β-dicarbonyl compounds, aldehydes, and ammonium acetate and the synthesis of fused 1,4-DHPs from dimedone in the presence of Preyssler HPA catalyst is reported under reflux conditions with good to excellent yields. Preyssler HPAs catalyst is easily prepared, stable (up to 300 °C), reusable, efficient, green, and inexpensive (Scheme 3.17) [57].

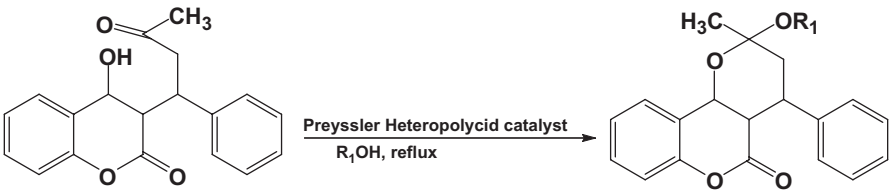


Ar=4-FC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

Scheme 3.17 Synthesis of fused 1,4-dihydropyridines and 1,4-dihydropyridines using green method

17 Catalytic Synthesis of Warfarin Acetals by Using Different Heteropolyacid Catalysts

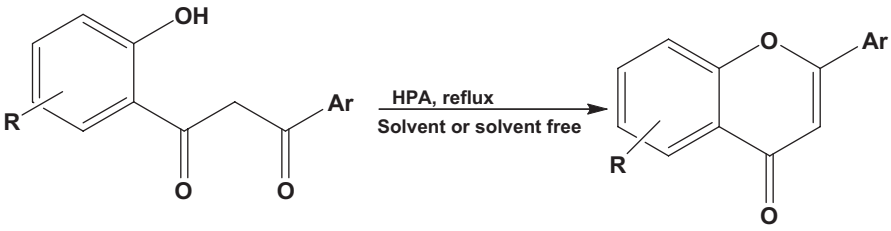
In this research, we report on the synthesis of warfarin acetals by using Preyssler's anion, $[NaP_5W_{30}O_{110}]^{-14}$, and HPA catalysts. This reaction was performed using methanol and ethanol at reflux temperature conditions. We have excellent yields and high selectivity under these conditions. Preyssler HPA catalyst was easily recycled, recovered, and reused without the loss of its catalytic activities. The synthesis of warfarin acetals has been achieved using the catalytic amounts of green, inexpensive, and eco-friendly Keggin HPA types. The products were obtained in high yields (Scheme 3.18) [58].



Scheme 3.18 Synthesis of warfarin acetals using green method

18 Effective Catalytic Synthesis of Substituted Flavones and Chromones Using Preyssler and Heteropolyacids as Catalysts

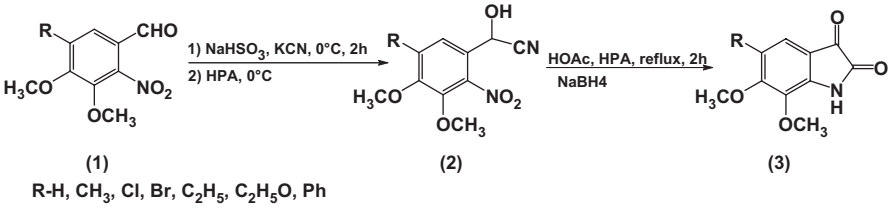
We report on the use of Preyssler's anion and HPA catalysts for obtaining substituted flavones and chromones for the cyclization of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones. The reactions were performed using chloroform as a solvent at reflux temperature conditions and in the absence of solvent, at 110 °C. We had excellent yields and high selectivity at these conditions. The presented synthetic method is a simple, clean, and environmentally friendly alternative for synthesizing substituted flavones and chromones (Scheme 3.19) [59].



Scheme 3.19 Synthesis of substituted flavones and chromones using green method

19 Novel Catalytic Synthesis of 6,7-dimethoxyisatin with the Use of Heteropolyacids as Acid Solid Catalyst

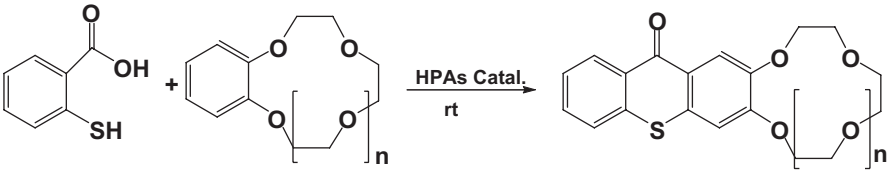
An efficient method for the preparation of 6,7-dimethoxyisatin and its derivatives was developed with good yield by using Preyssler-type HPA as an acid catalyst under green conditions. The comparison between Keggin-type HPAs, $H_3[PW_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$ and $H_4[SiMo_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$ and mineral acids with Preyssler's anion shows that the latter possess better catalytical activity than the other HPAs and no degradation of the structure was observed (Scheme 3.20) [60].



Scheme 3.20 Synthesis of 6,7-dimethoxyisatin derivatives using green method

20 A Method for Catalytic Synthesis of Convenient Thioxanthone Crown Ethers Using Wells–Dawson, $H_6[P_2W_{18}O_{62}]$, Preyssler $H_{14}[NaP_5W_{30}O_{110}]$, Heteropolyacid Catalysts

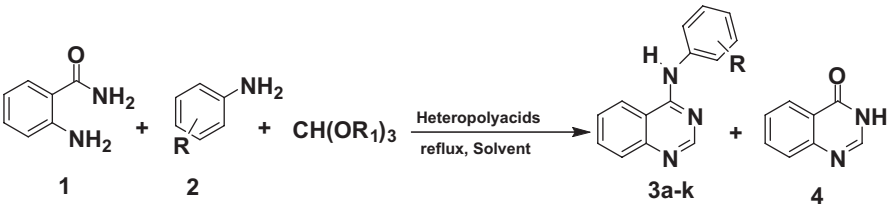
HPAs were used as an effective catalyst for the synthesis of thioxanthone crown ethers from the reaction of thiosalicylic acid and benzocrown ethers. This reaction was carried out subsequently via intramolecular electrophilic cyclization. The reaction was in mild and clean conditions, and has high selectivity with good yields (Scheme 3.21) [61].



Scheme 3.21 Synthesis of thioxanthone crown ethers using green method

21 Synthesis of 4-arylaminoquinazolines

Recently, Keggin-type HPAs including $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, and $H_3[PMo_{12}O_{40}]$ have been used for multicomponent synthesis of 4-arylaminoquinazolines from the reaction of 2-aminobenzamide, orthoesters, and substituted anilines. In all reactions, by-product was obtained in low yield. The effects of reaction conditions and different HPAs have been studied. It has been proved that Keggin-type HPAs are efficient, reusable, and eco-friendly heterogeneous inorganic catalysts. The advantages of this method are the easy workup procedure and high yields of products (Scheme 3.22) [62].

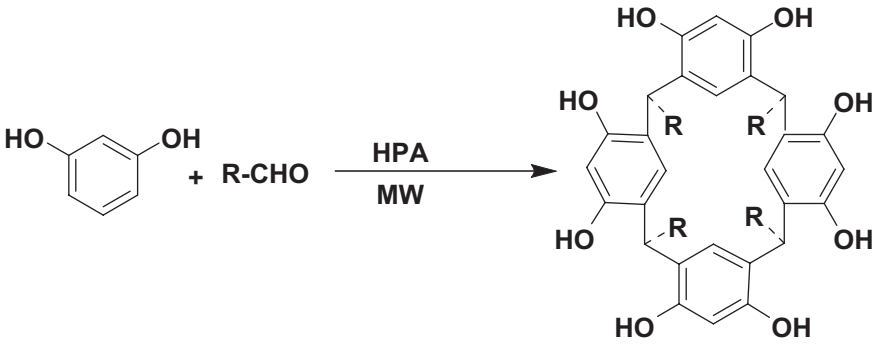


Scheme 3.22 Synthesis of 4-arylaminoquinazolines using green method

22 Synthesis of Calix[4]resorcinarenes

Interest in the chemistry of calixarenes has increased in recent years. Of particular significance has been the preparation of a range of calix[4]resorcinarene derivatives in high yields [63]. Self-assembled monolayers of resorcinarene derivatives on gold surfaces provide an important starting point for fabricating and operating nanoscale

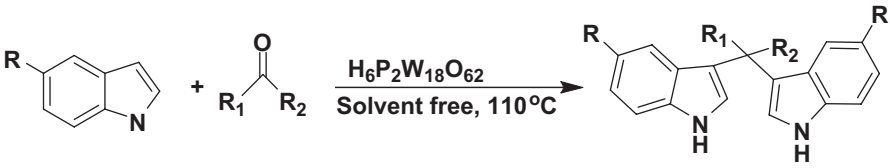
devices for advanced information technologies. Resorcinarene derivatives have also been used as a stationary phase in achiral capillary gas chromatography for the separation of positional isomers of substituted benzenes [64]. MW-assisted synthesis of calix[4]resorcinarenes by cyclocondensation of various aldehydes and resorcinol catalyzed by 12-tungstophosphoric acid-type Keggin ($H_3[PW_{12}O_{40}].13H_2O$) or concentrated HCl has been performed. Excellent isolated yields (up to 90%) were attained within short reaction times (typically, 3–5 min) when the reaction was performed under MW irradiation (Scheme 3.23) [65].



Scheme 3.23 Synthesis of calix[4]resorcinarenes using green method

23 Synthesis of Bis(indolyl)methanes

A simple, efficient, and convenient procedure for the synthesis of bis(indolyl)methane derivatives under solvent-free conditions in the presence of a catalytic amount of Wells–Dawson-type HPA has been developed. Some advantages of this procedure are: the experimental simplicity and the easy workup procedure; use of a green, easy to handle, and reusable catalyst; high yields; and the absence of volatile and hazardous solvents (Scheme 3.24) [66].

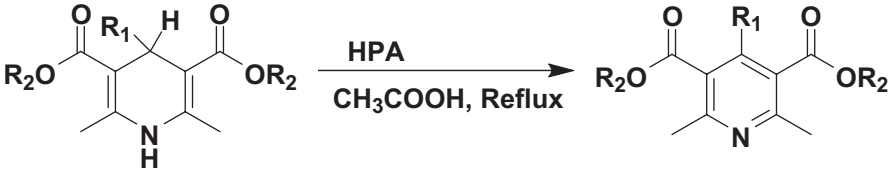


Scheme 3.24 Synthesis of bis(indolyl)methanes using green method

24 Oxidative Aromatization of Hantzsch 1,4-dihydropyridines

1,4-DHPs are a class of model compounds of NADH coenzyme and calcium channel antagonists (CCAs) [67]. These compounds have been established as one of the first-line drugs for treatment of hypertension because of their promising depressor effect and relatively good tolerability [68]. A variety of Hantzsch 1,4-DHPswere oxidized

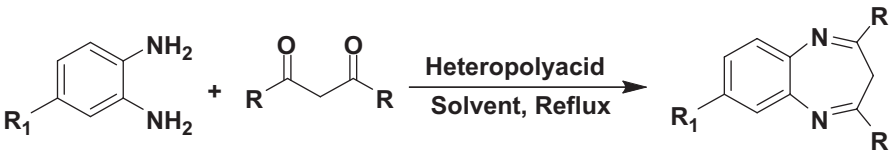
to the corresponding pyridines in high yields in the presence of acetic acid and Keggin-type HPA, $H_6PMo_9V_3O_{40}$, under reflux conditions. The HPA was found to be reusable. The effects of various solvents and HPAs were studied (Scheme 3.25) [69].



Scheme 3.25 Oxidative aromatization of Hantzsch 1,4-dihydropyridines using green method

25 Synthesis of 1,5-Benzodiazepine Derivatives

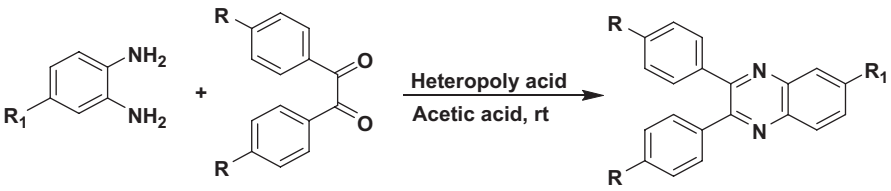
Benzodiazepines and their polycyclic derivatives are a very important class of bioactive compounds. They are finding numerous new applications and are widely used as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative, and antidepressive agents [70]. Benzodiazepines are also valuable intermediates for synthesis of fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, and furano-benzodiazepines [71]. A simple method for the condensation of *o*-phenylenediamines (*o*-PDA) with 1,3-diketones using a catalytic amount of different type of HPAs, including $H_{14}[NaP_5W_{29}MoO_{110}]$, $H_5[PMo_{10}V_2O_{40}]$, and $H_6[P_2W_{18}O_{62}]$, as the catalyst to synthesize 3*H*-1,5-benzodiazepines has been reported [72]. The results indicated that the nature of the catalyst played an important role in their catalytic activities. The highest yield of products has been achieved in the presence of $H_{14}[NaP_5W_{29}MoO_{110}]$ as catalyst, and $H_5[PMo_{10}V_2O_{40}]$ gave lowest yields (Scheme 3.26).



Scheme 3.26 Synthesis of 1,5-benzodiazepine derivatives using green method

26 Synthesis of Quinoxaline

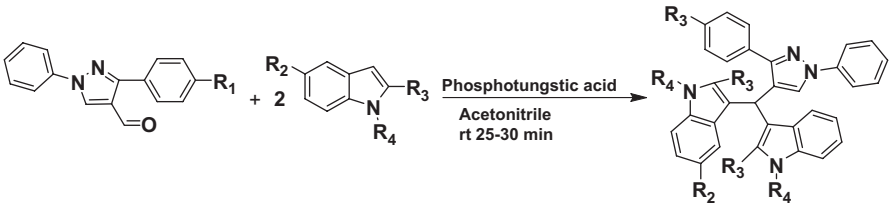
Well–Dawson HPA was used as an effective catalyst for the synthesis of biologically active quinoxaline derivatives from the condensation of 1,2-dicarbonyl compounds with *o*-phenylenediamine at room temperature in excellent yields [73]. The optimum yield of the products was obtained when 1 mol% of catalyst was used. Among the solvents tested for this reaction, including $CHCl_3$, CH_3CN, H_2O, and AcOH, the latter was found to be most efficient (Scheme 3.27).



Scheme 3.27 Synthesis of quinoxalines using green method

27 Synthesis and Antimicrobial Activity of Pyrazolylbisindoles

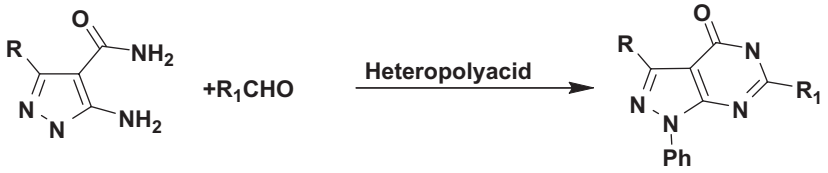
A series of pyrazolylbisindole derivatives have been synthesized by reacting substituted pyrazole aldehydes with substituted indoles using phosphotungstic acid, a Keggin-type HPA as catalyst. The synthesized pyrazolylbisindoles were evaluated for antimicrobial activities. The effect of pyrazolylbisindoles on the mycelial growth of plant pathogenic fungi was revealed (Scheme 3.28) [74].



Scheme 3.28 Synthesis of pyrazolylbisindoles using green method

28 Synthesis of 6-aryl-1*H*-pyrazolo[3,4-*d*] pyrimidin-4[5*H*]-ones

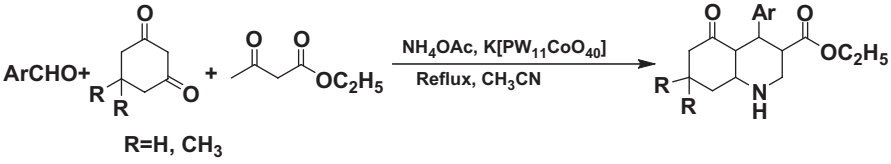
Pyrazolo[3,4-d]pyrimidines are of considerable chemical and pharmacological importance as purine analogues [75]. Various compounds with related structures also possess antitumor and antileukemia activities [76]. Therefore, the investigation about new methods and synthesis of new derivatives of these compounds attracted considerable amount of interest. Reaction of 5-amino-1-phenyl-1*H*-pyrazolo-4-carboxamide with aromatic aldehyde in the presence of HPAs, $H_3PW_{12}O_{40}$ and $H_{14}[NaP_5W_{29}MoO_{110}]$, gave derivatives of 6-aryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4[5*H*]-ones. It was confirmed that HPA with Preyssler structure shows higher activity and yields due to the higher number of acidic protons (Scheme 3.29) [77].



Scheme 3.29 Synthesis of 6-aryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4[5*H*]-ones using green method

29 1,4-dihydropyridyl Derivatives

In recent years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridyl compounds owing to their significant biological activities [78]. In particular, dihydropyridine drugs such as nifedipine, nicardipine, and amlodipine are effective cardiovascular agents for the treatment of hypertension [79]. In view of the importance of polyhydroquinoline derivatives, many classical methods for the synthesis of polyhydroquinoline derivatives were reported [80]. An easy and efficient method to prepare a variety of 1,4-dihydroquinoline derivatives from the reaction of different aryl aldehydes, 1,3-cyclohexanediones, ethyl acetoacetate, and ammonium acetate in the presence of catalytic amount of $K_7[PW_{11}CoO_{40}]$ under reflux condition as a clean, general, and inexpensive reaction has been successfully developed. Relatively short reaction times, very simple performance and workup procedure, and high yields were some of advantages of this procedure. The catalyst was recyclable and could be reused without significant loss of activity. $K_7[PW_{11}CoO_{40}]$ was also noncorrosive and environmentally benign and presents fewer disposal problems. The use of this solid acid catalyst allowed replacement of the usual soluble inorganic acids, contributing in this way to the reduction in wastes (Scheme 3.30) [81].

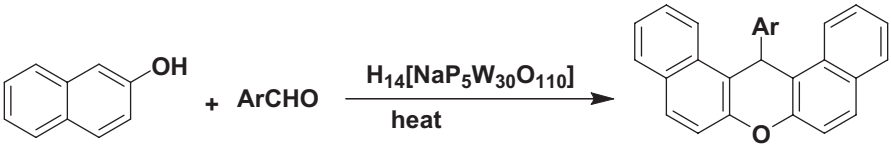


Scheme 3.30 Synthesis of 1,4-dihydropyridyl derivatives using green method

30 Synthesis of 14-aryl-14*H*-Dibenzo[*a, j*]xanthene

In recent years, much attention has been directed toward the synthesis of 14-substituted-14-*H*-dibenzo[*a, j*] xanthene derivatives due to the fact that these compounds possess a variety of biological and therapeutic properties, such as antibacterial [82], anti-inflammatory [83], antiviral activities [84] and as antagonism for paralyzing

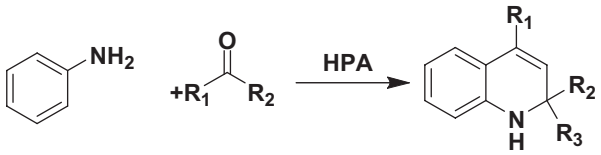
action of zoxazolamine [85]. Furthermore, these heterocycles show useful spectroscopic properties and are used as dyes [86] in laser technologies [87] and in fluorescent materials for visualization of biomolecules [88]. An efficient and facile synthesis of biologically active 14-substituted-14-*H*-dibenzo[*a, j*] xanthene derivatives were reported via three-component condensation reaction of α-naphthol and aldehydes in the presence of a catalytic amount of Preyssler-type HPA, under solvent-free conditions (Scheme 3.31).



Scheme 3.31 Synthesis of 14-aryl-14*H*-dibenzo[*a,j*]xanthene derivatives using green method

31 Quinoline Derivatives

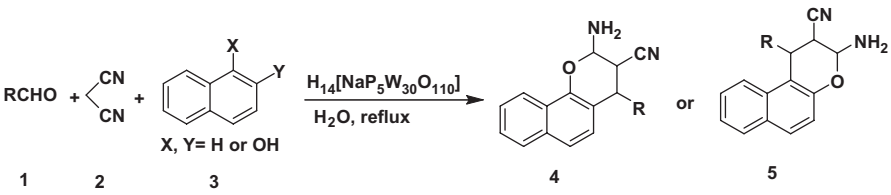
Dihydroquinoline moiety is found in a wide variety of natural products and they have attracted a lot of attention from synthetic organic chemists [89]. They form the parent bicyclic system for an extensive array of medicinally interesting compounds. Substituted dihydroquinolines have been used to produce potent drugs with bactericidal, antimalarial, and anti-inflammatory properties [90]. Substituted 2,2,4-dihydroquinolines have been synthesized in good yields from anilines and acetone and methyl ethyl ketone using silicotungstic acid as the catalyst. It was observed that acetonitrile was the best solvent in promoting the reaction (Scheme 3.32).



Scheme 3.32 Synthesis of quinoline derivatives using green method

32 Amino-4*H*-chromenes

2-Amino-chromenes represent an important class of compounds being the main components of many naturally occurring products. They can be utilized as cosmetics, pigments widely [91], and potential biodegradable agrochemicals [92]. These compounds have been of interest to the medicinal chemist for many years. $H_{14}[NaP_5W_{30}O_{110}]$ was used successfully as an efficient catalyst in the reaction of aldehydes, malononitrile, and α- and β-naphthol for the synthesis of 4 and 5 (Scheme 3.33).

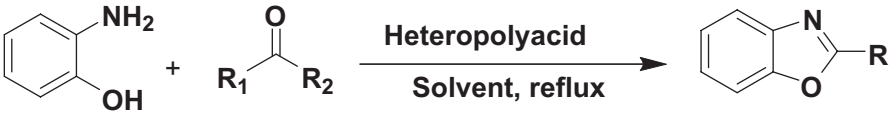


Scheme 3.33 Synthesis of amino-4*H*-chromenes using green method

This procedure offered several advantages including mild reaction conditions, cleaner reactions, high yields of products, as well as a simple experimental and workup procedure which made it a useful and attractive process for the synthesis of these compounds.

33 Synthesis of 2-arylbenzoxazoles

The use of three Keggin type of HPAs including, $H_4[PMo_{11}VO_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, and $H_3[PMo_{12}O_{40}]$ in the synthesis of benzoxazole derivatives from reaction of 2-aminophenol with benzaldehydes and benzoic acids and the effects of reaction parameters such as the type, amount of HPA, and solvent on the yield of reaction has been recently reported [93]. The comparison of these two methods for the synthesis of benzoxazole derivatives showed that condensation of 2-aminophenol with benzoic acids using HPAs under refluxing condition led to better yields than benzaldehydes. In addition, higher amount of HPA and more reaction time was required for the latter (Scheme 3.34).

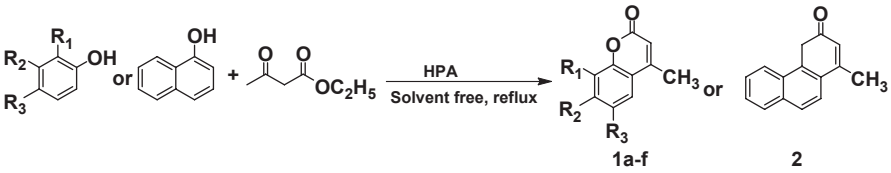


Scheme 3.34 Synthesis of 2-arylbenzoxazoles using green method

34 Synthesis of Coumarin Using Heteropolyacids Catalysts

Coumarin is the parent organic compound of a family of naturally occurring phytochemicals found in many plant species including lavender, sweet clover, strawberry, apricot, cherry, and cinnamon. The oxygen of this heterocycle is best known for its fragrance, described as a vanilla-like odor or the aroma of freshly mowed hay. It is also used to prepare other chemicals, in particular antioxidants [94]. Recently, the formation of 4-methylnaphtho-(1,2-b)-pyran-2-one (coumarin) from the condensation of α-naphthol and ethyl acetoacetate in a solvent-free system and under heating conditions, using a variety of heteropoly anions including: Keggin, Wells–Dawson, Preyssler, mixed addenda, and sandwich types, was performed.

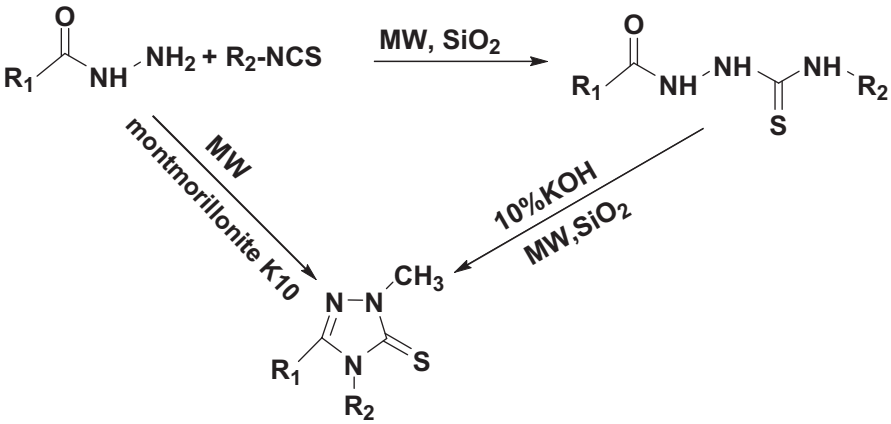
The obtained data vividly indicated that sodium 30-tungstopentaphosphate, $[NaP_5W_{30}O_{110}]^{14-}$, the so-called Preyssler's anion, with high hydrolytic (pH 0–12) and thermal stability is the catalyst of choice. This catalyst catalyzed the synthesis of other coumarin derivatives 1a–f and 2 in high yields and good selectivity [95] (Scheme 3.35).



Scheme 3.35 Synthesis of coumarin derivatives using green method

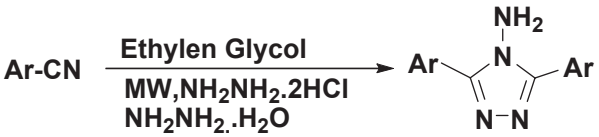
35 1,2,4-Triazoles

4,5-Disubstituted-1,2,4-triazole-3-thiones have been prepared in one stage from the reaction of acid hydrazide with alkyl or aryl isothiocyanate in the presence of a KOH (10%) solution on the surface of silica gel as well as on the surface of montmorillonite K10 under MW irradiation. These triazoles have also been prepared from the reaction of 4-substituted-1-aroyl thiosemicarbazides, with a KOH (10%) solution on the surface of silica gel under MW irradiation [96] (Scheme 3.36).



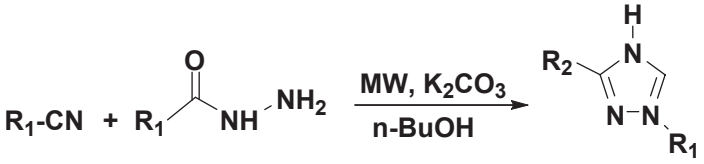
Scheme 3.36 Synthesis of 4,5-disubstituted-1,2,4-triazole-3-thiones using green method

Bentiss et al. [97] has synthesized 3,5-disubstituted-4-amino-1,2,4-triazoles from the reaction of aromatic nitriles with $NH_2NH_2.2HCl$ in the presence of $NH_2NH_2.2H_2O$ excess in ethylene glycol under MW irradiation (Scheme 3.37).



Scheme 3.37 Synthesis of 3,5-disubstituted-4-amino-1,2,4-triazoles using green method

An efficient MW-assisted one-pot and three-component synthesis of substituted 1,2,4-triazoles has been achieved utilizing substituted primary amines [98] (Scheme 3.38).



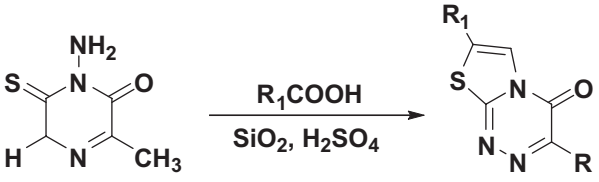
Scheme 3.38 Synthesis of substituted 1,2,4-triazoles using green method

36 Other Syntheses Using Green Methods

Kidwai et al. [99] synthesized new antifungal azoles including 1,2,4-triazole derivatives from substituted hydrazide using various solid supports under MW irradiation, as shown in Scheme 3.39.

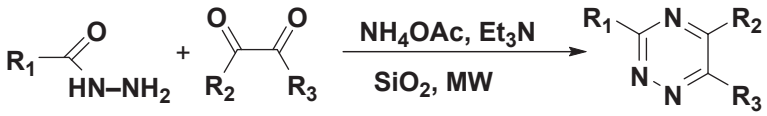
Scheme 3.39 Synthesis of azoles derivatives using green method

Heravi et al. [100] reported that the synthesis of [1,3,4]-thiadiazolo[2,3-*c*][1,2,4]-triazin-4-ones were one-pot condensation and cyclization of 4-amino-[1,2,4]triazine-3-thione-5-ones with various aromatic carboxylic acids in the presence of silica-gel/sulfuric acid in solventless condition (Scheme 3.40).



Scheme 3.40 Synthesis of [1,3,4]-thiadiazolo[2,3-*c*][1,2,4]-triazin-4-ones using green method

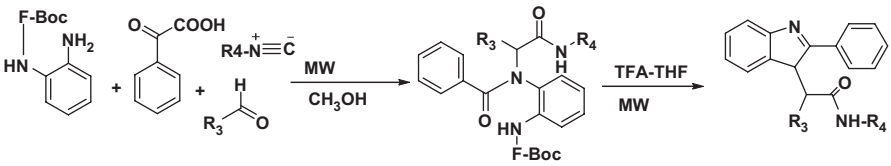
Rauf and coworkers synthesized the 3,5,6-trisubstituted-1,2,4-triazines from fatty acid hydrazides under MW assisted solvent-free conditions [101] (Scheme 3.41).



Scheme 3.41 Synthesis of 3,5,6-trisubstituted-1,2,4-triazines using green method

36.1 Benzimidazoles and Imidazoles with Green Method

The efficiency of an Ugi/de-Boc/cyclization strategy for construction of heterocyclic compounds has been improved through the incorporation of MW and fluorous technologies. In the synthesis of substituted quinoxalinones and benzimidazoles, a fluorous-Boc-protected diamine is employed for the Ugi reactions. Both the Ugi and the post-condensation reaction proceed rapidly under MW irradiation and the reaction mixtures are purified by solid-phase extraction (SPE) over fluoro flash cartridges (Scheme 3.42) [102].

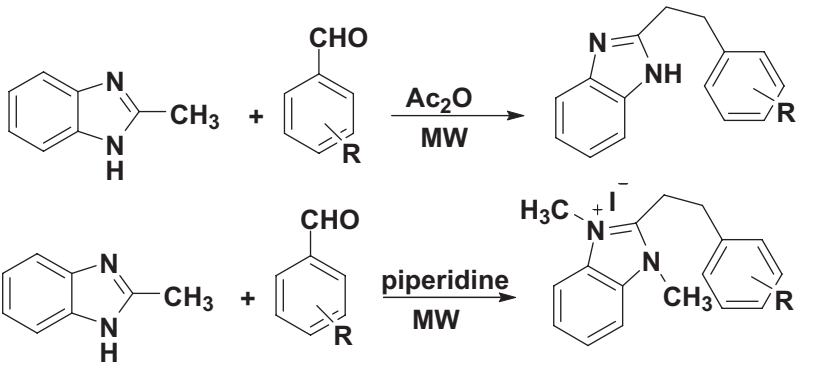


Scheme 3.42 The synthesis of substituted quinoxalinones and benzimidazoles using green method

An efficient and simple synthesis of several 2-arylbenzimidazoles from the reaction of 4-methyl-1,2-phenylenediamine and aromatic carboxylic acids in the presence of zeolite catalyst is reported. The reactions were performed under MW irradiation, and the catalyst could be recycled and used for several times [103] (Scheme 3.43).

Scheme 3.43 Synthesis of several 2-arylbenzimidazoles usong green method

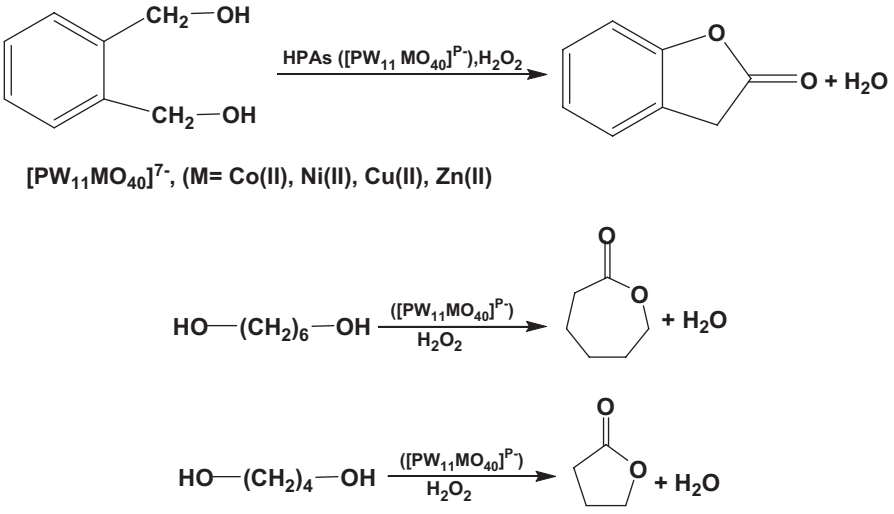
The reactions of 2-methylbenzimidazole or 2-methylbenzimidazolium iodide with aromatic aldehydes are accelerated under MW irradiation by using Ac_2O or piperidine as a dehydrant or catalyst in the absence of any solvent [104]. The approach provides an attractive and environmentally friendly pathway to several useful styryl dyes with benzimidazole nucleus (Scheme 3.44).



Scheme 3.44 The reactions of 2-methylbenzimidazole or 2-methylbenzimidazolium using green method

36.2 Lactonization of Various Diols, Using Transition Metal-Substituted Keggin Catalysts $[PW_{11}MO_{40}]^{7-}$, (M = Co(II), Ni(II), Cu(II), Zn(II))

Potassium salts of the monosubstituted Keggin POMs, $[PW_{11}MO_{40}]^{7-}$, (M = Co(II), Ni (II), Cu(II), Zn(II)), were used as catalysts for lactonization of 1,4-butane diol, 1,6-hexane diol, and 1,2-benzene dimethanol in the presence of hydrogen peroxide as an oxidant. The effects of various parameters such as amount of the oxidant and diol, solvent type, temperature, and reaction time have been studied. The results show that $[PW_{11}CoO_{40}]^{7-}$ as a catalyst in chloroform produce the highest yield of lactone [105] (Scheme 3.45).

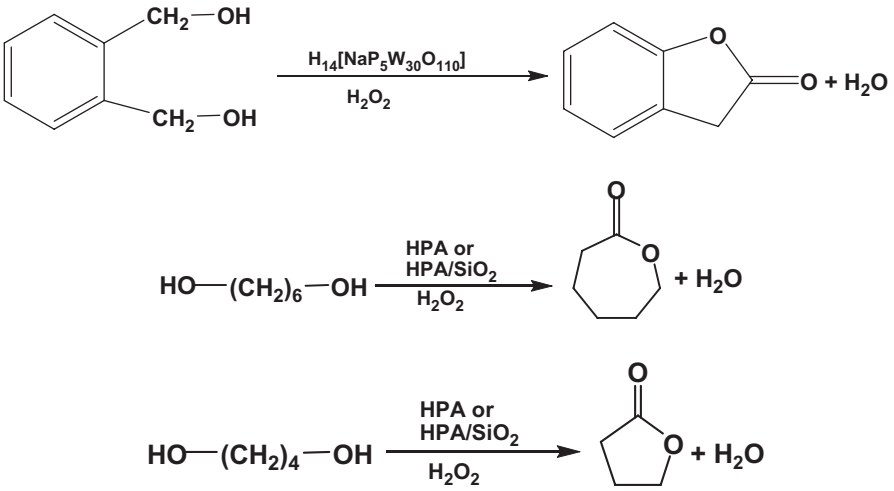


Scheme 3.45 Synthesis of γ-butyrolactone, ε-caprolactone and 2-cumaranone in the presence of transition metal-substituted Keggin catalysts

36.3 Condensation Reactions Using Heteropolyacids

36.3.1 A Catalytic Method for Synthesis of γ-butyrolactone, ε-caprolactone, and 2-cumaranone in the Presence of Preyssler's Anion, $[NaP_5W_{30}O_{110}]^{14-}$, as a Green and Reusable Catalyst

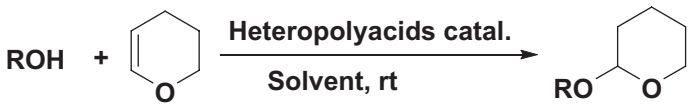
γ-Butyrolactone, ε-caprolactone, and 2-cumaranone are synthesized from related diols using Preyssler HPAs, $H_{14}[NaP_5W_{30}O_{110}]$ and $H_{14}[NaP_5W_{29}MoO_{110}]$ as catalyst, and hydrogen peroxide as oxidizing agent. The performance of eco-friendly Preyssler catalysts was compared with H_2SO_4 and the catalytic activity of H_2SO_4 is found to be lower than Preyssler catalysts. The effects of various parameters such as amount of diol, temperature, solvent, and time were studied. In all cases, the Preyssler catalyst was easily recovered and recycled with retention of their initial structure and activity [25] (Scheme 3.46).



Scheme 3.46 Synthesis of γ-butyrolactone, ε-caprolactone and 2-cumaranone in the presence of Preyssler's anion, $[NaP_5W_{30}O_{110}]^{14-}$

36.4 Catalytic Tetrahydropyranylation of Phenols and Alcohols Using Vanadium(V)-Substituted Polyoxomolybdates

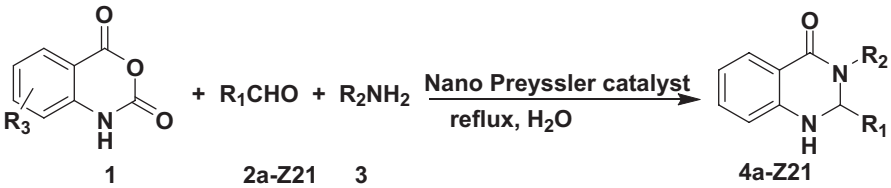
Alcohols and phenols were tetrahydropyranylated in the presence of $H_7[PMo_8V_4O_{40}]$ in good to excellent yields in acetonitrile and under solvent-free reaction conditions. A mild and convenient method for the formation and deprotection of ethers (tetrahydropyranyl (THP) ethers) is described. The formation of THP ethers from the corresponding alcohols was accomplished in the presence of acid-sensitive functional groups [106] (Scheme 3.47).



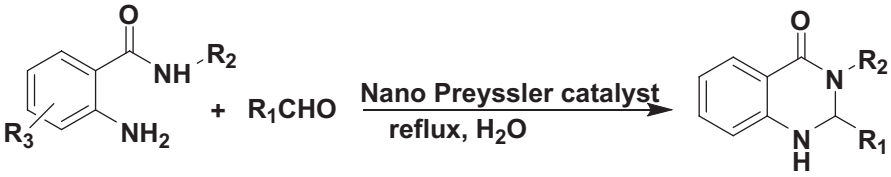
Scheme 3.47 Tetrahydropyranylation of phenols and alcohols usingHeteropolyacids catalysts

37 Synthesis of bis-2,3-dihydroquinazolin-4(1*H*)-ones and 2,3-dihydroquinazolin-4(1*H*)-ones Derivatives with the Aid of Silica-Supported Preyssler Nanoparticles

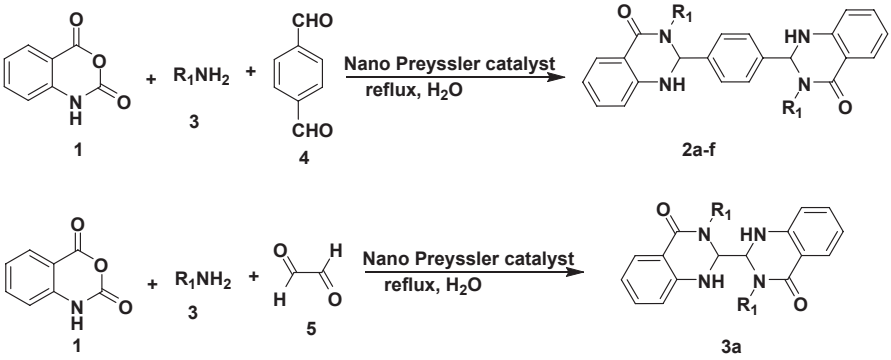
One-pot three-component condensation of isatoic anhydride with primary amines or ammonium carbonate and aromatic aldehydes in refluxing ethanol in the presence of catalytic amounts of silica-supported Preyssler nanoparticles (SPNP) afforded the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones in high yields, and bis-dihydroquinazolinones were synthesized for the first time by a novel pseudo-five-component condensation of isatoic anhydride, a primary amine, and a dialdehyde in water. The catalyst is reusable and can be applied several times without any decrease in product yield. In this method, a simple and environmentally friendly and novel one-pot three-component method for the synthesis of 2,3-dihydroquinazolinones is reported. High yields, ease of workup procedure, use of cheap and commercially available starting materials, convenient manipulation, and mild reaction conditions are the advantages of this new method. We believe that the present methodology addresses the current drive toward green chemistry due to high yields, atomic economy, and reusability of the catalyst. By the reaction of a range of amines and dialdehydes, novel libraries of bisdihydroquinazolinones could be obtained, which would make this method a suitable candidate for combinatorial and parallel synthesis in drug discovery [107] (Schemes 3.48, 3.49, and 3.50).



Scheme 3.48 Synthesized mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones using silica-supported Preyssler nanoparticles heteropolyacid under reflux conditions



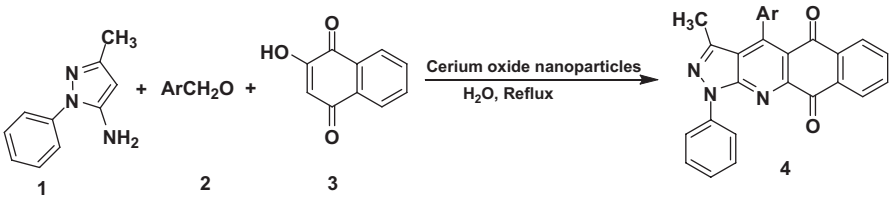
Scheme 3.49 Synthesized disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones using silica-supported Preyssler nanoparticles heteropolyacid under reflux conditions



Scheme 3.50 Synthesis of Bis-2,3-dihydroquinazolin-4(1*H*)-ones derivatives using Silica-Supported Preyssler Nanoparticles and primary amine and terphtaldehyde under reflux conditions

38 Catalytic Synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*] pyrazolo[3,4-*b*]quinoline-5,10-dione Derivatives Using Nano Cerium Oxide as Heterogeneous Catalyst in Green Conditions

We have developed a new methodology for the synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione derivatives in excellent yields. A new green chemistry protocol with the reusability of the nanoparticle as catalyst has been developed for the synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione derivatives via one-pot reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, arylaldehydes, and 2-hydroxynaphthalene-1,4-dione in water as green solvent and using cerium oxide nanoparticles (CONPs) as a heterogeneous catalyst. The present methodology affords several advantages such as simple procedure, excellent yields, and short reaction time. The catalyst is inexpensive, stable, easily recycled, and reused for several cycles with consistent activity [108] (Scheme 3.51).



Scheme 3.51 Synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones

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Chapter 4
Ammonium- and Phosphonium-Based Ionic Liquid: Green and Reusable Catalysts

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Contents

Abstract Recently, the use of ionic liquids (ILs) attracted an increasing interest in the field of organic synthesis because of its mild reaction condition, negligible vapor pressure, solvating ability, and easy recyclability. ILs are used as green reaction media due to their unique chemical and physical properties such as non-volatility, noninflammability, thermal stability, and controlled miscibility. Today, they have a wider scope, playing significant role in reactions as a solvent as well as catalyst. Several reactions have been recently reported using ILs as reaction media and rate enhancers. In chemical and pharmaceutical industries, there is always a demand for

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the development of more environmental friendly organic reaction methodologies using nonhazardous catalysis. Organic transformations using IL are gaining much attention due to simplified product isolation, mild reaction conditions, and high selectivity. ILs have received great attention in the past few years due to their broad range of potential uses and minimized use of hazardous chemicals by replacing the traditional organic solvents.

Several excellent reviews and books cover the field of IL and its applications. However, from the literature point of view, functionalized phosphonium- and ammonium-based ILs are less focused but are needed for their increasing role in different fields. In this chapter, we have highlighted recent developments towards phosphonium- and ammonium-based ILs.

Keywords Ammonium-based ionic liquid · Phosphonium-based ionic liquid

1 Introduction

Room-temperature ionic liquids (ILs) are salts with melting points close to or below room temperature, in which ions are present. ILs have many unique properties as a new and remarkable class of environmentally benign solvents. In recent years, the use of ILs in chemical research has gained considerable interest due to their unique and varied physicochemical properties. Reactions carried out in IL lead to improved process performance as compared to conventional solvents due to different thermodynamic–kinetic behaviors, better selectivity, and easy product recovery and recycling of catalysts. A number of comprehensive reviews that cover the history, properties, and applications of ILs are available [1–7]. With green chemistry becoming a central issue in both academic and industrial research in the twenty-first century, the development of environmentally benign and clean synthetic procedures has become the goal of present-day organic synthesis. Hence, the ILs are actively studied by several research groups worldwide working in all fields of chemistry. Numerous organic [8], organometallic [9], and biocatalyzed [10] reactions have been reported using IL [11].

ILs are quite well known for their unique property which makes them an attractive replacement for conventional solvents. ILs have unique properties such as lack of volatility, nonflammability, and polar, non-coordinating nature. They are also excellent solvents for organic, inorganic, and polymeric materials yet are insoluble in selected organic solvents. These solubility characteristics enable them to be easily recycled and used in biphasic applications and typical extraction processes.

2 Properties of Ionic Liquids

ILs are able to dissolve some nonpolar molecules as well as some very polar ones. They have negligible vapor pressure and excellent thermal stabilities, can act as "green solvents," and replace volatile organic solvents in several chemical reactions. Their physicochemical properties [12] can be modified by changing the cation, anion, or substituent (R-groups); hence, ILs can be used not only as reaction solvents but also as catalysts or catalytic solvents. ILs have also been referred to as "designer solvents" [13] as their physical and chemical properties such as solubility, density, refractive index, and viscosity can be adjusted by a careful choice of cation, anion, or both [14–16].

Chemical behavior and stability of the IL can be dramatically changed by the change of anion, while the change of cation has a profound effect on the physical properties such as melting point, viscosity, and density [17, 18]. Functionalized ILs are often designed for a particular use, e.g., for specific reactions, extractions, or separations, and are then referred to as "task-specific ILs" [19].

Combining these unique properties of ILs has resulted in the emergence of a green reaction media. The use of ILs as reaction media may offer a convenient solution to both the solvent emission and catalytic recycling problem. At present, both academic and industrial chemists are expecting a huge revolution of IL replacement for traditional organic solvent in signification process [20].

The melting points of IL compared with those of simple inorganic salts are the size difference between the ions and a molecular structure as well as high degree of asymmetry due to ion–ion packing by decreasing the coulombic attraction between the ions [21]. The water miscibility of IL can be controlled by changing the anion or the R-group of the cation. Hydrophobicity of ILs increases as alkyl chain length in the R-group increases. Lewis acidity or basicity of IL can be controlled through the selection and amount of the chosen anion. The specialized properties of IL can be introduced by the cation or anion and a special process can be achieved. In large-scale applications and electrochemical devices [22], viscosity is an extremely important parameter. To overcome this problem, functionalized anions have been shown to lower the viscosity.

The interest in ILs is mainly due to their peculiar properties such as absence of flammability, high thermal stability, very low vapor pressure, and good ability to dissolve organic, organometallic, and even some inorganic compounds. In many cases, Lewis acids showed limited or no solubility in conventional organic solvents that can be dissolved or immobilized in ILs. Recently, the ILs have been used in organic synthesis, pharmaceuticals, fine chemicals, biotechnology, medical sciences, nanotechnology, and environmental and nuclear sciences, including catalysis, materials science, and separation technology [23], etc. Due to its high polarity, the IL is able to dissolve many inorganic salts. Also, some insoluble polymers such as polyaniline and polypyrrole are highly soluble in IL [24].

The main physicochemical properties of room-temperature ILs are the following [25]:

1. They remain liquid over a temperature range of 200–300 °C.
2. They are catalysts as well as solvents.
3. They have high thermal stability and low volatility.
4. They have good electrical conductivity, high ionic mobility, and excellent chemical and electrochemical stabilities.
5. They have negligible vapor pressure.
6. They are noninflammable.
7. They are highly solvating—therefore, low volumes used.
8. Some ILs are water sensitive; others are hydrophobic and air stable.
9. They exhibit Brønsted, Lewis, Franklin, and super acidity.

3 Applications of Ionic Liquids

ILs are regarded as a new generation of catalysts in the chemical industry, with several uses in different commercial segments. The ILs are used in chemistry: as solvents in organic synthesis, catalyzed reactions, electrochemistry and spectroscopy, and room-temperature chemistry. Seddon et al. reported ILs as nonaqueous polar-like solvents for electrochemical and spectroscopic studies of transition metal complexes [26]. ILs used in liquid–liquid extractions form a biphasic liquid system with water.

The role of ILs in analytical chemistry is increasing substantially every year. Recent advances of IL in separations, mass spectrometry, spectroscopy, and electroanalytical chemistry have been reported [27]. In analytical chemistry, IL is used as matrices in mass spectrometry and stationary phase for high-performance liquid chromatography (HPLC). As some ILs are non-miscible with water, they could also be used in countercurrent chromatography in a biphasic liquid system. They have been used as stationary phases in gas chromatography [28] and mobile phases in liquid chromatography [29], as chiral stationary phases by dissolving chiral selectors [30], and also as unique running electrolytes in the separation of phenolic compounds by capillary electrophoresis [31]. For the separation of volatile nonpolar analytes, IL acts as nonpolar stationary phase in gas chromatography. ILs can be useful as high-temperature process solvents in mass spectrometry and other structural analyses. ILs have become the mainstream of analytical solvents and are used in various modes of chemical analysis [32].

Anticancer activity of phosphonium- and ammonium-based ILs were reported by Kumar et al. [33]. The anticancer activity and cytotoxicity of phosphonium- and ammonium-based ILs were reported in vitro human tumor cell lines. The chain length of alkyl substitution on the cations plays a crucial role towards antitumor activity and cytotoxicity of these ILs. They also reported that phosphonium-based ILs are more active and less cytotoxic as compared to ammonium-based ILs.

Andreani et al. [34] described the use of ILs as catalysts in the biodiesel production. Few studies reported the manufacture of biodiesel from vegetable oils or

animal fats. Literature studies reviewed that ILs act as great potential as catalysts for biodiesel production [34]. ILs are also used in engineering field as lubricants, coatings, dispersing agents, and plasticizers.

Recently, in the electrochemistry research, a combination of IL and nanotechnology has been used [35, 36]. The catalytic activities of palladium nanoparticles and IL in alkene hydrogenation were reported [37]. It is also used as an electrolyte in batteries, solar panels, fuel cells, etc. ILs, which show up as an alternative solvent for green process, are now not only used for replacement of traditional solvents but are also applied as material for other clean technology, for example, the fuel desulfurization and flow gas desulfurization [38–40].

ILs are widely used in transition metal chemistry, such as biphasic catalytic system in π-acceptor ligand [41]. Several reviews have been published in which ILs occupied a central theme due to their use in homogeneous and heterogeneous catalyses as well as for transition metal-mediated catalysis and organometallic reactions [42]. IL is used as a solvent in organic and bioorganic reactions [43, 44]; it also acts as an organocatalyst [45].

The reactions studied in ILs embrace catalytic hydrogenations, transfer hydrogenations, oxidations, hydroformylations, carbonylations, alkylations, acylations, nucleophilic substitutions, halogenations, condensations, Diels–Alder reactions, Michael additions, coupling reactions, and transformations in organophosphorus chemistry [46].

Recently, management of solvent use is the greatest improvement towards greener processes for the manufacture of pharmaceutical intermediates by efficient methods for recycling homogeneous catalysts. The use of ILs as novel reaction media may offer a convenient solution to both the solvent emission and the catalyst-recycling problem.

Isambert et al. [47] described the development of multicomponent reactions in the presence of task-specific ILs for the new eco-compatible methodologies for heterocyclic chemistry as environmentally benign reaction media as well as catalysts.

In 1995, Chauvin et al. [48] reported the role of ILs in asymmetric synthesis. Malhotra et al. [49] synthesized chiral ILs for enantioselective transformations. Recently, they reported that Ru nanoparticles dispersed in imidazolium ILs are efficient catalysts for selective partial hydrogenation of benzene to cyclohexene.

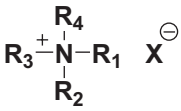
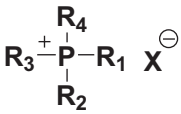
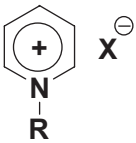
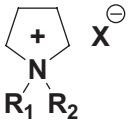
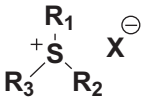
Room-temperature ILs have been widely used as green solvents for industrial applications [50–53] such as petrochemical, heavy chemicals, fine chemicals, agrochemicals, and pharmaceuticals industry [54], as well as to the nuclear industry [55]. Organic reactions that have been successfully studied in ILs include Friedel–Crafts [56], Diels–Alder [57], Suzuki coupling, halogenation, chlorination [58], sulfonation, nitration, chiral hydrogenation, enzyme catalysis reaction [59, 60], polymerization [61], cracking [62], redox reactions [63], diazotisation, *N*-alkylation and *O*-alkylation, hydrogenation [64], Heck reaction [65], oligomerization, Aldol condensation, etc.

Martins et al. [66] described the role of IL in synthesis of various heterocycles. IL is used in cyclocondensation reactions and three-membered heterocycles such as aziridines. It is used in the synthesis of five-membered heterocycles such as pyr-

roles, furans, thiophenes, pyrazoles, imidazoles, isoxazoles, oxazoles, oxazolines, oxazolidinones, thiazoles and thiazolidinones, etc. IL is also used as a green solvent as well as a catalyst in the synthesis of six-membered and seven-membered heterocycles, for example, pyridines, quinolines, acridines, pyrans, flavones, pyrimidines, pyrimidinones, quinazolines, β-carbolines, dioxanes, oxazines, benzothiazines, triazines, diazepines, thiazepine, etc.

4 Types of Ionic Liquid

Recently, the scope of ILs based on various combinations of cations and anions has been increased. Typically, IL consists of nitrogen- or phosphorous-containing organic cations and large organic or inorganic anions, for example, alkylammonium salts, alkylpyridinium salts, alkyl phosphonium salts, and *N,N*-dialkyl imidazolium salts. The common classes of IL comprise an ammonium-based IL, imidazolium-based IL, phosphonium-based IL, pyridinium-based IL, pyrrolidinium-based IL, and sulfonium-based IL.

Ammonium-based ionic liquid	
Phosphonium-based ionic liquid	
Imidazolium-based ionic liquid	
Pyridinium-based ionic liquid	
Pyrrolidinium-based ionic liquid	
Sulfonium-based ionic liquid	

Common inorganic anions (X^-) are halide, tetrachloroaluminate (also tetrachloroferrate and tetrachloroindate), tetrafluoroborate, hexafluorophosphate, and bis(trifluoromethylsulfonyl)imide, and common organic anions are derivatives of sulfate or sulfonate esters, trifluoroacetate, lactate, acetate, or dicyanamide. Substituents (R-groups) on the cation are usually alkyl chains, but can contain any of a variety of functional groups such as fluoroalkyl, alkenyl, methoxy, or hydroxyl [67–69]. Some typical examples of common anions are BF_4^-, PF_6^-, $B(CN)_4^-$, $CH_3BF_3^-$, $CH_2CHBF_3^-$, $CF_3BF_3^-$, $C_2F_5BF_3^-$, $nC_3F_7BF_3^-$, $nC_4F_9BF_3^-$, $CF_3CO_2^-$, $CF_3SO_3^-$, $N(CN)_2^-$, $C(CN)_3^-$, SCN^-, $CuCl_2^-$, $AlCl_4^-$, Cl^-, Br^-, I^-, etc.

The first IL was discovered by Walden in 1914 for new explosives; it was ethylammonium nitrate (EAN) $[EtNH_3][NO_3]$, with a melting point of 12–14 °C, and was prepared by neutralization of ethylamine with concentrated nitric acid [70]. The first use of this type of low-melting ILs as reaction media for organic synthesis was reported in 1986 as combined solvents and catalysts for Friedel–Crafts reactions. IL based on $AlCl_3$ is considered as the first generation of ILs. The hygroscopic nature of $AlCl_3$ has delayed the progress in their use in many applications since they must be prepared and handled under inert gas atmosphere. Wilkes and Zaworotko reported the preparation of new combinations of cations and anions, forming air- and moisture-stable ILs, considered as the second generation [71] of ILs, which attracted the use of ILs in various fields. The third-generation IL was introduced by Davis [72] in 2004.

There are many excellent reviews and books covering the field of IL and its applications [73–76]; however, literature setting a point of view from functionalization, particularly phosphonium- and ammonium-based ILs, is needed. In this chapter, we highlight recent developments towards phosphonium- and ammonium-based ILs.

5 Ammonium-Based Ionic Liquid

Recently, the use of ILs has increasing interest in the field of organic synthesis because of its mild reaction condition, negligible vapor pressure, solvating ability, and easy recyclability [77]. ILs are used as green reaction media due to their unique chemical and physical properties such as non-volatility, noninflammability, thermal stability, and controlled miscibility. They are playing a significant role in reactions as a solvent/catalyst. Several reactions have been recently reported to have used ILs as reaction media and rate enhancers [78].

ILs have been defined as salts which are liquids at or below room temperature or, more broadly, as salts which melt at, below, or around 100 °C. Over the past 10 years, there has been an exponential growth in publications and patents relating to ILs. The majority of reports investigate their use as alternative solvents for volatile organic compounds owing to their non-volatile properties. They also enhanced yields or increased reaction rates. ILs do not boil at elevated temperatures, but they do have upper thermal stability limits because of their nature.

5.1 Properties of Ammonium-Based Ionic Liquids

ILs—tetraethyl and tetrabutyl ammonium nitrate—were used as additives for protein refolding. Pure liquid tetra-alkyl ammonium nitrates were utilized to denature the protein. EAN is a colorless to slightly yellow-colored IL having no characteristic odor and works as an amphoteric solvent. EAN is a liquid electrolyte at room temperature and involves dissociable protons; thus, it is also called as protic IL [79–82], which can be used as medium electrolytes for fuel cells [83] and polymer membrane separators [84]. The properties and applications of EAN were recently reviewed in the literature [85]. EAN is miscible with water to form mixtures at any composition, and both the component ions favorably form hydrogen bonds with water [86].

5.2 Applications of Ammonium-Based Ionic Liquid

EAN has many potential applications in protein chemistry [87] because of its hydrophobic and ionic characters and the ability to form hydrogen bonds. It may be used as an additive, a detergent, a precipitating agent, or to deliver ligands into protein crystals. EAN has been used to enhance the recovery of denatured–reduced hen egg white lysozyme (HEWL). EAN has the ability to prevent aggregation of the denatured protein [88].

Kanzaki et al. [89] reported EAN composed of $C_2H_5NH_3^+$ and NO_3^- ions, which behave as an acid and a base, respectively, and reported that H_3O^+ is a stronger acid than HNO_3 in an EAN solution, unlike in water.

Zech et al. [90] reported high-temperature-stable microemulsions composed of the room-temperature IL EAN as polar phase. Byrne et al. [91] reported on the solubility of HEWL in aqueous EAN as a function of water content. The structure of micelles formed by nonionic polyoxyethylene alkyl ether nonionic surfactants in the room-temperature IL EAN by small-angle neutron scattering as a function of alkyl and ethoxy chain length, concentration, and temperature, was reported by Araos et al. [92].

EAN and ethylammonium formate [93] have been used as mobile-phase solvents for liquid chromatography. Methylammonium formate replaced methanol in reversed-phase liquid chromatography to lower viscosity. Poole et al. [94, 95] studied tetraalkylammonium nitrate and thiocyanate ILs in gas and liquid chromatography in the range of 150–180 °C, from room temperature to high temperature, because of its significant vapor pressure. The viscosity of these ILs is conveniently controlled by working at elevated temperatures or through dilution with a co-solvent. Alkylammonium salts are used as electroosmotic flow modifiers in some capillary electrophoreses [96–98].

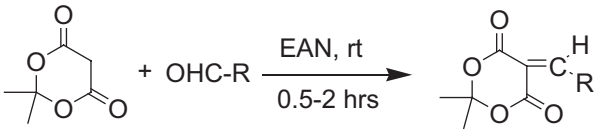
EAN has many potential applications in protein chemistry due to its hydrophobic and ionic characters as well as the ability to form hydrogen bonds [99]. EAN may

be used as an additive, a detergent, a precipitating agent, or to deliver ligands into protein crystals. Duvivier et al. [100] studied the thermodynamics of adsorption of dodecyltrimethyl ammonium bromide onto laponite in fused EAN and its aqueous solutions.

Abbott et al. reported moisture-stable Lewis-acidic ILs made from metal chlorides and quaternary ammonium salts that are commercially available. These offer required physical properties, e.g., melting point, viscosity, and conductivity, and to tune the Lewis acidity by choosing a different metal or indeed combination of metals [101].

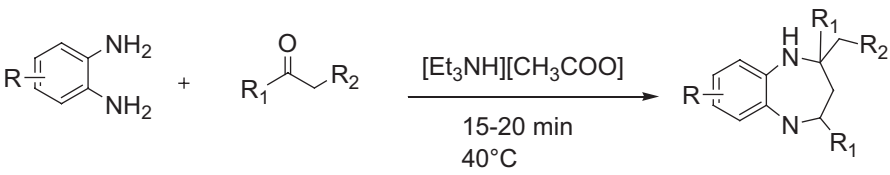
EAN IL was used in various reactions such as Biginelli reaction, condensation reaction, nitration of phenol, synthesis of β-amino ketone, etc. Nitration of phenol using ferric nitrate and clayfen in the IL, EAN, has been reported under ultrasound irradiation [102]. Jaeger and Tucker in 1989 reported the Diels–Alder reaction involving EAN IL [103]. IL EAN was prepared as per the literature method. EAN was found to be a more suitable solvent and catalyst for these reactions. In the presence of EAN, the reactions proceed in a shorter time, under milder conditions, and with excellent yield of products. EAN is liquid at room temperature and is miscible with water; thus, the separation and isolation of the product becomes easier. Its autoprotolysis constant is high, and the large electroactivity area and conductivity allow it to be used as a potential solvent. Araos et al. [104] reported the stability of a variety of lyotropic liquid crystals formed by a number of polyoxyethylene nonionic surfactants in the room-temperature IL EAN.

Ganeshpure et al. reported [105] the use of triethylammonium sulfate, triethylammonium dihydrogen phosphate, and triethylammonium tetrafluoroborate ILs as catalysts and media for the esterification of carboxylic acids with primary alcohols. Esterification of aliphatic carboxylic acids in the presence of triethylammonium sulfate gave the corresponding esters in excellent yield. Hu et al. [106] reported the condensation of Meldrum's acid with aldehydes using IL, i.e., EAN (Scheme 4.1), which can be used and reused as a green solvent as well as catalyst.



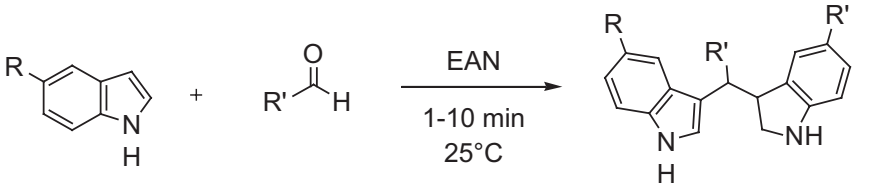
Scheme 4.1

Madje et al. [107] reported the Biginelli reaction using EAN as a solvent as well as catalyst with high yield of product. Triethylammonium acetate (TEAA) [Et_3NH] [CH_3COO] IL has been reported for the effective synthesis of 1,5-benzodiazepine (Scheme 4.2). This process benefits from the use of TEAA in organic reaction medium and as a catalyst [108].



Scheme 4.2

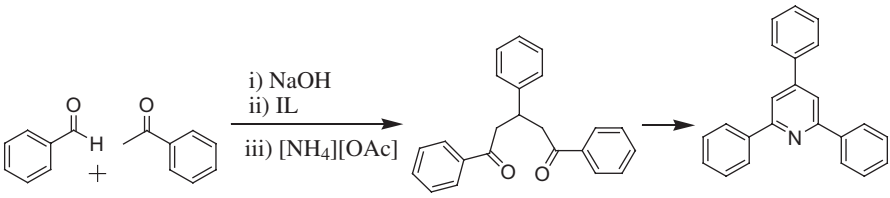
Mulla et al. [109] developed an efficient synthesis of bis(indolyl)methane in excellent yield using EAN as reusable IL at room temperature (Scheme 4.3). This method involves an electrophilic substitution reaction of indoles with several aldehydes. EAN acts as a reaction medium as well as a catalyst.



Scheme 4.3

Diels–Alder reactions occurring in high yield in Lewis acidic quaternary ammonium zinc- or tin-containing recyclable ILs has been reported by Abbott et al. [110].

Ingole et al. [111] synthesized a series of 2,4,6-triarylpyridines and their hydroxyl-substituted analogues using cheap IL, EAN, using the reaction of acetophenone and aryl aldehydes and ammonium acetate (Scheme 4.4). This method has several advantages like reducing the use of volatile organic solvents, simplicity of the process, good yields, and mild reaction conditions.

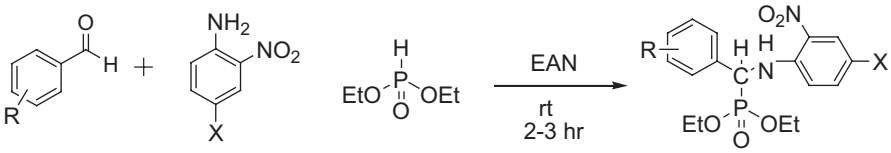


Scheme 4.4

5.3 Our Work Using Ammonium-Based Ionic Liquids

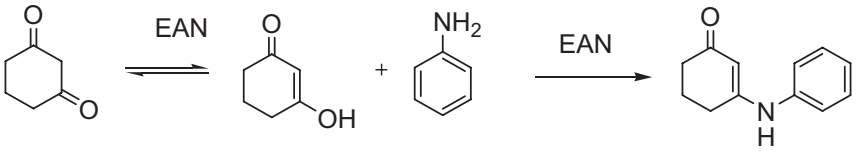
ILs act as catalysts in biomedicine mainly for the synthesis of pharmacologically active compounds. Dake et al. [112] developed a novel high-yield synthesis route for α-aminophosphonate derivatives via one-pot three-component reaction of aromatic aldehydes, amines, and diethylphosphite at room temperature (Scheme 4.5).

The reaction method is superior due to short reaction time, high reaction yields, recyclability, reusability, etc.



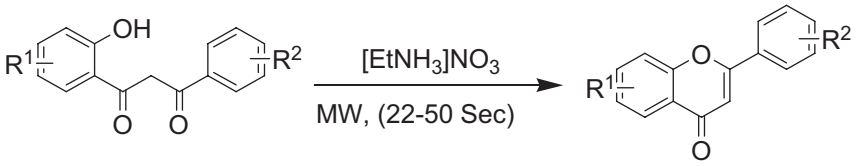
Scheme 4.5

We also reported synthesis of β-aminoketone using EAN as reusable IL at room temperature (Scheme 4.6). This method has several advantages like reducing the use of volatile organic solvents, simplicity of the process, high yields, and mild reaction conditions [113].



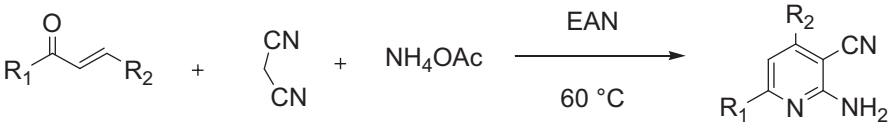
Scheme 4.6

We synthesized substituted corresponding 2-phenyl-4H-chromen-4-ones from 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones under microwave irradiations using $[EtNH_3]NO_3$ IL [114] (Scheme 4.7).



Scheme 4.7

We developed and described an efficient and mild protocol for the synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile [115] using EAN $[EtNH_3]NO_3$. Chalcones on condensation with malononitrile and ammonium acetate in the presence of the IL EAN affords the corresponding 2-amino-4,6-diphenylpyridine-3-carbonitrile in excellent yield (Scheme 4.8). The IL is recycled and reused several times. The method offers several advantages such as high yields, shorter reaction time, simple workup procedure, and cleaner reaction profiles.



Scheme 4.8

6 Phosphonium-Based Ionic Liquid

ILs have recently emerged as an alternative to organic solvents in traditional chemical reactions, mainly due to their stability, insolubility in organic solvents, low volatility, and easy recyclability. These advantages render the use of ILs more eco-friendly than the organic solvents. Green chemistry can be formulated as it utilizes (preferably renewable) raw materials, eliminates waste, and avoids the use of toxic or hazardous reagents and solvents in the manufacture and application of chemical products. Environmental pressure to reduce waste and reuse materials has driven studies into "green chemistry."

ILs have gained much attention as "designer solvents" for a diversity of chemical applications. The reason for this is the enormous selection of weakly bonding anion and cation combinations, which make up this special class of low-melting salts. It has been calculated that there are about 10^{18} possible single ILs, and the number of ILs increases still further when binary and tertiary ILs are included. Phosphonium-based ILs have attracted growing interest in the last few years due to their negligible vapor pressure, high thermal capacity, and wide liquid range.

6.1 Properties and Advantages of Phosphonium-Based Ionic Liquids

1. Phosphorus has larger radius and more polarizable lone pair of electrons that make it more nucleophilic than other amine-based ILs.
2. Phosphonium salts are thermally more stable than ammonium salts.
3. Important difference between imidazolium and phosphonium salts is the presence of acidic protons in the former.
4. Relative to phosphonium cations, imidazolium cations are not entirely inert and can interact with solutes either through hydrogen bonding interactions or through the aromatic nature of the ring system.
5. Phosphonium-based ILs tend to have higher viscosities than their ammonium counterparts, especially at or near room temperature.

Acidic ILs [116] that are quite not stable can be replaced by the Brønsted acidic IL (BAIL). Imidazolium-based ILs are unsuitable for reactions involving either active metals like Na or K or solutions that involve strong bases, since these reagents react with the imidazolium salts; for this purpose, phosphonium-based ILs have been de-

veloped recently, in which even Grignard reaction can be performed. Phosphonium-based ILs, most notably tetradecyl(trihexyl)phosphonium decanoate, are solvents for bases such as Grignard reagents, isocyanides, Wittig reagents (phosphoranes), and *N*-heterocyclic carbenes [117].

Phosphonium-based ILs are highly basic [118], having the generic formula [PR_3R'] X, where both R and R′ are alkyl groups, and X is a halide. Large radius and polarizable lone pair of electrons make them more nucleophilic. Phosphonium-based materials are one of the most thermally stable commercial ILs. Ultra-low vapor pressure and relatively high viscosity index make phosphonium-based ILs particularly attractive for high-temperature applications.

6.2 Applications of Phosphonium-Based Ionic Liquids

Phosphonium cation-based ILs, in some applications, offer superior properties as compared to nitrogen cation-based ILs such as their use as extraction solvents, chemical synthesis solvents, electrolytes in batteries and super-capacitors, in corrosion protection, etc. Phosphonium-based ILs have many industrial and pharmaceutical applications such as lubricants, entrainers, electrolytes, media for metal deposition, paramagnetic fluids, and extractants for sulfur-containing compounds.

Phosphonium salts are thermally more stable than ammonium salts. Phosphonium-based ILs have higher viscosities than the ammonium counterparts at room temperature. However, on heating at 70–100 °C, their viscosities generally decrease, whereas the addition of reactants or catalysts can also further reduce the viscosity. An important difference between imidazolium- and phosphonium-based ILs is the presence of acidic protons in the former. As compared to phosphonium cations, imidazolium cations are not entirely inert and interact with solutes either through hydrogen bonding or through the aromatic nature of ring system. Tetralkylphosphonium salts do not have such acidic protons or aromatic rings; consequently, they are less potent for interaction with solutes.

Kevin et al. [119] described some applications of phosphonium-based ILs that offer superior properties as compared to nitrogen cation-based ILs and their use as extraction solvents, chemical synthesis solvents, electrolytes in batteries and super-capacitors, and in corrosion protection.

Cieniecka et al. [120] synthesized bis(trifluoromethylsulfonyl)imide nitrate, dialkylphosphinate, trifluoromethanesulfonate, tetrafluoroborate, and hexafluorophosphate phosphonium ILs and tested for antimicrobial activity and anti-electrostatic properties. They reported that phosphonium salts, in contrast to their 1-alkyl-3-methylimidazolium analogues, both cation structure and the type of anion, have effects on their biological activity.

Atefi et al. [121] described the biodegradability of phosphonium-based ILs using the CO_2 headspace test (ISO 14593). Tetraalkylphosphonium cations, in which one of the alkyl substituents contained ester, ether, alcohol, or alkene functionality, were targeted in order to promote biodegradation. These cations were paired with halide,

triflimide, and octylsulfate anions. As compared to previously studied dialkylimidazolium and alkylpridinium ILs with ester moieties and octylsulfate anions, the phosphonium-based IL showed relatively low levels of biodegradability. Baumann et al. [122] described the degradation of phenol.

Karodia et al. reported [123] a convenient method for the acid-catalyzed Michael addition reactions of alcohols, thiols, and amines to methyl vinyl ketone, using the IL ethyltri-*n*-butylphosphonium tosylate. Recently, phosphonium-based ILs have been used [124] in the degradation of phenol, esterification, Wittig reaction, Heck reactions, Suzuki cross-coupling reactions, oxidation of benzyl halides [125], etc. Phosphonium tosylates are used as solvents in catalytic hydroformylation reactions; these catalyst systems are noncorrosive and can readily be recovered and reused [126].

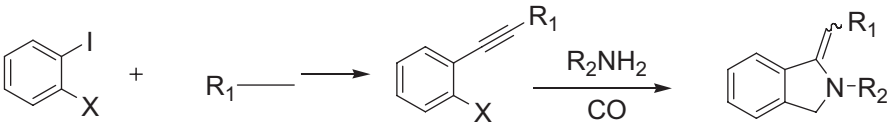
Recently, the application of ILs as solvents for transition-metal catalysis has increased and a wide range of reactions are under investigation because solubility of organometallic compounds increases in ILs. Various types of carbon–carbon bond-forming reactions of IL in conjunction with palladium in organic chemistry, such as the Heck, Suzuki, Stille, Negishi, Sonogashira coupling, etc., were reported [127].

Phosphonium-based IL-coated lipase (IL1-PS)-catalyzed reaction has been reported. IL1-PS was used as a catalyst in 2-methoxyethoxymethyl-(tri-n-butyl)-phosphonium bis(trifluoromethanesulfonyl)-amide for the transesterification of secondary alcohols [128]. McNulty et al. studied the anionic effect of Pd-catalyzed Buchwald–Hartwig amination reaction in phosphonium-based ILs [129].

Phosphonium-based ILs are also used in:

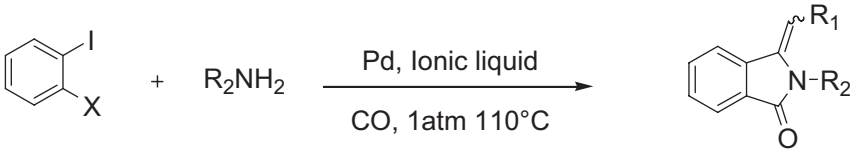
1. Hydroformylation [130]
2. Heck reactions [131]
3. Suzuki cross-coupling reactions [132]
4. Alkylation [133]
5. Esterification and transesterification [134]
6. Oxidation of benzyl halides
7. Diels–Alder reaction [135]
8. Wittig reaction [136]
9. Synthesis of cyclic carbonate [137], etc.

Synthesis of isoindolin-1-one derivatives in phosphonium-based ILs was described by Cao et al. [138]. The palladium-catalyzed carbonylation and hydroamination reaction of 1-halo-2-alkynylbenzene with amines afforded the substituted 3-methyleneisoindolin-1-ones in good yields and high selectivities in favor of the *Z*-isomers (Scheme 4.9).



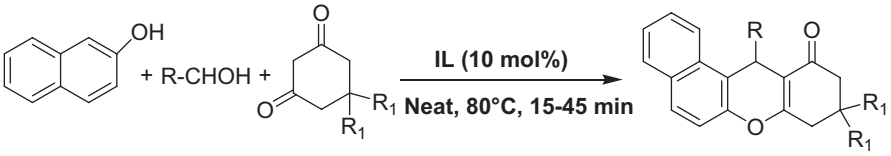
Scheme 4.9

Kevin et al. [139] reported palladium-catalyzed carbonylation–hydroamination reaction between 1-bromo-2-(phenylethynyl)benzene and benzylamine using phosphonium-based IL as the reaction solvent (Scheme 4.10).



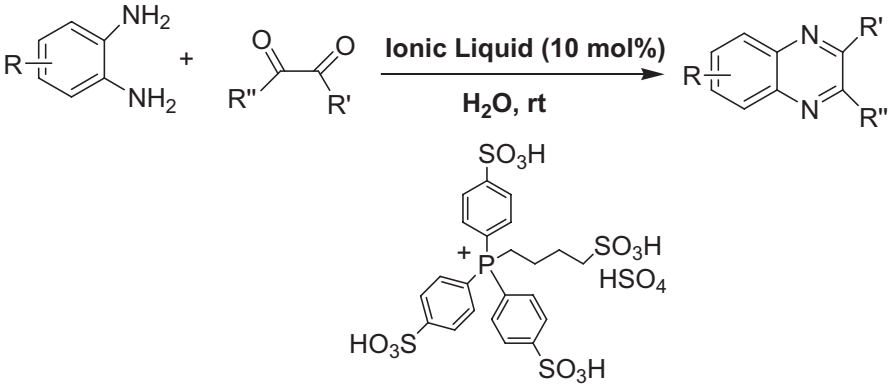
Scheme 4.10

An efficient and eco-friendly multicomponent one-pot synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones was achieved by the condensation of β-naphthol, aromatic aldehydes, and cyclic 1,3 dicarbonyl compounds (Scheme 4.11) using the BAIL (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulfate as a catalyst [140].



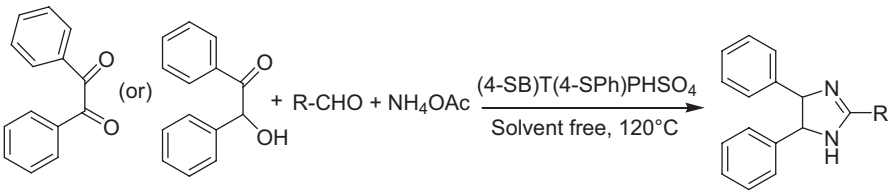
Scheme 4.11

The BAIL, (4-sulfobutyl)-tris-(4-sulfophenyl)-phosphonium hydrogen sulfate was reported [141] as a catalyst for the synthesis of 2,3-disubstituted quinoxaline derivatives via the one-pot condensation reaction of various *o*-phenylenediamine with 1,2-diketone derivatives (Scheme 4.12).



Scheme 4.12

The synthesis of 2,4,5-trisubstituted-1H-imidazoles via the one-pot three-component condensation of benzil/benzoin, aldehydes and ammonium acetate under solvent-free conditions has been achieved using the BAIL, (4-sulfobutyl)tris(4-sulfophenyl) phosphonium hydrogen sulfate as a catalyst [142] (Scheme 4.13).



Scheme 4.13

6.3 Our Work Using Phosphonium-Based Ionic Liquid

Our large interest towards phosphonium-based IL promotes us to develop an efficient and a green method using this type of IL. We developed a clean and efficient method for the synthesis of chalcones using phosphonium-based IL catalyst (PhosILCl). The method provides several advantages, such as mild reaction conditions, simple workup procedure, high yields, and eco-friendliness. In addition, the green solvent IL was recovered and reused several times in subsequent reactions [143].

We also reported a clean and efficient Michael addition reaction of thiols on chalcones using PhosILCl [144]. The method provides several advantages such as simple workup, environmental friendliness, mild conditions, and excellent yields. In addition, the IL was chosen as a green solvent, recovered, and reused several times in subsequent reactions.

Mild and selective oxidation of aryl halides to corresponding aldehydes using iodoxybenzoic acid as oxidizing agent and IL has been reported [145]. An efficient oxidation of benzyl halide was reported [146] using aqueous hydrogen peroxide (30%) in trihexyl(tetradecyl)phosphonium-tetrafluroborate IL; the protocol is simple and mild offering excellent yield of product.

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Chapter 5
An Approach Towards Green Switch Through Nanocatalysis for the Synthesis of Biodynamic Heterocycles

Anshu Dandia, Vijay Parewa and Amit Sharma

Contents

Abstract Heterocyclic structural architectures occur in many bioactive natural products and synthetic drugs, and these structural units serve as important intermediates in organic synthesis. Heterocyclic compounds are associated with a variety of biological activities. Most of the clinically important drugs available in the market are heterocycles. Therefore, organic chemists have been making extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among the variety of new synthetic transformations, catalyzed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds. The prologue of nanoscience and nanotechnology is providing the ability to fabricate proscribed structures and geometries to explore and optimize a broad array of catalytic processes. In this context, the present chapter focuses on the exploration of newer trends in the upcoming area of "nanocatalysis" by using more sustainable approaches for devising alternative, clean, efficient, economic, and nature-friendly methodology. This led to the progress of much greener catalysts

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with higher activity, selectivity, and greater ease of separation from the reaction medium.

Keywords Nanocatalyst · Biodynamic heterocycles

1 Introduction

The utilization of catalysis to achieve the goals of green chemistry has met with tremendous success [1]. Through the use of catalytic systems, the dual goals of attaining environmental and economic benefits simultaneously are being realized in applications ranging from very small-scale fine chemical synthesis to commodity petrochemical processes.

A homogeneous catalyst, where the catalyst is in the same phase as the reactants, is generally accepted by chemists [2]. One attractive property is that all catalytic sites are accessible because the catalyst is generally a soluble substrate. Furthermore, it is possible to tune the chemoselectivity, regioselectivity, and enantioselectivity of the catalyst. Homogeneous catalysts have a number of other advantages such as high selectivities, better yields, and easy optimization of catalytic systems. They are widely used in a number of commercial applications, but the difficulty of catalyst separation from the final product creates economic and environmental barriers to broadening their scope. To overcome the separation problems in homogeneous catalysis, chemists and engineers have investigated a wide range of strategies, and the use of heterogeneous catalyst systems appears to be the best logical solution [3]. Majority of the novel heterogenized catalysts display some advantageous properties such as excellent stability, good accessibility, and porosity. However, many potential applications of such immobilized catalysts are strongly hampered by leaching, and the amount of leaching depends strongly on the choice of support and linker material used for the preparation of the immobilized catalyst. The "leached catalyst" literally poisons the solution of substrates and products, which is the main obstacle for using such catalytic systems and products in pharmaceutical industries. Consequently, new catalytic systems that allow for rapid and selective chemical transformations with excellent product yields coupled with the ease of catalyst separation and recovery are highly desired for "greening" of chemical manufacturing processes.

Therefore, a green and sustainable catalyst should possess:

i) High activity
ii) High selectivity
iii) Efficient recovery from reaction medium
iv) Durability or recyclability
v) Cost-effectiveness
vi) Leach free

The fields of catalysis and nanoscience have been inextricably linked to each other for a long time. Thanks to the recent advances in characterization techniques, the old technology has been revisited with a new scope. The electronic structure and

chemical properties of compositionally identical materials are transformed when their dimensions are reduced from the macroscale through the nanoscale to the angstrom scale. A nanometer-sized particle, or nanoparticle (NP), can exhibit electronic and physical properties distinct from those of the corresponding bulk solid, and it should therefore display unique catalytic properties. Indeed, it is well known that the catalytic properties of NPs of a metal differ markedly from those of larger, bulk-like particles of the same metal. NPs have emerged as sustainable alternatives to conventional materials, as robust, high-surface-area heterogeneous catalysts [4], and catalyst supports [5]. The nano-sized particles increase the exposed surface area of the active component of the catalyst, thereby enhancing the contact between reactants and catalyst dramatically and mimicking the homogeneous catalysts. However, their insolubility in reaction solvents renders them easily separable from the reaction mixture like heterogeneous catalysts, which in turn makes the product-isolation stage effortless. Also, the activity and selectivity of nanocatalyst can be manipulated by tailoring chemical and physical properties like size, shape, composition, and morphology.

2 Synthesis of Active Nanocatalysts

The synthesis and structural characterization of transition-metal NPs are also topics of interest in which chemists strive to control chemical composition, particle size (quantum-size effects can play an important role), morphology, internal structure (such as alloyed or layered mixed-metal systems), as well as crystallographic structure, in order to achieve a better understanding of structure activity trends. It can be expected, in fact, that the effective control of the catalyst key features, either when used in the homogeneous phase or when anchored on heterogeneous supports, will also allow for successful applications at the industrial scale. In recent years, a number of approaches have been used for the synthesis of NP catalysts, including thermal evaporation in vacuum [6], electron-beam lithography and pulsed laser deposition [7], buffer-layer assisted growth [8], chemical vapordeposition [9], gas condensation, ionized cluster beam deposition [10, 11], electrochemical deposition methods [12], sol–gel or colloidal techniques [13], deposition–precipitation and impregnation methods [14], molecular cluster precursors [15], etc.

3 Enhancement of Catalytic Activity of NPs

3.1 Heterometallic NPs

Heterometallic NPs composed of two or more metal elements with various nanostructures (alloy/intermetallics, core–shell, heterostructure, etc.) via different synthetic approaches have presented improved physical and chemical properties com-

pared to their monometallic NPs in many fields, especially in catalysis [16, 17]. Since the properties of the catalyst surfaces are closely correlated with the catalytic activities, the precise modification of the catalyst surface by introducing another component or changing the morphology could facilitate the controlled tuning of the catalytic properties. In addition, for core–shell structured heterometallic NPs with the same shell composition, their catalytic activity can also be changed with the core metal due to the so-called ligand effect. Therefore, the catalytic activity in catalysis can be well tuned by combining two or more metals with various nanostructures. First principle studies have indicated that the synergistic effect on the performance of heterometallic nanocatalysts is subjected to surface electronic states, which are greatly altered by the change of catalysts for geometric parameters, particularly related to local strain and effective atomic coordination number at the surface [18].

3.2 Doping

Many attempts have been made to improve the performance of NPs as a catalyst. Different transition metals such as Co, Fe, and Mn have been investigated as promoter elements to develop new or improved catalytic systems [19]. Promoters are doping agents added to catalyst materials in small amounts to improve their activity, selectivity, and/or stability [20]. Some promoters interact with active components of catalysts and thereby alter their chemical effect on the catalyzed substance. The interaction may cause changes in the electronic or crystal structures of the active solid component. The commonly used promoters are metallic ions incorporated into metals and metallic-oxide catalysts, reducing and oxidizing gases or liquids, and acids and bases added during the reaction or to the catalysts before being used.

4 Catalytic Applications of Nanomaterials in the Synthesis of Heterocyclic Compounds

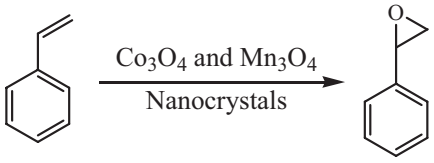
The catalytic efficiency, selectivity, and recyclability of nanocatalysts depend on the size, shape, composition, and assembly of the nanomaterials, as well as their interaction with the support. These fascinating phenomena enhance the appeal of well-defined nanostructured materials as green and sustainable heterogeneous catalysts in the synthesis of a wide variety of heterocyclic compounds. Hence, in this chapter, we focus on the use of nanocatalysis for green chemistry development, including more sustainable approaches for devising alternative, clean, efficient, economic, and nature-friendly methodology.

4.1 Synthesis of Three-Membered Heterocycles

4.1.1 Epoxides

Epoxides are valuable intermediates in organic chemical, fine chemical, and pharmaceutical syntheses. The epoxidation of olefins is one of the most efficient strategies for obtaining epoxides [21]. Although epoxides have been synthesized noncatalytically in small scale by peracids and in large scale using the chlorohydrin process, all new developments aim for catalytic processes in order to reduce byproducts, waste (chlorohydrin process), and expensive oxidants (peracids). Generally, a high atom efficiency is of utmost importance to make new processes feasible, from both economic and ecologic points of view.

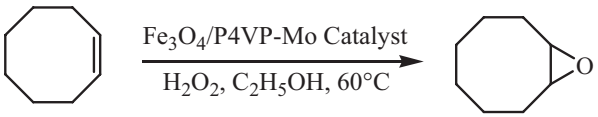
Morsali et al. [22] reported a simple sonochemical method to synthesize uniform sphere-like Co_3O_4 and Mn_3O_4 nanocrystals (Scheme 5.1). Epoxidation of styrene and cyclooctene by anhydrous tert-butyl hydroperoxide over the prepared Co_3O_4 and Mn_3O_4 nanocatalysts was investigated. The results of the conversion activity were compared with bulk Co_3O_4 and Mn_3O_4. Powder X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and Brunauer–Emmett–Teller (BET) surface area techniques were used to characterize and investigate the nanocatalysts. Under optimized reaction conditions, Co_3O_4 and Mn_3O_4 nanomaterials appear as very interesting and promising catalysts, having good activity for cyclooctene and styrene epoxidation in short times and rather at low temperatures with the advantages of being prepared under direct and inexpensive conditions, and they help to reach considerably higher conversion activities than these materials in bulk form.



Scheme 5.1

Magnetite/poly(4-vinylpyridine) (Fe_3O_4/P4VP) composite nanospheres with multiple Fe_3O_4 cores embedded in a P4VP shell were synthesized by mini emulsion polymerization and then used as recoverable supports for the $MoO_2(acac)_2$ complex [23]. Both strong magnetic response and abundant pyridine rings enabled them to serve as easily recyclable support for the immobilization of catalysts (Scheme 5.2). Fe_3O_4/P4VP composite nanospheres supported the $MoO_2(acac)_2$ complex and exhibited good catalytic activity for green cis-cyclooctene epoxidation system and strong magnetic response (48.3 emu/g), and basically maintained initial catalytic activity after eight runs. The content of Mo species in the recovered catalyst is

0.928 mmol/g, slightly lower than that in a fresh catalyst (0.975 mmol/g), indicating that the loss of Mo active sites bound to P4VP is minimal. In view of similar morphologies and infrared (IR) spectra for fresh and recovered catalyst, Fe_3O_4/P4VP composite nanospheres further turn out to be an outstanding support for the $MoO_2(acac)_2$ complex.



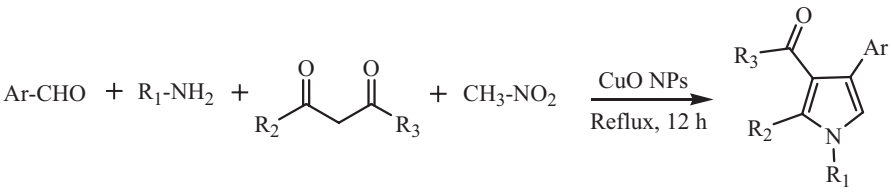
Scheme 5.2

4.2 Synthesis of Five-Membered Heterocycles

4.2.1 Pyrroles

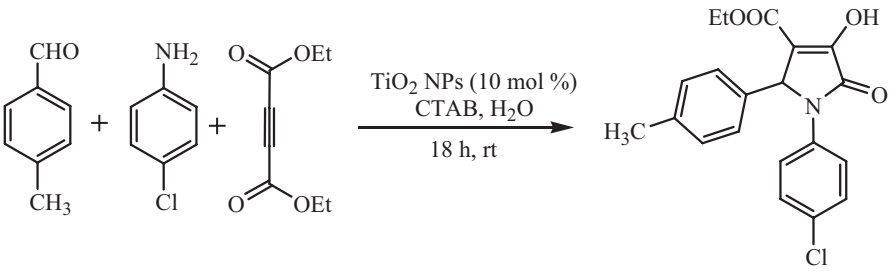
The pyrrole nucleus is the characteristic structural motif of numerous natural (storniamide A, lamellarin P, marinopyrrole B) and synthetic products [24]. Many polyfunctionalized pyrroles are known to display interesting biological activities [25]. In addition, pyrroles were observed to inhibit cytokine-mediated diseases and were also found to have some applications in materials chemistry [26]. The growing importance and wide usefulness of polysubstituted pyrroles have kept in focus the search for new methods for the efficient synthesis of these heterocycles.

A convenient one-pot four-component reaction of aromatic aldehydes, β-keto esters, and nitromethane, in the presence of an amine and 10 mol% CuO NPs for the synthesis of highly substituted pyrroles, is described [27] (Scheme 5.3). The nuclear magnetic resonance (NMR) spectrum was coupled with quantum chemical calculations in discrete Fourier transform (DFT) approach using the hybrid B3LYP exchange–correlation functional to confirm the structures of (1-benzyl-4-(4- chlorophenyl)-2-methyl-1*H*-pyrrol-3-yl)(phenyl)methanone and 1-(1-benzyl-4-(4- chlorophenyl)-2-phenyl-1*H*-pyrrol-3-yl)ethanone.



Scheme 5.3

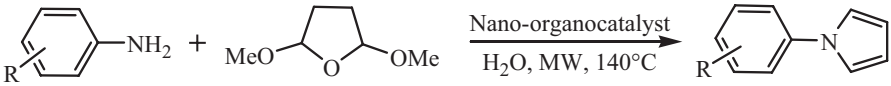
A multicomponent green methodology was developed [28] to synthesize 3-hydroxy-2-pyrrolidinones under admicellar catalysis by TiO_2 NPs at room temperature (30 °C). TiO_2 NPs in aqueous CTAB solution promote the formation of admicelles and the reaction occurs in an admicellar environment (Scheme 5.4).



Scheme 5.4

A variety of aldehydes and amines were used. Aromatic aldehydes with both electron-withdrawing and electron-donating substituents (like Cl, Br, NO_2, OMe, Me groups) at different positions of the aromatic ring resulted in good-to-excellent yields. The yield was also very high with aliphatic aldehydes and heteroaromatic aldehyde like pyridine-2-carboxaldehyde. With aliphatic aldehydes, the reaction was completed even at room temperature (25–28 °C) with stirring. Use of aniline, substituted anilines, heteroaromatic amine, and aliphatic amines increased the diversity of the products. No product was, however, obtained with two different aromatic amines. Dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate were used as but-2-ynedioate part and both of them are equally efficient for this reaction.

A novel concept of nano-organocatalyst was developed [29] by supporting totally benign and naturally abundant glutathione on magnetic NPs. The catalyst showed excellent activity for microwave-assisted Paal–Knorr synthesis of pyrroles (Scheme 5.5). The entire process was carried out in aqueous medium, without using organic solvent in the reaction or during the workup. This novel nano-organocatalyst bridges the gap between homogeneous and heterogeneous catalyses thus preserving the desirable attributes of both the systems.



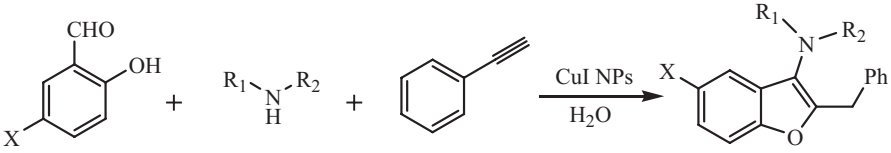
R = Alkyl, aryl, heterocyclic, etc.

Scheme 5.5

4.2.2 Furans

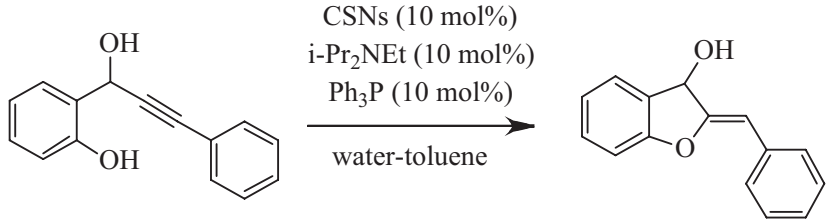
Highly substituted furans play an important role in organic chemistry not only as the key structural units in many natural products, common subunits in pharmaceuticals [30], and flavors [31] but also as useful building blocks in synthetic chemistry [32]. They have also found utilities as synthetic intermediates or synthons for numerous functional groups, carboxylic acids, α-keto esters, and aromatics [33]. For this reason, the efficient syntheses of highly substituted furans continue to attract the interest of synthetic chemists.

An efficient, facile, and economical method for the preparation of benzofuran derivatives has been developed using copper iodide (CuI) NPs as catalyst in aqueous media [34]. The products were obtained in excellent yields and the reaction times were significantly reduced in comparison with using bulk CuI. The present protocol represents a simple and remarkable method for the three-component reactions of aldehyde, amine, and phenylacetylene in order to synthesize some 2,3-disubstituted benzofuran derivatives in the presence of novel nano-scale materials (Scheme 5.6).



Scheme 5.6

Yao et al. [35] developed a highly efficient annulation of 2-(1-hydroxy-3-arylprop-2-ynyl)phenols leading to the key intermediates to synthesize aurones catalyzed by silver NPs/carbon black-supported silver NPs (Scheme 5.7). In the presence of a phosphine ligand, both the catalysts show excellent catalytic activities in the reaction and give the products with good yields as well as excellent regioselectivities and stereoselectivities in a water–toluene mixed solvent.



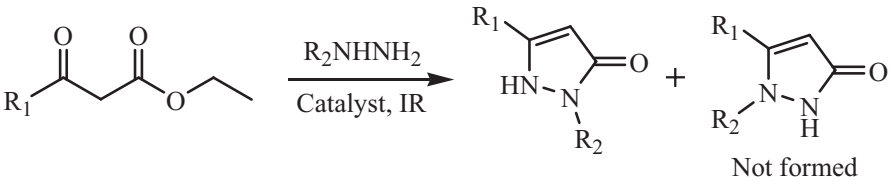
Scheme 5.7

4.2.3 Pyrazoles

Pyrazoles have a rich chemistry with numerous applications [36]. Of these, particularly interesting to medicinal chemists are highly substituted pyrazoles, which constitute the core structure of clinically used drugs, such as Celebrex, Viagra, and Rimonabant, as well as many developing molecules across a wide spectrum of therapeutic areas including anti-inflammation, analgesia, anti-infection, and anticancer [37]. These factors have assured a continually increasing attention on the synthesis of functionalized pyrazole derivatives and their biological explorations.

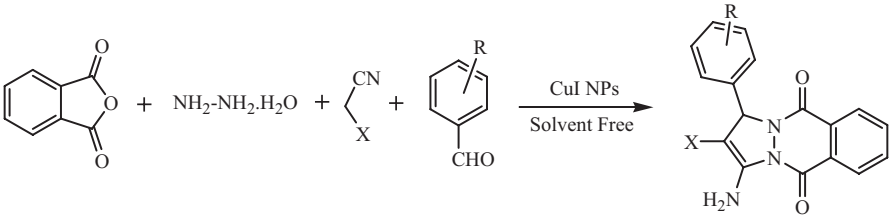
Cobalt-doped ZnS-NPs-catalyzed novel strategy has been developed to generate a diverse array of pyrazolones (with excellent regioselectivity) representing a privileged medicinal scaffold using IR irradiation as the heating mode [38]. The proposed

synthetic protocol allowed a straightforward preparation of an array of molecules spanning a broad range of molecular diversity (Scheme 5.8). About 40-fold higher catalytic activity was observed for a nanocatalyst under IR than that under a conventional method. The results suggested that IR and nanocatalyst had a synergistic effect. Catalytic processes with shorter reaction times safeguard the catalyst from deactivation and decomposition. The positive effect of cobalt doping on the reaction rate acceleration in the catalyst ZnS NPs was attributed to an increase in surface acidity.



Scheme 5.8

CuI NPs as efficient catalysts have been used for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones by the four-component condensation reaction of phthalic anhydride, hydrazine monohydrate, aromatic aldehydes, and malononitrile or ethyl cyanoacetate under solvent-free conditions in good-to-excellent yields [39] (Scheme 5.9). The advantages offered by this method include short reaction times, excellent yields, simple procedure, easy workup, and the employment of a cost-effective catalyst.

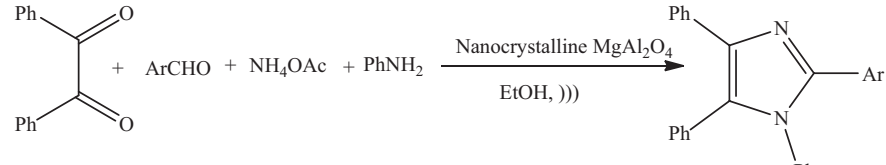


Scheme 5.9

4.2.4 Imidazoles

Imidazoles are an important group of five-membered nitrogen heterocycles that have attracted much attention because of the participation in the structure of biologically active molecules [40]. Compounds bearing the imidazole nucleus are known to show antiedema, anti-inflammatory, analgesic, anthelmintic, antibacterial, antitubercular, anti-fungal, antitumor, and antiviral activities. In addition, many of the substituted diaryl imidazoles are known as potential inhibitors of the p38 mitogen-activated protein (MAP) kinase [41]. This versatile applicability highlights the importance of the access to efficient synthetic routes to well-benign highly substituted imidazole derivatives.

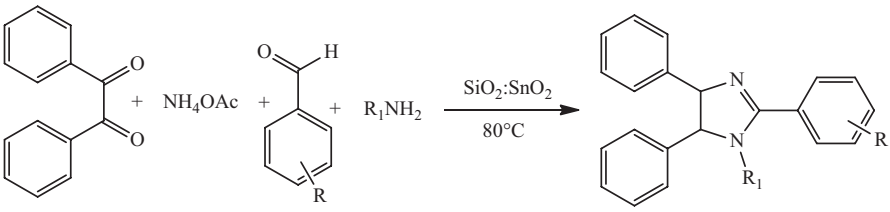
An efficient four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles have been described by Safari et al. [42] through one-step condensation of an aldehyde, benzil, ammonium acetate, and primary aromatic amine with nanocrystalline magnesium aluminate in ethanol under ultrasonic irradiation (Scheme 5.10). It seems that the existence of magnesium aluminate ($MgAl_2O_4$) as an acidic catalyst can accelerate this cyclocondensation reaction by increasing the reactivity of benzaldehyde derivatives and benzil. Magnesium aluminate spinel, used as catalyst, shows a relatively large surface area, small crystalline size, and special active sites, which can be controlled by its preparation method. The high activity of magnesium aluminate NPs is only because of their high effective surface. In other words, the high impact of these NPs is due to the high concentration of areas with low coordination and structural deficiencies in their surface.



Ar=C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-OHC_6H_4, 2-OHC_6H_4, 2-FC_6H_4, 3,4-$(OCH_3)_2C_6H_3$

Scheme 5.10

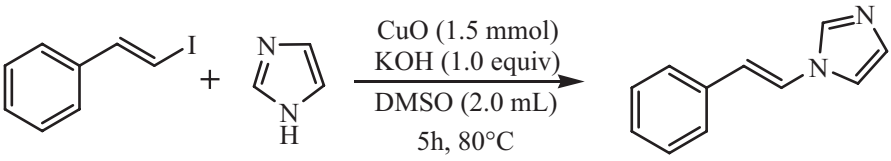
Borhade et al. [43] reported highly efficient and eco-friendly one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles and 2,4,5-trisubstituted imidazoles under solvent-free conditions using nanocrystalline, silica-supported tin oxide (SiO_2:SnO_2) as a catalyst (Scheme 5.11). Most importantly, this catalyst facilitates the reaction at 80 °C providing solid support in the reaction, enhances the reaction rate, and thereby the excellent yields of the products. Electron-donating groups influence the reaction and furnish the corresponding 1,3,4,5-tetrasubstituted imidazoles in high yield with less time, whereas electron-withdrawing substituents need a longer reaction time with good yield. Moreover, it has been observed that the electronic properties of the aromatic ring of aryl aldehyde have some effect on the yield and reaction time. Similar effects were observed for the synthesis of 2,4,5-trisubstituted imidazoles.



Scheme 5.11

Recyclable copper oxide NPs catalyzed most efficient and straightforward protocol for the vinylation of imidazoles with vinyl halides under ligand-free condi-

tions has been reported [44]. Utilizing this protocol, various imidazoles were cross-coupled with different substituted vinyl halides to get the corresponding products in excellent yields with the retention of configuration (Scheme 5.12). This protocol efficiently cross-coupled trans-β-iodostyrene having electron-rich, electron-neutral, and electron-poor functionalities with various imidazoles and benzimidazoles under the optimized reaction conditions, and generated the desired products in excellent yields. However, the reaction of imidazoles having electron-withdrawing substituents such as 4-nitrile imidazole with trans-β-iodostyrene did not proceed. Even in the case of 4-nitro imidazole, the product was obtained in very low yields. All attempts to couple alkyl vinyl iodides with imidazoles were unsuccessful. They further tested the coupling of trans-β-bromostyrenes with imidazoles under the same conditions. The reaction of trans-β-bromostyrenes with imidazoles proceeded smoothly to afford the desired product in a reasonable yield. However, the coupling reaction of various imidazoles with vinyl bromides required longer reaction times to get reasonable yields of N-vinylimidazoles, whereas shorter reaction times led to decreased yields. Furthermore, the double-bond geometry of the vinyl imidazoles was retained in all the cases, and the structures of all the products were determined from their analytical and spectral (IR, ^{1}H NMR, and ^{13}C NMR) data and by direct comparison with authentic samples.

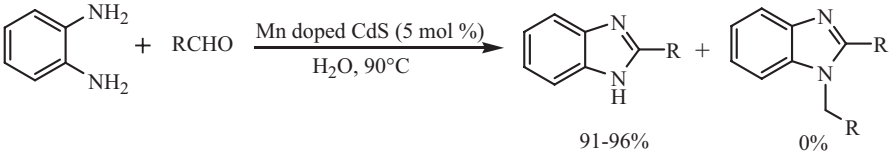


Scheme 5.12

CdS and Mn-doped CdS NPs of ~2 nm have been prepared by Dandia et al. [45] at room temperature by a wet chemical technique. The heterogeneous catalysts were fully characterized by XRD, TEM, energy-dispersive X-ray spectroscopy (EDX), inductively coupled plasma atomic emission spectroscopy (ICP-AES), and UV/VIS. These NPs were exploited by us to study their catalytic activities towards the chemoselective, aqueous-mediated synthesis of 2-aryl benzimidazoles (Scheme 5.13).

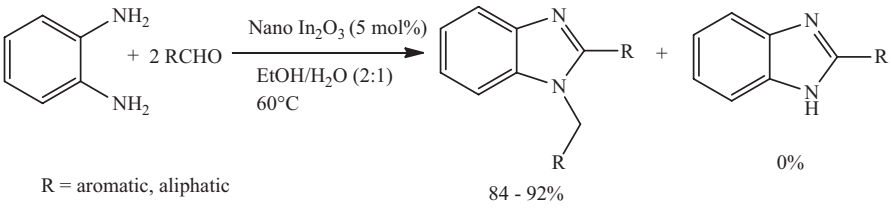
Literature reveals that in the oxidative cyclization of aldehyde and o-phenylenediamine, the formation of the required 2-aryl-1*H*-benzimidazole is accompanied by the occurrence of 1-benzylated 2-aryl-1*H*-benzimidazoles as side products [46], and sometimes these disubstituted derivatives have been isolated as the main product [47, 48]. The present protocol gives 2-aryl-1*H*-benzimidazole selectively. Further, we extended our studies on oxidative reactions of aldehydes with o-aminothiophenol. Although thiols are good nucleophiles and SET agents [49], in present studies, no substitution of the halogen atom or the nitro group, dealkylation/debenzoylation, took place as reported earlier [50–52]. Further, the dithioacetal formation is a common reaction of aldehydes with thiols [53]; no competitive dithioacetal formation was observed under the present conditions. Doping of Mn promotes the activity and

selectivity of CdS NPs as indicated by high turnover frequency (TOF) value, providing the products in good-to-excellent yields with good chemoselectivity.



Scheme 5.13

The synthesis of 1,2-disubstituted benzimidazoles has been developed by the condensation of diamine with aldehydes by Hajra et al. [54] using nano-In_2O_3 as an efficient catalyst under mild reaction conditions in aqueous media (Scheme 5.14). The procedure is applicable to aryl, aliphatic, and heteroaryl aldehydes. In_2O_3 NPs are recyclable without the loss of significant catalytic activity. A wide range of aliphatic, aromatic, heteroaryl, and α,β-unsaturated aldehydes were subjected to prove the general applicability of procedure. Several sensitive functionalities such as –OH, OMe, and halogen (Cl, Br) are unaffected under the present reaction conditions. Heteroaryl aldehydes such as pyridine-2-carboxaldehye and furfural also afforded desired products in good yields. α,β-Unsaturated aldehyde such as cinnamaldehyde reacted well under these conditions.



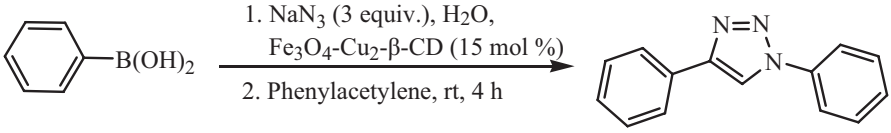
Scheme 5.14

4.2.5 Triazoles

Triazoles are an interesting class of heterocyclic units widely used in the discovery and modulation of drug candidates, development of new materials, supramolecular chemistry, design of new supported organocatalysts, and biotechnology area [55]. Therefore, several elegant methods for the synthesis of this classic nitrogen heterocyclic compounds have been reported by 1,3-dipolar cycloaddition of azides with alkynes under thermal [56] conditions as well as copper catalysis.

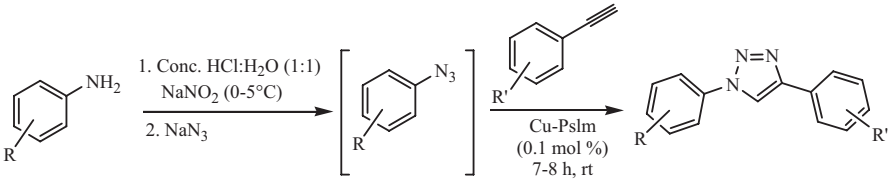
Kaboudin et al. [57] reported the preparation of an efficient, easily recoverable, and reusable Fe_3O_4 magnetic NP-supported Cu(II)-β-cyclodextrin complex catalyst for the synthesis of 1,2,3-triazoles from arylboronic acids in water, followed by a click cyclization reaction with an alkyne at room temperature in air without

any additives (Scheme 5.15). Fe_3O_4 magnetic NP-supported Cu(II)-β-cyclodextrin complex catalyst was characterized by TEM, XRD, vibrating sample magnetometer (VSM), thermal gravimetric analysis (TGA), and Fourier transform infrared (FT-IR) spectrometer. The reaction was initiated by the transmetalation of the aryl group from boron to copper via the attack of the hydroxide ligand to the oxophilic boron center. The resulting aryl copper intermediate undergoes subsequent reductive azidation to the aryl azide compound. The 1,2,3-triazole formation proceeds through the formation of copper acetylide, followed by coordination of the aryl azide to the copper center of the acetylide, and initiates an azide–alkyne 1,3-dipolar cycloaddition.



Scheme 5.15

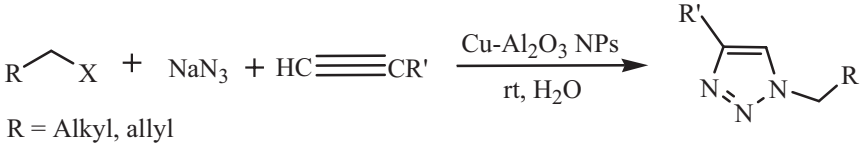
An efficient procedure for the one-pot synthesis of 1,4-disubstituted 1,2,3-triazole derivatives has been developed by the "click" reaction of azides generated in situ from anilines or amines and terminal acetylenes catalyzed by the polymer-anchored Cu(II) catalyst in water without using any additives [58] (Scheme 5.16). 2-Ethynyl-6-methoxy-naphthalene easily reacted with 2-nitrophenyl azide to form the corresponding triazole. Both electron-donating (OMe) and electron-withdrawing (CN, F) groups containing acetylenes react equally with various azides to form the corresponding products. All kinds of permutations and combinations of electron-donating and electron-withdrawing groups in both the aniline and acetylene reagents were applied. Most significantly, when 2-nitrophenyl azide formed in situ from 2-nitroaniline was made to react with excess (1.5 equiv.) of 1,4-diethynyl benzene, only the monotriazole product was formed keeping the other acetylene moiety intact, which indicates that the reaction is highly chemoselective. The heteroaryl-substituted acetylene, 2-ethynyl pyridine, reacted clearly with benzyl azide formed in situ from benzyl amine to form 2-(1-benzyl-1*H*- (1,2,3)triazole-4-yl)-pyridine.



R = H, 4-OMe, 2-NO_2, 3-OH, 2-I, 3-Cl, etc.
R' = H, 4-OMe, 4-F, 4-CN, etc.

Scheme 5.16

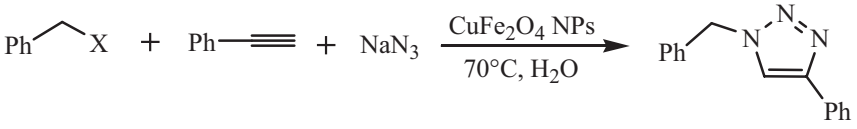
Kantam et al. [59] reported the synthesis of alumina-supported copper NPs from copper(II) acetylacetonate and aluminum isopropoxide precursors using aerogel protocol. The NPs were characterized by XRD, TEM, ^{27}Al MAS NMR, X-ray photoelectron spectroscopy (XPS), and ICP-AES. Cu–Al_2O_3 NPs are used for the preparation of 1,2,3-triazoles by the reaction of terminal alkynes, sodium azide, and alkyl/allyl halides (Scheme 5.17).



R = Alkyl, allyl
X = Cl, Br, I
R' = Aromatic, Aliphatic

Scheme 5.17

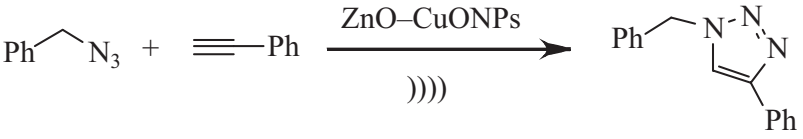
Kumar et al. [60] developed magnetically separable copper ferrite NPs as a catalyst for the synthesis of 1,2,3-triazoles (Scheme 5.18). This one-pot preparation of 1,2,3-triazoles involves initial substitution of benzyl halides with sodium azide to generate in situ benzyl azides, which is followed by copper ferrite-catalyzed cycloaddition reaction with alkynes in water at 70 °C. The present method described here is simple, facile, and can be applicable to a wide range of substrates with high functional-group tolerance. The method circumvents the problems encountered with the isolation of organic azides. The high activity, easy separation, commercial availability, and reusability are the salient features of the catalyst that make this as a competitive catalyst.



Scheme 5.18

Park et al. [61] synthesized ZnO–CuO core–branch hybrid NPs by copper oxide growth and controlled oxidation on ZnO nanospheres, and exhibited remarkable enhancement of catalytic activity and stability for ultrasound-assisted [3 + 2] azide–alkyne cycloaddition reactions under ultrasonic irradiation (Scheme 5.19). The surface species of the catalysts were investigated by XPS with the core level of Cu $2p_{3/2}$ before and after the reaction. The peaks are deconvoluted into two peaks, where the peak at lower binding energy is attributed to Cu(I) and that at higher binding energy is attributed to the Cu(II) species. Before the reaction, the

Cu(II) state mostly existed on the catalyst surface. However, after the reaction, the relative areal intensity ratio between Cu(I) and Cu(II) states remarkably increases up to more than 1:1. Note that the Cu(II) state after the chemical reaction might be formed by air oxidation during the sample preparation of the XPS measurement. Consequently, it is believed that the present cycloaddition reactions were proceeded by the Cu(I) species formed in situ during the reaction. The excess amount of phenylacetylene could behave as a reductant to convert Cu(I) from the activated Cu(II) surface, via the formation of Cu(II)–acetylide. Apparently, such a well-defined hybrid system with bifunctional components provides a new way to design high-performance catalysts with high activity and reusability for gas- and solution-phase reactions.



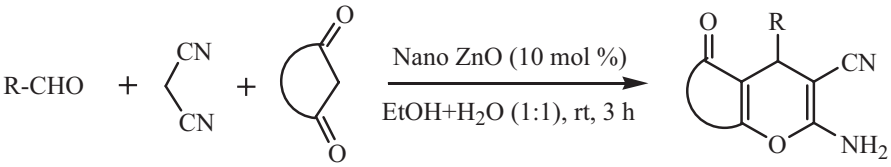
Scheme 5.19

4.3 Synthesis of Six-Membered Heterocycles

4.3.1 Pyrans

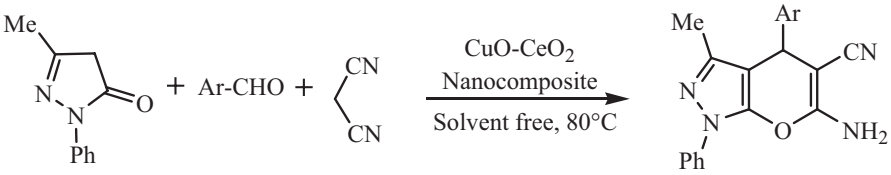
The synthesis of polyfunctionlized 4*H*-pyrans group is attractive to researchers as it is a constituent of various natural products [62] and exhibits a variety of biological and pharmacological activities [63]. These compounds are used as anticoagulants, anticancer agents, spasmolytics, anti-anaphylactics, etc. Moreover, these compounds can be used in various applications as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, as well as for the treatment of schizophrenia and myoclonus. Also, a number of 2-amino-4*H*-pyran derivatives are useful as photoactive materials [64].

A green and highly efficient protocol has been developed for the synthesis of 4*H*-pyran scaffolds installing a one-pot three-component coupling reaction of an aldehyde, malononitrile, and a 1,3-diketo compound using nanostructured ZnO as the catalyst in aqueous alcoholic medium [65] (Scheme 5.20). The optimized methodology tolerated a wide spectrum of aldehydes and dicarbonyl compounds with good-to-excellent yield of the targeted molecules. The aromatic aldehydes with electron-withdrawing groups reacted faster with slightly improved yields than their electron-donating counterparts. The method is also applicable to aliphatic aldehydes and heterocyclic aldehydes. The catalyst can be recycled five times without significant loss of the activity.



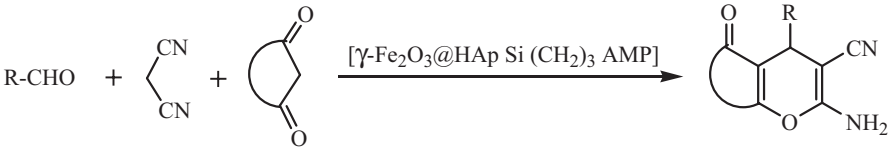
Scheme 5.20

$CuO–CeO_2$ is reported as a highly efficient and green recyclable catalyst for the multicomponent synthesis of 4*H*-benzo[*b*]pyran derivatives [66] (Scheme 5.21). The catalyst was synthesized by a co-precipitation method and characterized by XRD, BET specific surface area, environmental scanning electron microscope (ESEM), and energy-dispersive X-ray spectroscopy (EDX) analysis. The catalyst showed very good catalytic activity. This might be due to its small particle size, which provides a large surface area for reactant adsorption and therefore high catalytic activity.



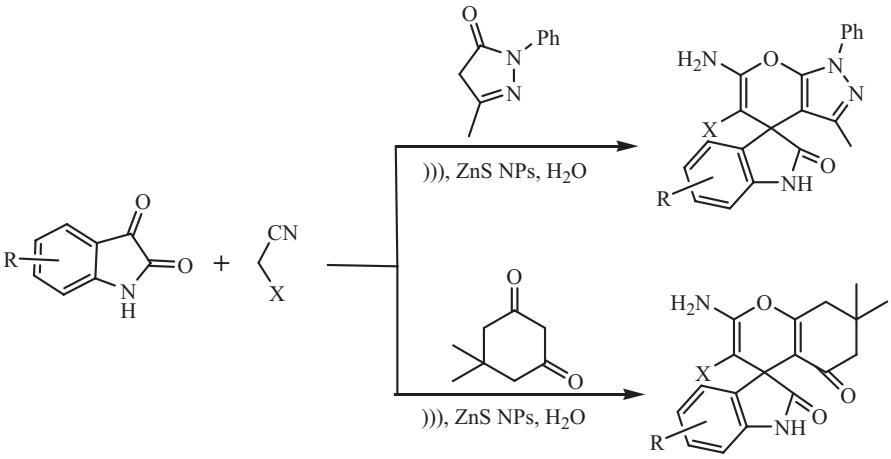
Scheme 5.21

Shafiee et al. [67] showed that (2-aminomethyl)phenol moiety supported on HAp-encapsulated-γ-Fe_2O_3 [γ-Fe_2O_3@HAp Si $(CH_2)_3$ AMP] was a novel and effective heterogeneous catalyst for the one-pot synthesis of 4*H*-benzo[*b*]pyran derivatives from commercially available starting materials (Scheme 5.22). The present method requires remarkably small amounts of nontoxic and environmentally friendly [γ-Fe_2O_3@HAp Si $(CH_2)_3$ AMP] as catalyst. In addition, the aqueous conditions, excellent yields, operational simplicity, practicability, product purity, cost efficiency, and environmental benefits are the worthy advantages of this protocol. The introduced magnetically inorganic–organic hybrid nanocatalyst supported on hydroxyapatite-encapsulated γ-Fe_2O_3 was highly stable and could be reused in ten successive runs with no significant structural change and loss of activity.



Scheme 5.22

Dandia et al. [68] described a novel and highly efficient protocol for the synthesis of structurally complex and diverse spirooxindole derivatives catalyzed effectively by ZnS NPs in aqueous medium (Scheme 5.23). ZnS NPs were well characterized by TEM and XRD techniques. Greenness of the process was well instituted as water was exploited both as a reaction medium as well as a medium for synthesis of catalyst (ZnS NPs). The particle size was determined by TEM and XRD. Compared with other methods for synthesis of spirooxindole derivatives, satisfactory results were obtained with high yields, short reaction time, with simple experimental procedure. After reaction course, the ZnS NPs can be recycled and reused without any apparent loss of activity.

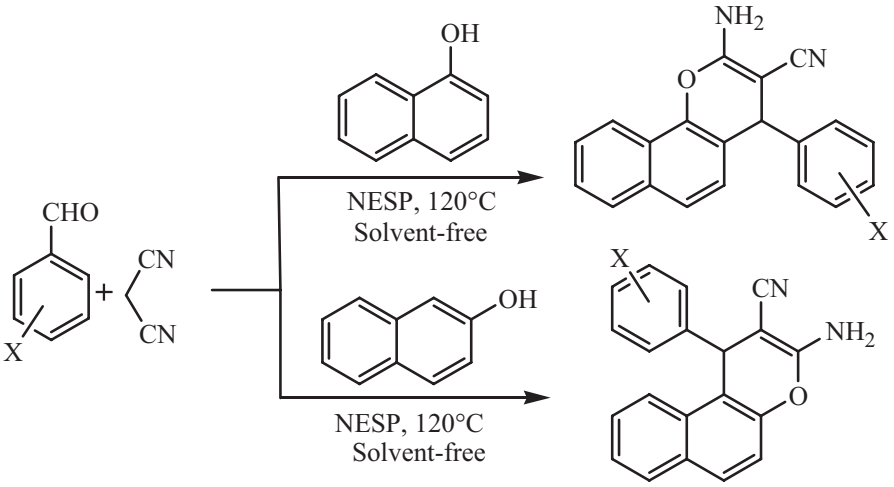


Scheme 5.23

4.3.2 Chromenes

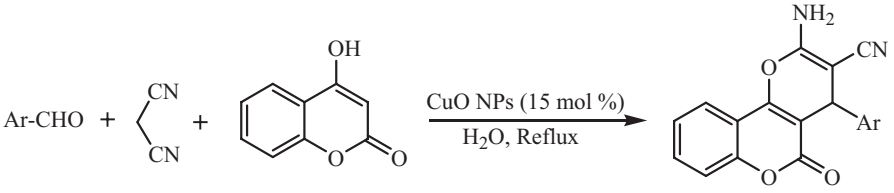
Chromene frameworks are commonly found in natural products [69]. Due to their useful biological activities and pharmacological properties [70], such as pro-apoptotic activity against cancer cells, anticoagulant, and spasmolytic, the synthesis of chromene derivatives, especially 2-amino-4*H*-chromene, has attracted much attention.

The nano eggshell powder (NESP) has been prepared by ultrasound irradiation and used as a novel and biodegradable catalyst with high catalytic activity and reusability in green synthesis of 2-aminochromenes via condensation of α- or β-naphathol, malononitrile and aromatic aldehydes at 120 °C under solvent-free conditions [71] (Scheme 5.24). NESP is a novel nanocatalyst based on eggshell waste, which can catalyze the organic transformation and reduce environmental problems, and it is the first use of this waste material as the nano-sized catalyst in organic synthesis.



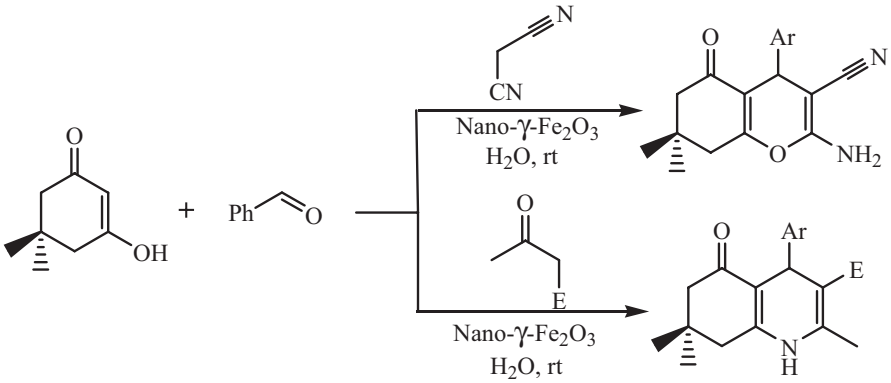
Scheme 5.24

Copper oxide NPs [72] showed excellent catalytic activity through three-component condensation reaction of aldehydes, malononitrile, and 4-hydroxycoumarin for the synthesis of 3,4-dihyropyrano[*c*]chromenes in water as a reaction medium in excellent yields and very short reaction times (Scheme 5.25).



Scheme 5.25

Water-dispersed magnetic NPs (DMNPs) of γ-Fe_2O_3 represent a simple and green catalyst for the rapid three-component synthesis of tetrahydro-4*H*-chromene and hexahydroquinoline carboxylate skeletons via single-pot domino Knoevenagel–Michael-cyclization reactions [73] (Scheme 5.26). A variety of annulated tetrahydro-4*H*-chromenes are accessible under mild conditions using this method. This rapid, green process, in which the catalyst can be recycled, should be an interesting alternative to other synthetic methods. The method offers several advantages, including high yields of products, recyclability of the catalyst, use of an environmentally favorable solvent, and an easy, experimental workup procedure.

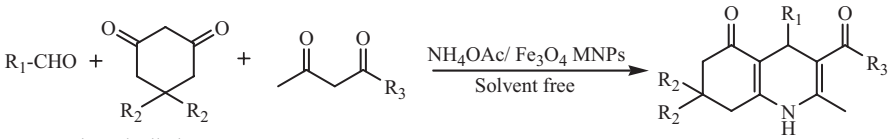


Scheme 5.26

4.3.3 Pyridines

Substituted pyridines are one of the most prevalent heterocycles in natural products [74], pharmaceuticals [75], and various kinds of functional materials [76]. Over the past decades, a variety of synthetic strategies have been developed to obtain substituted pyridines.

A green approach for efficient and rapid synthesis of biologically active, substituted Hantzsch 1,4-dihydropyridine derivatives using magnetic Fe_3O_4 NPs (Fe_3O_4 MNPs) as a recyclable catalyst under solvent-free conditions was reported [77] (Scheme 5.27). The catalyst was characterized by FT-IR, XRD, and TEM analyses. Acid-sensitive substrates such as 3-(2-nitrophenyl) acrylaldehyde proceeded well to give the corresponding 1,4-dihydropyridine without the formation of any side products. The results indicate the generality of the procedure because aliphatic, aromatic, heterocyclic, and α, β-unsaturated aldehydes were converted into the corresponding products in good-to-excellent yields in short reaction time.

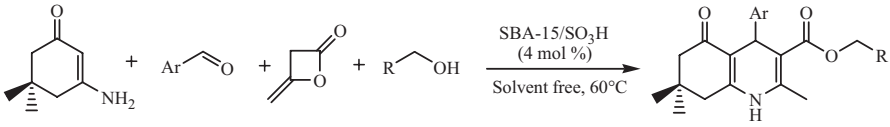


R_1 = Aryl, cycloalkyl
R_2 = Me, H
R_3 = OEt, OMe

Scheme 5.27

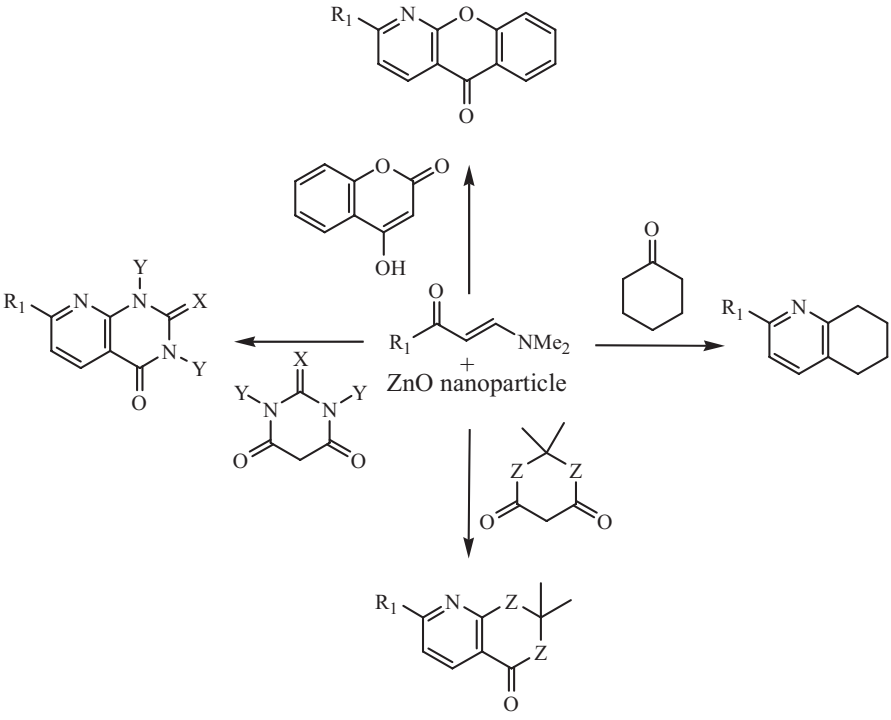
An efficient diketene ring-opening synthesis of dihydropyridine derivatives using SBA-15 sulfonic acid-modified mesoporous substrate as a green and reusable

catalyst in a single-pot four-component coupling reaction of diketene, alcohol, enamine, and aldehydes is reported [78] (Scheme 5.28). The advantages of the present method include the use of a small amount of catalyst, simple procedure with an easily filterable workup, waste-free, green, and direct synthetic method with an excellent yield of products, efficient use of catalyst, and a short reaction time.



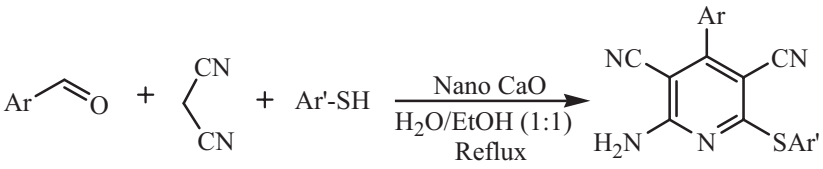
Scheme 5.28

Highly efficient ZnO NP-catalyzed one-pot solvent-free synthesis of novel pyridine derivatives by three-component reaction of β-enaminones, different active methylene compounds, and ammonium acetate via Michael addition, cyclodehydration, and elimination sequence is reported [79] (Scheme 5.29). The catalyst was recyclable up to six catalytic cycles without a significant loss in the catalytic activity. This new protocol has the advantages of environmental friendliness, higher yields, solvent-free, low loading of catalyst, shorter reaction times, and convenient operation procedure. ZnO NPs were characterized by XRD, SEM, and TEM analyses.



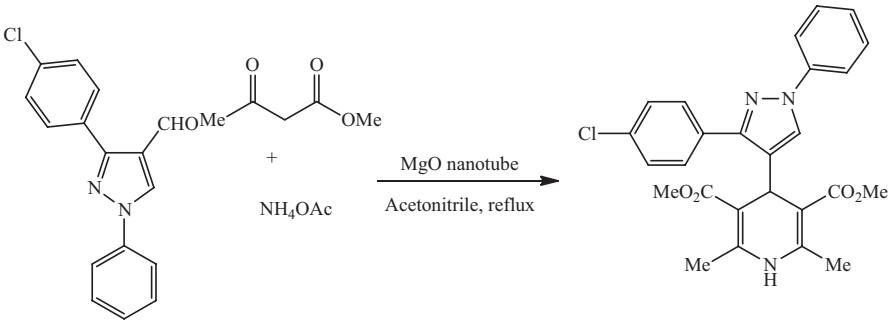
Scheme 5.29

An efficient one-pot three-component condensation of aldehydes, thiols, and malononitrile has been developed (Scheme 5.30) in the presence of calcium oxide NPs. Highly substituted pyridines as privileged medicinal scaffolds have been efficiently prepared via carbon–carbon and carbon–heteroatom bond formation [80].



Scheme 5.30

Magnesium oxide nanotubes (NTs) were prepared by electrospinning technique by Murugan et al. [81]. The activities of these NT catalysts have been investigated by promoting pyrazolyl 1,4-dihydropyridine syntheses (Scheme 5.31). Various advantages associated with these protocols are simple workup procedure, short reaction times, high yields, and reusability of the catalyst.



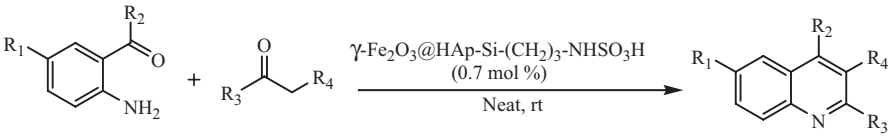
Scheme 5.31

4.3.4 Quinolines

Quinoline derivatives are an important class of nitrogen-containing heterocycles with a wide range of medicinal properties such as antimalarial, antiasthmatic, antihypertensive, antibacterial, anti-inflammatory, and tyrosine kinase inhibitors [82]. In addition to medicinal properties, quinolines are known to undergo hierarchical self-assembly into a variety of nanostructures and mesostructures with improved electronic and photonic functions.

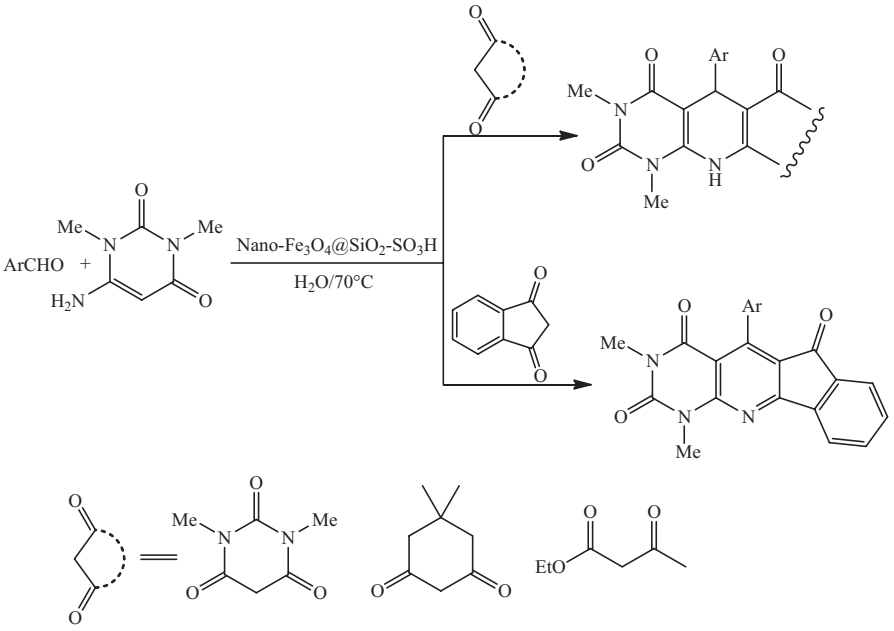
The preparation and characterization of n-propyl sulfamic acid, covalently supported on hydroxyapatite-encapsulated magnetic NPs [γ-Fe_2O_3-HAp-$(CH_2)_3$-$NHSO_3H$], was described [83]. A synthesized material acts as a powerful and "green" heterogeneous interphase catalyst for the preparation of substituted quinolines and α-aminophosphonates derivatives (Scheme 5.32). Hydroxyapatite is found

in teeth and bones within the human body. Thus, it is commonly used as a filler to replace amputated bone or as a coating to promote bone ingrowth into prosthetic implants. It contains more than 60 % of mammalian hard tissues and, in addition, it has a unique biocompatibility feature among phosphate groups. One of the reasons to use this biocompatible material as a catalyst support was that it has no pollution and is in the context of "green chemistry." This can make our new magnetic catalyst distinct from all of its present analogs.



Scheme 5.32

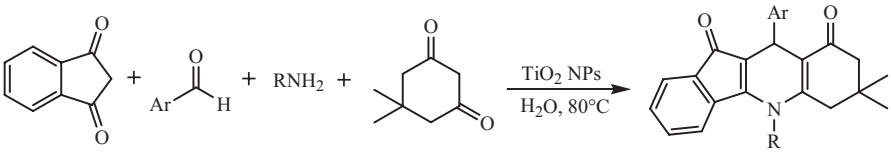
Nemati et al. [84] developed an efficient and eco-friendly method for one-pot synthesis of pyrimido[4,5-*b*]quinolines using nano-Fe_3O_4@SiO_2–SO_3H as a catalyst in water under mild conditions (Scheme 5.33). The catalyst is completely magnetically recoverable and the efficiency of the catalyst remains unaltered after three cycles.



Scheme 5.33

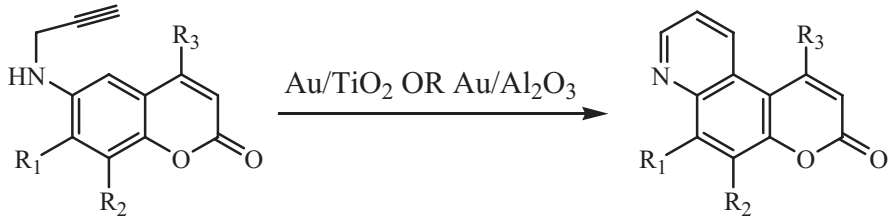
A simple, efficient, and high-yielding approach for the synthesis of indeno[1,2-*b*]quinolinediones has been developed by a one-pot, four-component, coupling reaction utilizing TiO_2 NPs (TiO_2-NPs) as a heterogeneous catalyst at 80 °C in aque-

ous media [85]. It is reasonable to assume that TiO_2NPs catalyze the formation of carbocation, which then undergoes a Knoevenagel condensation with enolized 1,3-indanedione, producing the alkene (Scheme 5.34). The enamine, obtained by the reaction of dimedone with primary amine, then adds to alkene to produce the Michael adduct. Intramolecular cyclization gives a product after dehydration of the intermediate.



Scheme 5.34

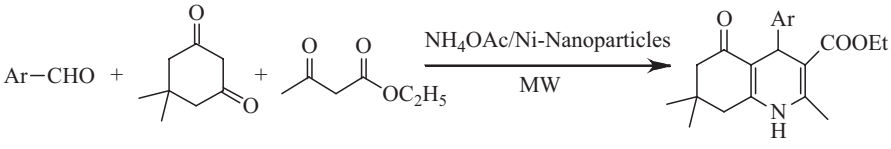
N-propargyl-anilines and coumarins were efficiently transformed into the corresponding quinolines catalyzed by gold NPs supported on TiO_2 and Al_2O_3 under mild conditions [86]. In all cases, pyridocoumarins and quinolines were obtained in high yields, via a synthetically useful procedure (Scheme 5.35).



1,3 a: R_1=R_2=R_3=H
c: R_1-R_2= $CH_2CH_2CH_2CH_2$, R_3=H
b: R_1=CH_3, R_2=R_3=H
e: R_1-R_2= CH=CH-CH=CH, R_3=CO_2Me
d: R_1-R_2= $CH_2CH_2CH_2CH_2$, R_3=CO_2Me
f: R_1-R_2= CH=CH-CH=N, R_3=CO_2Me

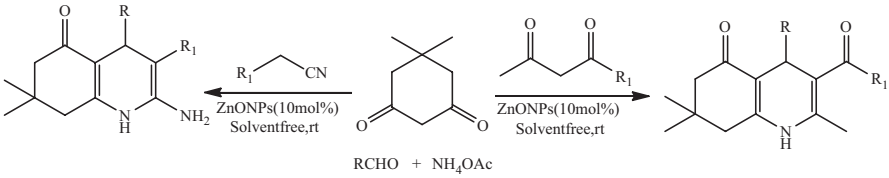
Scheme 5.35

Polyhydroquinoline derivatives have been prepared efficiently in a one-pot synthesis via Hantzsch condensation using nano-sized Nickel (Ni) as a heterogeneous catalyst under microwave irradiation by Shingare et al. [87] (Scheme 5.36).



Scheme 5.36

Kassaee et al. [88] used zinc oxide NPs as an effective and reusable catalyst for one-pot, four-component coupling of aldehydes, dimedone, active methylene compounds, and ammonium acetate to produce polyhydroquinoline derivatives under solvent-free conditions at room temperature (Scheme 5.37).



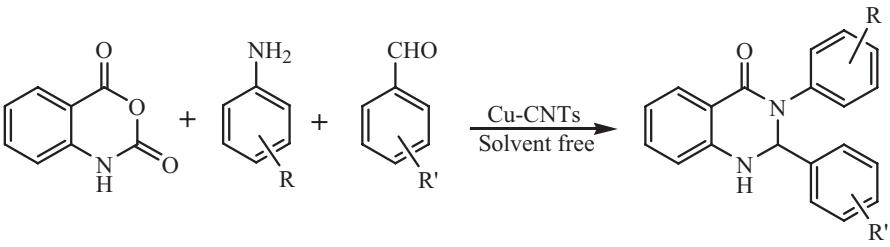
R=C_6H_5, 4-ClC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4 -OHC_6H_4, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-furyl, 2-thienyl, 2-$CH_3C_6H_4$, CH_3CH_2,
R_1 = CN, OEt, OMe, CO_2Et,

Scheme 5.37

4.3.5 Quinazolines

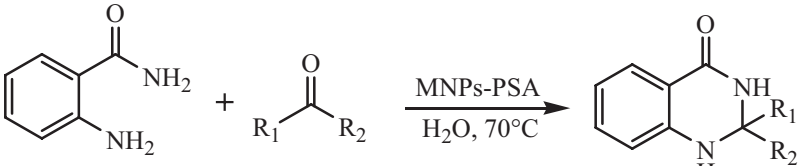
Quinazoline and its derivatives are important compounds found widespread in natural products and pharmaceuticals, which show interesting biological and physiological activities [89] such as antibacterial, antiviral, antitubercular, and anticancer activities. Therefore, a variety of synthetic methods have been developed to synthesize such type of compounds.

Safari et al. [90] successfully demonstrated for the first time that copper-supported carbon NTs (Cu-CNTs) nanocomposite could be used as an excellent and efficient catalyst for convenient synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives under solvent-free conditions and microwave irradiation (Scheme 5.38). Characterization of Cu-CNTs has been performed by XRD, TEM, and SEM. The protocol proves to be efficient and environmentally benign in terms of easy workup, high yields, and ease of recovery of catalyst. In addition, the present method is superior in terms of green media, the amount of catalyst, and reaction time.



Scheme 5.38

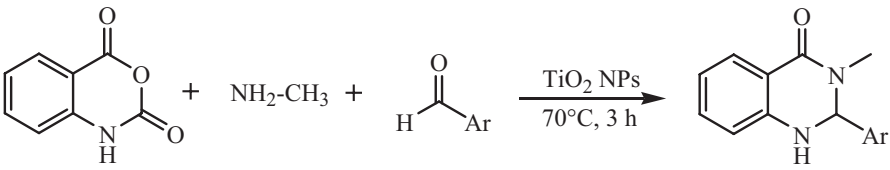
An efficient and eco-friendly method is reported for the synthesis of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones from direct cyclocondensation of anthranilamide with aldehydes and ketones using N-propylsulfamic acid supported onto magnetic Fe_3O_4 NPs (MNPs-PSA) as a recoverable and recyclable nanocatalyst in good-to-excellent yields in water at 70 °C [91] (Scheme 5.39). The characteristic advantages of this catalyst are rapid, simple, and efficient separation using an appropriate external magnet, which minimizes the loss of catalyst during separation, and reusable without significant loss of activity up to ten cycles. In addition, MNPs-PSA couples the advantages of heterogeneous and homogeneous SA-based systems, which make it as a promising material for industry.



R_1, R_2 = Alkyl, aryl, H

Scheme 5.39

Bharathi et al. [92] successfully synthesized the TiO_2 NPs using aqueous *Annona squamosa* peel extract (Scheme 5.40). These synthesized TiO_2 NPs were characterized using UV, XRD, and TEM and used as a catalyst for 2,3-dihydro-3-methyl-2-phenylquinazolin-4(1*H*)-one analog synthesis.



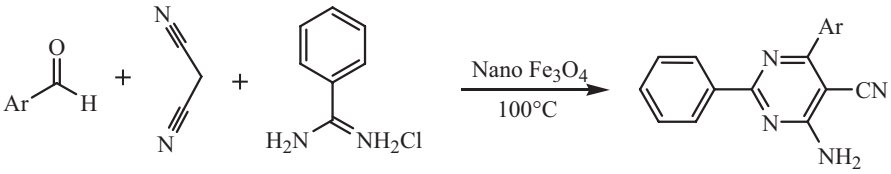
Scheme 5.40

4.3.6 Pyrimidine

Pyrimidine is an important heterocycle with a variety of biological activities. They are closely related to nucleic acids since they are very much alike in structure to the pyrimidine bases [93]. Perhaps, because of this structural similarity, compounds with such heterocycles in their molecular structure were reported as antitumor, interferon inducer, antiviral, antihypertensive, hypoglycemic, anticonvulsant, antinociceptive, and anti-inflammatory agents [94].

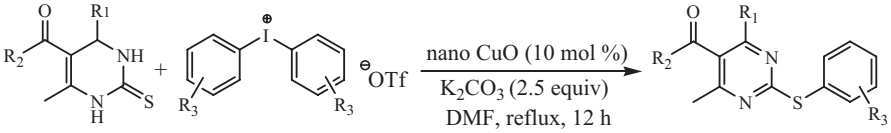
Rostamizadeh et al. [95] synthesized 4-amino-6-aryl-2-phenyl pyrimidine-5-carbonitrile derivatives through a one-pot, three-component reaction of an

aldehyde, malononitrile, and benzamidine hydrochloride in the presence of magnetic Fe_3O_4 NPs as a catalyst under solvent-free conditions (Scheme 5.41). The inhibitory property of the synthetic compounds against two gram-negative strains of bacteria, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae,* and two gram-positive bacteria *Staphylococcus aureus* and *Enterococcus raffinosus* were evaluated. Penicillin G was used as a reference antibacterial agent. Compounds exhibited weak-to-moderate antibacterial activity only against the gram-positive pathogens (MIC = 3.8–300 mmol/L). The bactericidal activity of the tested compounds against *E. raffinosus* (MIC = 3.8–202.5 mmol/L) was higher than that determined against the *S. aureus* (MIC = 12.3–300 mmol/L).



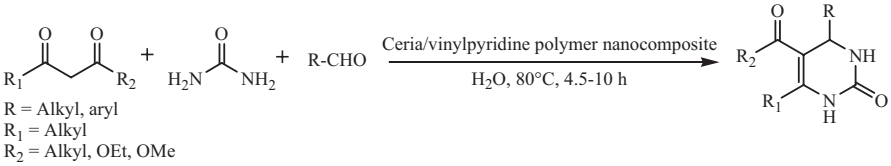
Scheme 5.41

Karade et al. [96] synthesized a wide range of Biginelli 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thiones to undergo ligand-free C–S cross-coupling with diaryl iodonium triflates in the presence of CuO NPs with the concomitant oxidative aromatization to form highly substituted 2-(thioaryl)pyrimidine (Scheme 5.42). The nano-CuO catalyst can be recycled and reused three times without any significant loss of catalytic activity. It is a unique example of CuO NP catalysis for a C–S cross-coupling reaction of thiocarbonyl functional groups of dihydropyrimidinones (DHPMs) with concomitant oxidative aromatization to produce pyrimidine. This method also offers significant advantages such as operational simplicity with a recyclable catalytic system. This is also a first report of a C–S cross-coupling reaction of diaryliodonium salts using a copper-based catalytic system.



Scheme 5.42

The three-component condensation of aldehydes, β-ketoesters, and urea has been carried out in water using ceria (cerium oxide, CeO_2) NPs supported on poly(4vp-co-dvb) as a catalyst for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones in good yields [97] (Scheme 5.43).



R = Alkyl, aryl
R_1 = Alkyl
R_2 = Alkyl, OEt, OMe

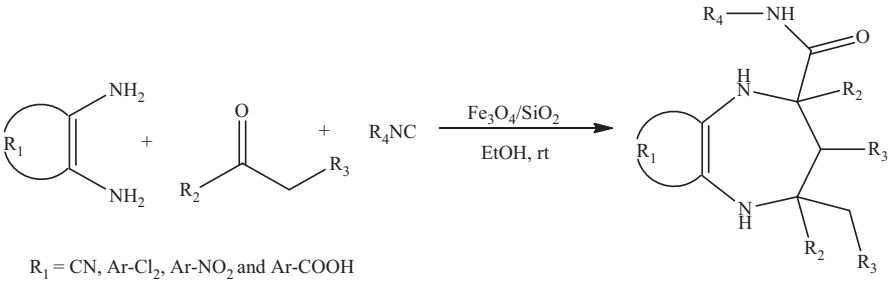
Scheme 5.43

4.4 Synthesis of Seven-Membered Heterocycles

4.4.1 Diazepines

Compounds containing privileged benzodiazepine ring system possess a wide range of pharmacological and biological activities [98]. They have been used as analgesic, sedative, anticonvulsant, antianxiety, antidepressant, hypnotic, and anti-inflammatory agents. 1,5-Benzodiazepines can be prepared by cyclization or cycloaddition of *o*-phenylenediamines with 1,3-diketones, α,β-conjugated alkenones, or β-haloketones or ketones in the presence of BF_3-etherate, $NaBH_4$, polyphosphoric acid, or SiO_2, MgO/PCl_3, $Yb(OTf)_3$, or Al_2O_3/P_2O_5 or AcOH under microwave irradiation [99]. Many of these processes suffer from a number of limitations. Therefore, Maleki et al. [100] investigated a new protocol for the one-pot multicomponent synthesis of diazepine derivatives using a 1,2-diamine, a linear or cyclic ketone, and an isocyanide in the presence of a catalytic amount of silicasupported iron oxide (Fe_3O_4/SiO_2) NPs at ambient temperature in excellent yields (Scheme 5.44).

Maleki et al. explored the scope and limitations of this reaction by varying the structure of the diamine and phenyl acetylene components. The reactions proceeded very cleanly under mild conditions at room temperature, and no undesirable side reactions were observed. In the case of unsymmetrical substituted diamines, inseparable regioisomeric mixtures were obtained.



R_1 = CN, Ar-Cl_2, Ar-NO_2 and Ar-COOH
R_2 and R_3 = acetone, cyclohexanone and acetophenone
R_4 = aliphatic, alicyclic and aromatic

Scheme 5.44

5 Conclusions

The emerging field of NP catalysis represents a burgeoning area with increasing use in heterocyclic synthesis, as reflected by the increasing number of publications devoted to nanocatalysis during the past decade. Nanomaterial-catalyzed transformations in an alternative reaction medium are one of the ideal solutions for the development of green and sustainable protocols. In this chapter, we have given a concise idea of the applicability of nanocatalyst in the heterocyclic synthesis. We would like to conclude with a buoyant view for the future exploration of nanocatalysts for the synthesis of biologically active heterocyclic compounds. This positive view comes from the conviction that the results reported here will be the beginning of a great advance in this promising field in the near future, and that this area of nanoscience will much more be applied in tomorrow's laboratory and industry.

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Chapter 6
Microwave-Induced Synthesis of Various Quinoline Derivatives: Green Methodologies in Organic Synthesis

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Contents

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Abstract In the present chapter, we have focused on microwave-assisted synthesis of quinoline-based heterocyclic compounds because this technique has gained popularity over nonconventional techniques for the rapid synthesis of products. With the help of this technique, many researchers have accelerated organic synthesis, and since the past couple of years a large number of research papers have appeared in scientific journals. This has proved the utility of microwave-assisted synthesis in various branches of chemistry. Microwave-assisted organic synthesis may be helpful to increase the yield, decrease reaction time and minimize the formation of hazardous by-products. With the help of this technique, solvent-free reactions can be easily carried out for eliminating toxicity and flammability issues, which are the major concerns with the use of classical solvents. Quinoline compounds serve both as biomimetics and as reactive pharmacophores of numerous drugs and are associated with several biological activities. Considering these facts and the several applications of microwave-induced synthesis in organic and pharmaceutical chemistry, in the present chapter, we have exclusively focused on the synthesis of various quinoline-based heterocyclic compounds.

Keywords Green chemistry · Quinoline · Microwave synthesis

1 Introduction

In the background of green chemistry, microwave irradiation (MWI) provides an alternative to the conventional methods for heating or introducing energy into the system. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave (MW)-assisted reactions are fast, clean, economic and eco-friendly, and this technique has been proposed as the "technology of tomorrow". Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances.

Solvent-free MW-assisted reactions have gained popularity as they provide potentialities to work in open vessels and the enhanced possibility of up-scaling the reactions on a preparative scale. Three types of solvent-free procedures can be coupled with MW activation [1, 2]:

1. Reactions between neat reactants, needing at least one liquid polar molecule [3], as liquid–liquid or liquid–solid systems. In the absence of a solvent, the radiation is absorbed directly by the reagents, so the effect of MWs is more marked.
2. Reactions between supported reagents on solid mineral supports in "dry media" by impregnation of compounds on alumina, silica or clays [4].
3. Phase transfer catalysis (PTC) conditions in the absence of an organic solvent when a liquid reagent acts both in a reactant and an organic phase [5].

Currently, organic transformations take place by either of the two ways.

Conventional heating: In this method of heating, reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and the reactants. This is a slow and inefficient method for transferring energy into the reacting system.

MW heating: Here, MWs couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in the temperature. Since the process is not limited by thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conductivity. Only the reaction vessel contents are heated and not the vessel itself; better homogeneity and selective heating of polar molecules might be achieved.

2 Fundamentals of Microwave Heating

MW digestion systems provide an accelerated heating phase and the possibility of simultaneous digestion of a number of different samples. They support unique applications, such as MW-assisted UV digestion and oxygen combustion. MW consists of electric and magnetic fields and thus represents electromagnetic energy. This energy can act as a nonionizing radiation that causes molecular motion of ions and rotation of the dipoles, but does not affect the molecular structure. The rotation of the dipoles in an alternating field causes friction, which produces heat up to 10 °C/s. More exactly, the applied MW field causes the molecules to temporarily spend slightly more time orienting themselves in the direction of the electric field rather than in other directions. When the field is removed, thermal agitation returns the molecules to a disordered state in the relaxation time and thermal energy is released. MW-assisted digestion, dissolution or extraction constitutes a thriving field gathering the thermal effects of MWs and their chemical effects (dielectric polarization) [6]. Under MWs, the energy transfer is not produced by conduction or convection, but by dielectric loss. The propensity of a sample to undergo MW heating depends on the dielectric properties, the dielectric loss factor (ε'') and the dielectric constant (ε'). The dielectric constant represents the ability of a substance to absorb MWs, while the dielectric loss factor represents the ability of a substance to transform this energy into heat. A high dissipation factor ($\tan \delta = \varepsilon''/\varepsilon'$) is responsible for a high susceptibility to MW energy. Dielectric parameters relevant to MW heating have recently been catalogued [7]. For example, the dielectric constants of acetone and ethanol are, indeed, in the same range, but ethanol possesses a much higher loss tangent. For this reason, ethanol couples better with MWI, resulting in a more rapid temperature increase. In this high frequency (2450 MHz) [6], the charge space polarization [8] can also intervene and can be of prime importance with semiconductors since it concerns materials, which contain free conduction electrons. This phenomenon is essential in heating solid particles, more or less magnetic, such as a variety of mineral oxides or metallic species [9].

3 Detailed Microwave Effects

It has long been known that molecules undergo excitation with electromagnetic radiations. This effect is utilized in household MW ovens to heat up food. However, chemists have only been using MWs as a reaction methodology for a few years.

Some of the first examples gave amazing results, which led to a flood of interest in MW-accelerated synthesis.

There are two general classes of MW effects:

(i) **Specific MW effects:** Specific MW effects are those effects that cannot be (easily) emulated through conventional heating methods. Examples include: (i) selective heating of specific reaction components, (ii) rapid heating rates and temperature gradients, (iii) the elimination of wall effects and (iv) the superheating of solvents. MW-specific effects tend not to be controversial and invoke "conventional" explanations (i.e., kinetic effects) for the observed effects.

(ii) **Nonthermal MW effects:** A nonthermal MW effect has been proposed in order to explain unusual observations in MW chemistry. As the name suggests, the effects do not require the transfer of MW energy into thermal energy. This effect is controversial.

MW effects result from material–wave interactions and due to the dipolar polarization phenomenon, the greater the polarity of a molecule, the more pronounced the MW effect when the rise in temperature is considered. In terms of reactivity, the specific effect has to be considered according to the reaction mechanism and particularly with regard to how the polarity of the system is altered during the progress of the reaction. Specific MW effects can be expected for the polar mechanism, when the polarity is increased during the reaction from the ground state (GS) towards the transition state (TS) [10]. The outcome is essentially dependent on the medium and the reaction mechanism. If stabilization by dipole–dipole electrostatic interactions of the TS is more effective than that of the GS, this results in an enhancement of reactivity by a decrease in the activation energy. Typically, some reactions that do not occur by classical heating or that lead to very low yields can be performed in good yields under MWI. Some authors suggest the existence of a specific effect derived from the MW field, recognized as the "MW effect", and not from rapid heating. Occasionally, MW effects on selectivities are found in the literature where the chemioselectivity or regioselectivity of reactions can be altered under MWI when compared to conventional heating. As a further consequence of these assumptions, it may be foreseen that MW effects could be important in determining the selectivity of certain reactions. When competitive reactions are involved, the GS is common for both processes. The mechanism occurring via the more polar TS could therefore be favoured under MWIs [11].

4 Microwave Apparatus: An Important Tool in Organic Synthesis

MWI frequently gives rise to products of higher purity and with a considerable decrease in reaction time, which is of great advantage over conventional heating methods, so this strategy has allowed the optimization of various synthetic processes. The most popular and cheap equipment in organic synthesis is the domestic oven (with limited power at 800–1000 W; Fig. 6.1a).

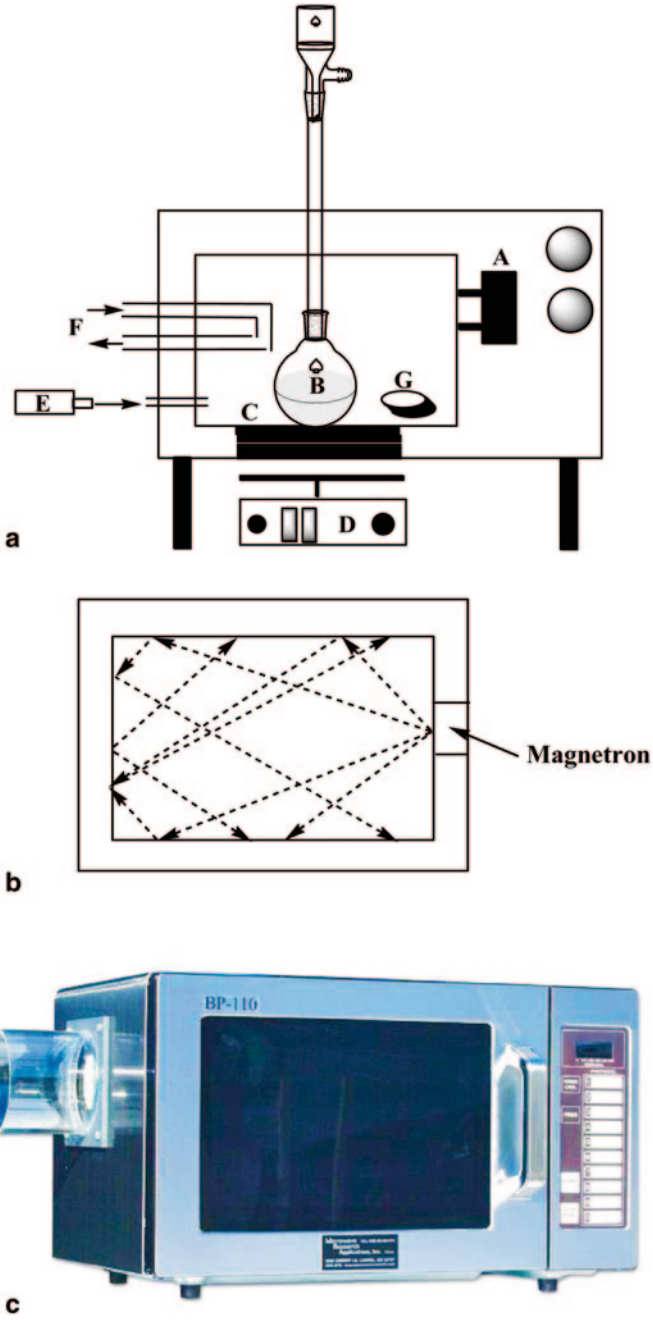


Fig. 6.1 **a** Domestic multimode oven. **b** A modified MW oven for MW photochemistry experiments. (*A*) Magnetron, (*B*) reaction mixture with the EDL and a magnetic stir bar, (*C*) aluminium plate, (*D*) magnetic stir, (*E*) infrared pyrometer, (*F*) circulating water in a glass tube and (*G*) dummy load inside the oven cavity. **c** Photochemistry a MW oven (the EDL floats on the liquid surface)

The distribution of electric field is heterogeneous. This distribution is complex and possibly unstable in the time, and their use for synthetic purposes requires a previous cartography to determine the hot spots of high energy using a filter paper sheet impregnated with a solution of cobalt chloride [12]. The power is not tenable and, in fact, the sample is always subjected to maximum power levels for varying periods of time. However, a variety of organic synthesis can be achieved with this simple, non-expensive apparatus. In order to carry out more accurately and safely organic reactions, domestic MW ovens can be simply modified by piercing a hole on the top of the cavity. This allows the introduction of a tube (acting as a air cooler) surmounted by a water cooler to maintain reactions under solvent reflux, or under inert atmosphere, or allowing the addition of compounds in multistep procedures. In the same order of idea, as a typical application for photochemistry experiments, a modified MW oven is usable as described by Klan et al. [13]. In a typical design (Fig. 6.1b and c), four holes were drilled into the walls of a domestic oven: One for a condenser tube in the oven top, another in the side for an infrared (IR) pyrometer and two parts for a glass tube with circulating water. Part of the oven bottom was replaced by an aluminium plate to enable magnetic stirring. The opening for the IR pyrometer could also serve as an external (additional) source of UV radiation.

The vessel was connected to a very efficient water-cooler by means of a long glass tube. This electrode-less (EDL) system was successfully exploited in a lot of photochemical MW-assisted reactions [14]. More sophisticated apparatus has to be used when more accurate and reproducible results are required. They use properties of progressive or stationary waves; the electromagnetic waves are focused (monomode system), with a subsequent homogeneous distribution of energy. They permit to have higher energy yields [15]. These reactors are commercially available as Synthewave 402® from Prolabo or CEM Discover and equipped with an optical fibre inside the product to permit the measurement of temperature or by IR detection [16] on the surface of the product with great precision, temperature control using power modulation from 15 to 300 W, monitoring of the reaction by a computer to program power or temperature. Monomode reactors lead to considerable improvement in yields of organic synthesis by preserving thermal stabilities of products with low emitted power and improved homogeneity in temperature.

5 Microwave Establishment with Solvent-Free Heterocyclic Reactions

MW-assisted synthesis has been carried out using standard organic solvents under open-vessel conditions. If solvents are heated by MWI at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the reaction temperature that can be achieved. In order to, nonetheless, achieve high reaction rates, high-boiling MW-absorbing solvents have been frequently used in an open-vessel

MW synthesis. Solvent-free methods are of large interest in order to develop conventional procedures making them more clean, safe and easy to perform.

Reactions on solid mineral support: Reactants are impregnated as neat liquids on solid supports such as alumina, silica, zeolite and clays or using their solutions in adequate organic solvent and for further solvent elimination in the case of solids, reaction in "dry media" is performed between individually impregnated reactants, followed by possible heating. At the end of the reaction, organic products are simply removed by elution with an appropriate solvent.

Solid–liquid solvent-free PTC: In case of solid–liquid mixtures, the reaction implies either solubilization of the solid in the liquid phase or adsorption of the liquid on the solid surface as an interfacial reaction and this method is specific for anionic reactions occurring between neat reactants in quasi-equivalent amounts in the presence of a catalytic quantity of tetra-alkyl ammonium salts or cation-complexing agents. When achieved in the absence of solvent, the liquid organic phase consists of an electrophilic reagent than possibly the reaction product. Nucleophilic anionic species can be generated in situ by reacting their conjugated acids with solid bases of increased strength due to ion-pair exchange with quaternary ammonium salts. These solvent-free processes can be thus employed with noticeable increase in reactivity and selectivity. These methodologies can moreover be improved to take advantage of MW activation as an advantageous alternative to conventional heating under safe and efficient conditions with large enhancements in yields and reductions in time period of the reaction. Among the most promising ways to attain this objective, solvent-free techniques hold a strategic position as solvents are very often toxic, expensive and difficult to use and remove. It is the most important reason for the development of such modern technologies. These approaches may allow experiments to be run without strong mineral acids when replaced by k10 or KSF clays that can in turn cause corrosion, safety, manipulation and pollution problems as wastes. In solvent-free conditions, recyclable solids, such as montmorillonite, bentonite, alumina, silica, etc., absorbing MWs can be used efficiently as supports and catalysts in MW-assisted chemistry. This method has considerably attracted industries and converts MW chemistry in an environmentally benign method.

6 Applications in Heterocyclic Chemistry

Heterocyclic chemistry is interpreted in its broadest sense as an interesting group closest to mainstream with synthetic organic chemistry.

The following themes have been prevalent in recent years:

- Synthesis and reactivity of heterocycles including mechanistic studies
- Practical applications of heterocyclic compounds
- Total synthesis
- Heterocyclic intermediates and reagents

In this chapter, we have focused our efforts on the applications of MWI under solvent-free conditions in heterocyclic synthesis essentially via cycloaddition and cyclocondensation reactions and other heterocyclic reactions. More than 300 papers related to heterocyclic synthesis and reactivity under MWs have been published. We also present, in our review, a template reaction in combinatorial chemistry and examples of *one-pot* heterocyclic reactions. It is clear that the applications of MW technology to rapid synthesis of biologically significant heterocyclic molecules under solvent-free conditions are very promising and numerous. This technology has recently been recognized as a useful tool for drug discovery program especially in combinatorial chemistry. It is well known that the heterocyclic system is an important structural element in medicinal chemistry showing a broad spectrum of pharmacological activities. We have selected several topics related to heterocyclic chemistry; many of those are linked to interesting pharmacological properties (antiviral, including anti-HIV, antiparasitic, antihistaminic, anticancer, antimalarial, etc.).

Organic synthesis is the preparation of a desired organic compound from available starting materials. MW-assisted organic synthesis has been one of the most researched applications of MWs in chemical reactions. Chemists have successfully conducted a large range of organic reactions. These include:

1. Diels–Alder reaction
2. Heck reaction
3. Suzuki reaction
4. Mannich reaction
5. Hydrogenation of β-lactams
6. Hydrolysis
7. Dehydration
8. Esterification
9. Cycloaddition reaction
10. Epoxidation
11. Reductions
12. Condensations
13. Protection and deprotection
14. Cyclization reactions.

MW-assisted organic synthesis is being widely applied in the pharmaceutical industry, particularly for developing compounds in the lead optimization phase of drug development. In this phase, chemists use diverse synthetic techniques to develop candidate drugs from lead compounds.

7 Introduction of Quinoline Moiety

Quinoline is a heterocyclic scaffold of paramount importance to human race. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Indeed,

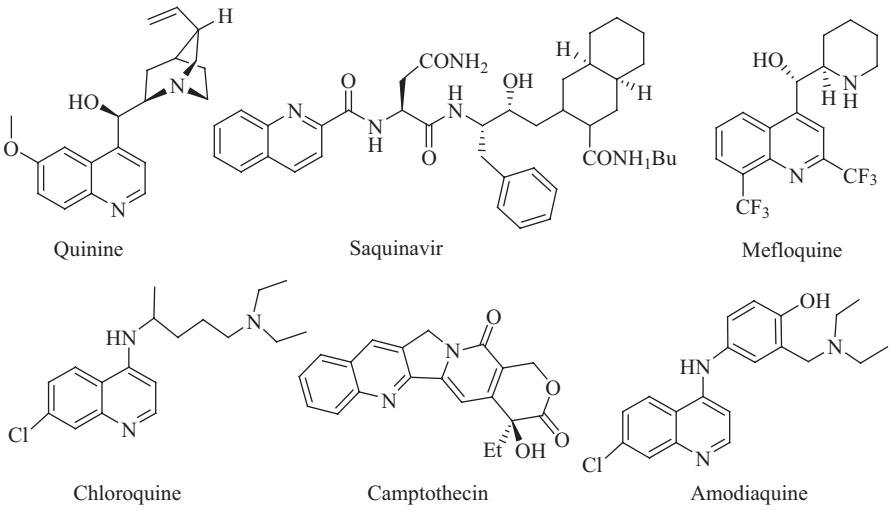


Fig. 6.2 Quinoline-based commercially available drugs

quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases. The bark of Cinchona plant (also known as Jesuit's or Cardinal's bark) containing quinine was utilized to treat palpitations [17], fevers and tertians since more than 200 years ago. Quinidine, a diastereoisomer of quinine was, in the early twentieth century, acknowledged as the most potent of the antiarrhythmic compounds isolated from the Cinchona plant [18]. Compounds containing the quinoline motif are most widely used as antimalarials [19], antibacterials [20], antifungals, [21] and anticancer agents [22]. Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavouring agents [23]. They are also used as polymers, catalysts, corrosion inhibitors, preservatives and as a solvent for resins and terpenes. Furthermore, these compounds find applications in chemistry of transition metal catalyst for uniform polymerization and luminescence chemistry [24]. Quinoline derivatives also act as antifoaming agents in refineries [25]. Owing to such significance, the synthesis of substituted quinolines has been a subject of great focus in organic chemistry. Several drugs which bear quinoline derivatives are described in Fig. 6.2.

The first formal synthesis was reported by Skraup over a century ago [26]. This involved the treatment of aniline with acrolein and hot sulphuric acid, but later several variations to the original Skraup synthesis have been reported [27].

Alternatively, several new methods were unfolded which eventually became conventional for synthesizing the structural core of quinoline. These are (a) Combes synthesis using anilines and β-diketones; (b) Conrad–Limpach synthesis employing anilines and β-ketoesters; (c) Doebner–Miller reaction involving anilines and α,β-unsaturated carbonyl compounds; (d) Friedlander synthesis using 2-aminobenzaldehyde and acetaldehyde; (e) Povarov reaction which involves reaction of an aniline, a benzaldehyde and an activated alkene also known as Aza-Diels–Al-

der reaction; (f) Camps quinoline synthesis utilizing a 2-acylaminoacetophenone and hydroxide ion and (g) Niementowski quinoline synthesis which is the reaction of anthranilic acids and ketones (or aldehydes) to form γ-hydroxyquinoline derivatives.

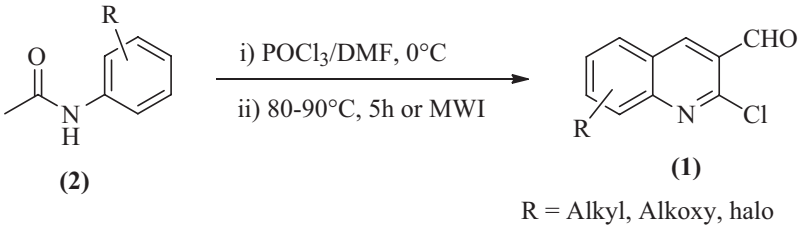
Although there has been tremendous development for obtaining several quinolone derivatives, different synthetic routes have been emphasized for various problems viz. (1) harsh conditions [28]; (2) multistep [29] and (3) a large amount of promoters such as a base [30], expensive reagents and/or harmful metals [31], the oxidants for the aromatization [32] and other additives [33]. Kouznetsov et al. reviewed some of the recent progress made in the synthesis of quinolines in 2005 [34]. They rightly mentioned that there are conceptually only two approaches towards the construction of quinoline. The first one relates to the use of aromatic primary amine as a nucleophilic component providing nitrogen as C–C–N unit whereas the second one employs ortho-substituted anilines as the C–C–C–N unit. Strikingly, since 2005 there has been an unusual increment in the number of publications describing the construction of quinolines decorated with a variety of functional groups at different positions. Although the basic two approaches described by Kouznetsov are universally relevant, the advancement generally concerns the use of new catalysts, medium or physical conditions for already known reactions. As a result, it was deemed suitable to make an effort to assimilate literature pertaining to the synthesis of quinoline derivatives.

The literature for the present review was obtained from the Sci-finder search using the keyword “Quinoline” from the period 2005 to 2007. In addition, other web resources available to us were also utilized to conduct searches related to the synthesis of quinoline derivatives. The scope of this review chapter is limited to the references describing the synthesis of quinoline core including dihydroquinolines and quinoline-annulated ring system. The referral to the bioactivity if described in the original report has been included herein. However, no discussion has been provided for several reports describing methodologies towards quinoline synthesis which are well established and robust. For the sake of convenience, we have classified all reports on the basis of participating carbon skeletons for the construction of quinoline.

8 Utility of Microwave-Induced Synthesis of Quinoline-Based Heterocyclic Compounds

8.1 Preparation of Quinoline (Vilsmeier–Haack Reaction) and Substituted Quinoline Derivatives Using Microwave

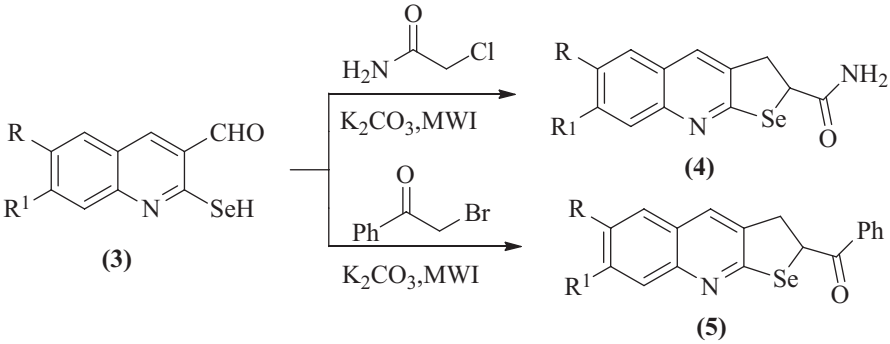
2-Chloroquinoline-3-carbaldehydes (**1**) were synthesized from acetanilides (**2**) via a Vilsmeier–Haack reaction either by traditional methods [35] or by MW [36] or ultrasonic irradiation (Scheme 6.1) [37].



Scheme 6.1

8.2 *A Facile One-Pot Microwave-Induced Synthesis of Some Novel Selenolo[2,3-b]quinoline Derivatives Under Solvent-Free Conditions*

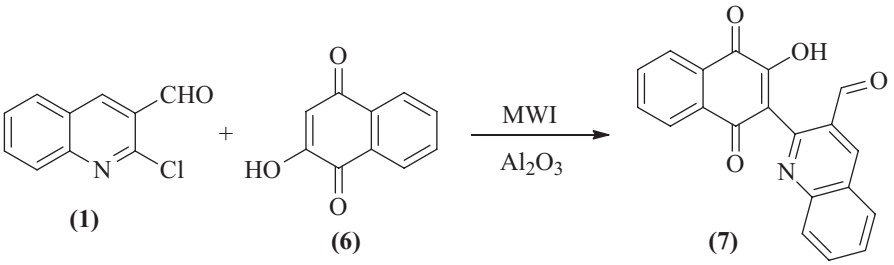
Raghavendra et al. have synthesized selenopheno[2,3-*b*]quinoline-2-carboxamide (**4**) and phenyl(selenopheno[2,3-*b*]quinolin-2-yl)methanone (**5**) in good yields by treating 2-(hydroseleno)quinoline-3-carbaldehyde (**3**) with 2-chloroacetamide and phenacyl bromide, under solvent-free MWI in one-pot reaction (Scheme 6.2) [38].



Scheme 6.2 Synthesis of selenopheno[2,3-*b*]quinoline-2-carboxamide **(4)** and phenyl(selenopheno [2,3-*b*]quinolin-2-yl)methanone **(5)**

8.3 *Alumina-Supported Synthesis of Antibacterial Quinolines Using Microwaves*

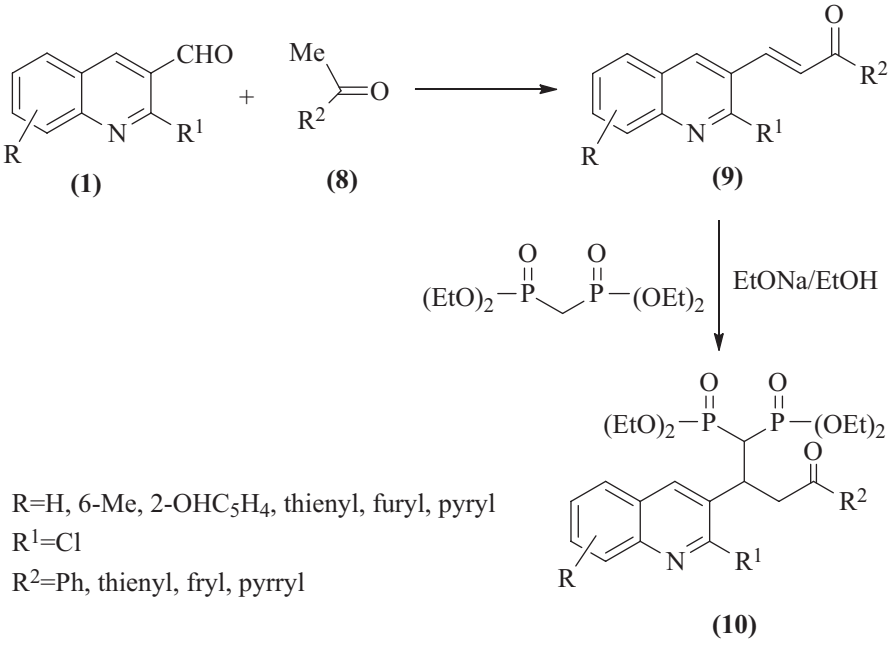
Kidwai et al. have synthesized 3-formyl-2-(3-hydroxy-1,4-naphthoquinon-2-yl)-quinoline (**7**) by the reaction of aldehydes (**1**) with 2-hydroxy-1,4-naphthoquinone (**6**) in basic alumina using MWI (Scheme 6.3). The synthesized compound showed promising antibacterial activity [39].



Scheme 6.3 Synthesis of 3-formyl-2-(3-hydroxy-1,4-naphthoquinon-2-yl)-quinoline **(7)** in basic alumina using microwave irradiation (MWI)

8.4 Synthesis of Bisphosphonate Adduct

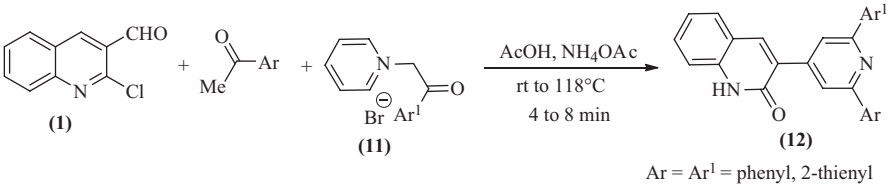
Abdou et al. have synthesized bisphosphonate adduct (**10**) by condensation of aldehydes (**1**) with aryl (heterocycles) methyl ketones (**8**) either by using MW under solvent-free conditions or by using conventional methods to give quinoline chalcones (**9**). Michael addition of tetraethyl methylenebisphosphonate to compound (**9**) (R = Cl, N_3, R^1 = Ph, thienyl, furyl, pyrryl) in EtOH/EtONa at refluxing temperature gave required compounds (Scheme 6.4) [40].



Scheme 6.4 Synthetic route for the preparation of bisphosphonate adduct **(10)**

8.5 Synthesis of 3-(2,6-diarylpyrid-n-4-yl)quinolin-2(1H)-ones

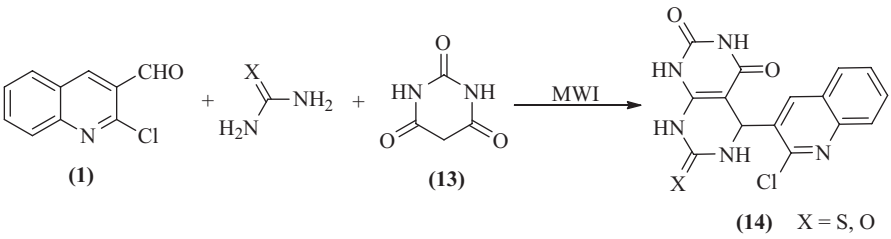
Ladani et al. have synthesized one-pot synthesis of 3-(2,6-diarylpyrid-n-4-yl)quinolin-2(1*H*)-ones (**12**) in high yield by cyclocondensation reaction under Kröhnke's reaction conditions using aldehyde (**1**), aryl methyl ketone and various *N*-phenacylpyridinium bromides (**11**) in a mixture of ammonium acetate and acetic acid under MWI (Scheme 6.5). The synthesized compounds were screened for their antimicrobial activity [41, 42].



Scheme 6.5 Synthesis of 3-(2,6-diarylpyrid-n-4-yl)quinolin-2(1*H*)-ones **(12)** using Kröhnke's reaction conditions

8.6 Synthetic Route for the Preparation of Pyrimido[4,5-d] pyrimidine Derivatives

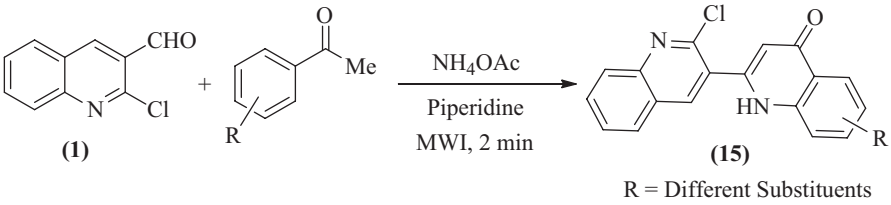
Similarly, Kategaonkar et al. and Kidwai et al. have synthesized pyrimido[4,5-*d*] pyrimidine derivatives (**14**) by the reaction of aldehyde (**1**), barbituric acid (**13**) and urea/thiourea using either solid support of alumina [43] or water [44] under MWI (Scheme 6.6).



Scheme 6.6 Synthetic route for the preparation of pyrimido[4,5-*d*]pyrimidine derivatives **(14)**

8.7 Synthesis of 2'-chloro-2,3'-biquinolin-4(1H)-ones by One-Pot Microwave- Mediated Multicomponent Reaction

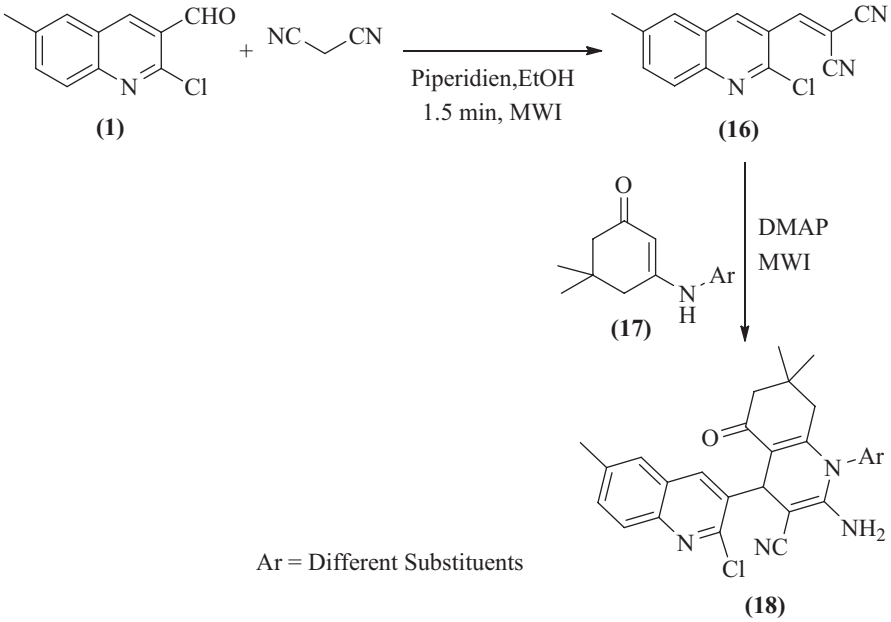
Patel et al. have synthesized 2′-chloro-2,3′-biquinolin-4(1*H*)-ones (**15**) by one-pot MW-mediated multicomponent reaction of aldehyde (**1**), aryl methyl ketone and ammonium acetate using piperidine as a catalyst (Scheme 6.7). The antibacterial activity of the synthesized compounds was determined against gram-positive and gram-negative bacteria, and their antifungal activity was also determined [45].



Scheme 6.7 Synthesized 2′-chloro-2,3′-biquinolin-4(1*H*)-ones **(15)** by one-pot microwave-mediated multicomponent reaction using piperidine as a catalyst

8.8 *Microwave-Assisted Synthesis of Some New Biquinoline Compounds Catalysed by DMAP and their Biological Activities*

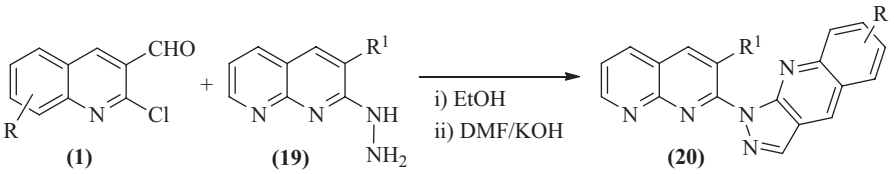
Nirmal et al. have synthesized biquinoline adducts (**18**) in high yields by the cyclization of [(2-chloro-3-quinolyl)methylene]methane-1,1-dicarbonitriles (**16**), which was provided from reaction between aldehyde (**1**) and malononitrile, with 3-arylamino-5,5-dimethyl-cyclohex-2-en-1-ones (**17**) under MWI catalysed by 4-(*N, N*-dimethylamino)pyridine (DMAP; Scheme 6.8). The synthesized compounds were screened for their antifungal and antibacterial activities [46].



Scheme 6.8 Synthesis of biquinoline adducts **(18)** bycyclization of [(2-chloro-3-quinolyl)-methylene]methane-1,1-dicarbonitriles **(16)** using DMAP as catalyst

8.9 Microwave-Assisted Synthesis of Pyrazolo[3,4-b]quinolines Containing 1,8-naphthyridine Moiety

Mogilaiah et al. have synthesized 1,8-naphthyridinyl pyrazolo [3,4-*b*]quinolines (**20**) by the reaction of 2-hydrazino-3-(4-methoxyphenyl)-1,8-naphthyridine (**19**) with aldehydes (**1**) followed by cyclization with DMF/KOH either by MWI or by conventional methods. The reaction rate is enhanced tremendously under MWI as compared to conventional method with improved yields (Scheme 6.9) [47].

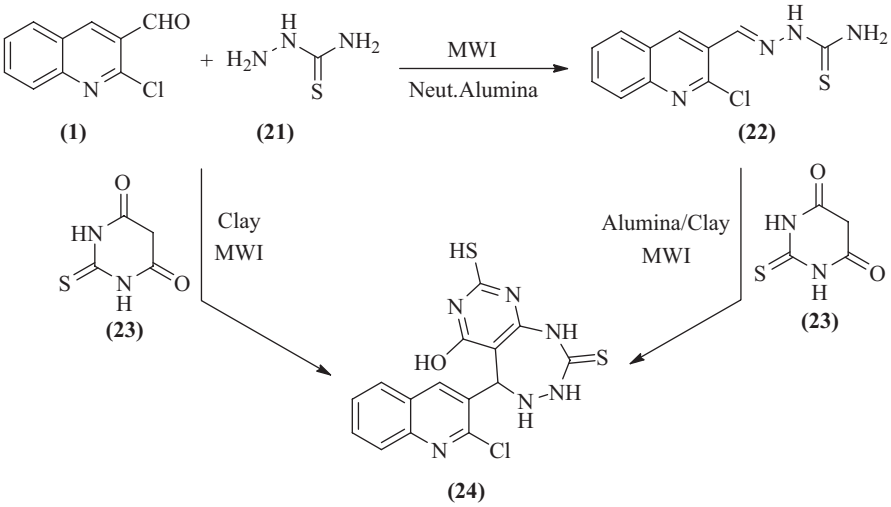


R = H, 6-Me, 7-Me, 8-Me, 8-MeO, 6-Cl, 6-Br; R^1 = 4-$MeOC_6H_4$

Scheme 6.9 Synthetic route for the preparation of 1,8-naphthyridinyl pyrazolo[3,4-*b*]quinolines **(20)**

8.10 Synthesis of 5-(2-chloroquinolin-3-yl)-6-hydroxy-8-mercapto-4,5-dihydro-1H-pyrimido[4,5-e][1,2,4] triazepine-2(3H)-thione (24) Under One-Pot Reaction Condition Using Montmorillonite K-10 Clay

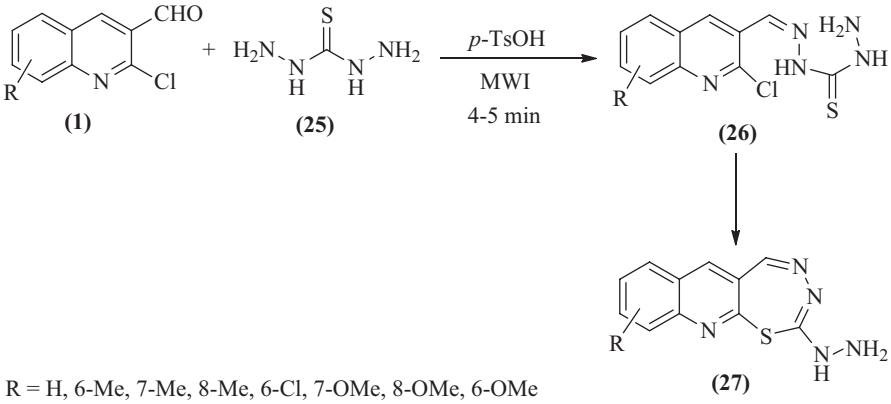
Kidwai et al. have synthesized 5-(2-chloroquinolin-3-yl)-6-hydroxy-8-mercapto-4,5-dihydro-1*H*-pyrimido[4,5-*e*][1,2,4]triazepine-2(3*H*)-thione (**24**) under MWI either by one-pot reaction of aldehyde (**1**), thiosemicarbazide (**21**) and thiobarbituric acid (**23**) using montmorillonite K-10clay or by two steps. Firstly, thiosemicarbazide (**21**) was condensed with aldehyde (**1**) using neutral alumina/montmorillonite K-10 clay resulting in thiosemicarbazone (**22**). Then, in the second step, the later compound was allowed to react with thiobarbituric acid (**23**), over alumina/clay that cyclized to afford target compounds (Scheme 6.10) [48].



Scheme 6.10 Synthesis of 5-(2-chloroquinolin-3-yl)-6-hydroxy-8-mercapto-4,5-dihydro-1*H*-pyrimido[4,5-*e*][1,2,4]triazepine-2(3*H*)-thione **(24)** under one-Pot reaction condition using montmorillonite K-10 clay

8.11 One-Pot Synthesis of Some New 2-hydrazino-[1,3,4] thiadiazepino [7,6-b]quinolines Under Microwave Irradiation Conditions

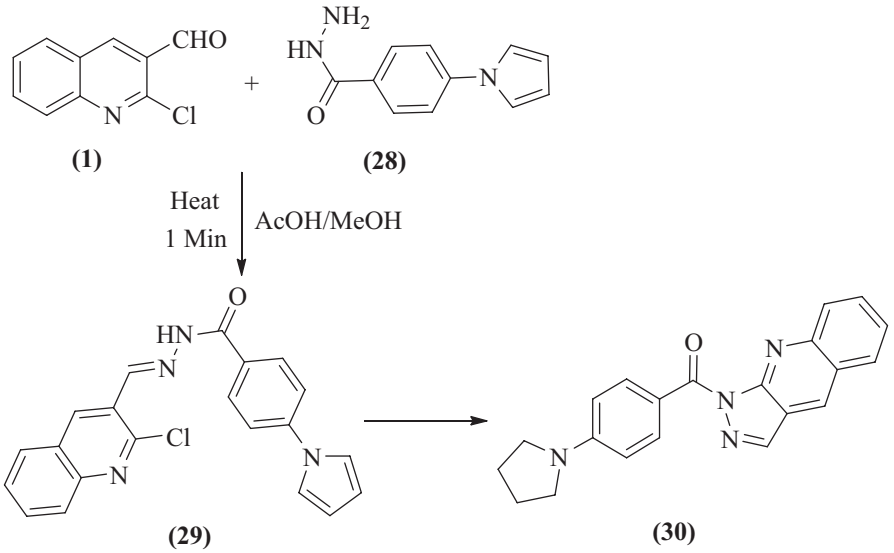
Raghavendra et al. and Gururaja et al. have synthesized 2-hydrazinyl[1,3,4] thiadiazepino[7,6-*b*]quinolines (**27**) in good yields by one-pot reaction of aldehyde (**1**) with carbidimide (**25**) in DMF in the presence of *p*-TsOH as a catalyst under MWI (Scheme 6.11) [49, 50].



Scheme 6.11 Synthetic route for the preparation of 2-hydrazinyl[1,3,4]thiadiazepino[7,6-*b*]quinolines **(27)** in DMF using *p*-TsOH as a catalyst

8.12 Synthetic Route for the Preparation of (4-(1H-Pyrrol-1-yl) phenyl)(1H-pyrazolo-[3,4-b]quinolin-1-yl)methanone

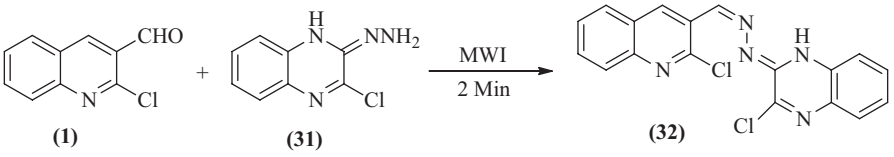
Joshi et al. have synthesized (4-(1*H*-Pyrrol-1-yl)phenyl)(1*H*-pyrazolo[3,4-*b*] quinolin-1-yl)methanone (**30**) by reaction of aldehydes (**1**) with 4-(1*H*-pyrrol-1-yl) benzohydrazide (**28**) in MWI to give *N*′-((2-chloroquinolin-3-yl)methylene)-4-(1*H*-pyrrol-1-yl)benzohydrazide (**29**) followed by intramolecular cyclization. Compound (**30**) exhibited moderate to good antibacterial and antitubercular activities (Scheme 6.12) [51].



Scheme 6.12 Synthetic route for the preparation of (4-(1*H*-pyrrol-1-yl)phenyl)(1*H*-pyrazolo-[3,4-*b*]quinolin-1-yl)methanone **(30)**

8.13 Preparation of 3-chloro-2-((2-chloroquinolin-3-yl) methylene)hydrazono)-1,2-dihydroquinoxaline

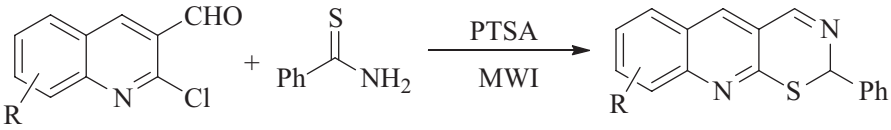
Dubey et al. have synthesized 3-chloro-2-((2-chloroquinolin-3-yl)methylene) hydrazono)-1,2-dihydroquinoxaline (**32**) from reaction of 3-chloro-2-hydrazono-1,2-dihydroquinoxaline (**31**) with aldehyde (**1**) under MWI (Scheme 6.13) [52].



Scheme 6.13 Synthetic route for the preparation of 3-chloro-2-((2-chloroquinolin-3-yl)methylene)hydrazono)-1,2-dihydroquinoxaline **(32)**

8.14 A Facile One-Pot Synthesis of Some New 2-phenyl-2H-[1,3] thiazino[6,5-b]quinolines Under Microwave Irradiation in Solvent-Free Conditions

Raghavendra et al. have synthesized 2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinolines (**33**) in good to excellent yields by one-pot reaction between aldehydes (**1**) and thiobenzamide using *p*-TsOH catalyst under MWI (Scheme 6.14) [53].

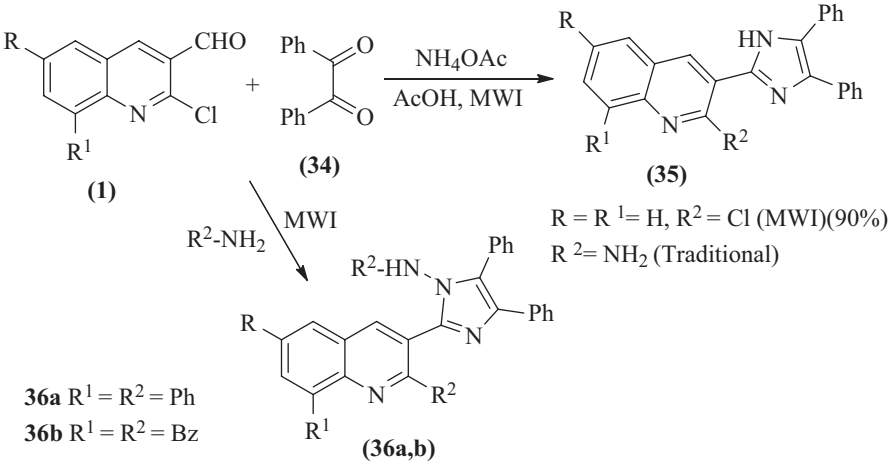


R = H, 7-Me, 8-Me, 7-OMe, 8-OMe, 7-Br, 7-Cl

Scheme 6.14 synthesis of 2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinolines **(33)** by one-pot reaction using *p*-TsOH catalyst

8.15 Synthesis of 2,4,5-trisubstituted Imidazoles and 1,2,4,5-tetrasubstituted Imidazoles

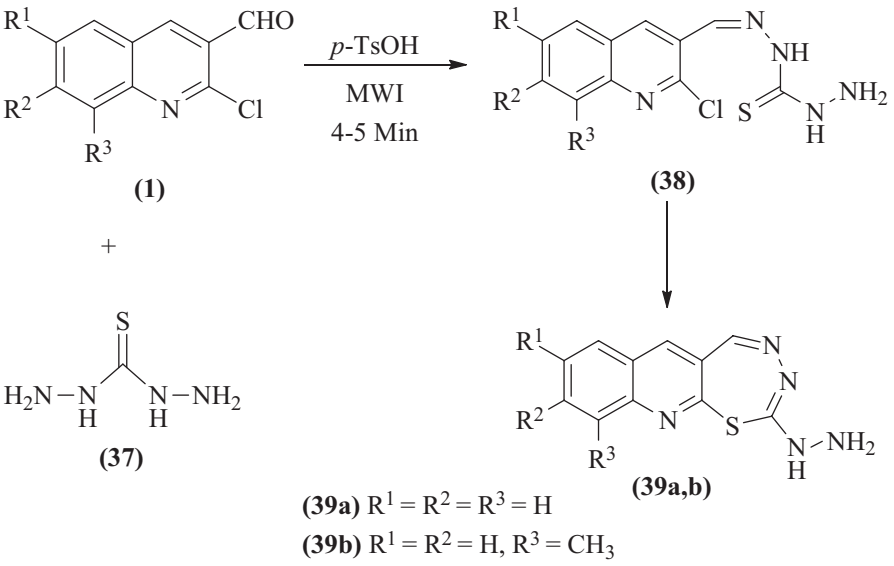
Kidwai et al. have synthesized 2,4,5-trisubstituted imidazoles (**35**) from reaction between benzyl (**34**), aldehydes (**1**) and excess of ammonium acetate either by traditional method using acetic acid or by solvent-free MWI. Similarly, 1,2,4,5-tetrasubstituted imidazoles (**36a, b**) were also obtained in high yields within few minutes by the four-component condensation of benzil, aldehyde (**1**), a primary amine and NH_4OAc under MWI (Scheme 6.15) [54]



Scheme 6.15 Synthesis of 2,4,5-trisubstituted imidazoles **(35)** and 1,2,4,5-tetrasubstituted imidazoles **(36a,b)** using four-component condensation

8.16 One-Pot Synthesis of Some New 2-hydrazino-[1,3,4] thiadiazepino[7,6-b]quinolines Under Microwave Irradiation Conditions

Raghvendra et al. have synthesized a simple, convenient MW-assisted synthesis of 2-hydrazino-[1,3,4]thiadiazepino[7,6-*b*]quinolines (**39a-h**) in the presence of *p*-TsOH catalyst from the reaction of substituted 2-chloro-3-formyl-quinoline (**1**) and carbidimide (**37**) in shorter time with good yield (Scheme 6.16) [55].

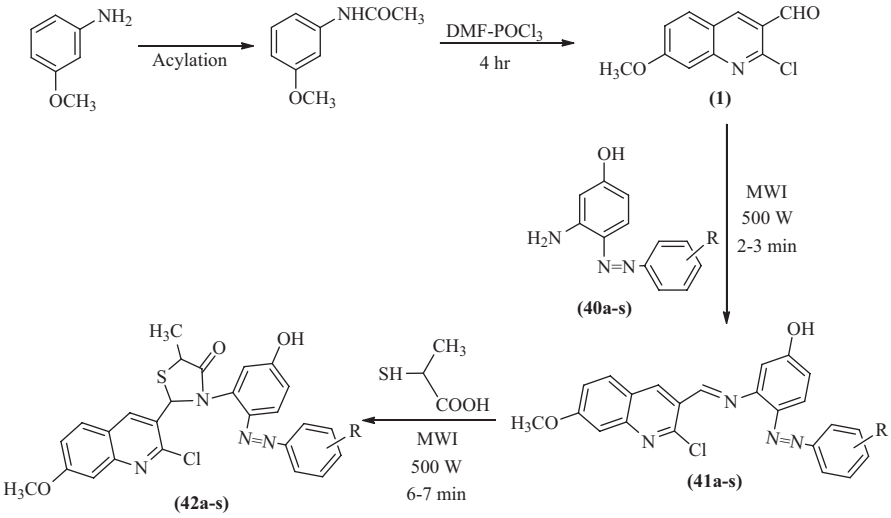


Scheme 6.16 Convenient microwave assisted synthesis of 2-hydrazino-[1,3,4]thiadiazepino[7,6-*b*] quinolines **(39a-h)** inpresence of *p*-TsOH as catalyst

8.17 Green Chemistry: Conventional and Microwave-Induced Synthesis of Various Thiazolidinone Derivatives from 3-{[(1E)-(2'-chloro-7'-methoxyquinoline-3'-yl)methylene] amino}-4-(substitutedphenyldiazenyl)phenol and their Antimicrobial Screening

Rana et al. have synthesized 2-[(2′-chloro-7′-methoxyquinoline-3′-yl)]-3-[3″ -hydroxy-6″-(substitutedphenyldiazenyl)phenyl]-5-methyl-1,3-thiazolidin-4-ones (**42a-s)** have been synthesized by the reaction of 3-{[(1*E*)-(2′-chloro-7′-

methoxyquinoline-3′-yl)methylene]amino}-4-(substituted phenyldiazenyl)phenols (**41a-s)** with thiolactic acid (Scheme 6.17). The reaction was carried out by both conventional and MW methods. The compounds have been screened for their antibacterial and antifungal activities against different microorganisms [56].

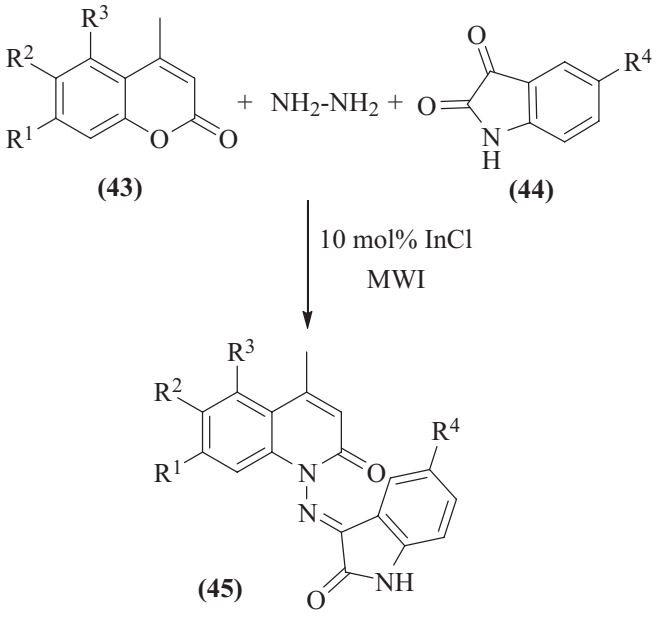


R = H, 2-OCH_3, 3-OCH_3, 4-OCH_3, 2-Br, 3-Br, 4-Br,2-Cl, 3-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2, 2-F, 3-F, 4-F

Scheme 6.17 Synthetic route for the preparation of 2-[(2'-chloro-7'-methoxyquinoline-3'-yl)]-3-[3''-hydroxy-6''-(substitutedphenyldiazenyl)phenyl]-5-methyl-1,3-thiazolidin-4-one **(42a-s)**

8.18 Moisture-Compatible and Recyclable Indium (III) chloride Catalysed and Microwave-Assisted Efficient Route to Substituted 1H-quinolin-2-ones

Siddiqui et al. have synthesized an efficient three-component synthesis of highly functionalized 4-methyl-1*H*-quinolin-2-ones in one-pot reaction from readily available coumarin, hydrazine and isatin catalysed by a recyclable and moisture-compatible $InCl_3$ under MWI. The synthesis involves a $InCl_3$ catalysed dehydrative nucleophilic substitution on the lactone moiety of coumarin by the isatin hydrazone resulting in the formation of *N*-substituted lactams, 6-substituted-4-methyl-1-(2-oxo-1,2-dihydroindol-3-ylidenamino)-1*H*-quinolin-2-ones (**45**). The coumarin-based transformation into substituted 1*H*-quinolin-2-ones proceeded smoothly with quantitative yields at ambient temperature (Scheme 6.18) [57].

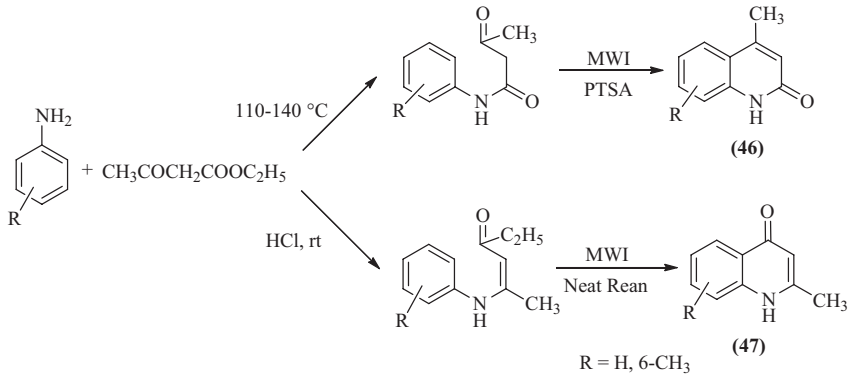


R^1 = H, OH, OCH_3; $R^2 = R^3$ = H, OH; R^4 = H, CH_3, NO_2

Scheme 6.18 $InCl_3$ catalyzed synthesis of 6-substituted-4-methyl-1-(2-oxo-1,2-dihydroindol-3-ylidenamino)-1*H*-quinolin-2-ones **(45)**

8.19 Moisture-Compatible and Recyclable Indium (III) chloride Catalysed and Microwave-Assisted Efficient Route to Substituted 1H-quinolin-2-ones

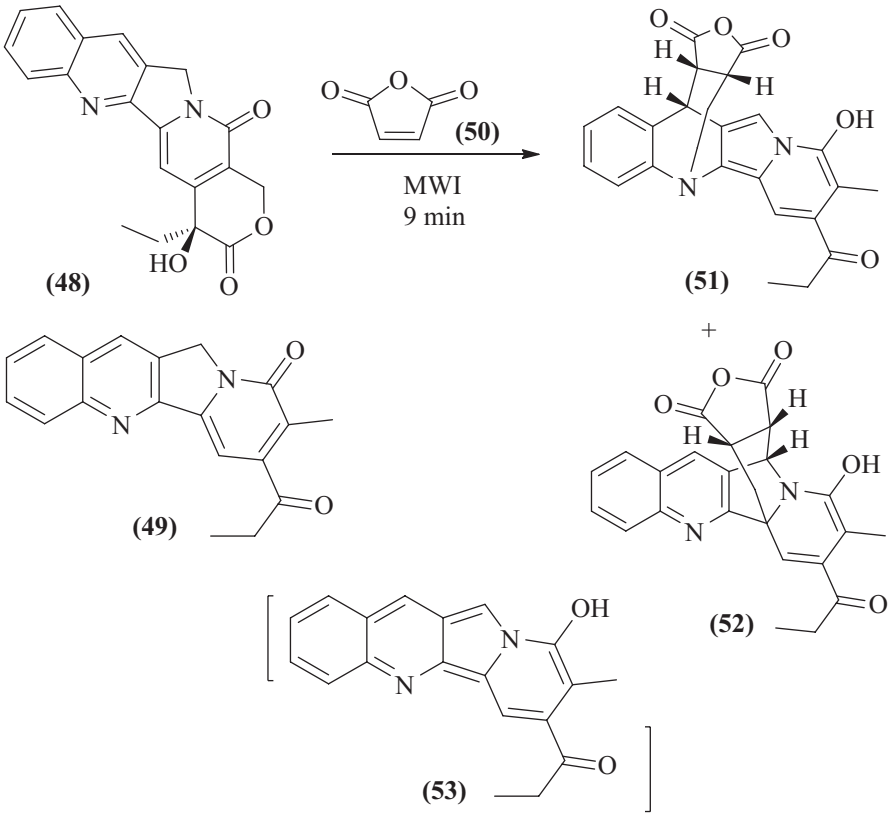
Nadaraj et al. carried out MW-assisted synthesis of 4-methyl-2-hydroxy-quinolines (**46**) and 2-methyl-4-hydroxyquiniolines (**47**) from aniline and ethyl acetoacetate (Scheme 6.19) [58].



Scheme 6.19 Microwave-assisted synthesis of 4-methyl-2-hydroxy-quinolines **(46)** and 2-methyl-4-hydroxyquiniolines **(47)**

8.20 *Microwave-Activated Solid Support Synthesis of New Antibacterial Quinolones*

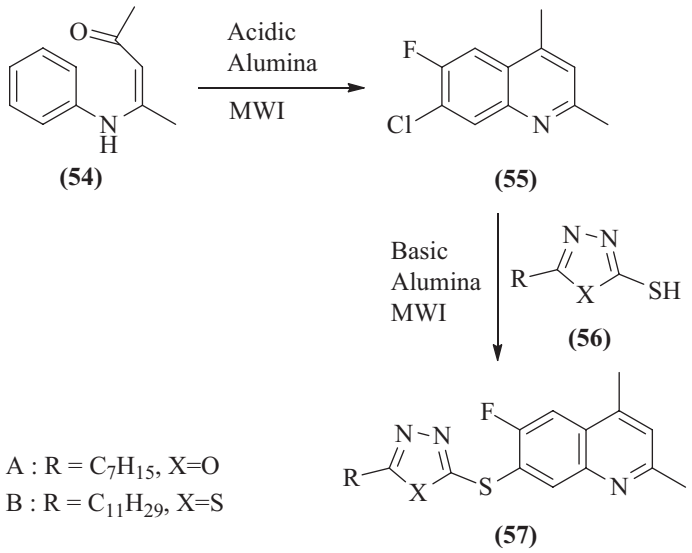
Das et al. [59] described the Diels–Alder reaction of the naturally occurring alkaloids, camptochecin (**48**) and mappicine ketone (**49**) with maleic anhydride (**50**) under solvent-free for 9 min of MWI in a commercial domestic oven (Scheme 6.20). Two unprecedented adducts, (**51**) and (**52**) were produced with yields of 81 % and 14 %, respectively. The first adduct was formed by the involvement of B-ring of camptochecin with maleic anhydride (**50**) while the second was formed by the involvement of the C-ring of the alkaloid with the dienophile. Mappicine ketone (**49**) also underwent similar reaction with maleic anhydride under MWI (9 min) to produce the same adducts (**51**) and (**52**) probably through a Diels–Alder reaction of intermediate (**53**).



Scheme 6.20 Diels–Alder reaction for the synthesis of adducts **(51)** and **(52)** through intermediate **(53)**

8.21 Alumina-Supported Synthesis of Antibacterial Quinolines Using Microwaves

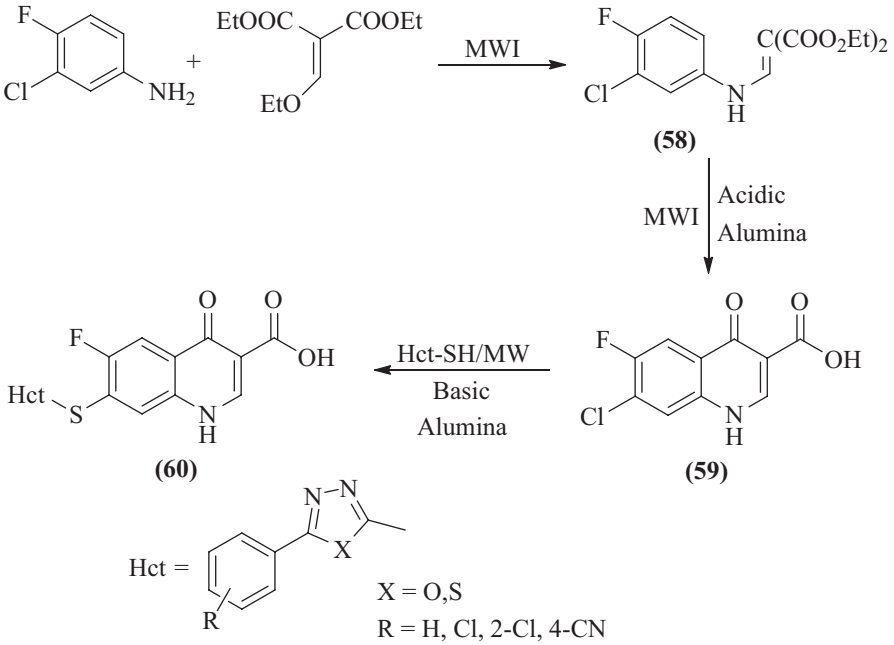
Kidwai et al. have developed a convenient synthesis of 7-(5-alkyl-1,3,4-thiadiazol/oxadiazol-2-ylthio)-6-fluoro-2, 4-dimethy lquinolines (**57**) from 5-alkyl-1,3,4-thiadiazol/oxadiazol-2-thiols (**56**) with 7-chloro-6-fluoro-2,4-dimethylquinoline (**55**) using basic alumina in MW (Scheme 6.21) [39, 60].



Scheme 6.21 Microwave assisted convenient synthesis of 7-(5-alkyl-1,3,4-thiadiazol/oxadiazol-2-ylthio)-6-fluoro-2,4-dimethylquinolines **(57)**

8.22 Microwave-Activated Solid Support Synthesis of New Antibacterial Quinolones

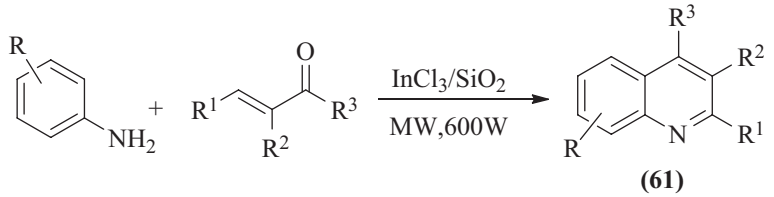
In this context, Kidwai et al. reported with the same method the synthesis of new antibacterial quinolones (**60**; Scheme 6.22) [61].



Scheme 6.22 Synthesis of new antibacterial quinolones **(60)** using alumina as catalysts

8.23 Microwave-Assisted Simple Synthesis of Quinolines from Anilines and Alkyl Vinyl Ketones on the Surface of Silica Gel in the Presence of Indium(III)chloride

The Skraup synthesis has a bad reputation as it involves very harsh conditions and produced very low yield of quinolines (**61**) when carried out conventionally. Recently, it has been reported by Ranu et al. that MW enhancement reduces the reaction time and gives high yields (Scheme 6.23) [62].

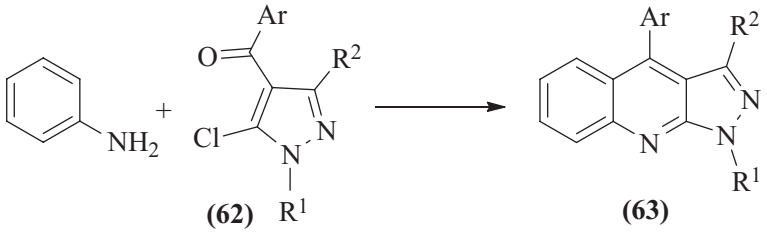


R^1 = H, CH_3, n-Pr; R^2 = H, Et; R^3 = CH_3, CH_3 -C_6H_4-OCH_3

Scheme 6.23 Microwave induced Skraup synthesis for the preparation of **(61)**

8.24 Microwave-Assisted Facile Route to 1H-pyrazolo[3,4-b] quinolines

Danel et al. have synthesized 1*H*-pyrazolo[3,4-*b*]quinolines (**63**) from anilines by reacting with 4-aroyl-5-chloro-1,3-disubstituted pyrazoles (**62**). The reaction preceded over 3 h at 200–220 °C and provided compound (**63**) with yields reaching 70 % depending on the identity of the starting materials (Scheme 6.24) [63].



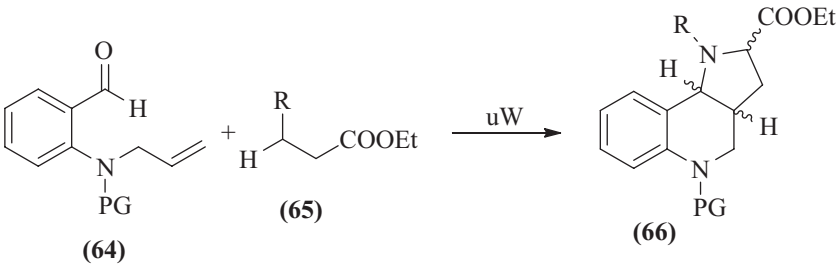
$R^1 = R^2$ = Different substituents

Ar = Different aryl groups

Scheme 6.24 Synthetic route for the preparation of 1*H*-pyrazolo[3,4-*b*]quinolines **(63)**

8.25 Microwave-Assisted Synthesis of Substituted hexahydropyrrolo[3,2-c]quinolines

Neuschl et al. have synthesized ethyl hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylates (**66**) from reaction between *ortho*-(3-alkenyl)amino benzaldehyde (**64**) with secondary amines (**65**) in MW. The reactions were carried out under solvent-free conditions and compared with the same reaction in the presence of a solvent and a catalyst (Scheme 6.25) [64].

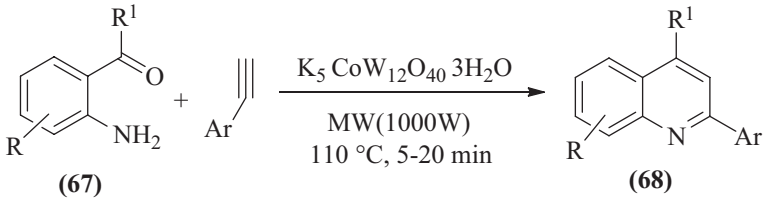


R = n-Bu, CH_3, Bn

Scheme 6.25 synthesis of ethyl hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate **(66)** under solvent-free conditions

8.26 Quinoline: A Versatile Heterocyclic

Iraj et al. synthesized 2,4-disubstituted quinolones (**68**) through a one-pot reaction of structurally diverse 2-aminoaryl ketones with various arylacetylenes in the presence of potassium dodecatugstocobaltatetrihydrate ($K_5CoW_{12}O_{40}.3H_2O$) as a reusable and environmentally benign catalyst under MWI and solvent-free conditions (Scheme 6.26) [65].



(67) **(68)**

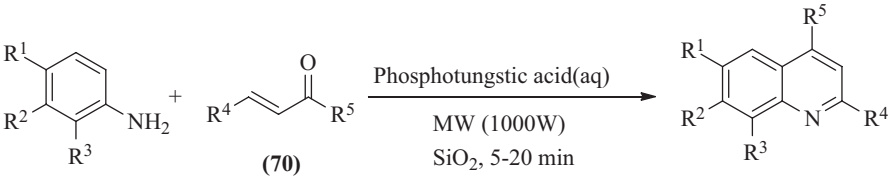
R = R^1 = Different substituents

Ar = Different aryl groups

Scheme 6.26 Synthesis 2,4-disubstituted quinolones **(68)** in the presence of potassium dodecatugstocobaltatetrihydrate ($K_5CoW_{12}O_{40}.3H_2O$)

8.27 Synthesis of Quinaldines and Lepidines by a Doebner–Miller Reaction Under Thermal and Microwave Irradiation Conditions Using Phosphotungstic Acid

Perumal et al. have used reactions of aromatic amines with α,β-unsaturated carbonyl compounds via Michael addition, cyclization and aromatization by conventional heating or MWI to afford the corresponding quinolines (**71**) in high yields as shown in Scheme 6.27 [66].



(69) **(70)** **(71)**

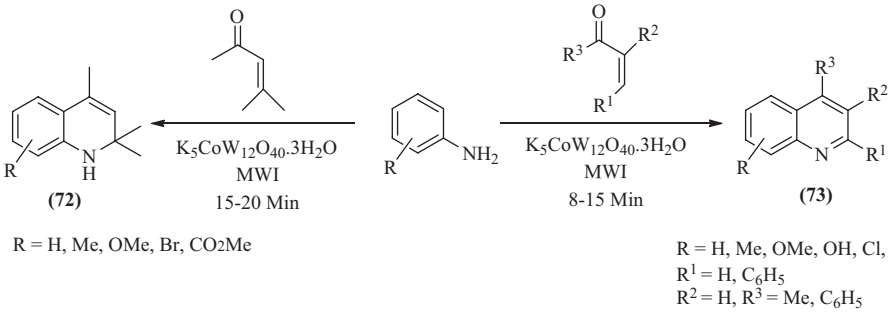
R^1 = H, Br, Cl, OH, OMe, NO_2; R^2 = H, Br, Cl, NO_2; R^3 = H, Cl, OH, OMe, NO_2

R^4 = H, Me; R^5 = H, Me

Scheme 6.27 Conventional heating or microwave irradiation were described to afford the corresponding quinolines **(71)**

8.28 High-Yielding Microwave-Assisted Synthesis of Quinoline and Dihydroquinoline Derivatives Under Solvent-Free Conditions

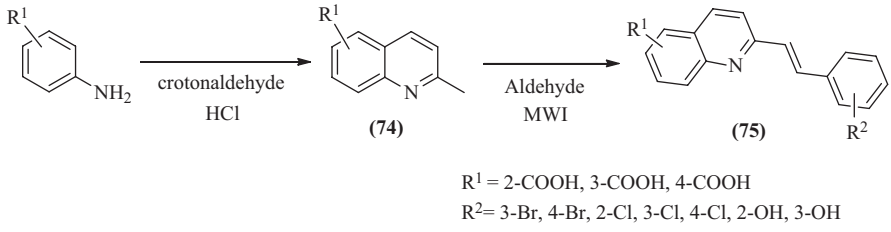
Bose et al. were also able to successfully achieve the microwave-assisted synthesis of quinoline (**72**) and dihydroquinoline (**73**) derivative under solvent-free condition via Skraup synthesis. They demonstrated that 25 mol% of $K_5CoW_{12}O_{40}$ (PDTC) was effective for one-pot reaction of aniline with alkyl vinyl ketones as shown in Scheme 6.28. This reagent was also demonstrated to be an effective catalyst for the Friedlander synthesis [67].



Scheme 6.28 Microwave-assisted synthesis of quinoline **(72)** and dihydroquinoline **(73)** derivative under solvent-free condition via Skraup synthesis

8.29 Investigating Biological Activity Spectrum for Novel Quinoline Analogues

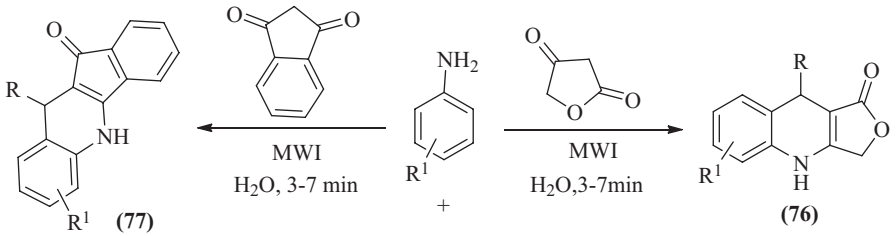
Polanski et al. carried out the synthesis of styryl-quinolines (**75**) via condensation of anilines with crotonaldehyde in the presence of HCl, followed by MWI of the resulting quinaldine (**74**) with aldehydes (Scheme 6.29). Some of the synthesized compounds exhibited photosynthesis inhibiting activity [68].



Scheme 6.29 Synthetic route for the preparation of styryl-quinolines **(75)**

8.30 A Simple Procedure for the Synthesis of 4-aza-podophyllotoxin Derivatives in Water Under Microwave Irradiation Conditions

Tu et al. have reported the synthesis of 4-aza-podophyllotoxin via a three-component reaction of an aldehyde, aniline and cyclic diones in H_2O under MWI. Use of tetronic acid as the cyclic diketone provided the 4-aza-podophyllotoxin derivatives (**76**) (Scheme 6.30). The reaction proceeded via the attack of Schiff's base, formed through the condensation between aldehyde and aniline, on tetronic acid resulting into an intermediate which underwent intramolecular cyclization and dehydration to yield the product. The scope of the strategy was enhanced by replacing tetronic acid with 1,3-indanedione to generate indenoquinoline derivatives (**77**) [69].

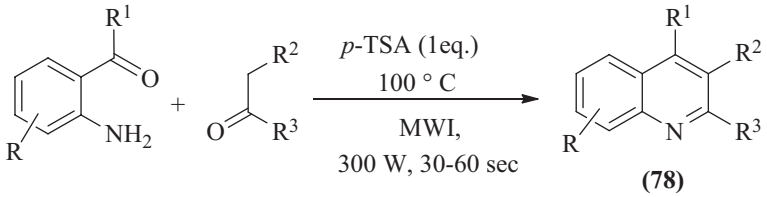


R = Bu, C_6H_5, 4-Br-C_6H_5, 4-Cl-C_6H_4, 4-F-C_6H_4, 3-NO_2-C_6H_4

Scheme 6.30 Synthesis of 4-aza-podophyllotoxinderivatives **(76)** via a three-component reaction

8.31 Rapid and Efficient Synthesis of Poly-Substituted Quinolines Assisted by p-toluene Sulphonic Acid Under Solvent-Free Conditions: Comparative Study of Microwave Irradiation Versus Conventional Heating

Wang et al. utilized *p*-TSA as the catalyst to demonstrate the synthesis of quinoline derivatives (**78**) under solvent-less condition. They carried out their reaction both under MW and conventional heating. Although yields of the products were excellent under both conditions, the reaction accomplished in the influence of MW was reported to be completed within a few seconds (Scheme 6.31) [70].



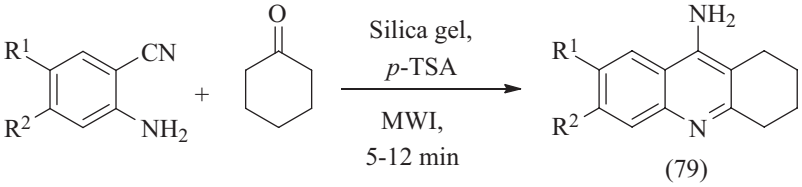
(78)

R = H, 2,4-$(Br)_2$; R^1 = H, Me, 4-F-C_6H_4;
R^2 = H, COOEt, CO_2Me; R^3 = Me, Cy-Pr

Scheme 6.31 *p*-TSA catalyzed synthesis of quinoline derivatives **(78)**

8.32 Synthesis of Tacrine Derivatives Under Solvent-Less Conditions

Recently Khalilzadeh et al. also utilized anthranilonitrile as a precursor for the synthesis of substituted tacrines (**79**). This was achieved by the condensation of substituted anthranilonitriles with cyclohexanone in the presence of silica gel / *p*-TSA as a catalyst under MWI (Scheme 6.32) [71].



(79)

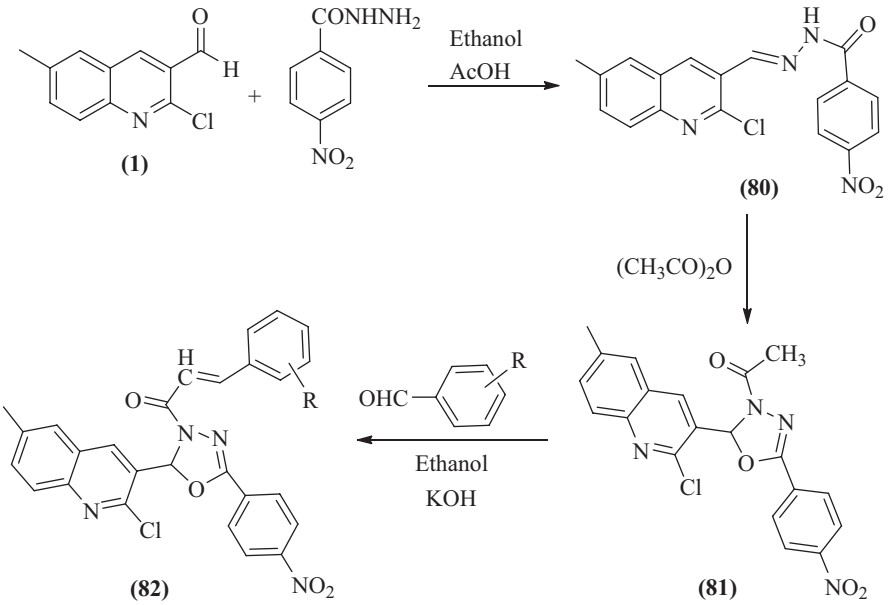
R^1 = H, Me, OMe, Cl, NO_2, NH_2;
R^2 = H, Me, OMe, Cl, NO_2, F

Scheme 6.32 Synthesis of substituted tacrines **(79)** using anthranilonitrile as a precursor

8.33 Conventional and Microwave Techniques for the Synthesis and Antimicrobial Studies of Novel 1-[2-(2-chloro-6-methyl(3-quinolyl))-5-(4-nitrophenyl)-(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones

Desai et al. have synthesized 1-[2-(2-chloro-6-methyl(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)-prop-2-en-1-ones (**82**) by using conventional and MW methods (Scheme 6.33) having better yield than the previously described

conventional method. These compounds were evaluated for their *in vitro* antimicrobial screening on different strains of bacteria and fungi [72].

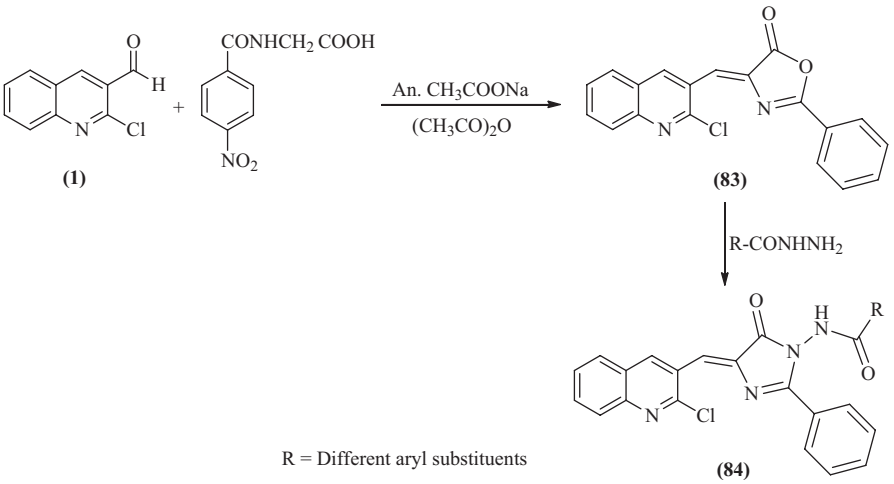


Scheme 6.33 Conventional and microwave methods for the synthesis of 1-[2-(2-chloro-6-methyl(3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)-prop-2-en-1-ones **(82)**

8.34 Green Synthesis of Novel Quinoline-Based Imidazole Derivatives and Evaluation of their Antimicrobial Activity

Desai et al. have synthesized *N*-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)(aryl)amides (**84**) by using conventional and MW methods (Scheme 6.34) and observed that the solvent-free MW thermolysis is a convenient, rapid, high-yielding and environmentally friendly protocol for the synthesis of quinoline-based imidazole derivatives when compared with conventional reaction in a solution phase. Antimicrobial activity of the newly synthesized compounds were screened in vitro on the following microbial cultures: *Escherichia coli* (MTCC443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323). All

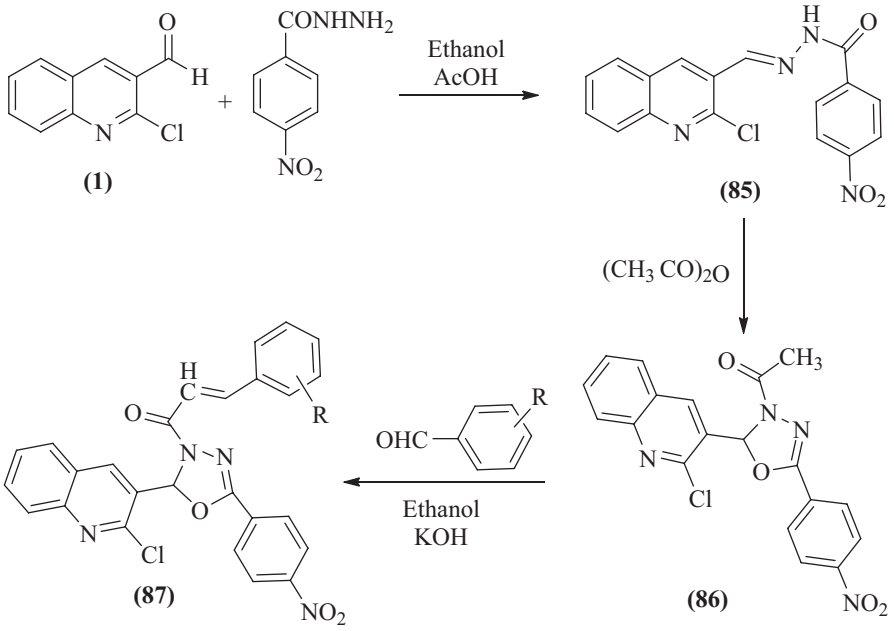
the synthesized bioactive molecules were tested for their in vitro antimicrobial activity by bioassay, namely serial broth dilution [73].



Scheme 6.34 Synthetic route for the preparation of *N*-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)(aryl)amides **(84)**

8.35 Conventional and Microwave Techniques for Synthesis and Antimicrobial Studies of Novel 1-[2-(2-chloro (3-quinolyl))-5-(4-nitrophenyl)-(1,3,4-oxadiazolin-3-yl)] -3-(aryl)prop-2-en-1-ones

Desai et al. have synthesized 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)-(1,3,4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones (**87**) by using conventional and MW techniques. These compounds were evaluated for their in vitro antimicrobial activities on different strains of bacteria and fungi (Scheme 6.35) [74].



Scheme 6.35 Synthesis of 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)-(1,3,4-oxadiazolin-3-yl)]-3-(aryl)-prop-2-en-1-ones **(87)** using conventional and microwave techniques

9 Conclusions

MW heating has achieved a wide-spread acceptance to academia and industry and has flourished into a useful technique for various applications in organic synthesis as well as in medicinal chemistry. In organic chemistry, MWIs provide rapid, reproducible and scalable processes to synthesize new bioactive molecules in excellent yields. In drug discovery and development, MW heating allows the medicinal chemists to furnish rapid synthesis for the development of large number of chemical libraries of bioactive molecules.

This eco-friendly solvent-free approach using MWI opens numerous possibilities for conducting rapid heterocyclic synthesis via cycloaddition and cyclocondensation reactions using a variety of supported reagents on mineral oxides and PTC conditions. The use of multimode oven, monomode reactor and conventional glass apparatus demonstrates the numerous practical applications in laboratory-scale experiments. Furthermore, there are different advantages of these solvent-free protocols as *Green Synthesis* since they provide absence of solvent thereby preventing

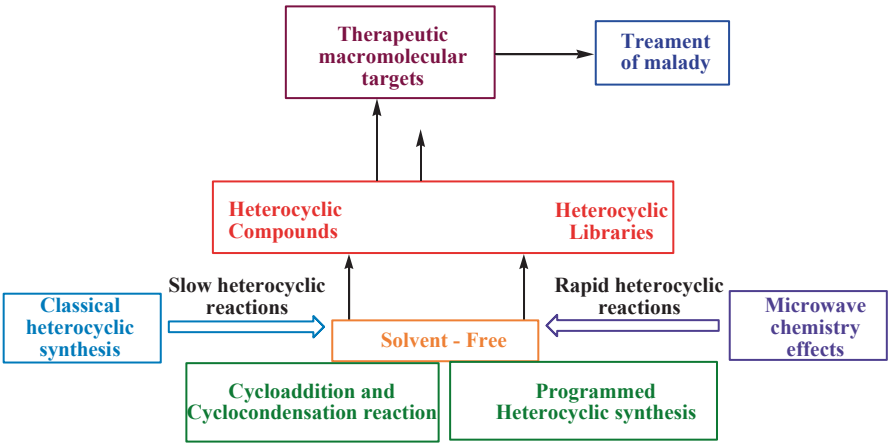


Fig. 6.3 Microwave-assisted solvent-free chemistry is a technique that has the power to accelerate the generation of organic molecules

pollution in organic synthesis. The absence of solvent clearly reduces the reaction time and generally improves the yields. In fact, it is noticeable that in several cases, thermal effects play a determinant part in the rates and in the chemioselective and regioselective or stereoselective heterocyclic synthesis. Additionally, there are many heterocyclic reactions with great potential for automated medicinal and combinatorial chemistry, which traditionally have been performed with long reaction times that might be dramatically accelerated by solvent-free MWI.

Today, new therapeutic hetero-macromolecular targets are increasingly being identified as drug targets. The lead generation and lead optimization processes must be accelerated. Traditional methods of organic heterocyclic synthesis are simply too slow to satisfy the future demands of compounds. MW-assisted solvent-free chemistry is a technique that has the power to accelerate the generation of organic molecules (Fig. 6.3).

10 Futuristic Road Map

In spite of the successful developments, there are still many challenges facing by this technique. The scalability, overall energy efficiency of MW-heating and instrument cost remain unresolved. Current MW reactors are able to synthesize small-scale MW chemistry from milligram or gram scale to multi-kilogram scale using batch or continuous-flow processing. All these challenges need more and dedicated input. The disadvantage associated with this technique is the equipment cost. Although the costs of MW reactors have dramatically reduced in the last decade or so, the current price range is still many times higher than that of conventional heating equipment. Continued efforts are devoted by several companies for the devel-

opment of newer and more readily available MW reactors as routine equipments of most laboratories. The multidisciplinary approaches of the scientists with MW heating encourage initiating new and unexplored areas of complex reactions in medicinal chemistry. Till today, MWI still requires to find promising and tempting combinations with more techniques to satisfy the increased synthetic demands in industry and academia. Looking at the several advantages associated with MW heating, it is undoubtedly a booming process for organic and medicinal chemists for the synthesis of newer compounds. Pharmaceutical industries are waiting for the successful production of compounds through this technique so that industries can reduce the time period and formation of hazardous by-products.

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Chapter 7
Imidazolium Ionic Liquids: An Environment-Friendly Medium for Various Applications

Satish A. Dake, Swapanil R. Sarda, Rajendra P. Marathe, Rajesh B. Nawale, Uday A. Deokate, Somshekhar S. Khadabadi and Rajendra P. Pawar

Contents

Abstract Imidazolium ionic liquid has been explored as a recyclable and reusable reaction medium. It not only acts as a reaction medium but also enhances the rate of reaction. The present chapter focuses on its use in different reactions for the synthesis of bioactive organic compounds.

Keywords Environmental-friendly medium · Green chemistry · Imidazolium · Ionic liquids

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1 Introduction

Recently, the world has been facing challenges of environmental safety; hence, wherever practicable, synthetic methodologies are designed to use and generate substances that possess little or no toxicity to human health and the environment. Synthetic methods are designed to maximize the incorporation of all materials used in the process into the final product. It is better to prevent waste than to treat or clean up waste after it is formed. Chemical products should end their function, do not persist in the environment, and break down into innocuous degradation products. For environmental and economic impacts, energy requirements should be minimized. Hence, synthetic methods should be conducted at an ambient temperature and pressure. Substances used in a chemical process should be chosen to minimize the chemical accidents, including releases, explosions, and fires.

All the desired chemical transformations with minimized by-products or waste and elimination of the use of conventional organic solvents, wherever possible, are the need of society. Nowadays, the scientific community is trying to develop new synthetic methods and uses of chemicals that reduce risk to humans and the environment. Organic solvents are high on the list of damaging chemicals because of their use in huge amounts and storage difficulty.

A reasonable working definition of green chemistry can be formulated as follows: Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste, and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.

The concept of "green chemistry" comprises the attempts to develop novel methodologies and technologies that are less harmful to the environment and human health on the planet. Environmental safety procedure to reduce waste and reuse of materials has driven studies into green chemistry hence covering the concept of green chemistry as:

- The designing of processes to maximize the amount of raw material that ends up in the product
- The use of safe, environment-benign substances, including solvents
- The designing of energy-efficient processes
- The best form of waste disposal: not to create it in the first place

Novel research in the field of organic chemistry has been one of the factors to lead the development of worldwide pharmaceutical fields. The demand for bioactive drugs has been growing, so the scale of manufacturing processes developed. Large-scale synthesis of potent drugs is now widespread. The concern for the welfare of our earth has never been so much to the forefront of everyone's minds. The overall ignorance towards issues such as pollutions (air, water, sound, soil, etc.) and global warming is diminishing. Green chemistry is defined as the design of chemical products and processes which reduce or eliminate the use and generation of hazardous substances [1]. Large-scale synthesis of drugs can lead to the production of mass amounts of harmful waste. The concept of "green chemistry" comprises the attempts to develop new cleaner technologies and methodologies that are less harm-

ful to the environment. In order to decrease or eliminate the use of harmful volatile organic compounds used in organic synthesis, chemists are trying to find out suitable alternatives, such as solvent-less conditions and use of ionic liquid (IL) in place of the use of these destructive solvents.

While working in the field of "green chemistry," 12 basic principles were derived by Clark and Macquarrie [2] in 2002. The work presented herein can be related to many of the principles.

2 The Principles of Green Chemistry

1. Waste of prevention materials
2. Atom economy
3. Less hazardous chemical process
4. Designing safer chemicals
5. Safer solvents and auxiliaries
6. Energy efficiency
7. Renewable feedstocks
8. Reduce derivatization
9. Catalysis
10. Design for degradation
11. Real-time analysis for pollution prevention
12. Safer chemistry for accident prevention

3 Ionic Liquids (ILs)

Recently, the use of Ionic Liquids (ILs) attracted an increasing interest in the field of organic synthesis because of its mild reaction condition, negligible vapor pressure, solvating ability, and easy recyclability. ILs are used as green reaction media due to their unique chemical and physical properties, such as nonvolatility, noninflammability, thermal stability, and controlled miscibility. They have a wider scope, playing significant role in reactions as a solvent/catalyst. Several reactions have been recently reported, using ILs as reaction media and rate enhancers.

In past few years, ILs have become alternative reaction media for organic transformations. The IL comprising ions differs from the classic definition of a molten salt [3]. More recently, melting point criterion has been proposed to distinguish between molten salts and ILs. Molten salts are usually defined as a highly-melting, viscous, and corrosive liquid medium. However, ILs are defined as compounds, consisting only of cations and anions (i.e., salts), which melt at or below 100 °C and have lower viscosity [4]. In some cases, ILs are free-flowing liquids at room temperature. Thus, they are referred as room temperature ionic liquids (RTILs). The great interest for such compounds relies on their several attractive properties,

such as chemical and thermal stability, negligible vapor pressure, nonflammability, high ionic conductivity, wide electrochemical potential window, and ability to act as catalysts. Further, many of their physicochemical properties are changed substantially by variation of the cation and anion. Eventually, they are applicable to the desired reaction; for this reason, ILs have been referred as designer solvents in many publications.

ILs have gained much attention as "designer solvents" for a diversity of chemical applications. The reason for this is the enormous selection of weakly bonding anion and cation combinations, which makes this special class of low-melting salts. It has been calculated that there are some 10^{18} possible single ILs, and the number of ILs increases still further when binary and tertiary ILs are included. In the last decade, ILs have been developed from curiosity to a new class of solvents with attractive properties. However, history of these salts goes back to the early twentieth century. In 1914, Paul Walden reported the synthesis of ethyl ammonium nitrate salt used as IL.

Diels–Alder reactions have been performed successfully in RTILs, such as [bmim][BF_4], [bmim][ClO_4], [emim][CF_3SO_3], [emim][NO_3], and [emim][PF_6] [5, 6] conventionally as well as under microwave (MW) conditions [7–9].

Literature survey reveals that the Michael addition reaction is highly accelerated in IL. Copper(II)triflate immobilized in [bmim]BF_4 IL is used as reaction medium for Michael addition of β-ketoesters to alkenes [10, 11]. [bmim]OH has been used in Michael addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles [12]. Michael addition of thiols and thiophosphate to conjugated alkenes in IL [pmim]Br [13] has been reported. Conjugate addition of azide ion to α,β-unsaturated carbonyl compounds and aza-Michael addition reactions are also reported [14–17]. Recently, Zare et al. [18] reported MW-assisted aza-Michael addition of aromatic sulfonamides to various α,β-unsaturated esters [19] in the presence of a catalytic amount of MgO or ZnO with [bmim]Br as the reaction solvent. Aryl nitriles can be synthesized via the Rosenmund von Braun reaction from the corresponding halides in IL under MW [20].

In the dehalogenation reactions, ILs used for debromination can be achieved by using a metal like Zn, Mg, or In, in an organic solvent, such as tetrahydrofuran (THF) or methyl alcohol (MeOH). Ranu et al. [21, 22] reported that IL [pmim][BF_4] can be used as a catalyst as well as a reaction medium for the stereoselective debromination of vicinal dibromides to the corresponding (*E*)-alkenes under MW irradiation.

In the protection of alcohol functionality in tetrahydropyranyl (THP) ether reactions, when ionic liquid (IL) was used, 2-(benzyloxy)-tetrahydro-2 H-pyran was obtained from alcohols using Lewis acid [bmim][$InCl_4$] IL as a catalyst in microwave (MW) promoted solvent-free synthesis [23, 24]. [bmim][$InCl_4$] maintained its catalytic activity well, even after five cycles.

Peng et al. [25] reported that IL [bmim]BF_4 catalyzed Biginelli reaction by the condensation reaction of benzaldehyde, ethyl acetoacetate in stoichiometric ratio, and urea.

Application of IL also used in the synthesis of α-amino phosphonates as a three-component reaction of aldehydes, amine, and diethyl phosphite-catalyzed

[bmim]PF_6 IL at temperature 26 °C was reported [26]. Peipei et al. [27] used chloroaluminate-based IL [bmim]Cl-$AlCl_3$ in one-pot coupling reaction of carbonyl compounds, amines, and diethyl phosphite to obtain α-amino phosphonates. α-hydroxyl aminophosphonates were used for three-component coupling reactions of aldehydes, hydroxylamines, and diethyl phosphite using 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ILs [28].

Formation of carbonyl compound derivatives: Hasan Mehdi et al. [29] reported the use of imidazolium ILs as solvents for organic transformations with tetravalent cerium salts. Urea-hydrogen peroxide in the presence of catalytic amount of magnesium bromide efficiently oxidizes primary and secondary benzylic alcohols into the corresponding aromatic aldehydes and ketones [30]. Margarida M. Antunes et al. [31] reported IL 1-butyl-3-methylimidazolium chloride ([bmim]Cl) as solvent, in the transformation of D-glucose into 5-(hydroxymethyl)-2-furaldehyde at 120 °C.

Use of IL in other reaction: 1-Alkyl-3-methylimidazolium cation-based ILs were used for *N-tert*-butyloxycarbonylation of amines with excellent chemoselectivity [32]. 1,3-dialkylimidazolium ILs such as [bmim][PF_6]. [bmTr][PF_6] and [bmTr][NTf_2] were reported for reaction media for the Baylis–Hillman reaction [33]. 1-butyl-3-methylimidazolium-based IL [bmim][NTf_2] is used as solvent for α-methylenations of carbonyl compounds [34]. M. L. Kantam et al. described copper-catalyzed cross-coupling reaction of arylboronic acids with sulfonic acid for alkylaryl and diaryl sulfones using IL [35].

4 History of Ionic Liquids (ILs)

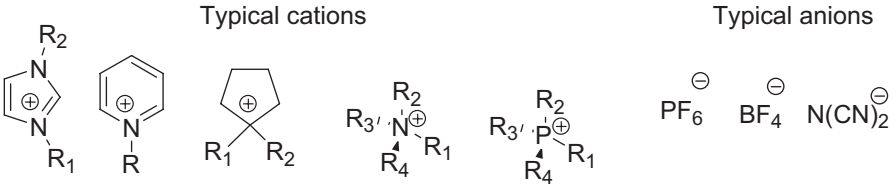
IL has been developed an interest to a new class of solvents with attractive properties. However, history of these salts goes back to the early twentieth century. In 1914, Paul Walden reported the synthesis of ethyl ammonium nitrate salt [36]. He reported the physical properties of ethyl ammonium nitrate [$EtNH_3$]NO_3 which has a melting point of 12 °C formed by the reaction of ethylamine and concentrated nitric acid. This interesting property could not attract lot of interest, until it was observed that the mixture of $AlCl_3$ and *N*-alkyl pyridium halide salt could be liquid at room temperature. The first research into chloroaluminate IL was oriented towards its use in electrochemistry. For example, the first IL with chloroaluminate ion such as ethyl pyridinium bromide/$AlCl_3$ was developed in 1948 by Hurley and Wier at the Rice Institute as bath solution for electroplating aluminum [37]. The real breakthrough occurred in 1992 when Wilkes and Zaworotko [38] reported the first air- and moisture-stable ILs based on 1-ethyl-3-methylimidazolium cation with either tetrafluoroborate or hexafluorophosphate as anions. Unlike the chloroaluminate these ILs could be prepared and safely stored outside of an inert atmosphere. Welton is one of the highly cited authors in the field of ILs [39]. Wasserscheid is an active member of the IL community and focuses on the preparation and characterization of ILs for use in the biphasic catalysis [40].

Use of chloroaluminate ILs was a blossoming field to attract both fundamental and applied research. However, these systems were not studied further until the late 1970s when the groups of Osteryoung and Wilkes rediscovered them. They synthesized and studied chloride system butyl pyridinium chloride/$AlCl_3$, which was not stable towards reduction, limiting its use as an electrolyte [41]. The discovery by Wilkes and Hussey in 1982 is that a mixture of dialkyl imidazolium chloride salts and $AlCl_3$ formed ILs [42]. Through the 1980s, chloroaluminate ILs were studied by the groups of Scheffler and Hussey et al. [43] and Seddon et al. [44] as solvents for transition metal complexes, mainly through electrochemical and spectroscopic investigations. The first report on the use of this type of low melting ILs as reaction media for organic synthesis was reported in 1986, as combined solvent and catalysts for Friedel–Crafts reactions [45]. Their first applications as solvents for biphasic catalysis came in 1990 by Chauvin et al., who reported the dimerisation of propene by nickel complexes dissolved in acidic chloroaluminate melts [46], and Osteryoung reported the polymerization of ethylene by Ziegler–Natta catalysts [47].

ILs based on $AlCl_3$ can be regarded as the first generation of ILs. The hygroscopic nature of $AlCl_3$-based ILs has delayed the progress in their use in many applications since they must be prepared and handled under inert gas atmosphere. Thus, the synthesis of air- and water-stable ILs, are considered as the second generation of ILs, attracted further interest in the use in various fields. Generally, these ILs are water insensitive; however, the exposure to moisture for a long time can cause some changes in their physical and chemical properties. This is due to the formation of HX as a result of decomposition of the IL in the presence of water. Therefore, ILs based on more hydrophobic anions such as trifluoromethanesulfonate ($CF_3SO_3^-$),bis-(trifluoromethanesulfonyl)imide[$(CF_3SO_2)_2\ N^-$] and tris-(trifluoromethanesulfonyl)methide [$(CF_3SO_2)_3C^-$] were developed [48–50]. In contrast to chloroaluminate ILs, these systems offer high tolerance versus functional groups which open a larger range of applications especially for transition metal catalysis. Besides Osteryoung, Wilkes, Hussey and Seddon who are pioneers in the field of ILs, there are several scientists, e.g., Wasserscheid, Rogers, MacFarlane, Ohno, Endres Jr, Abbott, Welton, Davis, and others, who entered this field having a strong impact in introducing the ILs in many applications. Davis introduced the concept of "task-specific ionic liquids" (TSILs) in the field of ILs. Abbott has recently developed a range of ionic compounds, which are fluid at room temperature. These ILs are based on simple precursors such as choline chloride (vitamin B_4) which is cheap and produced on a multi-tone scale hence, these ILs/deep eutectic solvents can be applied to large-scale processes for the first time. Using these liquids, a number of applications are now under development such as electrodeposition of metals, electropolishing, and ore processing. The physical properties through catalysis, synthesis and electrochemistry, and industrial applications of IL have been also explained [51–53].

RTILs and their polymeric derivatives are convenient green catalysts and recyclable for acetylation of various transformations of alcohols, phenols, amines, thiols to α,β-unsaturated esters and acrylonitrile and Michael additions of amines.

Heteroatomic cations such as imidazolium, pyridinium, ammonium, and phosphinium ions are the most widely used cations of the IL family, with applied synthetic strategy involving the cationization of the heteroatomic compound followed by anion metathesis.



Among them, imidazolium-based RTILs are widely used. In various fields. This review section describes the properties and applications of imidazolium-based RTILs in various organic transformations.

5 Properties of Imidazolium-Based Ionic Liquids

Imidazolium-based ILs have been increasingly used as green solvents to replace the volatile and relatively toxic organic solvents, in homogeneous and heterogeneous catalysis, material science, nanomaterials, lithium-ion batteries, and separation technology.

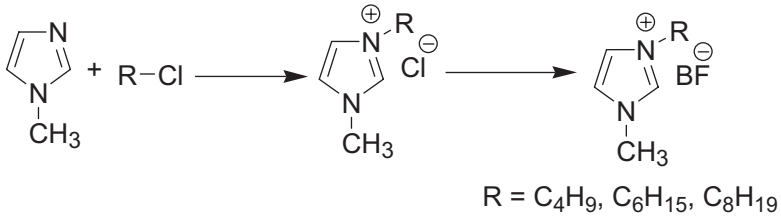
Many reviews had shown the importance of IL such as in supercritical fluid applications by Seda Keskin et al. [54]. Measurements of thermochemical properties of imidazolium-based ionic liquid (ILs) carried out has been reported [55]. Tamar L. Greaves et al. [56] explained the properties and applications of protic ILs. Revisiting characteristics of ILs are explained by Rusen Feng [57]. Recently, room-temperature ILs are being used as lubricants [58], i.e., tribology, because ILs possess excellent properties such as non-volatility, nonflammability, and thermo-oxidative stability.

ILs have been used in different areas of chromatography separations and in the extraction as IL-supported membranes, as mobile phase additives and surface-bonded stationary phases [59]. Mathieu Ratel et al. reported the imidazolium-based IL surfaces for biosensing [60]. Thermophysical properties of imidazolium-based lipidic ILs 1-oleyl-3-methylimidazolium bistriflimide, 1-ethy1-3-methylimidazolium bistriflimide, and 1-linoleyl-3-methyl-imidazolium bistriflimide were described by Samuel M. Murray et al. [61].

An important property of the imidazolium halogenoaluminate salts is their physical properties such as viscosity, melting point, and acidity could be adjusted by changing the alkyl substituents and the imidazolium and halide/halogenoaluminate ratios. The miscibility of ILs with water or organic solvents varies with side-chain lengths on the cation and with the choice of anion [62]. They can be functionalized to act as acids, bases, or ligands, and used as precursor salts in the preparation of stable carbenes. Imidazolium tetrafluoroborate ILs are stable up to 300 °C. Some imidazolium tetrafluoroborates with an allylic side chain showed wider voltage windows on the platinum electrode, better conductivities, and lower viscosities as compared to the corresponding ILs containing the saturated side chains [63].

6 Synthesis of Imidazolium-Based Ionic Liquids

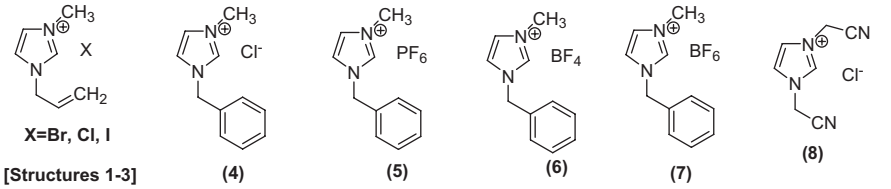
In general, 1-alkyl-3-methylimidazolium chlorides are synthesized by reacting 1-methylimidazole with 1-alky chloride. After exchanging anion by reacting sodium tetrafluoroborate, 1-alkyl-3-methylimidazolium tetrafluoroborate is synthesized. Similarly, different imidazolium-based IL has been also synthesized by exchanging anion [64].

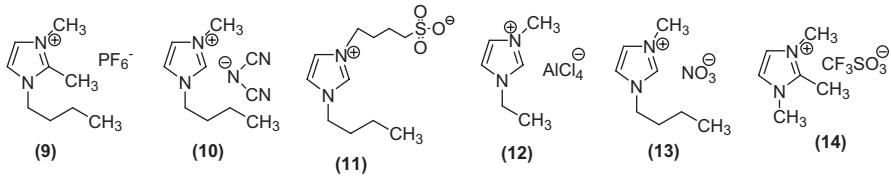


7 Structures of Some Common Imidazolium-Based Ionic Liquids

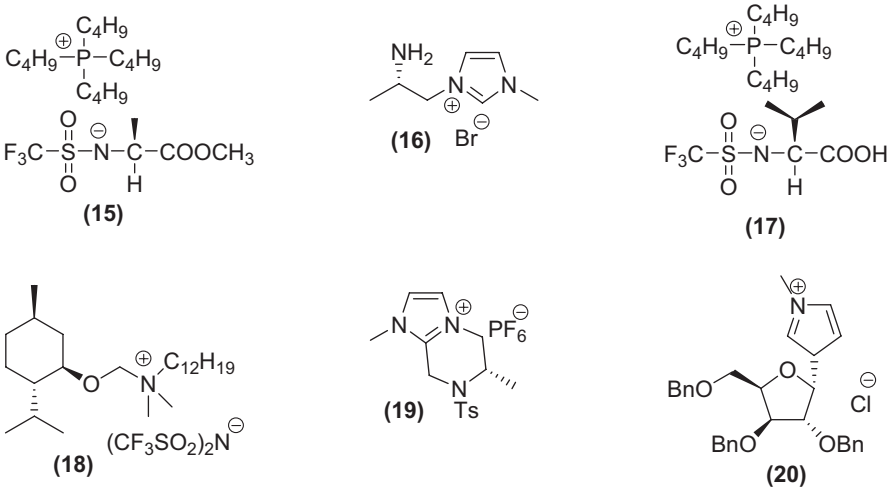
1-allyl-3-methylimidazoliumbromide($C_7H_{11}BrN_2$), 1-allyl-3-methylimidazolium chloride ($C_7H_{11}ClN_2$), 1-allyl-3-methylimidazolium iodide ($C_7H_{11}IN_2$) (**1–3)**, 1-benzyl-3-methylimidazolium chloride ($C_{11}H_{13}ClN_2$) (**4**), 1-benzyl-3-methylimidazolium hexafluorophosphate ($C_{11}H_{13}F_6N_2P$) (**5**), 1-benzyl-3-methylimidazolium tetrafluoroborate ($C_{11}H_{13}BF_4N_2$) (**6**), 1-benzyl-3-methylimidazolium hexafluoroborate ($C_{11}H_{13}BF_4N_2$) (**7**), 1,3-bis(cyanomethyl)imidazolium chloride ($C_7H_7ClN_4$) (**8**), 1-butyl-2,3-dimethylimidazolium hexafluorophosphate ($C_9H_{17}F_6N_2P$) (**9**), 1-butyl-3-methylimidazolium dicyanamide ($C_9H_{17}F_6N_2P$) (**10**), 4-(3-butyl-1-imidazolio)-1-butanesulfonate ($C_{11}H_{20}N_2O_3S$) (**11**), 1-ethyl-3-methylimidazolium-tetrachloro

aluminate ($C_6H_{11}AlCl_4N_2$) (**12**), 1-butyl-3-methylimidazolium nitrate ($C_8H_{15}N_3O_3$) (**13**), 1,2,3-trimethylimidazolium trifluoromethanesulfonate (**14**). Similarly, a number of ILs are available commercially [65].





Some typical examples of Chiral Ionic Liquids [66–70]



8 Antimicrobial Activities of Ionic Liquids

The toxicity studies highlighted previously raises issues over the validity of the classification of ILs as "green" compounds. However, the toxicity property may be utilized in number of other applications. For example, in the development of antiseptics, disinfectants and anti-fouling reagents [71]. Literature survey reveals that compounds with an alkyl chain substituent of 12 carbon atoms on the cation exhibited the highest antimicrobial activity across all groups of ILs tested, for a range of test microorganisms.

Pernak et al. [72] studied a series of 3-alkoxymethyl-1-methylimidazolium ILs bearing [Cl], [BF_4], and [PF_6] anions and tested against a range of bacterial species, as well as fungi. This study showed that a shorter cationic alkyl chain substituent resulted in reduced antimicrobial activity as compared to the imidazolium compounds containing 10, 11, 12, and 14 carbon atoms in their alkoxy group, confirming earlier findings. Another study showed that 1,3-(dialkloxymethyl)-substituted imidazolium ILs also exhibited a broad spectrum of antimicrobial activity against various bacterial rods, cocci, and fungi.

Pyrrolidinium ILs with varying alkyl chain substituents were possessed good antimicrobial activity against rods, cocci, and fungi. Compounds exhibiting the greatest antimicrobial activity were having 14 carbon atoms in the alkyl chain. In a recent study, Pernak and coworkers [73] tested a range of trigeminal tricationic ILs for antimicrobial activity. In addition to broad-spectrum antimicrobial activity, their potency was much better than the commercially available benzalkonium chloride. Further study on chiral ammonium-based ILs [74] revealed that compounds with 11 carbons in alkyl substituent showed the most activity against a range of bacteria and fungi. Docherty and Kulpa studied number of ILs with varying anions [75]. It was found that improved antimicrobial activity resulted from increasing alkyl group chain length as well as increasing the number of alkyl groups substituted on the cation ring. Varying the anion present in the compound did not significantly alter the toxicity. Recently, the antimicrobial activity of multifunctional long-alkyl-chain quaternary ammonium azolate-based ILs has been described.

These ILs, based on didecylmethylammonium, benzalkonium, domiphen, and hexadecyltrimethlammonium cations combined with benzotriazole, 1,2,4-triazolate, 4-nitroimidzolate, or 2-methyl-4-nitroimidazolate anions, exhibited a broad spectrum of antibacterial and antifungal activity, which was comparable or superior to that of the original benzalkonium chloride. Antimicrobial potency of IL depends on the substituent alkyl chain length, indicating a general mechanism for antimicrobial activity. Several ionic liquid (ILs) have similar structure to cationic surfactants whose primary mode of action is membrane-bound protein disruption. Another suggested mechanism of toxicity and antimicrobial activity is the inhibition of the

enzyme acetylcholinesterase, as illustrated in studies of the inhibitory effects of imidazolium and pyridinium ILs.

Pernak and Chwala [76] reported an antimicrobial activities of five new groups of choline-like quaternary ammonium chloride ILs and an evaluated against a range of Gram-positive and Gram-negative bacteria, which showed good antimicrobial activity and confirmed that lipophlicity was the main factor in determining antimicrobial activity. Recently, ILs 1-alkyl-3-methylimidazolium chloride and 1-alkylquinolinium bromide had shown antibiofilm activities [77, 78].

9 Application of Ionic Liquid in Various Fields

9.1 Applications of Ionic Liquid in Biotechnology

The use of RTILs is promising in the area of biotechnology, particularly in chemistry involving biocatalytic processes. A variety of examples have shown the application of RTILs in biocatalytic processes in recent reviews [79, 80]. In the reaction converting 1,3-dicyanobenzene to 3-cyanobenzamide and 3-cyanobenzoic acid catalyzed by whole cells of *Rhodococcus* R312, the biphasic 1-butyl, 3-methyl imidazolium hexafluorophosphate/water medium decreases the substrate and the product inhibition observed in water by acting as a reservoir for the substrate and product [81]. In another example, an isolated enzyme has been used to catalyze reactions in IL medium [82].

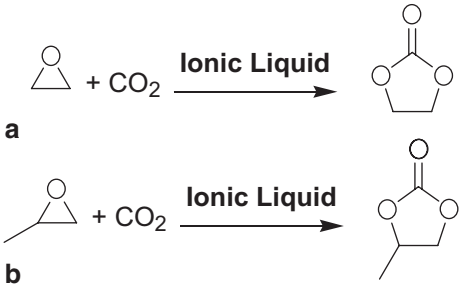
9.2 Applications of Ionic Liquid in Silver Nanowires

The demand for a transparent electrode in such fields as flat panel displays, touch panels, solar cells, etc. has been increasing. The imidazolium ILs associated with specific anions adaptable to the fabrication of metal nanostructures [83–89]. Recently, the material for the transparent electrode used includes a metal oxide such as indium tin oxide (ITO) for vacuum deposition. However, ITO has a number of drawbacks, such as rising cost of indium, the brittleness of ITO, toxicity, carcinogenicity [90], and the high temperature processing in its production. Deposition of nanostructured thin films from the liquid phase for the flexibility and low-temperature processing polymer [91] and graphene [92] films has been studied. The most common material used to date has been metal nanowire and carbon nanotuebes. Transparent conductive film is manufactured by nanostructure silver on a plastic film.

9.3 *Applications of Ionic Liquids in Organic Transformations*

9.3.1 Cycloaddition Reactions

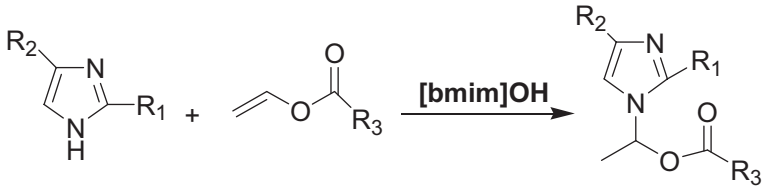
Recently, 1-n-butyl-3-methylimidazolium and n-butylpyridinium salts [bmim]BF_4 IL were used for catalytic media for the cycloaddition of carbon dioxide to propylene oxide reported by Blanchard L. A. et al. and Sergei V. D. et al. [93, 94] (Scheme 7.1a and b).



Scheme 7.1

9.3.2 Addition Reaction

Xu J. M. et al. [95] in 2006 described the Markovnikov addition of *N*-heterocycles to vinyl esters using IL, i.e., 1-methyl-3-butylimidazolium hydroxide ([bmim]OH) catalyst (Scheme 7.2).

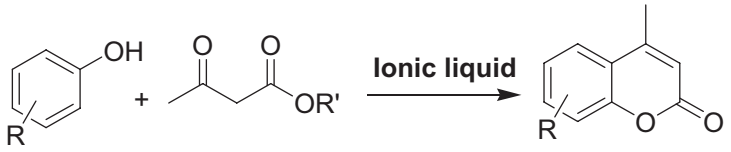


Scheme 7.2

9.3.3 Pechmann Reaction

The Pechmann reaction [96] normally refers to an acid-catalyzed condensation of phenols with β-ketoesters. It is widely applied for the synthesis of coumarins. A large number of reagents were used for this reaction, including sulfuric acid, phosphorus pentoxide, aluminum chloride, trifluoroacetic acid, $SnCl_2$ [97], oxalic acid

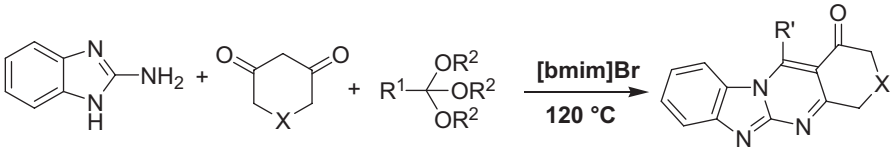
[98], alum ($KAl(SO_4)_2 \cdot H_2O$, silica triflate, iodine, [99] etc., which are preferred for the reaction. Recently, a number of studies have also shown that ILs, either neutral [100] or acidic [101–103], promoted coumarin synthesis via the Pechmann condensation. Sing et al. [104] studied the combination of an IL and MW irradiation using Brønsted acidic [bmim][HSO_4] IL (Scheme 7.3).



Scheme 7.3

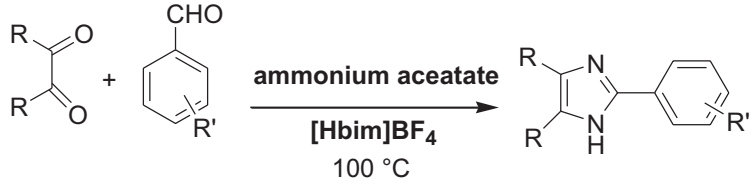
9.3.4 Synthesis of Imidazole Derivatives

3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2 H)-ones in the presence of 3-butyl-1-methyl imidazolium bromide IL at 120 °C were reported by Shaabani et al. [105] (Scheme 7.4).



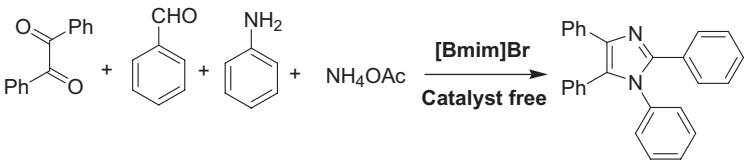
Scheme 7.4

Khan M. S. et al. [106] synthesized 2,4,5-trisubstituted imidazoles from aryl aldehydes and 1,2-diketones or α-hydroxyketone using [Hbim]BF_4 IL (Scheme 7.5).



Scheme 7.5

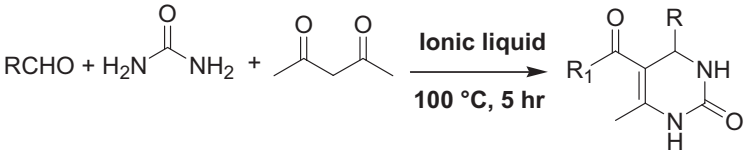
[bmim]Br IL was used in the one-pot four-component methodology for the synthesis of 1,2,4,5-substituted imidazoles from benzil, aldehydes, amines, and ammonium acetate under conventional heating and MW irradiation by Hasaninejad et al. [107] (Scheme 7.6).



Scheme 7.6

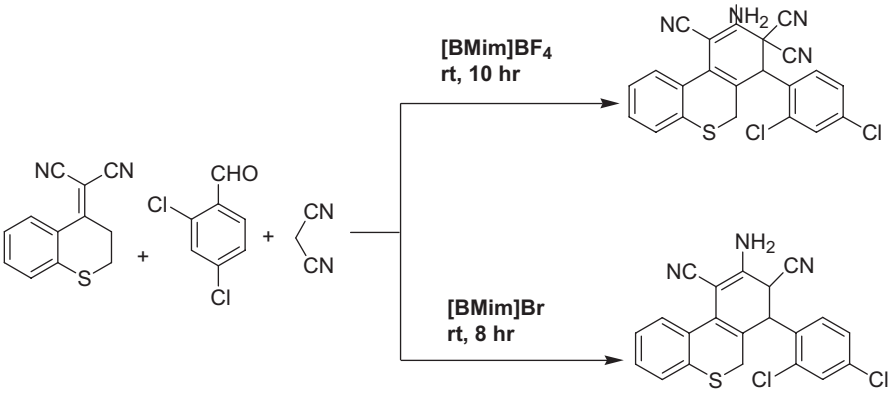
9.3.5 Multicomponent Reaction

Peng et al. [108] reported ILs $BMImBF_4$-catalyzed Biginelli reaction by the condensation reaction of benzaldehyde and ethyl acetoacetate in stoichiometric ratio and urea (Scheme 7.7).



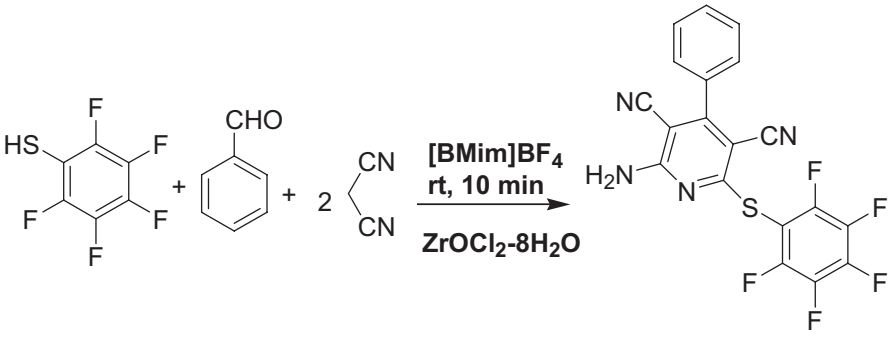
Scheme 7.7

Yanlong Gu et al. [109] summarized recent results of a multicomponent reaction obtained in nonconventional media including water, ILs, polyethylene glycol, and bio-based solvents. Wang et al. [110] have recently reported a three-component reaction in IL (Scheme 7.8).



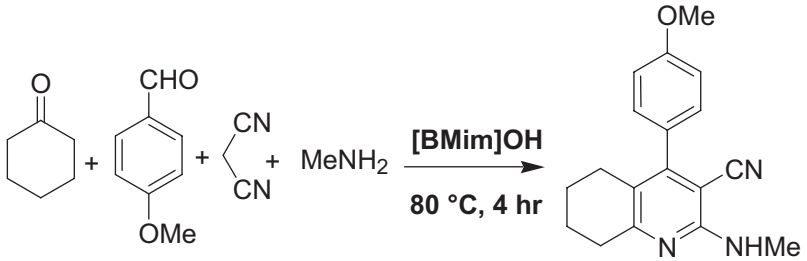
Scheme 7.8

Heravi et al. [111] described synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives using the pseudo-four-component condensation of aldehydes, thiophenols, and malononitrile in [BMIm]BF_4 catalyzed by $ZrOCl_2 \cdot 8H_2O$/$NaNH_2$ under ultrasound irradiation at room temperature (Scheme 7.9).



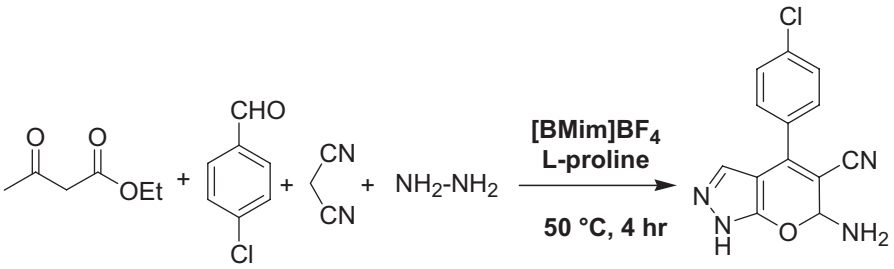
Scheme 7.9

A four-component, one-pot reaction of aromatic aldehyde, cyclohexanone, malononitrile, and amines was reported in basic IL [BMIm]OH, providing *N*-methyl or *N*-aryl-substituted 2-amino-4-aryl-5,6,7,8-tetrahydroquinoline-3-carbonitriles in excellent yields [112] (Scheme 7.10).



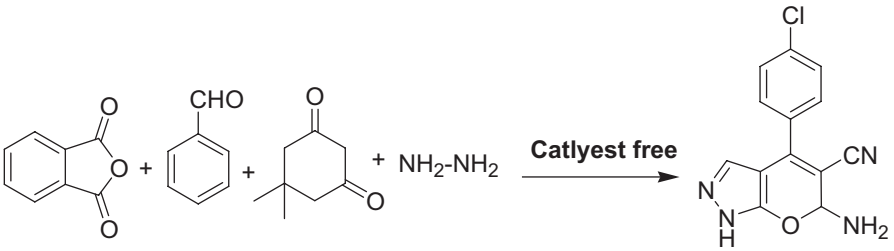
Scheme 7.10

Synthesis of 4 H-pyrano[2,3-c]pyrazoles has been reported [113] via a four-component cyclocondensation of hydrazine monohydrate/phenyl hydrazine, ethyl acetoacetate, aldehydes, and malononitrile by using L-proline as catalyst in IL [BMIm]BF_4 (Scheme 7.11).



Scheme 7.11

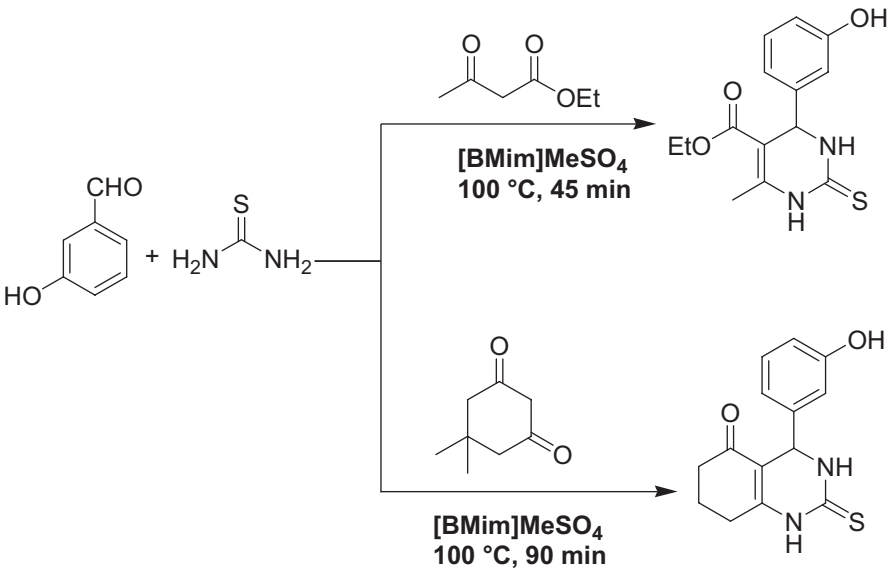
A one-pot four-component reaction of aldehyde, phthalic anhydride, hydrazinium hydroxide, and dimedone under ultrasonic irradiation in IL [BMIm]Br has been described, which generated various 2 H-indazolo[2,1-b]phthalazinetriones in good yields under neutral and catalyst-free conditions [114] (Scheme 7.12).



Scheme 7.12

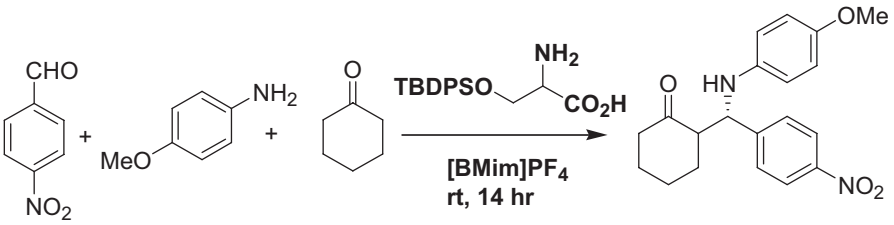
4-Substituted-spiro-1,2-dihydroquinazolines were synthesized by direct reaction of 2-aminobenzophenones, isatin, or 1,2-diketone derivatives and ammonium acetate in the presence of dual role catalyst/solvent IL, 1-methylimidazolium trifluoroacetate [HMIm]TFA.231. In the presence of the same IL, [HMIm]TFA, a three-component condensation reaction between 2-aminobenzophenone derivatives, aromatic aldehydes, and ammonium acetate efficiently provides substituted quinazoline. The IL was separated from the reaction mixture by simple extraction and was recycled three times without considerable loss in activity [115].

Recently, Roy S R et al. [116] reported [BMIm]-based ILs in the Biginelli reaction of aldehydes, β-keto ester or β-diketone, and urea or thiourea (Scheme 7.13). It was found that both counter anion and 1,3-disubstituted imidazolium moiety played a key role in determining the catalytic activity of the IL. The best IL was proved to be [BMIm]$MeSO_4$, and a very small amount of the IL (1 mol%) was sufficient enough to finish the Biginelli reaction at 100 °C for 30 min, affording dihydropyrimidinones in good yields.



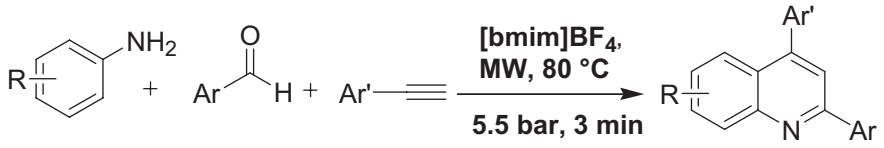
Scheme 7.13

3-(*N*, *N*-dimethyldodecylammonium)propanesulfonic acid hydrogen sulfate ([DDPA]HSO_4) IL used in a three-component Mannich-type reaction of aromatic aldehydes, amines, and ketones at room temperature to give various β-amino carbonyl compounds in good yields [117] (Scheme 7.14). In [BMIm]PF_6, an asymmetric direct three-component Mannich reaction of aromatic aldehyde, aniline, and ketone proceeded well in the presence of a siloxy-L-serine organocatalyst, (2S)-2-benzyloxycarbonylamino-3-(*tert*-butyldiphenyl-silanyloxy)-propionic acid, furnishing the β-amino carbonyl scaffold in high enantioselectivities and diastereoselectivities. The siloxy serine organocatalyst in [BMIm]PF_6 can be recycled up to three times with comparable enantioselectivities [118].



Scheme 7.14

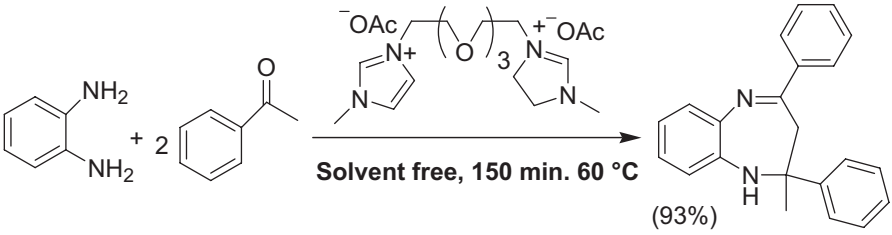
Synthesis of 2,4-disubstituted quinolines-catalyzed $Yb(OTf)_3$ in a three-component reaction of aldehydes, alkynes, and amines under MW irradiation in an IL has been reported (Scheme 7.15) [119].



Scheme 7.15

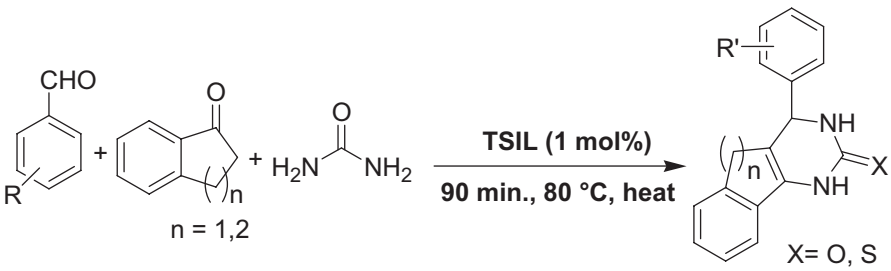
9.3.6 Other Applications of Imidazolium Ionic Liquids

The Jadhav A H et al. approach (2014): Dicationic RTILs based on 1-methylimidazolium salts were used for the synthesis of 1,5-benzodiazepine derivatives under a solvent-free reaction condition (Scheme 7.16). All novel synthesized imidazolium-based dicationic RTILs showed efficient yields and selectivity of benzodiazepine derivatives [120].



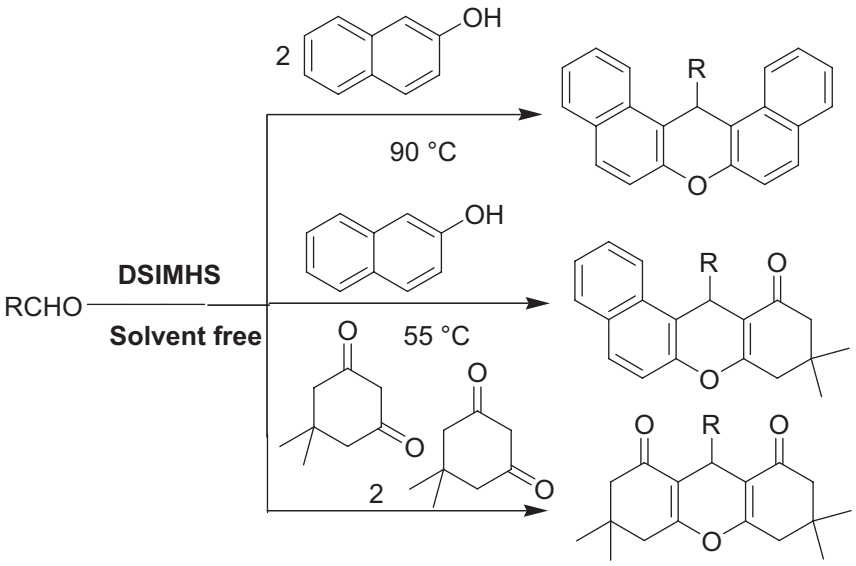
Scheme 7.16

The Rahman M et al. approach (2014): In the Biginelli reaction, IL [1-methyl-3-(4-sulfobutyl)imidazolium-4-methylbenzenesulfonate] was used in catalytic amount for the synthesis of benzoquinazolin-2-one derivatives using α-tetralone, aldehyde, and urea/thiourea (Scheme 7.17) in excellent yields within a short reaction time [121].



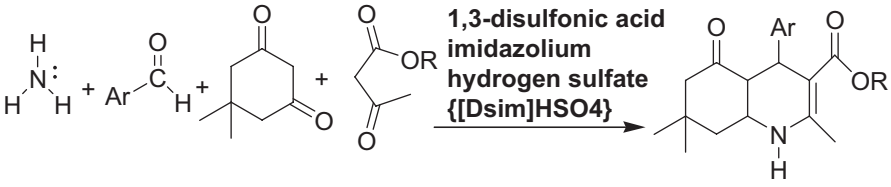
Scheme 7.17

The Shirini F et al. approach (2013): I**L** 1,3-disulfonic acid imidazolium hydrogen sulfate (DSIMHS) is used for the synthesis of xanthenes under solvent-free conditions (Scheme 7.18) [122].



Scheme 7.18

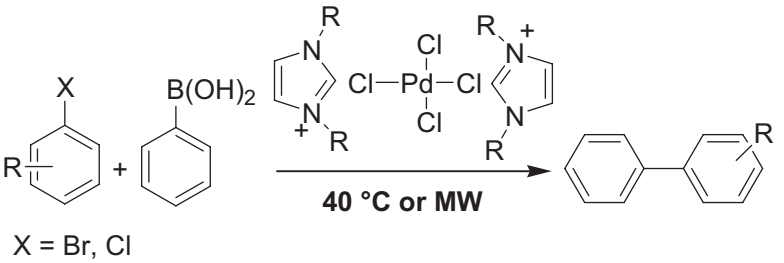
The Zare A et al. approach (2013): Brønsted acidic IL 1,3-disulfonic acid imidazolium hydrogen sulfate {[Dsim]HSO_4} is utilized for the preparation of hexahydroquinolines via the one-pot multicomponent condensation of arylaldehydes, dimedone (5,5-dimethylcyclohexane-1,3-dione), β-ketoesters, and ammonium acetate under solvent-free conditions (Scheme 7.19) [123].



Scheme 7.19

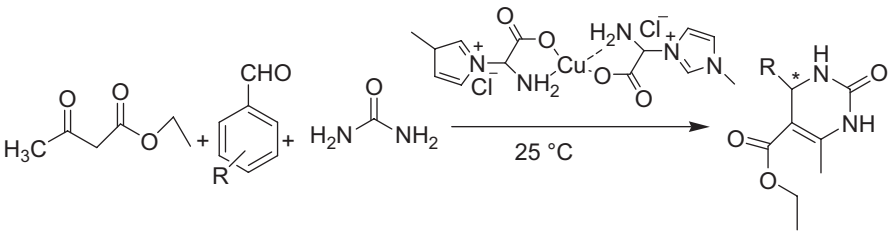
The Silarska et al. approach (2013): Palladium complexes of the type $[IL]_2[PdCl_4]$ (IL = imidazolium cation) were found to be active catalysts for the Suzuki–Miyaura reaction of 2-bromotoluene with phenylboronic acid carried out in 2-propanol or 2-propanol/water at 40 °C using normal heating or MW (Scheme 7.20). In

the presence of 2-propanol, the highest yields (89 and 85%) were obtained for $[dmiop]_2[PdCl_4]$ and $[dmdim][PdCl_4]$ (dmiop = 1,2-dimethyl-3-propoxymethyl imidazolium cation, dmdim = 3,3′-[1,7-(2,6-dioxaheptane)]bis(1,2-dimethyl-imidazolium)cation) containing cations substituted at the C2 carbon with a methyl group. In the presence of water, all $[IL]_2[PdCl_4]$ complexes produced ca. 90% of 2-methylbiphenyl [124].



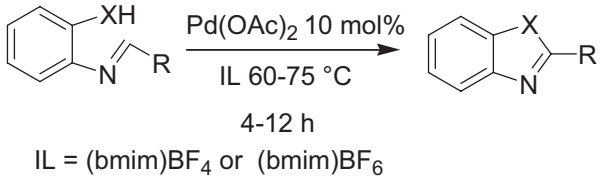
Scheme 7.20

The Karthikeyan P et al. approach (2013): In the Biginelli reaction, a novel 1-glycyl-3-methyl imidazolium chloride-copper(II) complex [[Gmim]Cl–Cu(II)] was synthesized (Scheme 7.21). This was also further studied as organocatalyst for enantioselective-substituted 4,6-dimethyl-2-oxopyrimidine-5-carboxylate derivatives under solvent-free condition at 25 °C [125].



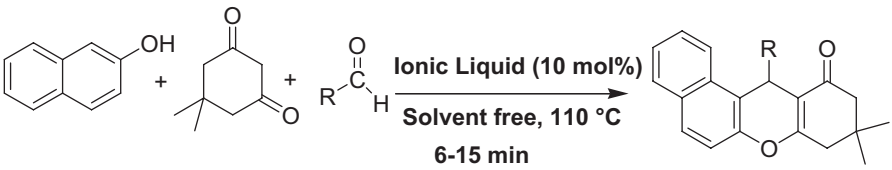
Scheme 7.21

The Kalkhambkar R G et al. approach (2012): The synthesis of 2-aryl- and 2-heteroaryl-benzoxazoles and benzothiazoles from Schiff bases by using catalytic amounts of $Pd(OAc)_2$ in imidazolium ILs $(bmim)BF_4$ and $(bmim)PF_6$ without ligands and/or additives has been reported (Scheme 7.22) [126].



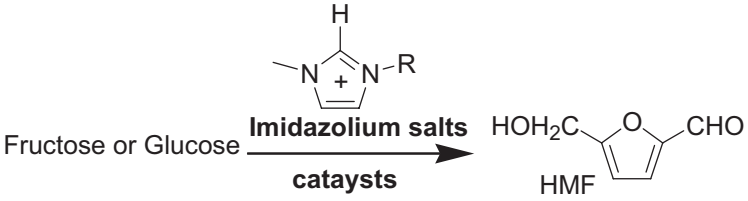
Scheme 7.22

The Zolfigol M A et al. approach (2012): A novel sulfonic acid-functionalized imidazolium salts (SAFIS) were used as new ILs for synthesis of tetrahydro-benzo[*a*] xanthene-11-ones from β-naphthol, arylaldehydes, and dimedone (Scheme 7.23) [127].



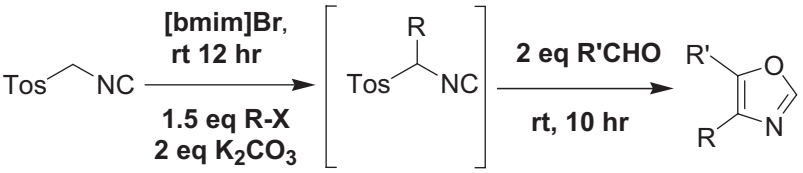
Scheme 7.23

The Cao Q et al. approach (2011): 5-hydroxymethylfurfural (HMF) has been synthesized from fructose and glucose in the presence of various imidazolium ILS, including 1-butyl-3-methylimidazolium chloride (BmimCl), 1-hexyl-3-methyl-imidazolium chloride (HmimCl), 1-octyl-3-methylimidazolium chloride (OmimCl), 1-benzyl-3-methylimidazolium chloride (BemimCl), 1-butyl-2,3-dimethylimidazo-lium chloride (BdmimCl), and 1-butyl-3-methylimidazolium *p*-toluenesulfonate (BmimPS) (Scheme 7.24) [128].



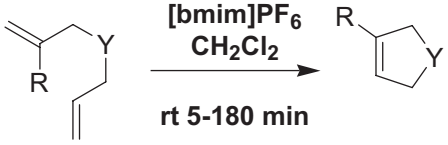
Scheme 7.24

Synthesis of 4,5- disubstituted oxazoles using ILs (Scheme 7.25) has been re-ported by Wu B et al. [129].



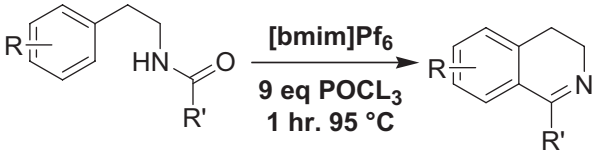
Scheme 7.25

The Wakamatsu et al. approach (2008): An IL-supported ruthenium carbene complex can be used for ring-closing metathesis in the construction of five- to eight-membered rings [130] (Scheme 7.26).



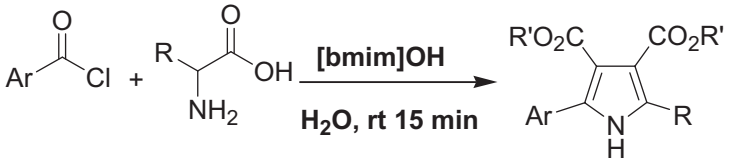
Scheme 7.26

3,4-dihydroisoquinolines derivatives through the Bischler–Napieralski cyclization using 1-butyl-3-methylimidazoliumhexafluorophosphate IL ([bmim]PF_6) (Scheme 7.27) were reported by Judeh et al. [131].



Scheme 7.27

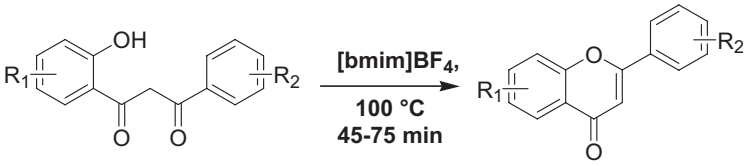
Yavari et al. approach (2008): The use of 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) [132] has been reported for the synthesis of pyrroles via condensation reaction of acid chlorides, amino acids, and dialkyl-acetylenedicarboxylates in water (Scheme 7.28).



Scheme 7.28

F. Shi et al. [133] reported carbonylation of aniline by using palladium and IL catalyst. The Beckmann rearrangement of cyclo-hexanone oxime in IL [Bmim]BF_4 has been described [134–136]. K. Qiao et al. [137] described the synthesis of ethyl iso-valerate and ethyl tertvalerate $Pd(PPh_3)_2Cl_2$ catalyst for hydroesterification of *tert*-butyl alcohol using IL. A new, base-stable, imidazolium IL has been used for the addition of Grignard reagents [138] to carbonyl compounds. These reactions occur readily at ambient temperature to afford the alcohol products in good to excellent yield. S. Morrissey et al. [139] described selective hydrogenation of *trans*-cinnamaldehyde in imidazolium ILs.

R. S. Bhosale et al. [140] synthesized flavones using imidazolium-based ILs [bmim]BF_4 at 100 °C temperature (Scheme 7.29).



Scheme 7.29

10. Conclusion

Imidazolium ILs can serve an alternative for organic solvent as a green medium in several organic transformations. Still, there is a need to continue the research work on it and to find out their environmentally friendly approaches in various fields.

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Chapter 8
Water: A Benign Solvent for the Synthesis of Various Organic Moieties

Chetna Ameta and K. L. Ameta

Contents

Abstract Water is the nature's solvent and all biological syntheses are being carried in aqueous medium. It is an essential element of life on our planet. Water possesses unique structural form, which bestows distinguished physical and chemical properties. It exhibits powerful hydrogen bonding, large dielectric constant, high heat capacity, as well as a broad temperature range to remain in liquid state. In view of the advantages derived by the utilization of water as a solvent medium, there is an increasing trend in performing organic synthesis in water. Apart from being eco-friendly, water also has the potentiality to become a universally acceptable solvent

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due to its abundance and low cost. However, several reactions are employing organic cosolvents to increase the solubility of organic compounds in water. Introduction of polar functional groups on reactant molecules to enhance water solubility is another manipulation. Moreover, organic reactions in aqueous medium can also be conducted in either heterogeneous or homogeneous phase in which volume of water may differ from moderate to large quantity.

Keywords Water · Eco-friendly · Heterocycles

1 Introduction

Approximately 70% of the earth's surface is comprised of water, making it the most abundantly existing liquid solvent. In fact, for many hundreds of years, water was the only solvent available to chemists to carry out their reactions. It was not until organic solvents came into use that a whole new area of chemistry was born and many types of reactions were conducted and compounds made that previously had not been thought possible. Nevertheless, in the most recent decades, chemists have begun to reinvestigate the possibility of using water as a solvent for organic reactions.

The concept of efficient and selective synthesis in water has been confirmed as the rates, yields, and selectivity were observed for many reactions. Some of the reactions that were only considered possible in organic solvents are now being conducted using water as solvent, and this is very much at the forefront of solvent-replacement research following green chemistry principles. The low solubility of substrates in pure water at room temperature can often be overcome by use of organic cosolvents, ionic derivatization, surfactants, or hydrophilic auxiliaries.

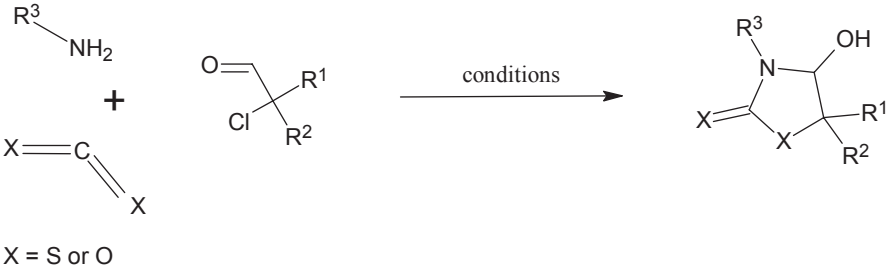
Why use water as solvent? Not only is water nontoxic and readily available at a low cost, it is also nonflammable and environmentally benign, providing opportunities for clean processing and pollution prevention. Therefore, synthetic organic reactions in aqueous media at ambient or slightly elevated temperatures have become of great interest as water as a solvent for organic reactions often displays unique reactivity, selectivity, and exploitation of so-called hydrophobic effects. Significant advances have been made in this area, directing the selectivity of synthetic organic reactions in water through the interaction of nonpolar or hydrophobic regions of the reactants. These forces are normally too weak to compete with any steric and electronic effects in organic solvents. In water, on the other hand, hydrophobic surfaces associate strongly to nonpolar species and thus minimize the Gibbs energy of solvation, a phenomenon known as the hydrophobic effect.

2 Water-Mediated Synthesis

2.1 Five-Membered Heterocycles

Starting with the development of new multicomponent reactions (MCRs) in water, hydroxy thiazolidinethiones and oxazolidinones were prepared efficiently in a one-pot procedure [1] (Scheme 8.1). The reaction was carried out under mild conditions, consistent with the principles of "green chemistry." These precursors were converted into different dienes containing terminal C–C double bonds by modifying the hydroxy group in one- or two-step sequences. A final ring- closing metathesis (RCM) reaction led to various classes of unsaturated bicycles.

The new one-pot procedure using $KHCO_3$ as a source of CO_2 is a very mild and inexpensive method. Therefore, this technique may find enormous use in heterocyclic chemistry.



Scheme 8.1

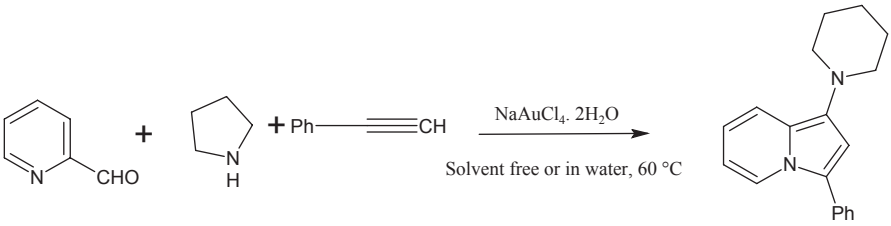
Initial experiments suggested that the addition of a base would lead to a more successful reaction (Table 8.1, entries 1–3). Of the two bases tested (K_2CO_3 and Et_3N), Stalling et al. [1] found that K_2CO_3 gave the best yield of thiazolidinethione. In terms of reaction time, the best result was achieved after 2 h (Table 8.1, entry 7). Longer or shorter times led to lower yields (Table 8.1, entries 5 and 8). Heating has a significant negative influence on the yield (Table 8.1, entries 13 and 14). Furthermore, long reaction times and heating promote the formation of two by-products. To summarize, the best yield (60 %) was obtained after stirring for 2 h at room temperature by using K_2CO_3 as base (Table 8.1, entry 7) and water as solvent.

A gold(III)-catalyzed multicomponent coupling/cycloisomerization reaction of heteroaryl aldehydes, amines, and alkynes under solvent-free conditions or in water has been developed as shown in Scheme 8.2 [2]. This methodology provides rapid access to substituted aminoindolizines with high atom economy and high catalytic efficiency. Especially, the coupling of enantiomerically enriched amino acid derivatives produces the corresponding *N*-indolizine-incorporated amino acid derivatives without loss of enantiomeric purity.

Table 8.1 Synthesis of thiazolidinethione ($R^1 = R^2 = H$; R^3 = allyl) under different conditions

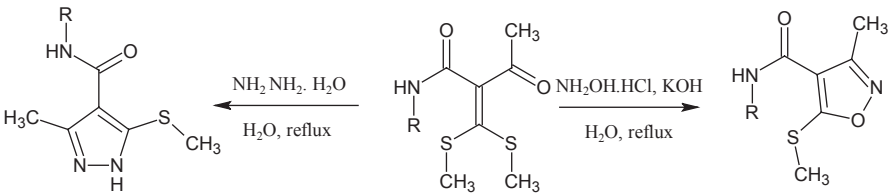
Entry	Molar ratio [mmol][a]	Base[b]	Conditions	Solvent	Yield [%]
1	1.5:3.0:1.0	–	Room temp., 2 h	THF	14
2	1.5:3.0:1.0	–	Room temp., 2 h	H_2O	35
3	1.5:3.0:1.0	–	Room temp., 1 h	H_2O	27
4	1.5:3.0:1.0	Et_3N	Room temp., 1 h	H_2O	30
5	1.5:3.0:1.0	K_2CO_3	Room temp., 1 h	H_2O	34
6	1.5:3.0:1.0	Et_3N	Room temp., 2 h	H_2O	46
7	1.5:3.0:1.0	K_2CO_3	Room temp., 2 h	H_2O	60
8	1.5:3.0:1.0	K_2CO_3	Room temp., 3 h	H_2O	50
9	30:60:20	K_2CO_3	Room temp., 2 h	H_2O	42
10	30:60:20	K_2CO_3	Room temp., 2 h	H_2O	34
11	1.5:3.0:1.0	K_2CO_3	Room temp., 2 h	H_2O	33
12	3.0:6.0:2.0	K_2CO_3	Room temp., 2 h	H_2O	41
13	3.0:6.0:2.0	K_2CO_3	35–41°C, 2 h	H_2O	44
14	3.0:6.0:2.0	K_2CO_3	Room temp., 2 h; 80°C, 15 min	H_2O	31

[a] Amine/CS_2/aldehyde
[b] 0.5 equiv



Scheme 8.2

A small library of alkyl, sulfone, and carboxamide-functionalized pyrazoles and isoxazoles has been developed via a rapid sequential condensation of various R-acylketene dithioacetals with hydrazine hydrate or hydroxylamine hydrochloride, followed by oxidation of sulfide to sulfone using water as the reaction medium [3] (Scheme 8.3). An efficient and safe oxidation of sulfides to the corresponding sulfones using sodium per borate system in aqueous medium has also been reported. The concise and two-step synthesis of trisubstituted pyrazoles and isoxazoles was investigated under a variety of reaction conditions. The newly developed methodology has the advantage of excellent yield and chemical purity with short reaction time using water as a solvent.



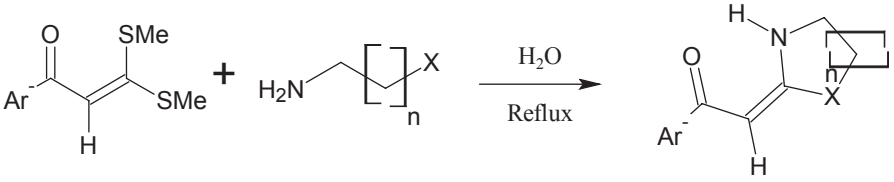
Scheme 8.3

Table 8.2 Synthesis of 3-methyl-5-(methylthio)-*N*-phenyl-1*H* pyrazole-4-carboxamide using variety of solvents

Entry	Solvent	Time (h)	Yield (%)
1	Isopropyl alcohol	2.8	85
2	Methanol	4.0	81
3	Ethanol	3.5	83
4	Tetrahydrofuran	4.5	79
5	Acetonitrile	4.0	75
6	Dioxane	3.5	80
7	Water	3.0	97

The condensation reaction in water requires 3.0 h with 97% yield of desired product (entry 7, Table 8.2). On the other hand, the reaction was relatively fast when *i*PrOH was used as a solvent with 12% lower yield (entry 1, Table 8.2). The yield of the desired product was reasonable when methanol (MeOH), ethanol (EtOH), and dioxane were used as solvents (entries 2, 3, and 6, Table 8.2). The other solvents, tetrahydrofuran (THF) and acetonitrile, gave lower yield with higher reaction time (entries 4, and 5, Table 8.2). Thus, it was clear from the aforementioned experiments that the best yield of pyrazoles could be obtained by employing water as a solvent without using any phase-transfer catalyst.

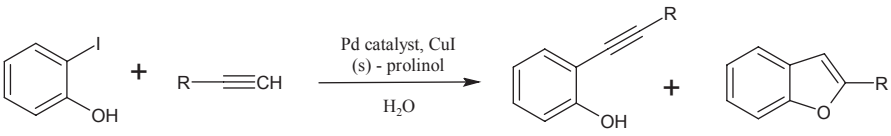
An easy and efficient green methodology for "water"-mediated highly regioselective synthesis of heterocyclic *N, N-, N, O-,* and *N, S*-acetals have been described as shown in Scheme 8.4 [4]. The general methods described here were very convenient for the synthesis of dihydroimidazoles, hexahydropyrimidines, 1,3-oxazolidines, 1,3-oxazines, and 1,3-thiazolidines with readily available starting materials, mild conditions, easy operation, and a broad range of substrates.



Scheme 8.4

An efficient synthesis of 2-alkyl/aryl-substituted benzo[*b*]furans/nitrobenzo[*b*]furans in water has been accomplished via Pd/C-catalyzed reaction of *o*-iodophenols with terminal alkynes in the presence of PPh_3, CuI, and prolinol [5] (Scheme 8.5). This method is used for a variety of functional groups present in the alkynes as well as base labile nitro group in the *o*-iodophenols. The protocol does not require the use of a phase-transfer catalyst or water-soluble phosphine ligands and is free from the use of any organic cosolvent. Palladium-catalyzed reactions in aqueous media have attracted much attention because water-based synthetic processes are naturally safer as well as inexpensive. Therefore, the use of water-soluble catalysts and water-soluble phosphine ligands, e.g., sulfonated phosphines, has been explored successfully. The use of Pd/C-CuI-PPh3 as a catalyst system for efficient Sonogashira coupling of aryl halides with terminal alkynes has also been reported [5]. When compared to the most frequently used expensive palladium catalysts (e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$

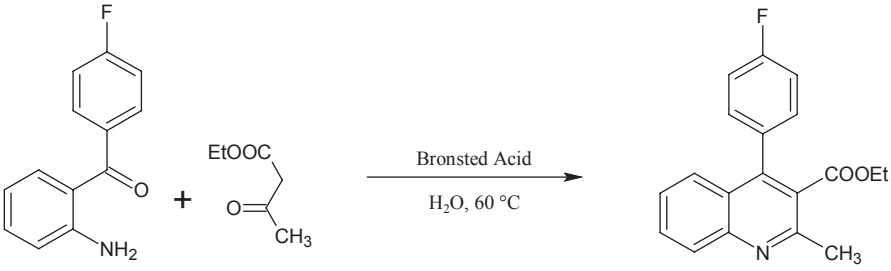
etc.), Pd/C-based methods have an economic advantage and hence remain attractive in large or industrial-scale preparations. Nevertheless, all these Pd-catalyzed reactions are usually carried out in an aqueous–organic media and a cosolvent such as acetonitrile or dimethyl ether (DME) is often required for these coupling reactions.



Scheme 8.5

2.2 Six-Membered Heterocycles

An environmentally friendly and highly efficient procedure for the preparation of substituted quinoline derivatives was developed by a simple Friedlander reaction of 2-aminoarylketone or 2-aminoarylaldehyde with carbonyl compounds in the presence of hydrochloric acid utilizing water as the solvent [6] (Scheme 8.6).



Scheme 8.6

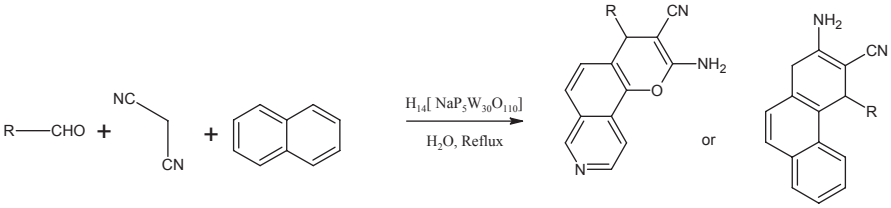
That is, a straightforward, highly efficient, and cost-effective synthesis of biologically active quinolines can be achieved by HCl-catalyzed Friedlander reaction in water. The current method presents a very appealing synthetic process for quinolines because of the following advantages: (1) use of water as environmentally benign reaction media, (2) use of very cheap and readily available hydrochloric acid, (3) high yield and shorter reaction time, (4) straightforward and easy workup procedure, and (5) no use of any metal catalyst or phase-transfer catalyst or surfactant.

A simple, clean, and environmentally benign route to the synthesis of 2-amino-4H-chromenes has been described using Preyssler-type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, as a green and reusable catalyst in water [7]. $H_{14}[NaP_5W_{30}O_{110}]$ serves as an efficient catalyst for the synthesis of 2-amino-4H-chromenes as biologically and pharmacologically active compounds as shown in Scheme 8.7. This procedure offers several advantages, including mild reaction conditions, cleaner reaction, high yields of products, as well as a simple experimental and workup procedure

Table 8.3 Synthesis of 3-amino-2-cyano-1-(phenyl)-1H-benzo[f]chromene in different solvents in the presence of $H_{14}[NaP_5W_{30}O_{110}]$

Entry	Solvent	Time (h)	Yield (%)
1	HOAc	8	50
2	CH_3CN	6	80
3	H_2O	5	91

which makes it a useful and attractive process for the synthesis of these compounds. Most importantly, water has been chosen as a green solvent for these reactions.

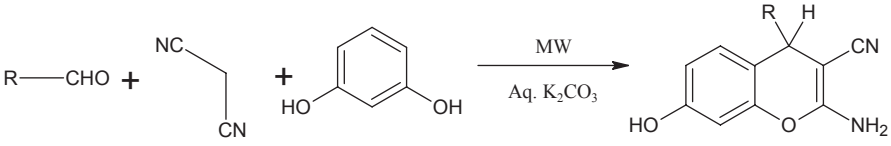


Scheme 8.7

A screening of three different solvents was performed in order to define the best solvent as a solvent of choice. As reported in Table 8.3, water was found to be the superior one affording the desired product in 91 % yield.

An easier, practically convenient, and eco-friendly green synthesis of substituted 2-amino-4H-chromene and benzo[e]chromene derivatives has been developed that avoids the use of harsh and highly environment-contaminating conditions, viz., classical heating, use of expensive and toxic reagents, solvents, and catalyst [8] (Scheme 8.8).

Moreover, it offers benefits like elimination of solvent, simplification of the workup procedures, and savings in energy consumption, and in addition giving higher yields of products and enhancement in reaction rate. Further, the use of water as a green solvent combined with the exploitation of the multicomponent strategy open to this process suggests good prospects for its industrial applicability.

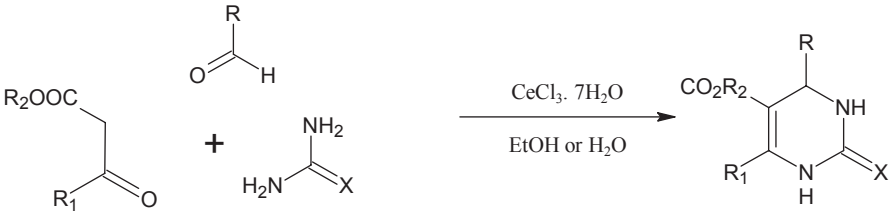


Scheme 8.8

A general and practical green chemical route to the Biginelli cyclocondensation reaction using cerium(III) chloride as the catalyst (25 %mol) has been described under three different sets of reaction conditions [9]. Three different sets of reaction conditions were examined: (1) traditional ethanol reflux, (2) water reflux, and (3) solvent-free conditions. The second and third set of conditions provides an efficient and much improved modification of the original Biginelli reaction reported in 1893, in terms of high yields, short reaction times, and simple workup procedure, and it

has the ability to tolerate a wide variety of substitutions in all three components, which is lacking in existing procedures.

This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the dihydropyrimidine-2(1*H*)-ones (Scheme 8.9).



Scheme 8.9

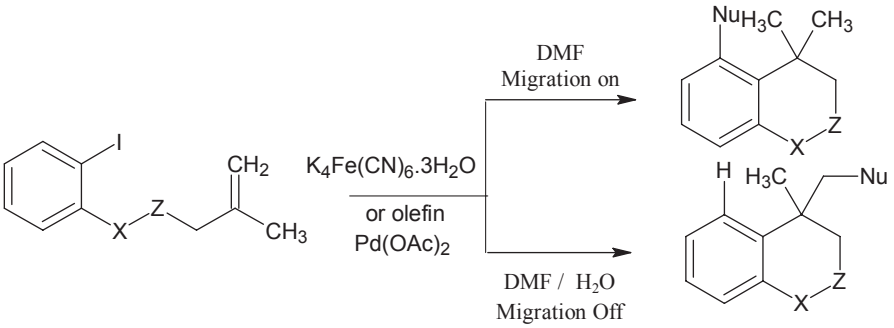
In a typical general experimental procedure by using traditional conditions, a solution of α-dicarbonyl compound, an aldehyde, and urea in ethanol was heated under reflux in the presence of a catalytic amount of $CeCl_3.7H_2O$ (25 mol%) for a certain period of time required to complete the reaction (TLC), resulting in the formation of dihydropyrimidinone derivatives. The reaction mixture was then poured into crushed ice and the solid product separated was filtered and recrystallized.

To reduce the employment of ecologically suspected solvents, Bose and coworkers [9] have chosen to carry out the reactions in water. Indeed, water is recognized as an attractive medium for many organic reactions. The Biginelli reaction using water as a solvent showed a significant improvement upon the isolated product yields ranging from 73 to 90% in the presence of $CeCl_3.7H_2O$ (1 mmol). Additionally, difficulties were still encountered in the use of -NO_2-substituted benzaldehydes. However, these reactions were confounded from the green perspectives by the requirements for extractive isolation followed by recrystallization to afford material of a suitable quality.

In the final series of experiments, they set out to examine the solvent-free reaction. α-ketoester, aldehyde, urea, and $CeCl_3.7H_2O$ (30 mol%) were mixed together and the heterogeneous mixture was stirred rapidly and refluxed for 10 h. The corresponding dihydropyrimidinones were afforded in a typically good yield (65–80%) with the notable exception of the reaction with 2-nitrobenzaldehyde. The solvent-free approach afforded good yields of most of the other nitrobenzaldehydes examined during the course of this study. This method offers several advantages including high yields, short reaction times, and a simple workup procedure, and it also has the ability to tolerate a wide variety of substitutions in all three components, which is lacking in existing procedures. Further, the present procedure is readily agreeable to parallel synthesis and the generation of combinatorial dihydropyrimidinone libraries.

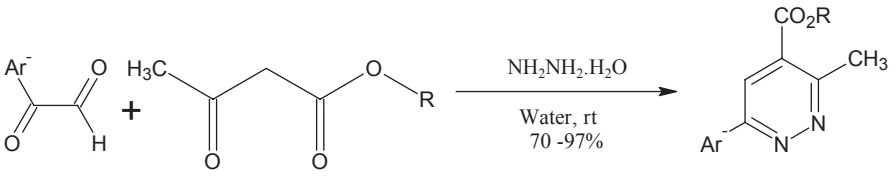
A palladium-catalyzed domino reaction involving a C–H activation process to synthesize diverse carbo and heterocyclic skeletons was developed [10] (Scheme 8.10). H_2O was used to control the regioselectivity as the cosolvent. The palladacycle intermediate was successfully trapped by cyanation, Heck reaction, secondary C–H activation, and Suzuki coupling. The regioselectivity was controlled by manipulating the reac-

tion conditions to give either an arylfunctionalized product with yields in the 47–95% range or an alkyl-functionalized product with yields in the 60–95% range. Moreover, these conditions avoided using expensive bases, which are usually employed in C–H activation, and phosphorus ligands, which are usually not friendly to the environment. Diverse products can be prepared starting from the same substrate using this method.



Scheme 8.10

Rimaz and Khalafy [11] reported a novel and efficient arylglyoxal-mediated synthesis of new alkyl 6-aryl-3-methylpyridazine-4-carboxylates from *β*-ketoesters and hydrazine in water (Scheme 8.11). Considering the availability of the starting materials, the simple procedure at room temperature, and the robust nature of this chemical process provided a very straightforward route to construct various trisubstituted pyridazines without using an acidic condition or metal catalysts.



Scheme 8.11

The Knoevenagel condensation is one of the most important, useful, and widely employed methods for carbon–carbon bond formation in organic reactions. Treating carbonyl compounds with active methylene compounds in the presence of acids or bases in organic solvents effects Knoevenagel condensation. These condensation reactions in organic solvents require an acid or base catalyst and prolonged heating. With the present growing concern about controlling important, and protecting future resources, design of routes having environmentally benign characteristics has attracted considerable interest in organic synthesis.

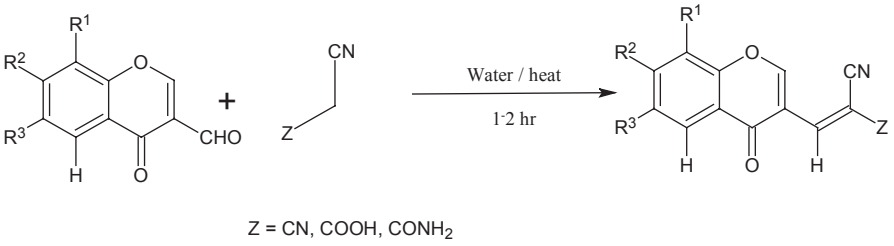
Scheme 8.12 shows a simple, efficient, and environmentlly eco-friendly route for the synthesis of ylidenenitriles of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde by the condensation of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde with active methylene compounds viz. malononitrile, cyanoacetic acid, and cyanoacetamide in distilled

Table 8.4 Yield range of ylidenenitriles of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde in different solvents

Solvent	Yield (%)
Water	90–94
DMF	86–91
DMSO	87–91
MeOH	86–89
EtOH	86–89
Toluene	8–13

water without a catalyst at 90°C for 1–2 h with quantitative yields and higher selectivity [12].

The substrate 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde has three active sites: an α, β-unsaturated carbonyl group i.e., the pyrone ring, a carbon–carbon double bond, and CHO group; the formyl (CHO) group has the highest reactivity towards active methylene compounds in a completely aqueous medium under catalyst-free conditions. In this methodology, the ylidenenitriles were isolated by simple filtration, as a result of which yield losses were avoided. The literature reveals that acids or bases facilitate the Knoevenagel condensation but prolonged heating is required for completion. In the present methodology, the reactions were completed in a shorter time and under milder reaction conditions. By considering these aspects, our method shows the following advantages: (i) cleaner synthesis, (ii) shorter time, (iii) higher selectivity, (iv) catalyst free, (v) high yields, (vi) eco-friendly, and (vii) economical. Thus, this is an excellent method for the preparation of ylidenenitriles (Table 8.4).



Scheme 8.12

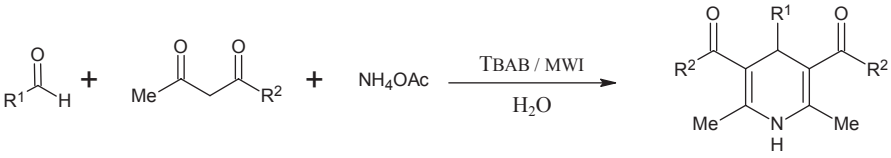
The synthesis of various substituted 1,4-dihydropyridines has been achieved by the reaction of aldehydes, ethyl/methyl acetoacetates, and ammonium acetate in water using a phase-transfer catalyst (tetrabutyl ammonium bromide) under microwave irradiation (Scheme 8.13) [13]. Compared to the classical Hantzsch reaction conditions, this new method consistently has the advantage of good yields and short reaction times.

The use of microwave ovens in organic synthesis has been the selection of solvent for the reaction, due to the possible loss of the solvent and volatile reactants, apart from fire hazards. Hence, water could be a safe alternative to organic solvents in such reactions. Water is a cheap, readily available nontoxic solvent for use in chemistry. There are, however, problems with the use of water, such as solubil-

Table 8.5 Comparative study for synthesis of 2-(2-oxoindolin-3-ylidene)hydrazinecarbothioamide under different reaction conditions

Entry	Reaction conditions	Method	Time (min/h)	Yield (%)
1	Ethanol/methanol	Conventional	5 h	54
2	Montmorillonite K10	MW	5 min	80
3	Water containing acetic acid	MW	4 min	82
4	Water containing montmorillonite K10 clay	MW	3 min	84

ity of substrates in water, but these problems have been overcome by the use of phase-transfer catalysts (tetrabutyl ammonium bromide) and the design of novel heterogeneous catalysts.



Scheme 8.13

In conclusion, the present procedure of the synthesis of 1,4-dihydropyridines in water using phase-transfer catalyst under microwave irradiation provides an efficient and improved modification of the Hantzsch reaction with high yields and short reaction times. In addition, it is possible to apply the belief of green chemistry to the generation of biologically interesting Hantzsch products using aqueous-medium approaches that is less expensive and less toxic than those with organic solvents.

A multicomponent condensation of substituted phenylthiourea/urea, aqueous formaldehyde, and substituted aromatic/heterocyclic amines lead to 2-thioxohexahydro-1,3,5-triazines in aqueous medium under microwave irradiation in 30–60 s in a quantitative yield with reasonable purity [14]. Further, triazolo[4,3-a]triazines were also prepared by a one-pot reaction of "in situ" synthesized triazinyl hydrazine with CS_2.

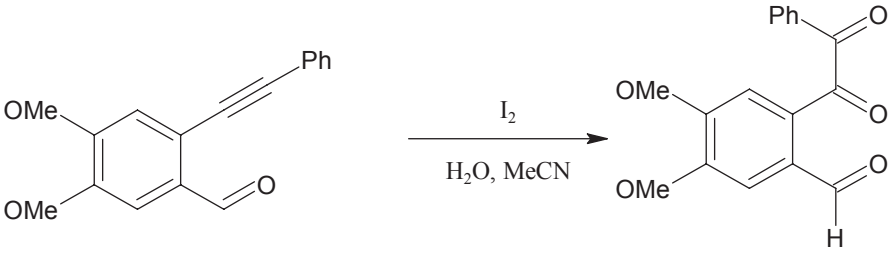
Rapid and highly efficient one-pot green chemical synthesis of substituted 6-(2-aminophenyl)-4-(4-substitutedphenyl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(*2H*)-one and 8-substituted-3,5-dihydro-2*H*-[1,2,4]triazino[5,6-*b*]indole has been carried out in the aqueous medium under microwave irradiation [15]. Improved synthesis of potent bioactive Schiff and N-Mannich bases of hexahydro-1H-indole-2,3-dione has also been reported. The operational simplicity, environmentally benign conditions, and high yield achieved in a very short reaction time are major benefits that meet the requirements of green production, including saving energy and high efficiency.

Table 8.5 shows that as conditions change from ethanol to water, time reduces and yield increases. The use of water gives environmental benefits, i.e., no atmospheric pollution by escaping solvents and easy waste treatment. For this reason, this methodology represents an important improvement for the production of this kind of fine chemicals following environmentally benign procedures.

2.3 Oxidation Reactions

A facile iodine / water-mediated oxidation of the triple bond of *o*-alkynylaroyl compounds to furnish tricarbonyl compounds has been reported by Sakthivel and Srinivasan (Scheme 8.14) [16]. The reaction proceeds through the formation of isochromenol intermediates by the assistance of the neighboring aroyl group. The product tricarbonyl compounds were versatile synthetic precursors that, upon treatment with mono and diamines, hydrazines, and aminoalcohols, afford various heterocyclic scaffolds such as isoindolinones, phthalazines, benzimidazoisoquinolinones, quinoxalines, and benzimidazole–quinoxaline hybrid compounds.

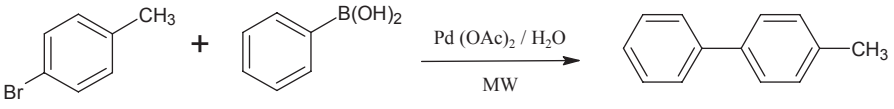
They developed a simple, environmentally benign procedure for the oxidation of a variety of *o*-alkynylarene aldehydes and ketones into the corresponding tricarbonyl compounds using an iodine/water system. The facile nature of the reaction is attributed to the involvement of isochromenol intermediates formed through intramolecular nucleophilic attack of the neighboring carbonyl oxygen on the triple bond. The tricarbonyl compounds resulting from the present oxidation methodology are potential precursors of various nitrogen heterocycles, including isoindolinones and a natural product, aristolactam BII.



Scheme 8.14

2.4 Suzuki Reactions

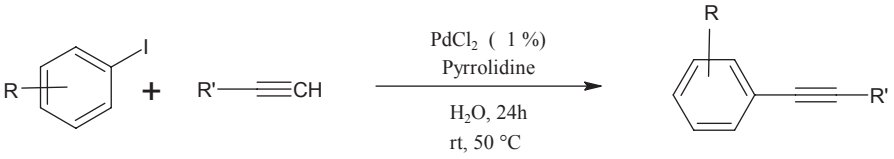
Leadbeater and Marco [17] developed a methodology for the ligand-free microwave-mediated Suzuki coupling of boronic acids and aryl halides in water and have shown the application of this for the synthesis of a number of biaryls starting from a range of aryl halides (Scheme 8.15). The methodology has the advantage of low catalyst loadings, rapid reaction times, ease of reaction (no need for anaerobic conditions), and use of a nontoxic, nonflammable solvent (H_2O). The methodology is currently being used in other C–C coupling reactions and further enhancements in reactivity will be possible.



Scheme 8.15

2.5 Sonogashira Coupling

A mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal acetylenes in water under aerobic conditions has been developed as shown in Scheme 8.16 [18]. The use of 1 mol% $PdCl_2$ in the presence of pyrrolidine allows the coupling reaction to proceed at room temperature or 50°C with good to excellent yields. One of the complications with the Sonogashira couplings was that the reaction needed degassed solvents, and had to be carried out under an inert atmosphere. This was particularly inconvenient when the reactions were carried out in multiple vessels for library generation. Therefore, the development of a convenient method was an important objective in this effort.

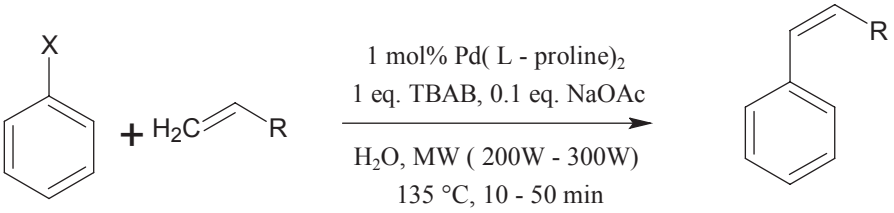


Scheme 8.16

The reaction of 2-amino-3-(2-propynyl)thiazolium bromide with various iodobenzenes, catalyzed by Pd/Cu, in the presence of sodium lauryl sulfate as surfactant and cesium carbonate as base, in water, leads to the formation of 6-substituted imidazo[2,1-b]thiazoles [19].

2.6 Heck Reaction

The Heck reaction (also called the Mizoroki–Heck reaction) is the chemical reaction of an unsaturated halide with an alkene in the presence of a base and a palladium catalyst (or palladium nanomaterial-based catalyst) to form a substituted alkene. An efficient and simple protocol for phosphine-free Heck reactions in water in the presence of a Pd(L-proline)$_2$ complex as the catalyst under controlled microwave irradiation conditions is versatile and provides excellent yields of products in short reaction times (Scheme 8.17) [20]. The reaction system minimizes costs, operational hazards, and environmental pollution.

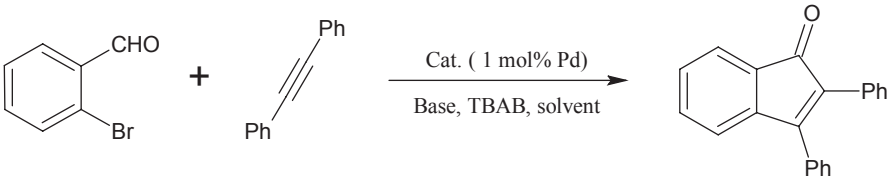


Scheme 8.17

A facile surfactant-mediated Heck and Suzuki coupling procedure in water has been developed using ligand-free Pd catalysts. The procedure which involves nanometric palladium colloids is operationally simple, environmentally benign, and synthetically as efficient as conventional procedures using organic solvents [21].

Imidazolium–styrene copolymers were prepared by copolymerization of 1-vinyl-3-butylimidazolium-based ionic liquids ([VBIm]X, X=Cl^-, BF_4^-, and PF_6^-) with styrene, which were used as polymeric supports to immobilize $Pd(OAc)_2$ using a method of alcohol reduction [22]. It was demonstrated that Pd existed in the form of Pd nanoparticles (NPs) on these imidazolium–styrene copolymers. Using the [VBIm]Cl–styrene copolymer as a support, Pd NPs of less than 6 nm were formed, which was particularly interesting, as usually only a Pd carbene complex was formed when $Pd(OAc)_2$ was treated with 1,3-dialkyimidazolium ionic liquids containing a halide anion. The copolymer-supported Pd catalysts were found to be efficient and reusable catalysts for the Heck reaction in water in the absence of a phosphine ligand and phase-transfer catalyst.

Alacid and Najera [23] demonstrated the Mizoroki–Heck reaction in organic and aqueous solvents promoted by a polymer-supported Kaiser oxime-derived palladacycle as shown in Scheme 8.18.



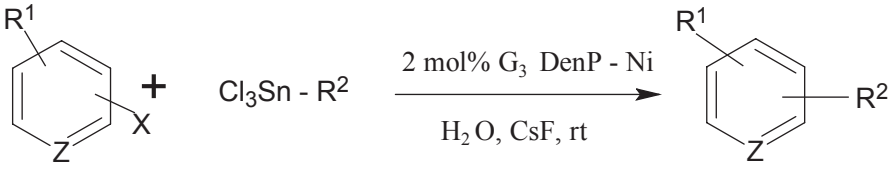
Scheme 8.18

As conclusion, the high catalytic efficiency of the polymeric palladacycle derived from Kaiser oxime resin similar to that of related unsupported dimeric palladacycles was observed in the Mizoroki–Heck reaction. This polymer showed a good catalytic activity, not only in organic but also in aqueous media, for aryl iodides, bromides, and activated chlorides with high turnover numbers (TONs), under aerobic conditions at relatively lower temperature.

2.7 Stille Reaction

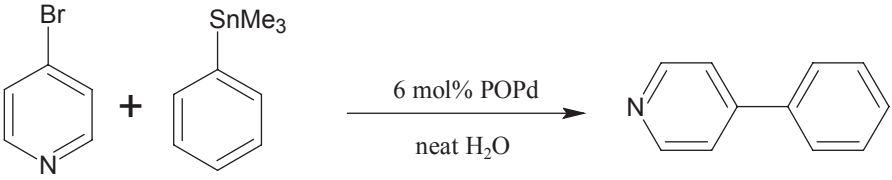
The Stille reaction (Migita–Kosugi–Stille coupling) is a chemical reaction widely used in organic synthesis which involves the coupling of an organotin compound (also known as organostannanes) with a variety of organic electrophiles via palladium-catalyzed coupling reaction. Wu et al. [24] reported the first application of nano-sized nickel catalysts (phosphine dendrimer-stabilized nickel nanoparticles) for the Stille coupling reaction in water (Scheme 8.19). The nickel NPs were found to be highly active and recyclable in the reactions at ambient temperature in water

medium, without cocatalyst, affording the biaryls with good to excellent yields. The catalytic process was proved to be heterogeneous, occurring on the surface of nickel NPs based on parallel experiments with molecular complexes and metal-leaching tests in recycling experiments as well as transmission electron microscopy (TEM) morphology of recovered nanocatalysts.



Scheme 8.19

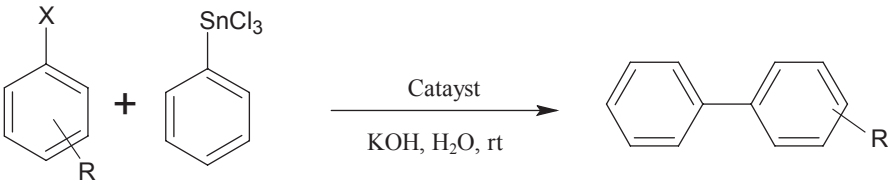
An efficient Stille cross-coupling reaction using a variety of aryl halides in neat water has been developed [25]. Employing palladium-phosphinous acid catalyst $[(t\text{-}Bu)_2P(OH)]_2PdCl_2$ allows formation of biaryls from aryl chlorides and bromides in good to high yields (Scheme 8.20). Functional groups such as ketones and nitriles are tolerated and organic cosolvents are not required. The air stability and solubility in water of the palladium complexes used in this study facilitate operation of the coupling reaction and product isolation. The feasibility of catalyst recycling has also been demonstrated.



Scheme 8.20

The performance of several palladium precatalysts, like palladium(II) acetate, palladium(0)NPs encapsulated into poly(amidoamine) (PAMAM) dendrimers (Pd DENs) and palladium(II)–PAMAM complexes, in the Stille reaction between trichloro(phenyl)stannane and iodoarenes in water was compared [26]. The reactivity of Pd DENs is similar or inferior to that of palladium(II) acetate, although the presence of the dendrimer suppresses the formation of homocoupling products and allows catalyst recycling. It is suggested that the reaction catalyzed by Pd DENs occurs via palladium species which are leached from the NP but which remain coordinated to the dendritic macromolecule.

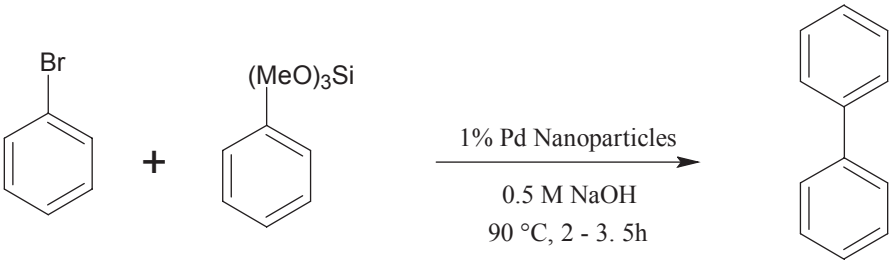
Garcia-Martinez et al. [27] also reported that dendrimer-encapsulated Pd NPs having a diameter of ~ 1.7 nm are effective and general catalysts for coupling aryl halides to organostannanes (the Stille reaction) under mild conditions (Scheme 8.21). This reaction was catalyzed by dendrimer-encapsulated Pd NPs in very good yield and in aqueous solution at 23°C using only 0.100 atom% of Pd as catalyst.



Scheme 8.21

2.8 Hiyama Reaction

The Hiyama reaction is a palladium-catalyzed cross-coupling reaction of organosilanes with organic halides to form carbon–carbon bonds. An efficient synthesis of Pd NPs in water has been developed using a Fischer carbene complex of tungsten as the reductant and polyethylene glycol (PEG) as the capping agent (Scheme 8.22) [28]. These Pd NPs efficiently catalyze Hiyama cross-coupling reactions performed in water. Excellent yields of products were obtained with a wide range of substrates.



Scheme 8.22

A new β-diketiminatophosphane Pd catalyst was found to be highly effective in the mono and double Hiyama coupling reactions of unactivated aryl chlorides in water [29]. A water-soluble ionic palladium(II) nitrogen-containing chelating complex, [palladium(II) 1-(4-*N, N′, N″*-trimethylbutylammonium)-4-(2-pyridyl)-1*H*-1,2,3-triazole dichloride] chloride, was prepared through the click reaction of 1-chloro-4-bromobutane, sodium azide, and 2-ethynylpyridine, followed by the quaternization of Me_3N and subsequent reaction with [Pd(cod)Cl_2] (cod = 1,5-cyclooctadiene). The catalytic performances of the chelating complex were preliminarily evaluated through Suzuki–Miyaura and Hiyama cross-coupling reactions of aryl bromides; excellent catalytic activity in water was observed [30]. TEM analysis revealed that small palladium NPs with a narrow size distribution were formed after the catalytic reaction. The NPs were stabilized by the synergetic effect of coordination and electrostatic interactions from the ionic, bidentate, nitrogen-containing ligand; no palladium black was detected after the aqueous solution of palladium NPs was stored in air for months. The use of palladium(II) 1-(4-*N, N′, N″*-trimethylbutylammonium) -4-(2-pyridyl)-1*H*-1,2,3-triazole-dichloride]chloride as a precursor in the formation

of palladium NPs was further explored by using $NaBH_4$ and hydrogen as reductive reagents. The resulting NPs displayed different sizes, surface properties, and catalytic performances in the Suzuki–Miyaura cross-coupling reaction in water.

A $Pd(NH_3)_2Cl_2$/cationic bipyridyl catalytic system catalyzed the cross-coupling reaction of aryl bromides with arylsiloxanes in water under aerobic conditions in the presence of NaOH to afford biaryls in good to high yields has been studied [31]. The reaction was performed at 120°C and the loading amount of catalyst can be as low as 0.001 mol%. After extraction, the residual aqueous phase can be reused several times with only a slight decrease in activity.

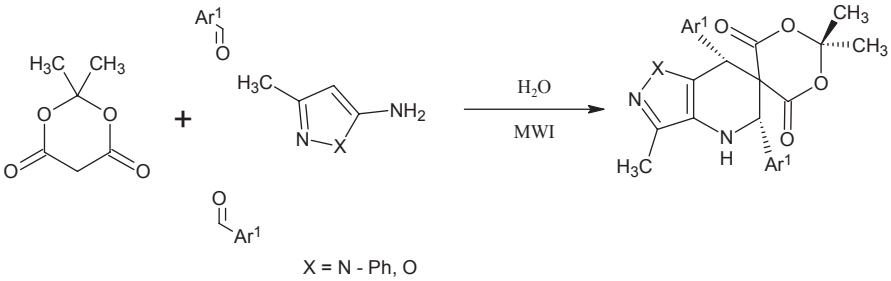
Fluoride-free Hiyama cross-coupling reactions of phenyltrimethoxysilane with aryl halides was performed in water using sodium hydroxide as activator at 110°C under microwave heating [32]. The reaction was catalyzed by poly (N-vinyl-2-pyrrolidone) (PVP)-stabilized colloidal palladium NPs. The reaction proceeds quickly under microwave heating (6 min).

2.9 Diels–Alder Cycloaddition

Peptide–oligonucleotide conjugates incorporating all the nucleobases and trifunctional amino acids were obtained by Diels–Alder reaction between diene-modified oligonucleotides (2′-deoxyribo- or ribo-) and malemide-derivatized peptides. Both reagents are easily synthesized by on-column derivatization of the corresponding peptides and oligonucleotides [33]. The cycloaddition reaction was carried out under mild conditions, in aqueous solution at 37°C, affording the desired peptide–oligonucleotide conjugate with high purity and yield. The speed of the reaction depends on the size and composition of both reagents, but it is accelerated by the presence of positively charged amino acids in the peptide fragment. However, a small excess of maleimide-derivatized peptide may be required in some cases to complete the reaction within 8–10 h.

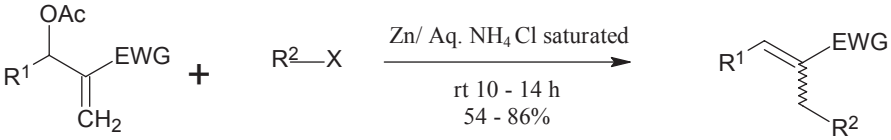
2.10 Stereoselective Synthesis

New multicomponent domino reactions (MDRs) have been established for the synthesis of spiro{pyrazolo[1,3]dioxanopyridine}-4,6-diones, spiro{isoxazolo[1,3] dioxanopyridine}-4,6-diones and pyrazolo[3,4-*b*]pyridines [34] (Scheme 8.23). The MDRs were conducted by reacting readily available and inexpensive starting materials in aqueous solution under microwave irradiation with a broad substrate scope and high overall yields (76–93%). A new mechanism has been proposed to explain the reaction process and the resulting chemo-, regio- and stereoselectivities. The present green synthesis shows attractive characteristics such as the use of water as the reaction medium, one-pot conditions, short reaction periods (9–13 min), easy workup/purification, and reduced waste production without the use of any acids or metal promoters.



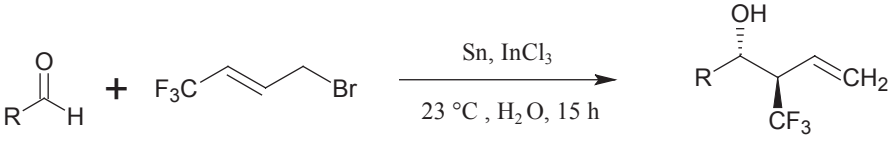
Scheme 8.23

Treatment of the acetyl derivatives of the Baylis−Hillman adducts 3-hydroxy-2-methylene-alkanoates and 3-hydroxy-2-methylene-alkanenitriles with unactivated alkyl halides in the presence of Zn in saturated aqueous NH_4Cl solution at room temperature afforded (2*E*)-2-substituted-alk-2-enoates in the first case and (2*Z*)-2-substituted-alk-2-enenitriles with high (*Z*)-selectivity in the second case has been reported [35] as shown in Scheme 8.24.



Scheme 8.24

A tin-mediated, indium trichloride promoted allylation reaction provided β-trifluoromethylated homoallylic alcohols, the building blocks of biologically active substances, in high yields and excellent stereoselectivity (R = H, Cy, Ar, COOH) (Scheme 8.25). Since the syntheses can be carried out in water, the reactive OH groups do not need to be protected, and even compounds that are insoluble in organic solvents can be used [36].



Scheme 8.25

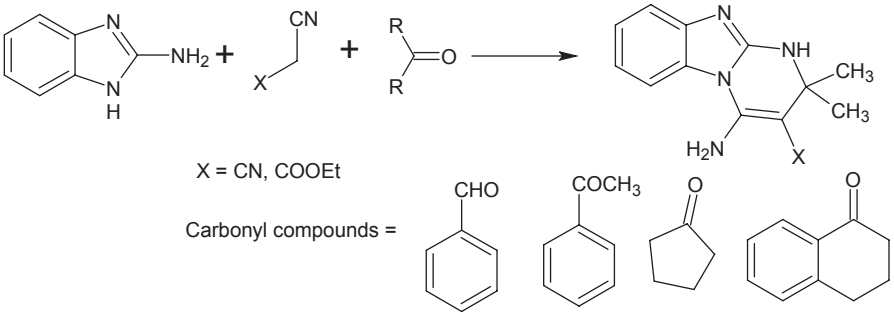
3 Reactions in Near-Critical Water

Organic reactions in water, without the use of any harmful organic solvent, are of great interest, because water is nontoxic, nonflammable, abundantly available, and inexpensive. Thus, water as the reaction medium is generally considered a cheap,

safe, and environmentally benign alternative to synthetic solvent. Furthermore, because of the low solubility of common organic compounds in water, the use of water as a solvent often makes the purification of product very easy by simple filtration or extraction.

With its high dielectric constant, water is potentially a very useful solvent for microwave-mediated synthesis. When water is heated using microwave heating above its boiling point in sealed vessels, organic substrates can become more soluble resulting in rate enhancement effects. Only a small number of publications that deal with microwave-assisted organic chemistry in water above 200°C exist due to the pressure limit of 20 bar for most of the commercially available microwave instruments. Pure water, for example, reaches an autogenic pressure of 50 bar at 250°C. Reactions in the near-critical water (NCW) region between 200 and 300°C have to be performed in one of the few accessible dedicated instruments with higher pressure limits (80–100 bar).

A convenient and clean water-mediated synthesis of a series of 4-amino-2-aryl-1,2-dihydro pyrimido[1,2-a]benzimidazoles has been reported using alternative nonconventional energy sources [37]. The products were obtained in shorter times with excellent yields (78–89%) from the multicomponent reaction of 2-aminobenzimidazole, malononitrile/ethylcyanoacetate, and carbonyl compounds (Scheme 8.26). The procedure does not involve the use of any additional reagent/catalyst, produces no waste, and represents a green synthetic protocol with high atom economy. The combination of microwave irradiation, ultrasonic irradiation, and aqueous-mediated conditions using multicomponent reactions leads to enhanced reaction rates, higher yields of pure products, easier workup, and sometimes selective conversions. Consequently, this protocol should be welcome in these environmentally aware days.



Scheme 8.26

The facile reaction occurs in neat condition in the absence of any solvent and catalyst under microwave irradiation but the product required further purification and recrystallization with suitable solvents, giving comparatively lower yield. Further, although a reaction in ethanol also occurs smoothly, it requires due precautions and modifications in microwave oven for operational safety. However, reaction in aqueous medium offer better results under both microwaves and ultrasonic waves,

probably because of the beneficial hydrophobic effect/ solvophobicity and hydrogen bonding in water described previously.

For microwave-irradiated reactions, the crystalline product was separated after the reactions by cooling yields were high, with no need for further purification and crystallization. Further comparison reactions were also studied under conventional conditions and in the absence of catalyst. No reaction occurred in ethanol, whereas in an aqueous medium, long reaction times with lower yield were observed.

To further improve the procedure, the reaction was also studied using cetyl trimethyl ammonium bromide as a phase-transfer catalyst, but no change in yield was observed. Although the reaction time was reduced slightly, it may be concluded that the aqueous medium is the perfect method for the synthesis of pyrimido[1,2-a]benzimidazoles.

The advantages of water mediated synthesis such as (i) no requirement of additional reagent/catalyst, (ii) nonflammable and nontoxic reaction medium, (iii) high yields, (iv) virtually no waste generation, and (v) ease of product isolation/purification, fulfill the philosophy of green chemistry and make the present methodology environmentally benign.

4 Conclusions

In general, organic synthetic processes are conducted in a solvent medium, which is toxic, inflammable, and hazardous in nature. They involve evaporation as well as recycling resulting in environmental pollution, which has become a major issue at the global level. Another important criterion is the use of solvent media in an industrial process causing health hazards directly affecting the people around. In view of such issues involved, the use of wide range of volatile, nonvolatile, polar as well as nonpolar, design and development of environmentally benign sustainable reaction processes involving nonconventional reaction media like water is widely accepted to become a global necessity. The expanding area of aqueous medium organic synthesis shows the significance of water as a medium to conduct organic reactions for the benefit of environmental sustainability by reducing the application of toxic organic solvents towards the reaction processes and further research in this field will contribute to attain newer goals.

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Chapter 9
Synthesis and Synthetic Applications of Biologically Interesting Rhodanine and Rhodanine-Based Scaffolds

Sadegh Rostamnia and Esmail Doustkhah

Contents

Abstract Rhodanine and thiazolidinone (TZD) heterocycles are attractive targets in organic and medicinal chemistry owing to their potency in a wide spectrum of biological activities and can also serve as synthetic intermediates for many kinds of pharmaceuticals or drug precursors. Consequently, looking for efficient and concise green methods for the synthesis of these types of compounds is a major challenge in chemistry. As a result, many green methods have been used to synthesize structurally complex and diverse rhodanine and TZDs in recent years. The purpose of this chapter is to discuss the recent green synthesis of the rhodanine and TZD heterocyclic scaffolds including aqueous medium synthesis, ionic liquid, microwave, ultrasonic irradiation, solvent-free methods, solid catalysts, such as mesoporous, magnetic nanoparticles, etc.

Keywords Rhodanine · Thiazolidinone (TZD) · 5-Oxo-2-thioxo-3-thiophene carboxylate · Heterocycles

Dedicated to Prof. Abdolali Alizadeh on the occasion of his 48th birthday.

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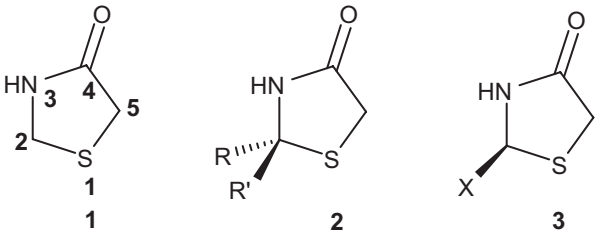
1 Introduction

Rhodanine is a heterocyclic compound which belongs to thiazolidinone (TZD) family. Discovery of TZD heterocycles and related derivatives goes back to more than 50 years, as bioactive compounds which are applied extensively in the pharmaceutical cases. TZDs are derivatives of thiazolidine with a carbonyl group. Substituents in the 2-, 3-, and 5-positions may be varied, but the greatest difference in structures and properties is exerted when attached group in the 2-position is varied (R and R′ in **2** or X in **3**). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by **2** and **3** (Scheme 9.1).



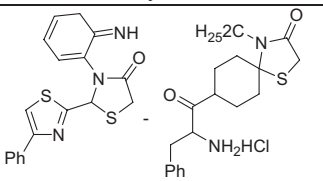
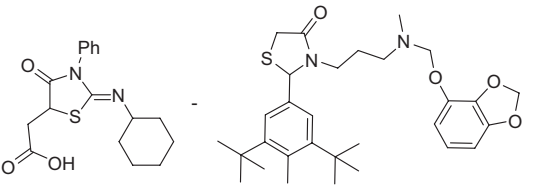
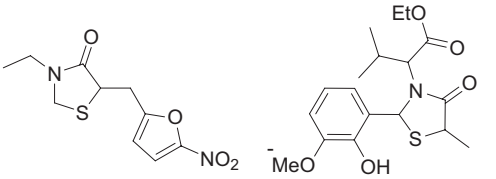
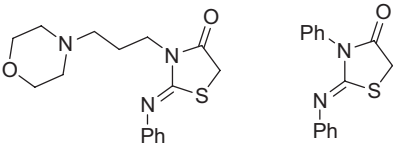
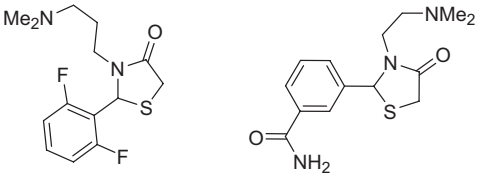
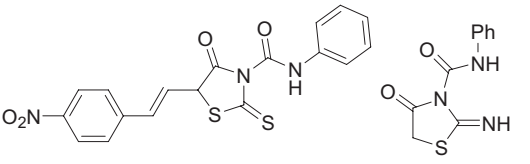
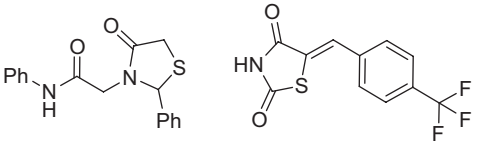
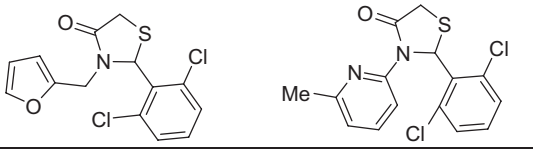
Scheme 9.1

Over the past decades, various types of TZD-based compounds were synthesized by several methods, which are applicable in the pharmaceutical and dye industries. For instance, they are known to exhibit antidiabetic activities [1] and anti-inflammatory activities [2]. There were investigations on the behavior of various analogues of substituted 5-benzyl thiazolidine-2,4-diones, which have euglycemic activity for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Examples of TZD derivatives include: (1) ciglitazone, (2) troglitazone, (3) englitazone, (4) pioglitazone, and (5) rosiglitazone.

For example, troglitazone is found to have anticancer activity. These kinds of compounds suppress the growth of several cancer cells such as colon, breast, and prostate [3–5]. These compounds are also used as free radical scavengers. Free radicals damage cell structure and consequently interfere with performance of enzymes and critical macromolecules. In addition to these important pharmaceutical effects of TZDs derivatives, they have also other several essential pharmaceutical effects including antiarthritic activity, oncostatic activities inhibiting angiogenesis, and potential chemopreventive action against tongue and gastric carcinogenesis [6].

Several studies have been done on the biological activity of 4-TZDs. Their bioactivity includes their anticonvulsant, hypnotic, antitubercular, anthelmintic, cardiovascular, anticancer, antibacterial, antifungal, antihistaminic, antiviral, anti-inflammatory, and follicle-stimulating hormone (FSH) receptor agonist activities. Table 9.1 indicates a number of important bioactive compounds in this area [7].

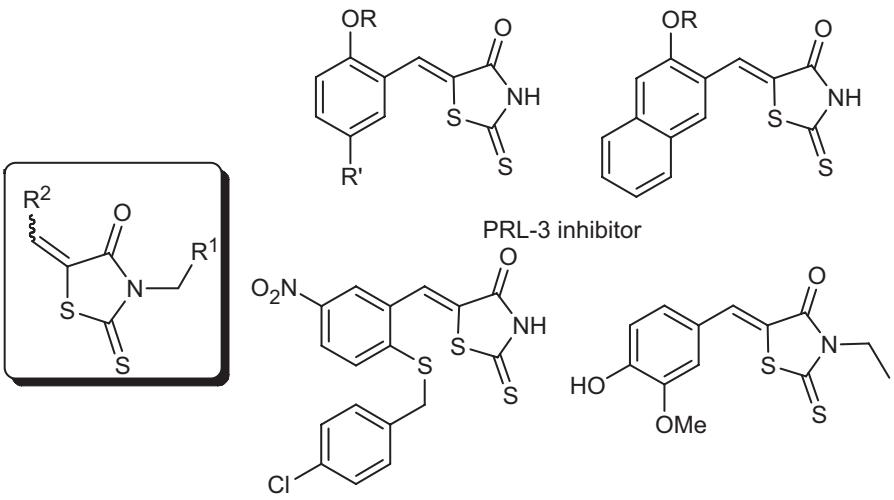
Table 9.1 Representative bioactive heterocycles of TZD family

Antifungal activity	
Cardiovascular activity	
Antitubercular activity	
Hypnotic activity	
Antihistaminic activity (H1-agonist)	
Anthelmentic activity	
Anticancer activity	
Antiviral activity	

As depicted in entry 6 of Table 9.1, 3-methyl-5-[(4-nitrophenyl)azo]rhodanin nitrodan is a potent anthelmintic compound [8]. It was reported that this compound was effective when administered in feed against *Hymenolepis nana*and *Syphacia obvelata* infections in mice, *Asceridia galli* infections in chickens, and *Toxocera canis*, *Ancylostoma caninum*, and *Uncinaria stenocephala* infections in dogs, pigs, and horses, respectively [7].

2 Rhodanine and Rhodanine-Based Scaffolds

Rhodanine (5-oxo-2-thioxo-3-thiophenecarboxylates) and rhodanine-based heterocyclic skeleton, in particular, are known to possess multiple biological activities (Scheme 9.2) including the inhibition of numerous targets such as HCV NS3 protease [9], β-lactamase [10], PMT1 manosyl transferase [11], and PRL-3 and JSP-1 phosphatases [12]. Typical examples of bioactive rhodanine-based heterocycle scaffolds are also indicated in Table 9.2 [13–16].

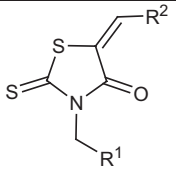


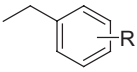
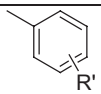
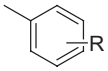
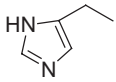
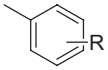
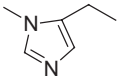
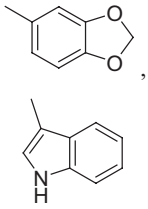
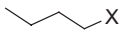
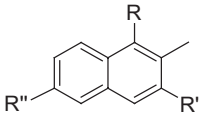
Scheme 9.2

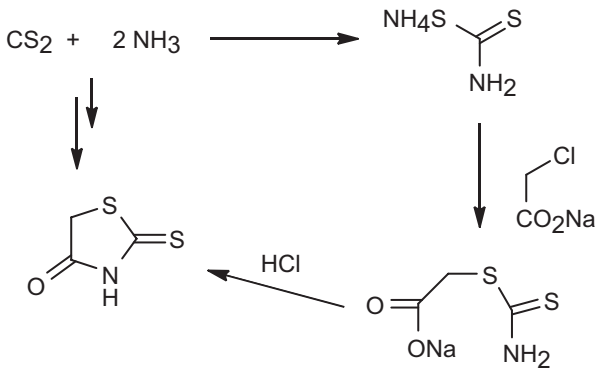
2.1 Synthesis of Rhodanine

Early synthesis of rhodanine refers back to 1910, which was reported by Homberg (Scheme 9.3). This synthesis began with the reaction of gaseous ammonia with carbon disulfide in 95% ethanol immersed in an ice bath until the end of reaction. This reaction led to the formation of ammonium dithiocarbamate, which subsequently reacted with a solution of sodium chloroacetate. After the completion of the reaction, rhodanine was obtained in 87% yield [17].

Table 9.2 Rhodanine-based compounds with different functionalities

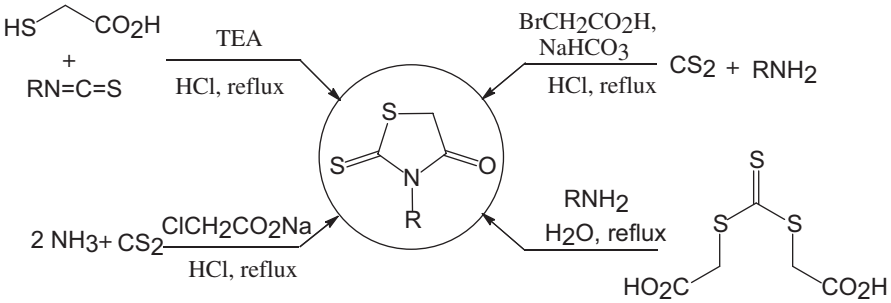


Entry	R_1	R_2	X, Z, R
1			R = 4-Methoxy, H, 4-OH R' = H, *ter*-butyl
2			Z = O, S R = H, 3,4-dichloro
3			-
4			R = OMe, H
5			-
6			-
7			X = OMe, H, C_5H_{11}
8		—COOH	R = H, Br, NO_2, OMe R' = H, Br, Cl, OCH_3 R = H, OCH_3



Scheme 9.3

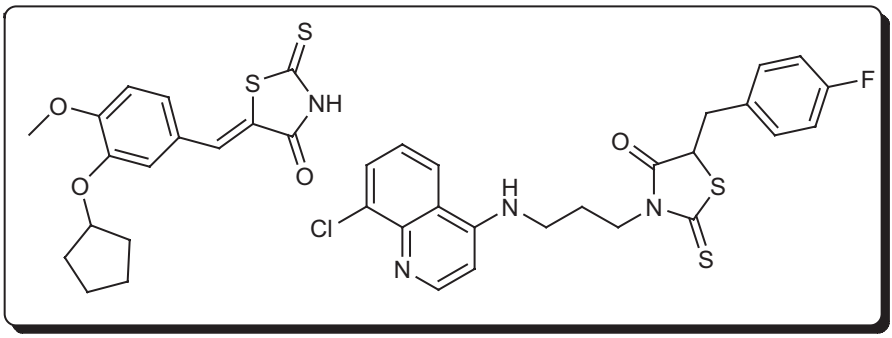
Classical methods for the preparation of rhodanine need several steps. Recent methods are limited by the requirement of highly reactive functional groups in the substrates or none smooth and mild condition media. Several methods have been reported for the synthesis of rhodanines. However, they suffer from multistep processes, harsh conditions, low yields, and long reaction times (Scheme 9.4). Thus, development of new synthetic methods remains an attractive goal.



Scheme 9.4

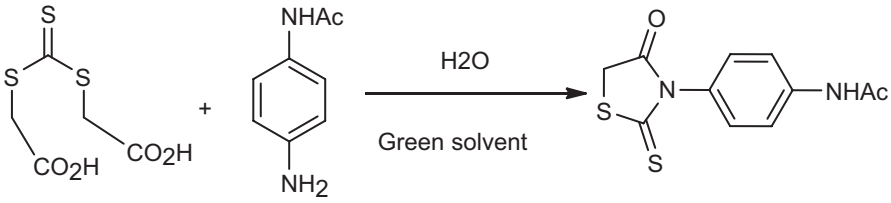
2.2 Synthesis of Rhodanine-Based Scaffolds

One of the main objectives of organic and medicinal chemistry is the design, synthesis, and production of molecules having value as human therapeutic agents. Rhodanine scaffold is a powerful tool for the medicinal chemist and has a broad substrate scope for the synthesis of various heterocyclic moieties (Scheme 9.5) with a wide range of pharmacological activities, such as antimalarial, antimicrobial, antiviral, antidiabetic, and anticonvulsant effects [18].



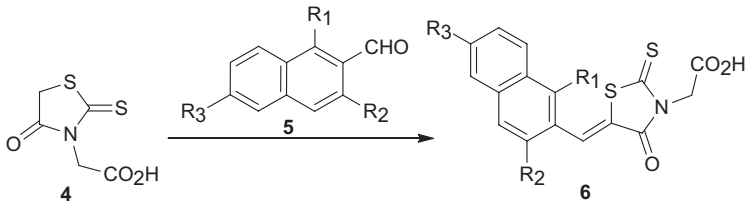
Scheme 9.5

Later, the discovery of new rhodanine-based compounds was achieved by researchers to develop new scaffolds of bioactive compounds. Strube prepared a new derivative of rhodanine, namely *N*-(*p*-acetylaminophenyl)rhodanine by the Holmberg procedure in aqueous solution (Scheme 9.6). This method begins with *p*-aminoacetanilide and trithiocarbodiglycolic acid in the presence of water as a solvent under heating conditions to give target molecule 49–53 % yield [19].



Scheme 9.6

A series of 2-(5-((naphthalen-6-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid analogues have been prepared as aldose reductase inhibitors. In vitro inhibitory activities of bovine lens aldose reductase were determined by a conventional method (Scheme 9.7).



Scheme 9.7

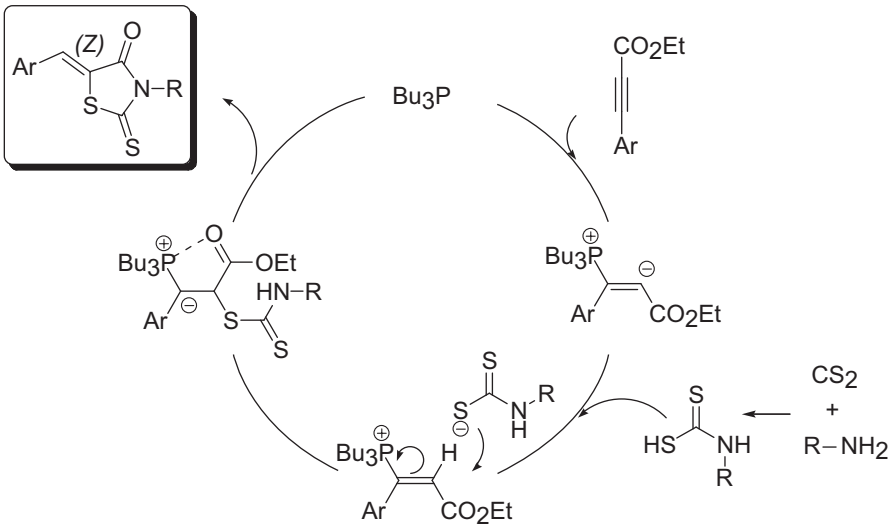
Table 9.3 In vitro IC_{50} values (nM) of aldose reductase inhibition with different substituents

R_1	R_2	R_3	IC_{50}
H	H	H	96
OCH_3	H	H	9
Br	H	H	11
NO_2	H	H	79
H	OCH_3	H	20
H	Br	H	15
H	H	OCH_3	67

In comparison, 1-naphthyl-substituted derivatives were more potent inhibitors (IC_{50} = 10 nM) with similar activity to epalrestat. 4-Oxo-2-thioxo-5-(2-naphthylmethylene)-3-thiazolidine-acetic acids were obtained by the condensation of substrate **4** with appropriate 2-naphthaldehydes. Results of in vitro studies related to these two classes of compounds are represented in Table 9.3 [16].

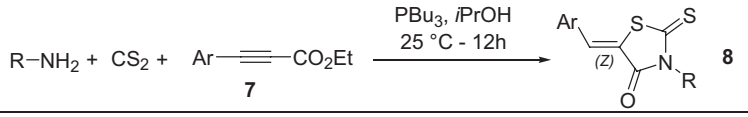
Although, there are methods for obtaining rhodanine derivatives such as Knoevenagel condensation, the one-pot method for synthesis of these derivatives is a prevailing option to reduce the synthetic steps and raise efficacy of the method. For example, the reaction of dithiocarbamates (prepared in situ from amines and CS_2) and arylpropiolates in the presence of PBu_3 as a catalyst (Table 9.4) led to alkylidine rhodanine-based scaffolds [20].

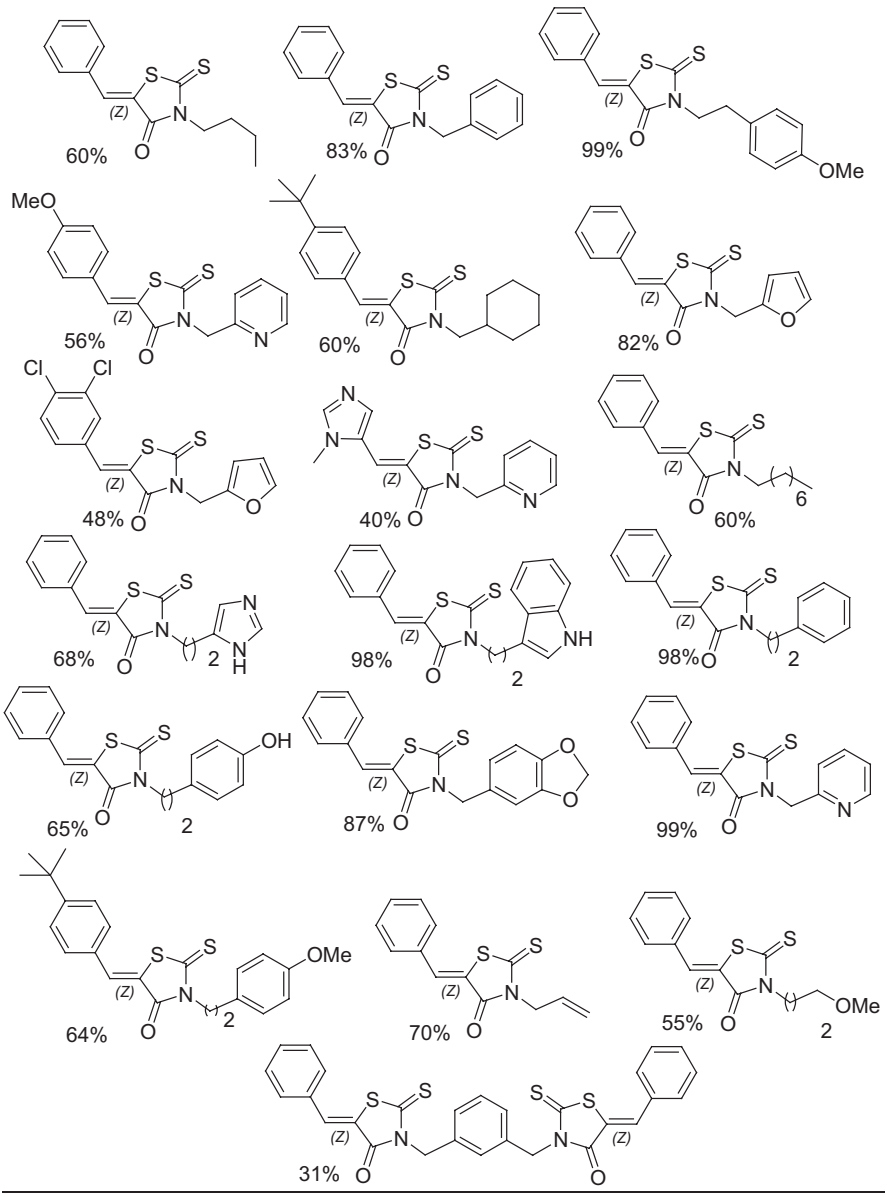
According to Taran's green catalytic method, one of the crucial points for the success of such an approach is chemoselectivity (Scheme 9.8). The strong nucleophilic character of the thiol function can facilitate a chemoselective Bu_3P-catalyzed *S*-addition of the bifunctional nucleophile on the alkyne (N vs. S). The resulting umpolung adduct then undergoes cyclization due to the close proximity of the second nucleophile with respect to the ester group resulting in the formation of arylidene rhodanine heterocycle.



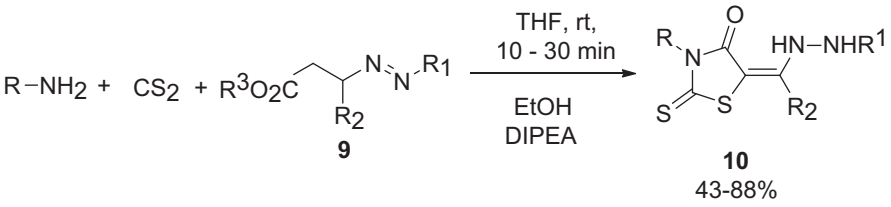
Scheme 9.8

Table 9.4 One-pot green method for the synthesis of rhodanine-based scaffolds



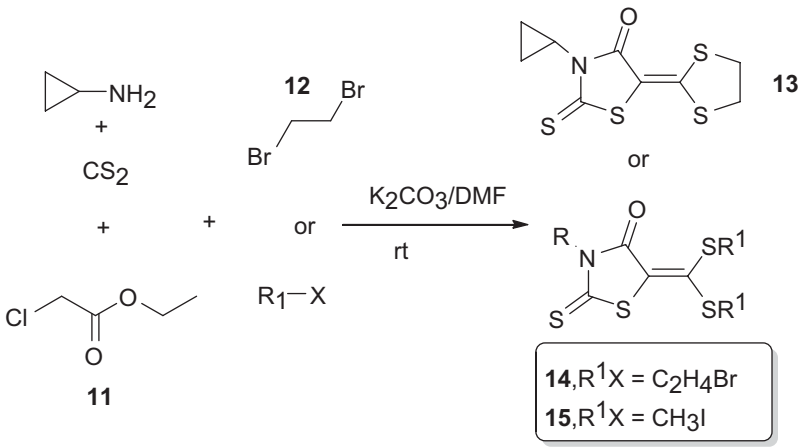


Another approach to reach rhodanine derivatives is depicted in Scheme 9.7, which begins with the reaction of aliphatic primary amines, carbon disulfide, and 1,2-diaza-1,3-dienes **9** (Scheme 9.9). Finally, this reaction leads to 5-hydrazinoalkylidene rhodanine derivatives **10** [21].



Scheme 9.9

Recently, the one-pot four-component synthesis of rhodanine derivatives was also reported. In this chapter, a novel multicomponent synthesis of ketene dithioacetal rhodanines was reported by the reaction of primary amine, carbon disulfide, ethyl chloroacetate, and alkyl halide in dimethylformamide (DMF; Scheme 9.10). When 1,2-dibromoethane **12** is used as an alkyl halide, 1,3-dithiolane is formed at the 5-position and linked by a double bond. According to the literature, potassium carbonate was the best candidate for catalyzing the reaction in moderate-to-good yields at room temperature [22].

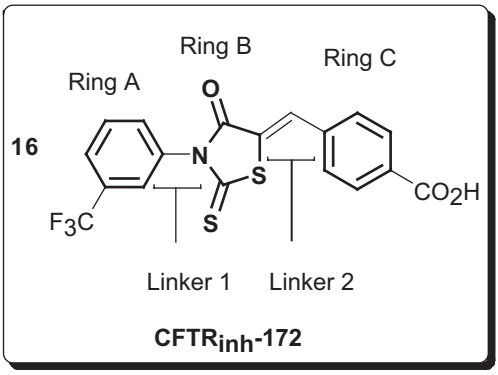


Scheme 9.10

The cystic fibrosis transmembrane conductance regulator (CFTR) is a cyclic adenosine monophosphate (cAMP)-regulated chloride channel whose mutation can generate the hereditary disease cystic fibrosis. CFTR inhibition is a therapeutic potential approach to secretory diarrhea [23–25]. 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone ($CFTR_{inh}$-172; Schemes

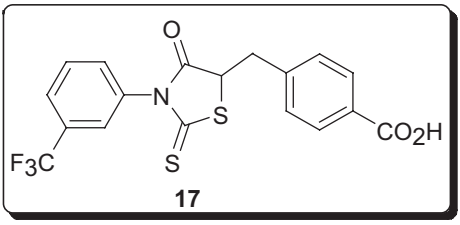
9.11 and 9.16) blocks CFTR chloride conductance fully with IC_{50}<0.5 µl. In vivo analysis of $CFTR_{inh}$-172 indicated efficacy in reducing cholera toxin-induced intestinal fluid secretion in rodent models [26]. $CFTR_{inh}$-172 was found to have low toxicity, renal excretion with minimal metabolism, and intestinal accumulation by enterohepatic recirculation [27]. $CFTR_{inh}$-172 has been used extensively to block CFTR chloride channel function in a variety of cell culture, tissue, and in vivo systems [28].

Limitations of $CFTR_{inh}$-172 include its low water solubility and oral bioavailability. $CFTR_{inh}$-172 is a weak acid with one negative charge at neutral pH, which undergoes precipitation in an acidic environment. Also, the concentration of $CFTR_{inh}$-172 in cytoplasm, where it acts, is likely reduced in a Nernstian manner compared with its extracellular concentration because of the interior-negative membrane potential of its target epithelial cells.



Scheme 9.11

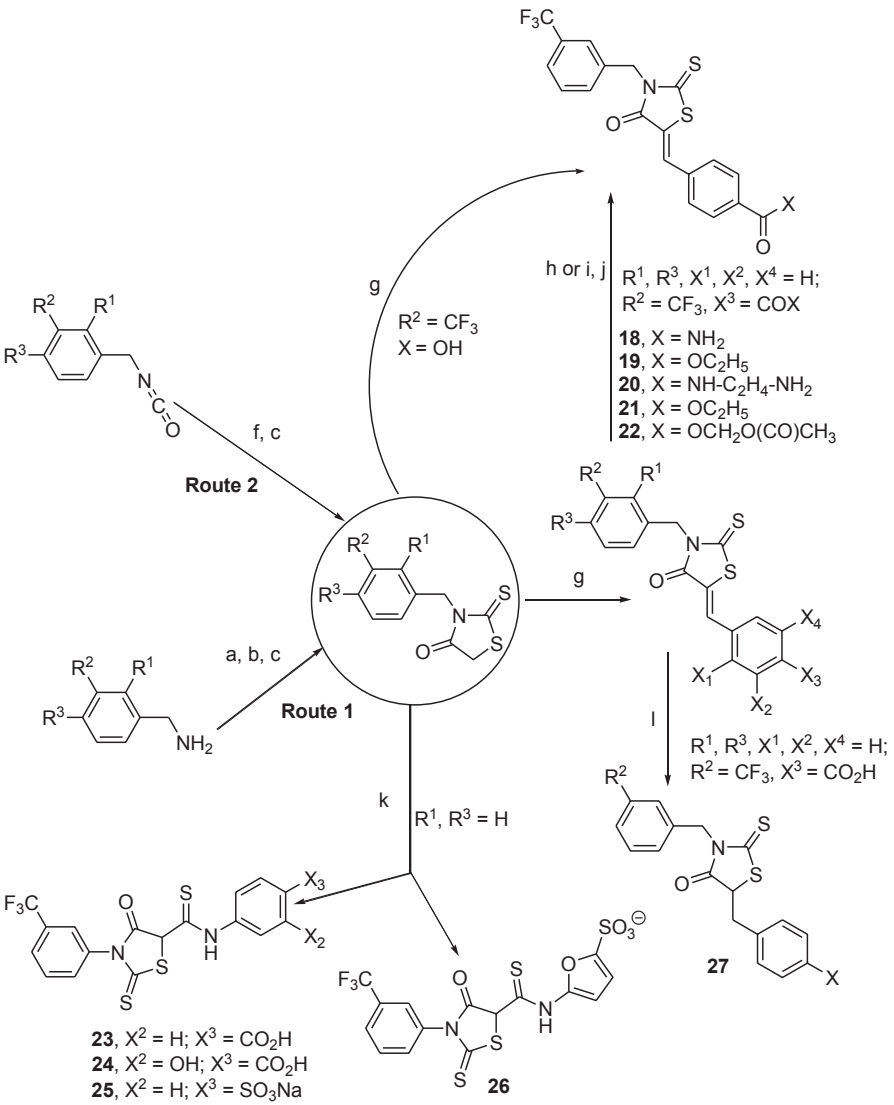
Sonawane and coworkers synthesized and characterized modified $CFTR_{inh}$-172 analogues to increase water solubility and to retain CFTR inhibition potency [29]. CFTR analogues with >10fold higher water solubility than $CFTR_{inh}$-172 and only mildly reduced potency were synthesized and characterized (Scheme 9.12).



Scheme 9.12

They revealed that compounds containing 3-CF_3 on Ring A, TZD (rhodanine) core as Ring B, and 4-carboxy at Ring C had the most CFTR inhibition potency. Polar ionizable substituent such as carboxyl or hydroxyl, which created a negative

charge on Ring C, gave the most inhibition activity, whereas nonpolar substituents were embedded on Ring A. There were several reported pathways for every class of rhodanine derivatives which are illustrated in Scheme 9.13. The results of these targets (IC_{50}) are explained in Table 9.5. These results exhibit the effect of substituents on the biological activities of rhodanine derivatives.

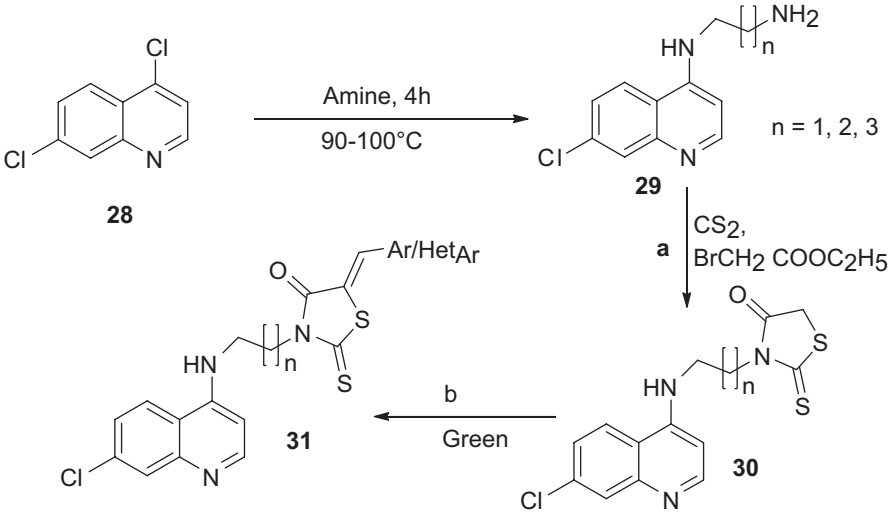


Scheme 9.13 (a) CS_2, TEA, EtOAc, rt, 12 h (b) $BrCH_2CO_2H$, $NaHCO_3$, rt, 2h; (c) HCl, reflux, 2 h; (d) $COCl_2$ or $SOCl_2$, 10 °C, 2 h; (e) Triphosgene, $CHCl_3$, reflux, 3 h; (f) $HSCH_2CO_2H$, TEA, 4 h; (g) Aldehyde, piperidine/ethanol, reflux, 2 h; (h) $SOCl_2$, DMF, rt, 2h; (i) DCC, *N*-hydroxysuccinimide, rt; (j) HX-R, pyridine, 0 °C-rt, 12 h; (k) SCN-($3X_2$-$4X_3$-Ph) or sodium 5-SCN-furan-2-sulphate (for 12), DBU, THF, rt, 2 h; (l) $LiBH_4$, pyridine, rt, 12 h

Table 9.5 IC_{50} results of rhodanine derivatives

Compound	IC_{50} (μM)
18	Inactive
19	Inactive
20	Inactive
21	Inactive
22	Inactive
23	9
24	11
25	25
26	27
27	27

Quinoline-based hybrids such as aminoquinoline–isatin, aminoquinoline–clotrimazole [30, 31], aminoquinoline–pyrimidine [18, 32], quinoline–thiazolidin-4-one [33], aminoquinoline–ferrocene-based hydrazones [34] and recently enone and chalcone–chloroquine hybrid analogues [35], and 15-membered azalide-4-aminoquinoline [36] were reported in the literature as anti-infective agents. Novel 4-aminoquinoline-rhodanine hybrid was synthesized and demonstrated as having potent in vitro antimalarial and antitubercular activities with low toxicity [18]. The most potent compounds in this series contains Ar/HetAr group as *p*-fluorophenyl and $n=2$ in **31**, which exhibited nanomolar activity against resistant strain of *Plasmodium falciparum* with the high selectivity ($IC_{50}=13.2$ nM; Scheme 9.14).

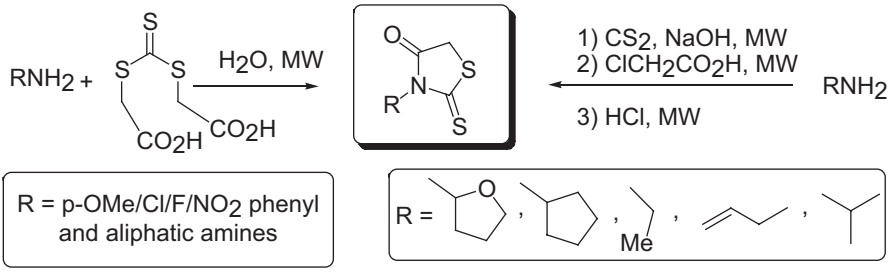


Scheme 9.14 (a) Acetonitrile, rt, 3-5 h, (b) Acetic acid, ammonium acetate, aromatic/hetero-aromatic aldehydes, 90 °C, 4-6 h

3 Green Synthesis of Rhodanines and TZDs

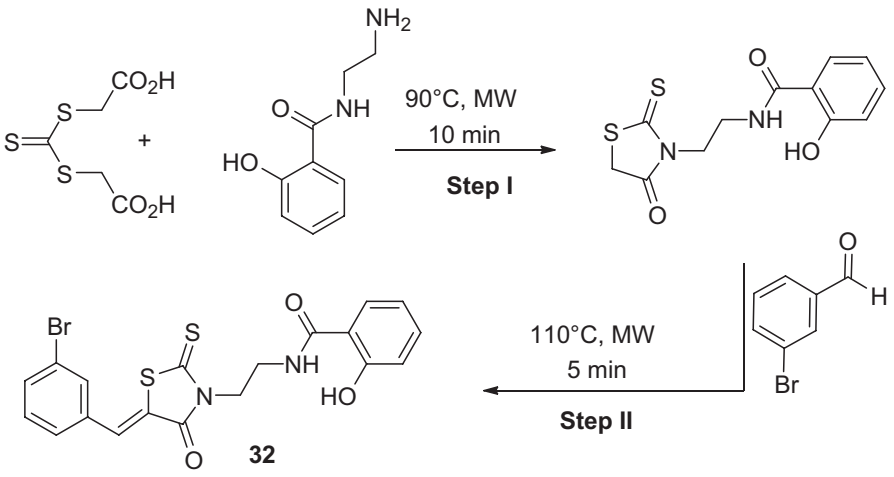
In recent years, there is a growing concern for providing safe and pure pharmaceutical products by green protocols. Green chemistry drives synthetic procedures of chemicals and drugs to be devoid of toxic solvents and heavy transitional metals as catalysts. Efforts in this area include developing green media such as ionic liquids (ILs), fluorinated solvents, and aqueous conditions; green catalysts such as zeolites, mesoporous nanomaterials;, and biopolymer supports in catalysis. In this part, we have described some green methods applied for the synthesis of rhodanine-based compounds. Part of our group's efforts is to develop chemical synthesis procedures of rhodanine-based compounds to green and eco-friendly methods. In this part, we have overviewed some of our papers and some other reports which are green and eco-benign pathways.

Recently, Nitsche and Klein developed two earlier methods of rhodanine synthesis to aqueous, one-pot, microwave-assisted methods [37]. They obtained different derivatives of *N*-substituted rhodanines from alkyl and benzylamines with an atom-efficient one-pot, three-step protocol started from carbon disulfide and chloroacetic acid in short reaction times and good to excellent yields. An alternative, microwave-assisted one-pot process included the reaction of bis(carboxymethyl) trithiocarbonate with alkyl-, benzylamine, and aniline in water to give *N*-arylrhodanines (Scheme 9.15).



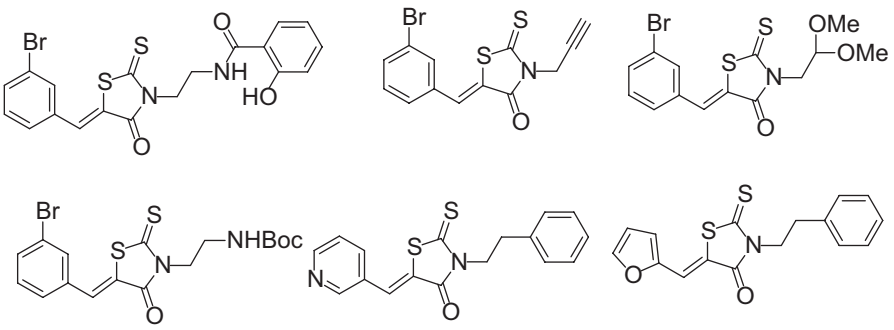
Scheme 9.15

Radi et al. [38], reported a novel microwave-assisted green approach for alkylidine rhodanine heterocycles . Their method was a fast and efficient protocol for the generation of substituted 5-arylidene rhodanines **32** in a sequential one-pot two-step process combining the Holmberg method and the Knoevenagel condensation under microwave irradiation. In this method, favored products were obtained in high yield and purified after a simple precipitation from methanol, in which the microwave irradiation results in a facile, practical, and rapid way to execute the procedure (Scheme 9.16).



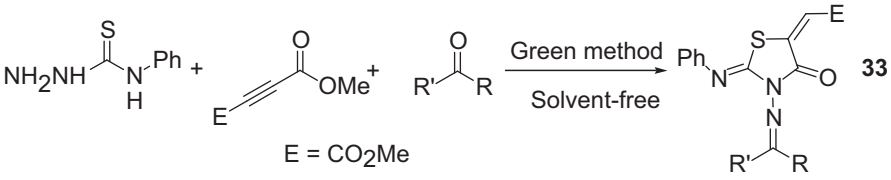
Scheme 9.16

That green method can be applied to heterocyclic or aryl aldehydes in combination with phenylethyl, benzyl, and aliphatic amines. The authors used a variety of amines as a library of this combinatorial method. Propargylamine gave a product that could be further elaborated via click-chemistry approaches; *N*-Boc-ethylenediamine gave a product whose exocyclic amine moiety could be further reacted to give potential DDX3 inhibitors (Scheme 9.17).



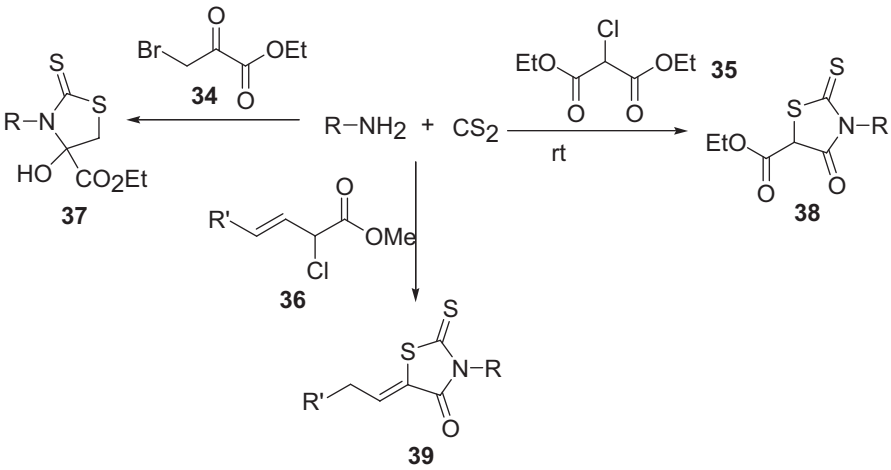
Scheme 9.17

Recently, Yavari et al. [39] reported a solvent-free green method for the synthesis of highly functionalized TZD-based thiazolidine-4-one **33**. In this three-component method, phenylthiosemicarbazide reacts smoothly with dimethylacetylenedicarboxylate in the presence of aldehydes or ketones under solvent-free conditions to produce thiazolidine-4-ones as indicated in Scheme 9.18.



Scheme 9.18

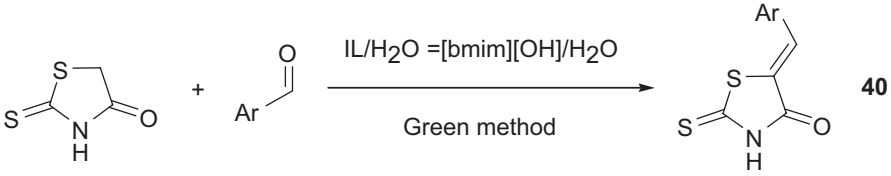
An efficient solvent-less green synthesis of 2-thioxo-1,3-thiazolanes **37** and ethyl 3-alkyl-4-oxo-2-thioxo-1,3-thiazolane-5-carboxylates **38** as new TZD-based heterocycle via reaction of primary amines with CS_2 in the presence of ethyl bromopyruvate **34** and diethyl 2-chloromalonate **35** was reported by Yavari et al. [39, 40]. These new multicomponent reactions were done in a green method in which the yields of biologically interesting structure are typically 90%. 5-(*Z*)-Alkylidene-2-thioxo-1,3-thiazolidin-4-ones **39** (rhodanine derivatives) were prepared by the reaction of in situ generated dithiocarbamates [41] with racemic *α*-chloro-*β*,*γ*-alkenoate esters **36** (Scheme 9.19).



Scheme 9.19

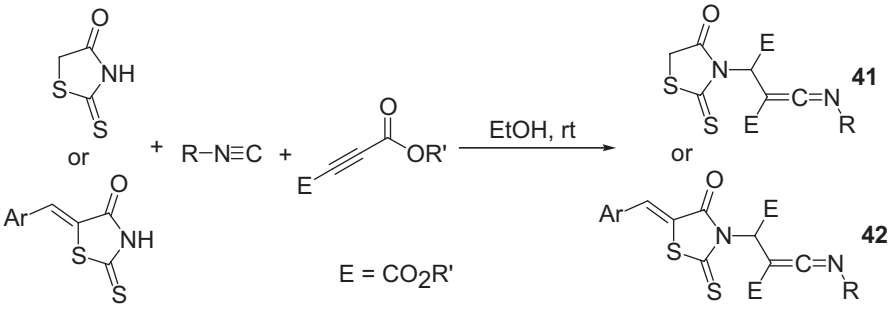
ILs have attracted extensive research interest in recent years as environmentally benign solvents of their favorable properties. Liu and coworkers prepared a basic IL, which was soluble in water and thus they used it for the synthesis of some interesting rhodanines. In their work, a basic functionalized IL, 1-butyl-3-methylimidazolium hydroxide ([bmim][OH]), catalyzed the Knoevenagel condensation of rhodanine with aromatic aldehydes (Scheme 9.20). It proceeded smoothly in water to afford the 5-benzylidene rhodanine derivatives in high yields at room temperature.

Application of IL/H_2O as catalyst offers several advantages such as excellent yields, short reaction times, and simple procedure. The catalyst can be reused at least five times [42].



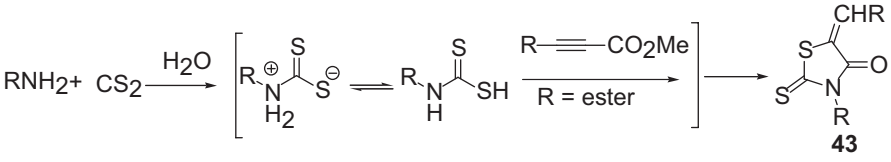
Scheme 9.20

Recently, multicomponent modification of the rhodanine or functionalized rhodanine to *N*-functionalized rhodanines containing ketenimine moiety has been reported [43]. New biologically interesting rhodanine-based heterocyclic scaffolds **41** and **42** are synthesized in one step by a green procedure at room temperature and mild conditions (Scheme 9.21).



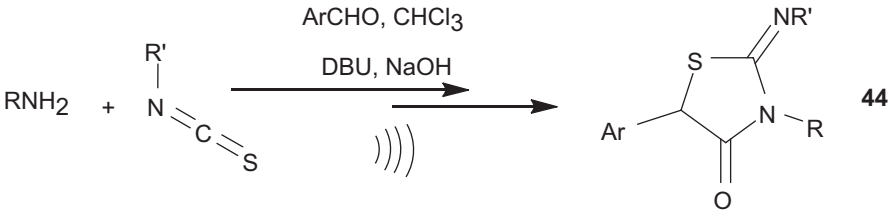
Scheme 9.21

An aqueous, green, simple, and direct synthetic procedure was reported by our group in 2009 for the synthesis of rhodanine derivatives via the three-component method, which began with the reaction of carbon disulfide, primary amines, and acetylenic esters under neutral conditions [44] to give rhodanine **50**. This procedure was completely a green and eco-friendly method (Scheme 9.22).



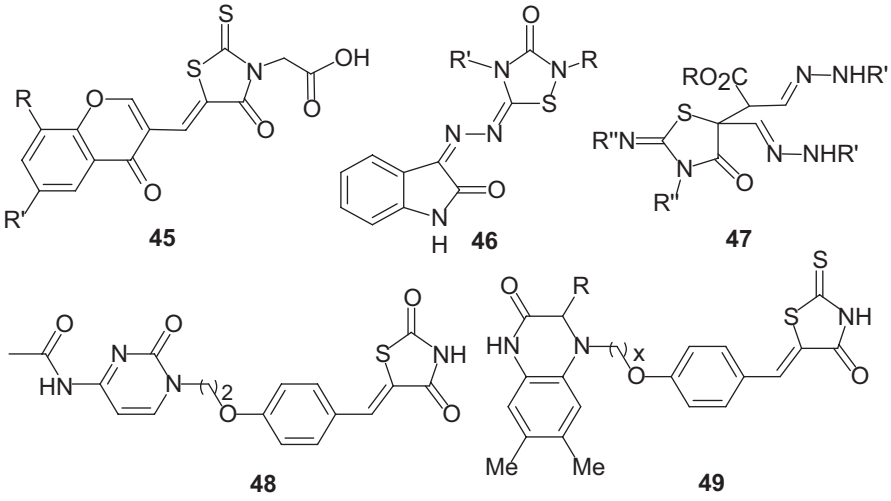
Scheme 9.22

In 2011, Mamaghani et al. reported a convenient one-pot green protocol for the synthesis of 2-imino-1,3-thiazolidin-4-ones **44** [45] by the reaction of amines, isocyanates, aldehydes, and chloroform in the presence of sodium hydroxide under ultrasonic conditions (Scheme 9.23). TZD-based 2-Imino-1,3-thiazolidin-4-ones were synthesized in high yields (75–91 %) and shorter reaction times (12–15 min).



Scheme 9.23

Some biologically and pharmacologically interesting rhodanine and TZD-based heterocycles were synthesized by partially green methods (Scheme 9.24). Chromonyl-rhodanine **45** with aldose reductase-inhibitory activity [46], indole-diones **46** with antituberculosis activity relationship [47], fused and spiro-heterocycles of cycloalkenyl-diazenes **47** [48], pyrimidinone-containing TZD-based derivatives **48** [49], quinoxalinyl–rhodanine derivatives as potent euglycemic and hypolipidemic agents **49** [50] are the examples for green synthesis of new scaffolds.



Scheme 9.24

As a part of our ongoing research in this field, a series of papers were published by our research group on using the one-pot three-component reaction in sonochemical,

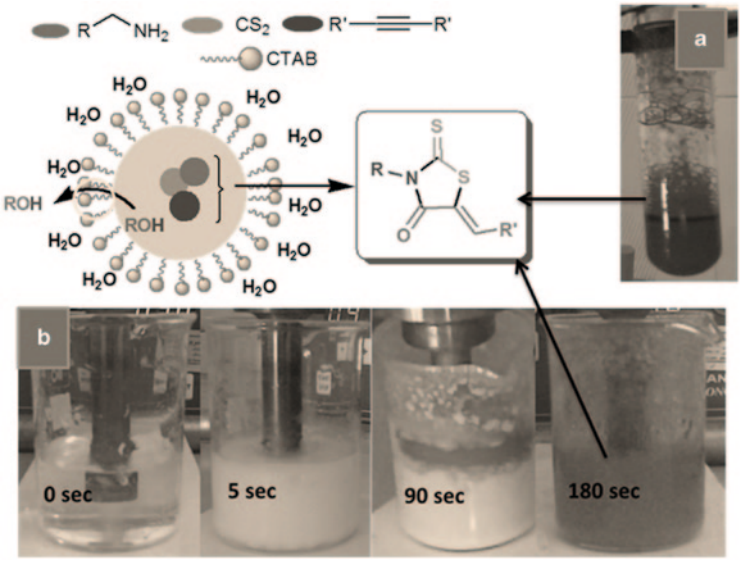


Fig. 9.1 Ultrasound-mediated synthesis of rhodanine derivatives; a) after reaction completion, b) before the reaction

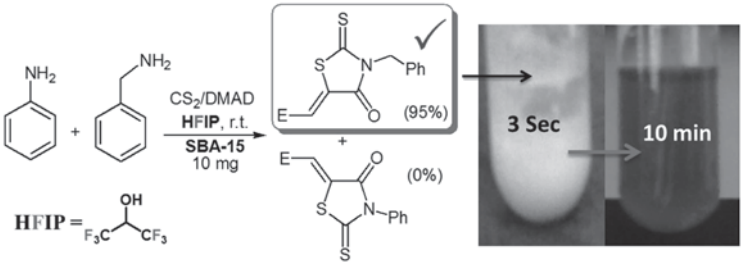


Fig. 9.2 SBA-15 (HFIP/SBA-15)-catalyzed synthesis of rhodanines

dispersed magnetical nanoparticles (DMNPs) of γ-Fe_3O_4 and heterogeneous porous nanomaterial application conditions. These green methods are explained in this chapter.

After our first report in 2009, later, we provided another green, but rapid and high-yielding method for the synthesis of alkyl rhodanines in water using ultrasonic irradiation [51]. The procedure was promoted by sonication. One-pot and rapid production of rhodanine derivatives and its facile isolation by a simple filtration were advantages of this method. In this method, we synthesized a large scale of rhodanines under ultrasonic irradiation (Fig. 9.1b). Aqueous cetyltrimethylammonium bromide-surfactant (CTAB) micelles were also found to be an efficient green and rapid reactor system for the synthesis of rhodanine [52] as illustrated in Fig. 9.1a.

SBA-15 nanomaterial is described as a nanoporous material, which has many applications in catalytic cases. Hexafluoroisopropanol dispersed into catalytical

Fig. 9.3 Nano γ-Fe_2O_3-catalyzed synthesis of rhodanines

amount of SBA-15 (HFIP/SBA-15) was the next catalytic condition for the synthesis of rhodanine-based compounds (Fig. 9.2). The advantages of this method included the ultrafast and waste-free conditions. In addition, low catalyst loading, simple procedure, waste-free and direct synthetic approach to excellent yield of rhodanines, high reusability of the catalyst, low reaction time, and chemoselectivity were the other advantages of this green method. Also, the reaction was achieved under the neutral conditions, in which there was no activation and modification of the substrates. The solid SBA-15 and hexafluoro-2-propanol (HFIP) were recovered and reused for recycling [53].

Recently, our research interest has been focused on the development of useful organic reactions in the presence of the nanocatalysts. EtOAc-dispersed magnetic nanoparticles (DMNPs) of γ-Fe_2O_3 were a representation of a green catalyst for the rapid three-component synthesis of 5-oxo-2-thioxo-3-thiophenecarboxylates as rhodanine skeletons via a single-pot domino process [54].

Rhodanines were prepared by magnetic nanoparticles of γ-Fe_2O_3 without any modification or additives (Fig. 9.3). Dispersed nano-γ-Fe_2O_3 has many advantages, such as stability in air, reusability, reactions with high efficiency, simple separation with magnetic external field from mixture reactions, chemical stability, and low toxicity.

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Chapter 10
Molecular Iodine: Mild, Green, and Nontoxic Lewis Acid Catalyst for the Synthesis of Heterocyclic Compounds

Anshu Dandia, Shyam L. Gupta and Shuchi Maheshwari

Contents

Abstract The synthetic uses of molecular iodine are described. This chapter discusses the versatile uses of iodine in heterocyclic synthesis. Iodine is a universal oxidizing agent, a mild and nontoxic Lewis acid catalyst, and it catalyzes various organic reactions with high efficiency and selectivity. Also, iodine acts as an electrophile–nucleophile dual activator in the reactions. Further applications are the introduction of protecting groups, deprotection, iodocyclization, C–C bond formation, and formation of heterocycles. It is quite clear from the growing number

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of emerging publications in this field that the possibility to utilize this technology allows accessing the reaction conditions that is valuable for heterocyclic synthesis. The present chapter focuses on literature reports for the period of 2003–2013.

Keywords Iodine · Green catalyst · Heterocyclic synthesis

1 Introduction

Iodine is a chemical element with symbol **I** and atomic number 53. The name is derived from the Greek word ἰοειδής *ioeidēs,* meaning violet or purple, due to the color of elemental iodine vapor. Iodine and its compounds are primarily used in nutrition and, industrially, in the production of acetic acid and certain polymers. Iodine's relatively high atomic number, low toxicity, and ease of attachment to organic compounds have made it a part of many X-ray contrast materials in modern medicine. Iodine is dissolved easily in most organic solvents such as hexane or chloroform owing to its lack of polarity, but is only slightly soluble in water [1].

Molecular iodine has gained considerable importance as a mild and nontoxic Lewis acid catalyst since it catalyzes various organic reactions with high efficiency and selectivity. Iodine has several advantages over the vast majority of other Lewis acid catalysts, especially the metallic catalysts. Its catalytic potential is intriguingly broad; it is a water-tolerant, relatively cheap, and environmentally friendly catalyst. Another distinctive feature of iodine is its high catalytic activity in dilute solutions, under highly concentrated reaction conditions (HCRC) as well as under solvent-free reaction conditions (SFRC). The later reaction conditions are particularly important in terms of green chemistry; they contribute to waste- and health-hazard minimization and cost efficiency. Iodine was established as a good mediator and reagent in organic synthesis [2, 3].

The numerous advantages and the mild Lewis acid character of iodine triggered us to review and investigate its catalytic influence. Iodine acts as an electrophile–nucleophile dual activator [4] in the reductive amination reaction. It carries out both electrophilic activation by coordinating the electrophilic center of molecular iodine with electronegative atoms such as N, O, etc. and nucleophilic activation through H bonding between electron-rich centers of molecular iodine and H atom. A three-point interaction model is shown in Fig. 10.1. It involves both electrophilic and nucleophilic activation.

Molecular iodine has recently been reported to be a Lewis acid imparting high regioselectivity and chemoselectivity in various transformations. For the last decade, the use of iodine as Lewis acid has been increasing exponentially due to its

1. High tolerance to air and moisture
2. Low cost and ready availability
3. High catalytic activity in dilute and highly concentrated conditions as well as under SFRC
4. Non-requirement of stringent dry conditions

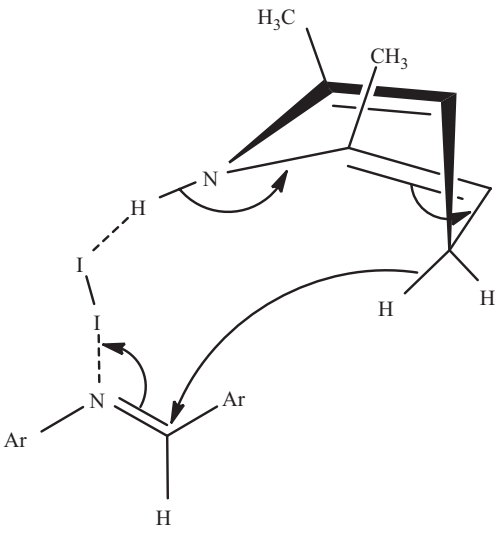


Fig. 10.1 Dual activation role of iodine in direct reductive amination (DRA)

Recently, Jereb et al. [5] published a review on iodine-catalyzed transformation of molecules containing oxygen functional groups. Iodine is capable of catalyzing the formation and scission of a broad range of different bonds, regardless of the hybridization of the atom. Earlier, Mphahlele et al. [6] published a review on molecular iodine-mediated cyclization of tethered heteroatom-containing alkenyl or alkynyl systems, and this review showed that iodine is an efficient, readily available, and easy-to-handle electrophilic reagent to effect halocyclization reactions to afford novel iodofunctionalized heterocyclic molecules that serve as versatile intermediates in synthetic organic chemistry. The combined electrophilic and oxidative potential of iodine can be exploited to synthesize novel aromatic and heteroaromatic compounds that would be difficult to synthesize.

Literature survey revealed that the history of heterocyclic chemistry began in the 1800s, in step with the development of organic chemistry. After World War II, there was an enormous explosion in research in the field of heterocycles. Out of the 12.5 million chemical compounds currently registered, about one half contain the heterocyclic system [7]. Heterocycles form, by far, the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only biologically and industrially but also for the functioning of any developed human society as well [8−10]. Most of the significant advances against diseases have been made by designing and testing new structures, which are often heteroaromatic derivatives. Heterocyclic compounds offer a high degree of structural diversity and have proved to be economically useful as therapeutic agents [11−13].

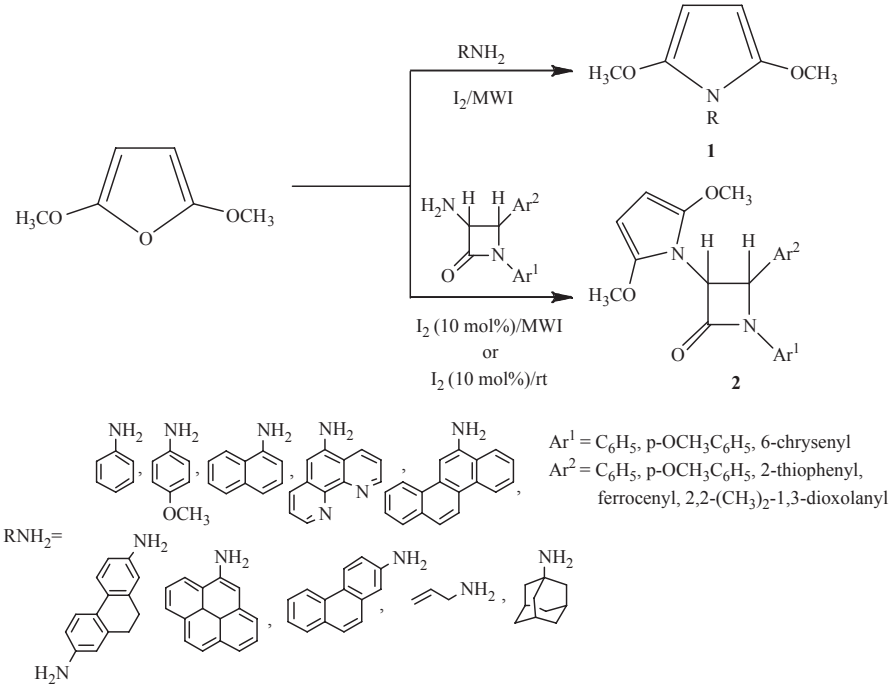
It is, therefore, easy to understand why the development of new methods and the strategic deployment of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry. For the sake of brevity and clarity, the text has been divided into various classes depending upon the construction of the size of heterocyclic ring system using iodine as a catalyst.

2 Five-Membered Heterocycles with One Heteroatom

2.1 Pyrroles

Pyrroles are key molecules of life, such as hemoglobin, chlorophyll, vitamin B_{12}, porphyrins, bile pigments, coenzymes and, more recently, as components of pharmaceuticals (currently, one of the best-selling drugs Lipitor (atorvastatin) has a pyrrole in its core) [14]. Pyrrole derivatives have also been reported as antimicrobial and antioxidant [15, 16], anti-HIV [17], anticancer [18, 19], antagonists of 5-HT7 receptor [20], antihepatitis [21], and as antifungal agents [22] as well as cognition enhancers [23]

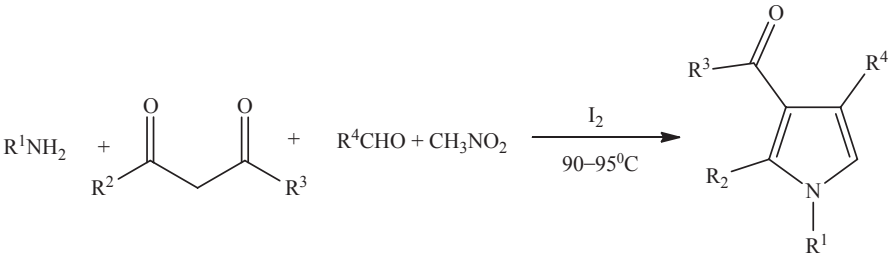
Banik et al. [24] reported an expeditious synthesis of *N*-substituted pyrroles **1** by reacting 2,5-dimethoxy tetrahydrofuran and several amines under microwave irradiation using iodine as a catalyst. 2-Azetidinones and pyrroles are two highly important classes of molecules in organic and medicinal chemistry. A green and practical method for the synthesis of 3-azetidinone-substituted pyrroles **2** using catalytic amounts of molecular iodine under microwave irradiation has been developed by the same group [25]. The extreme rapidity with excellent reaction yields is believed to be the result of a synergistic effect of the Lewis acid catalyst (molecular iodine) and microwave irradiation (Scheme 10.1). The reaction yields the products extremely well in the absence of any solvent. Both aliphatic and aromatic amines produce pyrroles in very high yield. A diamine and a heteropolyaromatic amine required higher temperature and longer reaction times, probably due to the diminished availability of the lone pair of nitrogen atom of amine.



Scheme 10.1

The methoxy groups in 2,5-dimethoxytetrahydrofuran can be deprotected under mild acidic conditions and microwave irradiation.

Pal et al. [26] reported an iodine-catalyzed four-component reaction of 1,3-dicarbonyl compounds, amines, aldehydes, and nitroalkanes affording polysubstituted pyrroles **3** under a metal-free condition. This is the first example of Grob and Camenisch's pyrrole synthesis [27] catalyzed by iodine via one-pot four-component reaction (Scheme 10.2).



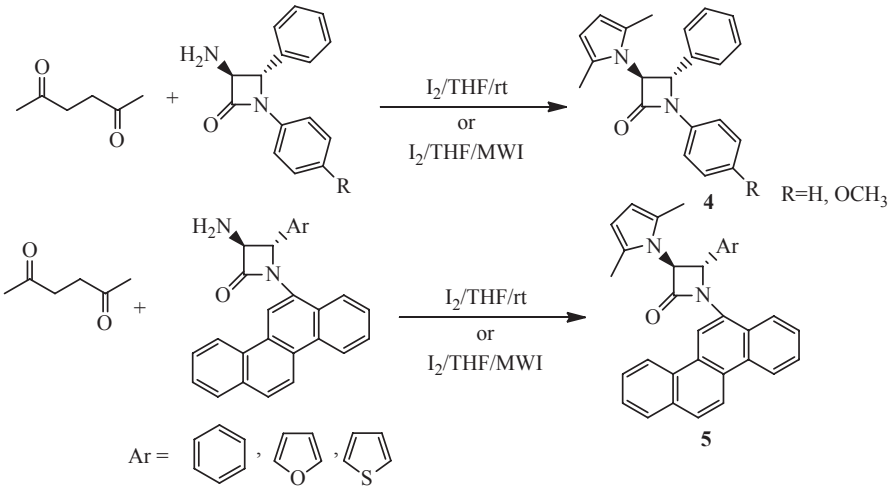
3

R_1 = $PhCH_2$, (R)-$Ph(CH_3)CH$, (S)-$Ph(CH_3)CH$,
1-Naphthyl, $HOCH_2CH_2$, Cyclohexyl
R^2 = CH_3; R^3 = CH_3, OC_2H_5
R^4 = C_6H_5 , 2,6-diF-4-BrC_6H_2, 3-BrC_6H_4, 4-BrC_6H_4,
2-IC_6H_4, 4-FC_6H_4,

Scheme 10.2

They used different catalysts for the synthesis of the desired product such as *p*-toluenesulfonic acid (*p*-TSA), CF_3SO_3H, and solid-supported catalyst such as $NaHSO_3$−SiO_2, but these were found to be less effective. The desired product was isolated only in 25–30% yield and the use of iodine increased the product yield significantly. The reaction was carried out using 0.1 mmol of iodine. The yield of the product was decreased when 0.05 mmol of iodine was used or suppressed when the reaction was performed at room temperature. The effect of solvents, e.g., DMF or tetrahydrofuran (THF) was also examined and found to be counterproductive.

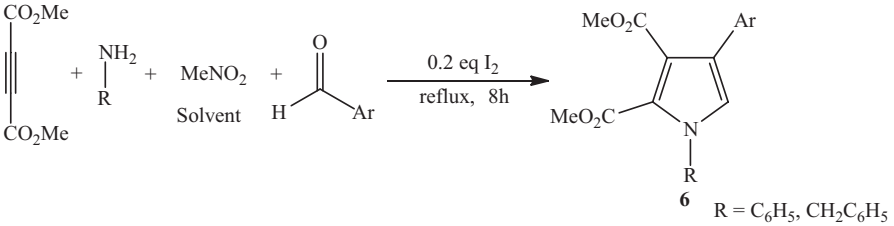
The synthesis and biological evaluation of various β-lactams as anticancer agents have been demonstrated by Banik et al. [28]. The anticancer activities of these compounds have prompted them to study the synthesis of pyrroles bound to the β-lactams **4** and **5**. They identified an expeditious synthetic method for the preparation of pyrroles fused with β-lactams by the reaction of 3-amino β-lactams with acetonylacetone in the presence of catalytic amounts (5 mol%) of molecular iodine at room temperature (Scheme 10.3).



Scheme 10.3

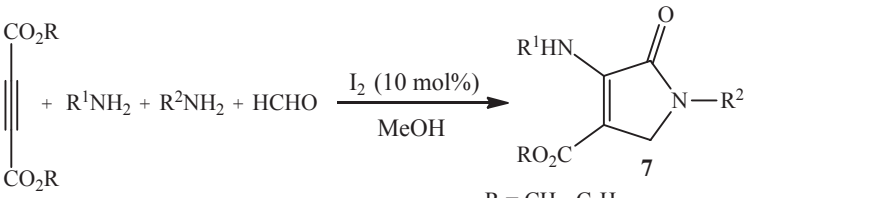
The reaction did not proceed at all without iodine even after 10 min of microwave irradiation. The presence of a small amount of iodine (5 mol%) is necessary for the occurrence of the reaction.

Das et al. [29] developed a simple, efficient, cost-effective, and metal-free four-component coupling reaction of aldehydes, amines, dialkyl acetylenedicarboxylates, and nitromethane for the synthesis of corresponding 1,2,3,4-tetra-substituted pyrroles **6** using molecular iodine as a catalyst (Scheme 10.4).



Scheme 10.4

Khan et al. [30] synthesized multifunctionalized dihydro-2-oxypyrrole **7** using one-pot four-component domino reaction from dialkylacetylene dicarboxylate, amines, and formaldehyde by employing molecular iodine as the catalyst. The salient features of this methodology were that it is simple, straightforward, cost-effective, and environmentally benign, with no need of column chromatographic separation and applicable for a broad range of substrates (Scheme 10.5).

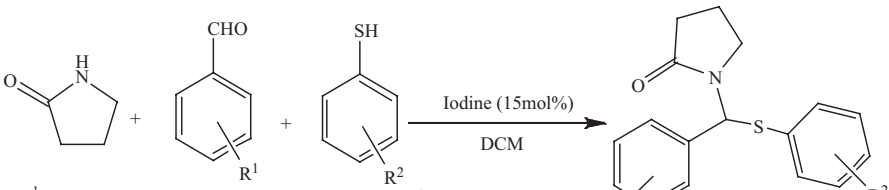


R = CH_3, C_2H_5
$R^1 = R^2 = C_6H_5$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$C_2H_5C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4,

Scheme 10.5

2.2 Pyrrolidinones

Sathiyanarayanan et al. [31] developed a simple and efficient three-component domino reaction of γ-butyrolactam (2-pyrrolidinone), aromatic aldehyde, and substituted thiophenol catalyzed by iodine for the synthesis of 1-((phenylthio)(phenyl) methyl)pyrrolidin-2-one derivatives **8**. The stability of the synthesized analogs was evaluated in stimulated gastric fluid (SGF) and bovine serum albumin (BSA; Scheme 10.6).



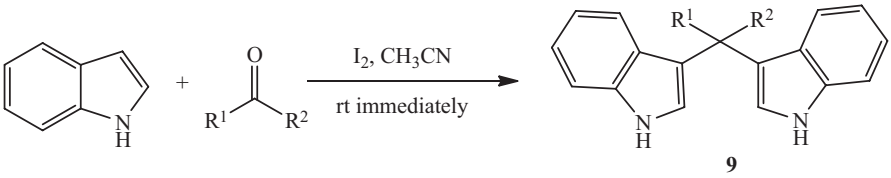
R^1 = H , 2-CH_3 , 4-CH_3 , 2-OCH_3, 4-OCH_3, 2-F,4-Cl, 2-OC_2H_5, 4-Br, 1-napthyl, terephthyl, 4-benzoyloxy
R^2 = 4-OCH_3, 4-Br

Scheme 10.6

2.3 Indoles

Indole ring is present in various marine or terrestrial natural compounds having useful biological properties [32, 33]. Substituted indoles show significant antibacterial, analgesic, anti-inflammatory, antipyretic, antitumor, anti-hypertensive, and antidepressant activities [34, 35].

Bandgar et al. [36] developed a rapid and efficient method for the electrophilic substitution reactions of indoles with various aldehydes and ketones using I_2 in CH_3CN to afford the corresponding bis(indolyl)methanes **9** in excellent yields (Scheme 10.7).



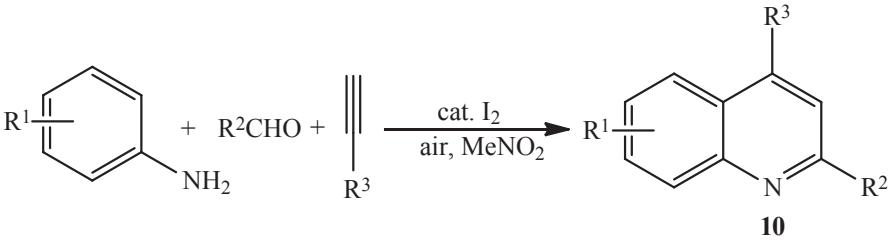
Scheme 10.7

3 Six-Membered Heterocycles with One Heteroatom

3.1 Quinolines

As a privileged fragment, quinoline is a ubiquitous subunit in many quinoline-containing natural products with remarkable biological activities [37]. Members of this family have wide applications in medicinal chemistry, being used as antimalarial, anti-inflammatory, antiasthmatic, antibacterial, anti-hypertensive, and tyrosine kinase-inhibiting agents [38, 39].

Lin et al. [40] developed a one-pot synthesis of quinolines **10** via molecular iodine-catalyzed and air-mediated tandem condensation/imino-Diels–Alder/isomerization/oxidation of amines, aldehydes, and alkynes (Scheme 10.8). They found that nitromethane was the most suitable solvent for this transformation as compared to acetonitrile, toluene, THF, dichloromethane (DCM), and ethanol (EtOH).



R^1 = H, 4-OCH_3, 4-Cl, 4-NO_2, 4-CH_3

R^2 = H, $CO_2C_2H_4$, C_6H_5, 4-$CH_3C_6H_4$, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 2-OHC_6H_4, 3,4-(-OCH_2O-)C_6H_4,

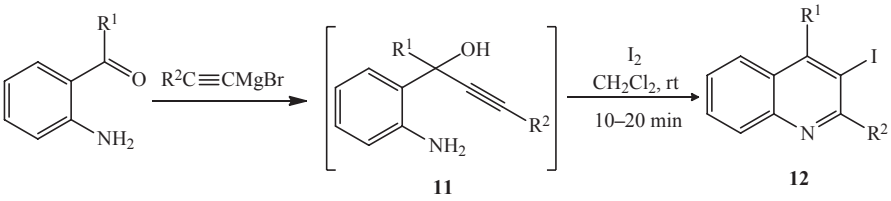
R^3= C_6H_5, 3-BrC_6H_4, 4-$CH_3C_6H_4$

Scheme 10.8

The versatility of this transformation was assessed by altering aldehydes. Isolated yield was tuned as a property of the presence of substituted groups on aldehydes. In case of aromatic aldehydes, the reaction was carried out under reflux condition. When the aromatic aldehyde carried an electron-donating group or an electron-withdrawing

group (except in the case of 4-nitrobenzaldehyde), isolated yields were comparable to those of ethyl glyoxalate (R^2 = COOEt). When an aliphatic aldehyde was used instead of the aromatic ones, the product was isolated in low yield (32%). Use of alkyne as a dienophile is suitable in this reaction and the key step of the mechanism may be an imino-Diels–Alder reaction.

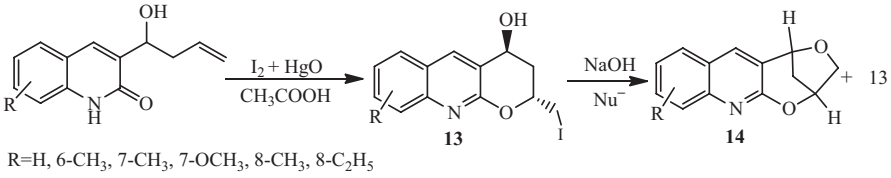
Reddy et al. [41] developed a method for the synthesis of substituted quinolines **12** from 2-aminoarylketones (via 1-(2-aminoaryl)-2-yn-1-ols **11**) using mild and simple reaction conditions. They used different iodine sources (I_2, NIS, and ICl) and I_2 was found to work efficiently for the synthesis of 3-iodoquinolines (Scheme 10.9).



Scheme 10.9

The pyranoquinoline moiety is an important structural feature of many alkaloids isolated from Rutaceae family [42] for example, flindersine, oricine, and verprisine [43] which have attracted great attention of synthetic as well as medicinal chemists.

A new and efficient method has been developed for the synthesis of furo[2′,4′:4,6] pyrano[2,3-*b*]quinolines **14** via a domino cyclization approach by Singh et al. [44] using iodine and mercuric oxide as a catalyst in acetic acid (Scheme 10.10).

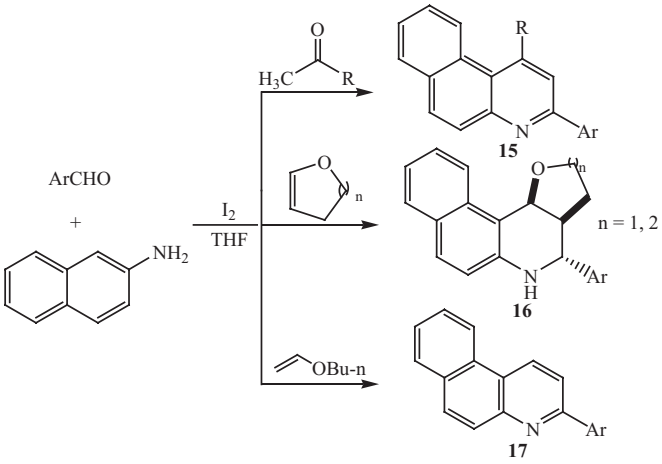


Scheme 10.10

In the presence of I_2/HgO, the less stable chair conformation of *cis*-pyranoquinolines **13**, in which 2-iodomethyl and 4-hydroxyl groups are axial, will predominate rather than the more stable chair conformation in which the 2-iodomethyl and 4-hydroxyl groups are equatorial. The 2-iodomethyl and 4-hydroxyl groups are in close proximity in the less stable conformation and undergo cyclization via nucleophilic benzylic oxide displacement of iodine to give the tetracyclic pyranoquinoline **14**.

Wang et al. [45] synthesized benzo[*f*]quinoline derivatives **15** via a three-component reaction of arylaldehyde, naphthalen-2-amine, and acetone or acetophenone**.** They [46] also explored the reaction of 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran in place of acetone or acetophenone for the synthesis of pyranoquinoline and

furoquinoline derivatives **16**. This methodology selectively formed the exo isomer of the product. They also expanded the scope of their reaction using chain vinyl ethers, *n*-butylvinyl ether with aromatic aldehyde, and naphthalen-2-amine to obtain *trans*-1-butoxy-1,2,3,4-tetrahydro-3-arylbenzo[*f*]quinoline derivatives, but surprisingly the butoxy group was not found in the ^{1}H NMR with aromatized 3-arylbenzo[*f*]quinolines **17** being obtained in high yields (Scheme 10.11).

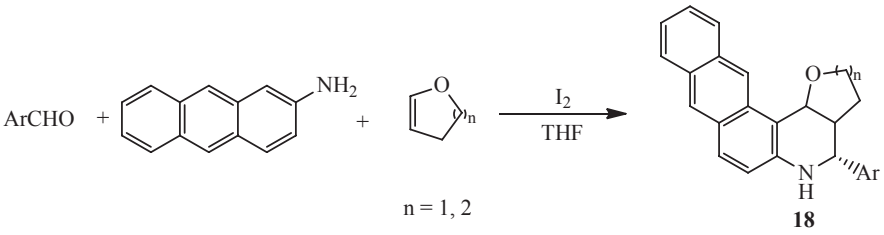


R = CH_3, C_6H_5, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4

Ar = 4-$CH_3OC_6H_4$, 2,3-$(CH_3O)_2C_6H_3$, 3,4-$(CH_3)_2C_6H_3$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-BrC_6H_4, 3-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 3-ClC_6H_4, 2-Thiophenyl

Scheme 10.11

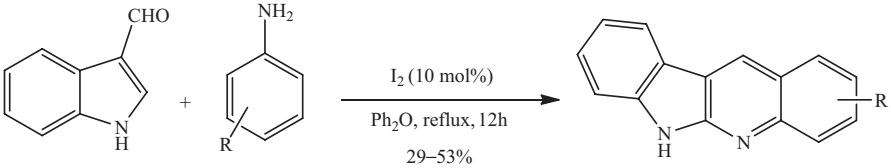
It was found that 5 mol% of I_2 at reflux in THF was sufficient to push the reaction forward. More amount of the catalyst did not improve the yields. They also extended the scope of the present reaction using naphthalen-2-amine, anthracen-2-amine, and selectively obtained exo-naphtho[2,3-*f*]furo(pyrano) [3,2-*c*]quinoline derivatives **18** (Scheme 10.12).



Ar = 4-$CH_3OC_6H_4$, 2-$CH_3OC_6H_4$, 2,3-$(CH_3O)_2C_6H_3$, 3,5-$(CH_3O)_2C_6H_3$, 3,4-$(CH_3)_2C_6H_3$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 3-BrC_6H_4, 2-BrC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 4-OHC_6H_4, 2,3-$Cl_2C_6H_3$, C_6H_5

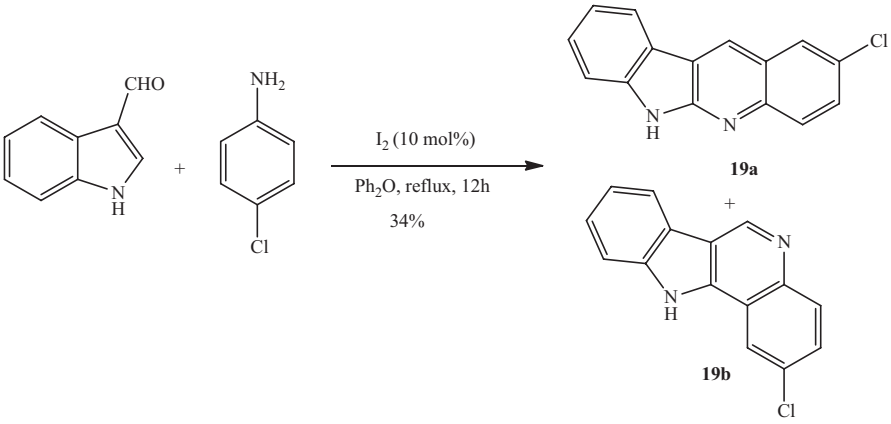
Scheme 10.12

Parvatkar et al. [47] developed a facile one-pot synthetic methodology of substituted linear and angular indoloquinoline derivatives **19** by the reaction of indole-3-carboxaldehyde and substituted anilines in the presence of iodine as a catalyst (Scheme 10.13). Some indolo[2,3-*b*]quinolines were tested against human hepatocellular carcinoma HepG2 and human breast carcinoma MCF-7 cells. In an antiproliferative assay against human hepatocellular carcinoma HepG2 and human breast carcinoma MCF-7 cells, methyl-substituted 6*H*-indolo[2,3-*b*]quinoline was found to be most active.



Scheme 10.13

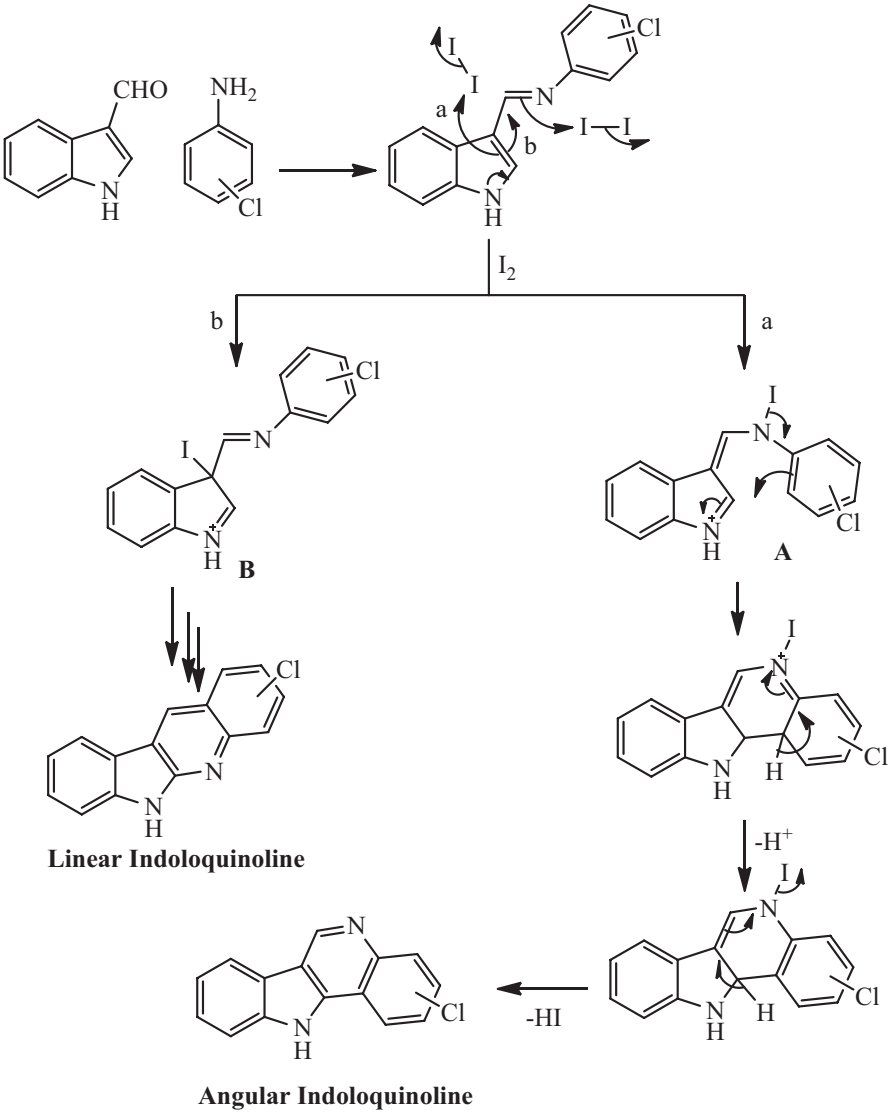
Earlier Parvatkar et al. [48] described the mechanistic pathway for the exclusive formation of linear indoloquinoline derivatives. However, in case of chloro-substituted anilines, the formation of both linear **19a** and angular indoloquinolines **19b** indicated that a different mechanism occurred for the formation of angular indoloquinoline (Scheme 10.14).



Scheme 10.14

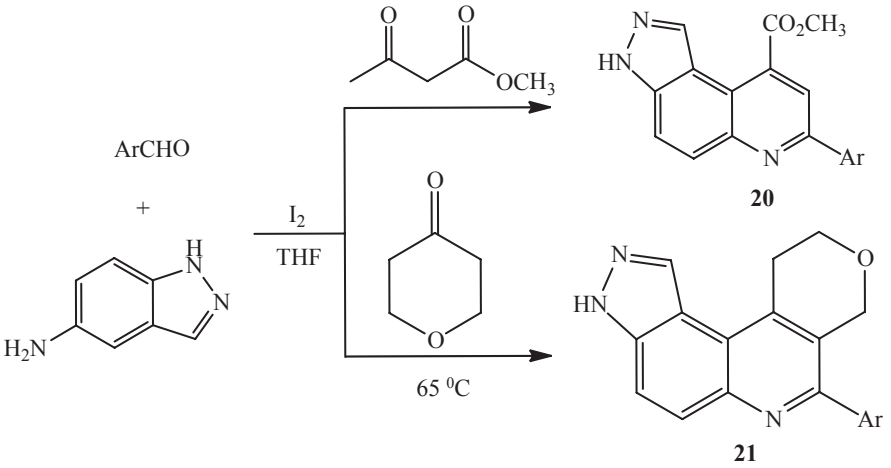
Initial electrophilic addition of iodine may lead to the formation of *N*-iodo-indolonium intermediate **A** (route a) and 3-iodo-indolinium cation **B** (route b). The formation of intermediate **A** may be facilitated due to the presence of the

electron-withdrawing chloro-substituent. Intramolecular cyclization of intermediate **A** led to the formation of angular indoloquinoline while that of intermediate **B** furnished the linear indoloquinoline (Scheme 10.15).



Scheme 10.15

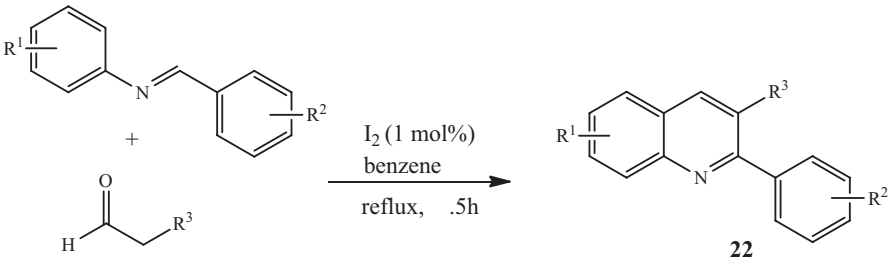
Wang et al. [49] developed a highly regioselective Povarov reaction of an aromatic aldehyde, 1*H*-indazol-5-amine, and methyl 3-oxobutanoate catalyzed by iodine. This novel reaction selectively gave 3*H*-pyrazolo[4,3-*f*]quinolin-9-yl acetates **20**, rather than 3*H*-pyrazolo[4,3-*f*]quinoline-8-carboxylate derivatives. Further, they [50] also extended the reaction using tetrahydropyran-4-one instead of methyl-3-oxobutanoate for the synthesis of 7-arylpyrano[3,4-*c*]pyrazolo[3,4-*f*]quinoline derivatives **21** (Scheme 10.16).



Ar = 4-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 4-$CH_3C_6H_4$, 3,4-$(CH_3)_2C_6H_3$, 3-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 3,4-$Cl_2C_6H_3$, Piperonyl

Scheme 10.16

Substituted quinolines **22** had been synthesized via molecular iodine-catalyzed one-pot domino reaction of imines with enolizable aldehyde by Yan-Guang et al. [51] (Scheme 10.17). They examined different solvents but benzene gave the best result and there was no product formation without using iodine. Different aniline and enolizable aldehydes were tested to afford the corresponding products but with enolizable acetophenone, instead of the aliphatic aldehydes, expected quinoline formation did not occur.

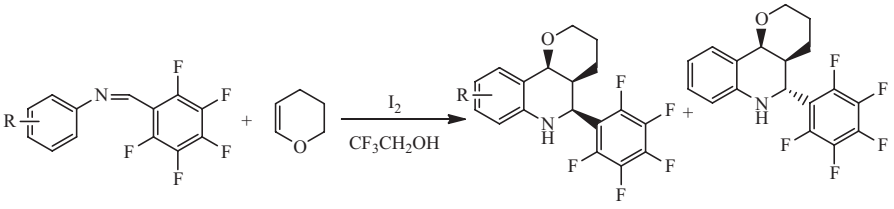


22

R1 = H, 4-OCH_3, 4-OC_2H_5, Br, 4-CH_3;
R2 = H, 4-Br, 4-CH_3, 3, 4-diCH_3, 4-Cl
R3 = n-$C_8H_{17}CH_2$, n-$C_7H_{15}CH_2$, n-$C_6H_{13}CH_2$
n-$C_5H_{11}CH_2$, n-$C_4H_9CH_2$, i-$C_3H_7CH_2$, $C_6H_5CH_2$

Scheme 10.17

Zhang et al. [52] used iodine to catalyze the hetero-Diels–Alder reaction of pentafluorobenzylidineaniline ($C_6F_5CH{=}NAr$) with enol ethers to afford the corresponding tetrahydroquinoline derivatives **23** and **24** as a mixture of *cis/trans* stereoisomers. Mild and neutral reaction conditions, facile experimental procedure, and the use of iodine made this method attractive for practical synthesis of many fluorinated tetrahydroquinoline derivatives (Scheme 10.18).

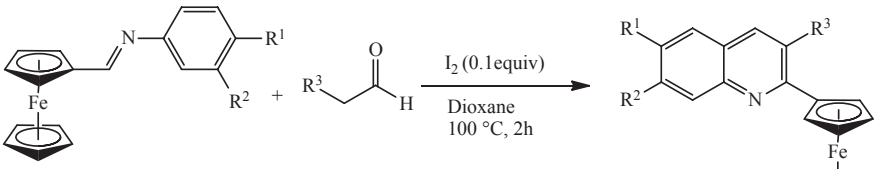


R = H, 4-CH_3, 4-OCH_3, 2,3-diCH_3, 4-Cl

23 24

Scheme 10.18

Zora et al. [53] synthesized ferrocenyl-substituted quinolines **25** via molecular iodine-catalyzed reaction of ferrocenylimines with enolizable aldehydes (Scheme 10.19) yielding only one regioisomer but interestingly when imines with $R^1{=}H$ and $R^2{=}CH_3$ and aldehydes with $R^3{=}CH_3$ were used, it resulted in a complex mixture and 2-ferrocenyl-3,7-dimethylquinoline was isolated in low yield (25%). Formation of polymeric by-products as well as the partial hydrolysis of starting imine lowered the yield of the product.

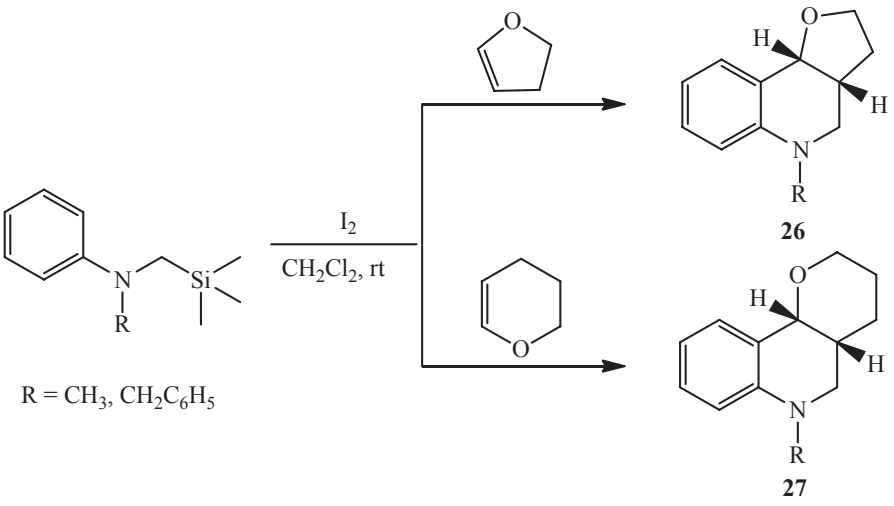


R^1 = H, Cl, Br
R^2 = H, CH_3
R^3 = H, CH_3

Scheme 10.19

Imines can be activated by iodine and similarly, in the presence of iodine, aldehydes can be easily equilibrated with their enols. The reaction between in situ-generated enol and iodine-activated imine through subsequent steps involving intramolecular Friedel–Crafts reaction and dehydration leading to the formation of dihydroquinoline and the aerobic oxidation of dihydroquinoline yields the expected quinoline derivative.

Reddy et al. [54] developed a method involving in situ-generated aza-diene, from *N*-[methyl-*N*-(trimethylsilyl)methyl]aniline using catalytic amount of molecular iodine which undergoes smooth [4+2] cycloaddition with electron-rich enol ethers, such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran to afford the corresponding hexahydropyrano **26** and furo[3,2-*c*]quinoline derivatives **27**, respectively, in good yields (Scheme 10.20).



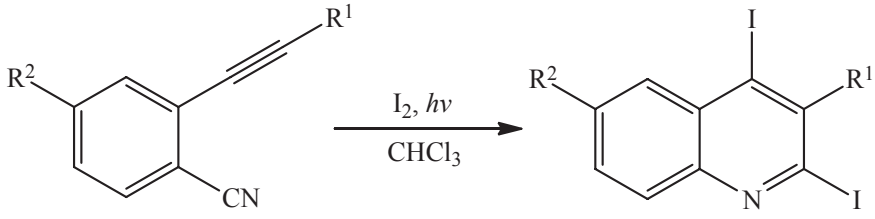
R = CH_3, $CH_2C_6H_5$

Scheme 10.20

The catalytic efficiency of various Lewis acids, such as $InCl_3$, $BiCl_3$, $ZnCl_2$, and $FeCl_3$ was tested for this transformation. The reactions were not clean with the above Lewis acids and also the products were obtained as a mixture of isomers while molecular iodine was found to be the most effective. In the absence of iodine, the reactions did not proceed even after 12 h indicating that molecular iodine is essential to facilitate the reaction. Out of the solvents studied, DCM appeared to give the best results.

Mechanistically, iodine reacts initially with *N*-arylamino-*N*-alkylsilane to generate an iminium ion, which subsequently undergoes [4+2] cycloaddition to afford a desired bicyclic quinoline derivative.

Akiya et al. [55] developed a photoirradiated method for the synthesis of *o*-alkynylaryl isocyanides in the presence of iodine via the intramolecular cyclization of *o*-alkynylaryl isocyanides affording the corresponding 2,4-diiodoquinolines **28** (Scheme 10.21). 2,4-Diiodoquinolines can be used in different cross-coupling reactions catalyzed by transition metal catalysts.



$R^1 = C_6H_5$, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, $CH_3(CH_2)_3$, $(CH_3)_3Si$, 1-cyclohexynyl

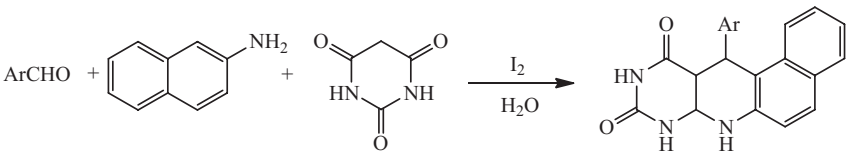
$R^2 = H, CH_3, CF_3$

28

Scheme 10.21

Upon photoirradiation, isocyanide underwent iodocyclization to afford corresponding product selectively. The yield of **28** increased with the increase in the amount of I_2. In contrast, no reaction took place in the dark. Further, they also demonstrated the synthetic application of 2,4-diiodoquinolines for palladium-catalyzed cross-coupling reactions to afford a wide variety of multifunctionalized quinoline derivatives.

Wang et al. [56] developed a one-pot iodine-catalyzed synthesis of benzo[*f*]pyrimido[4,5-*b*]quinoline derivatives **29** via a three-component reaction of benzaldehydes, naphthalen-2-amine, and barbituric acid at room temperature in aqueous media (Scheme 10.22). The reaction was carried out in water at room temperature to avoid a ring-opening reaction. It was observed that no reaction occurred without using the catalyst. Then, reaction was attempted by changing the mol% of I_2. The results showed that 5 mol% I_2 at room temperature in water was sufficient to push the reaction forward. Increased loading of the catalyst did not improve the yield to a great extent.

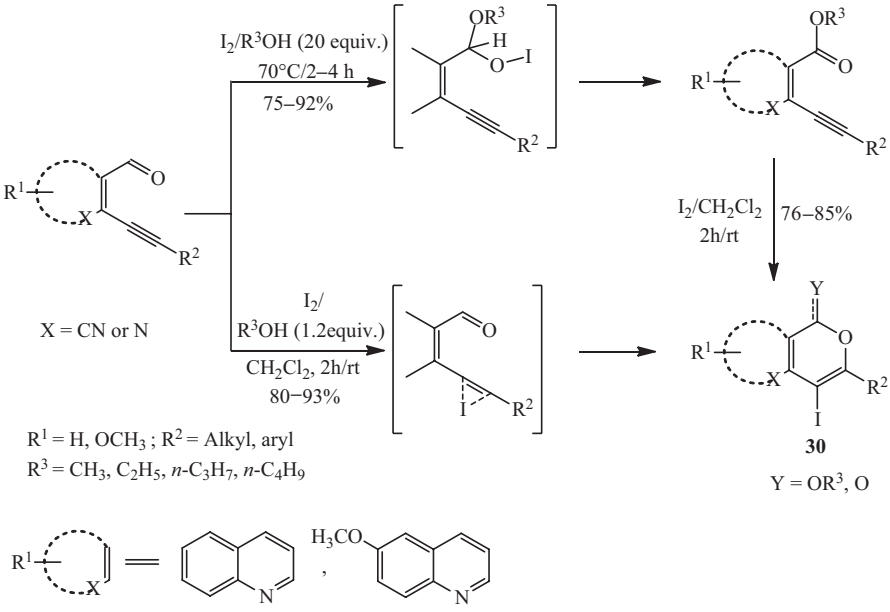


29

Ar = 2,3-$Cl_2C_6H_3$, 3-BrC_6H_4, 2,4-$Cl_2C_6H_3$, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 2,3-$(CH_3O)_2C_6H_3$, 3-$NO_2C_6H_4$, 3,4-$(CH_3)_2C_6H_3$, C_6H_5, 2-$CH_3OC_6H_4$, 3,5-$(CH_3O)_2C_6H_3$, 2-BrC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 4-HOC_6H_4, 4-$NO_2C_6H_4$

Scheme 10.22

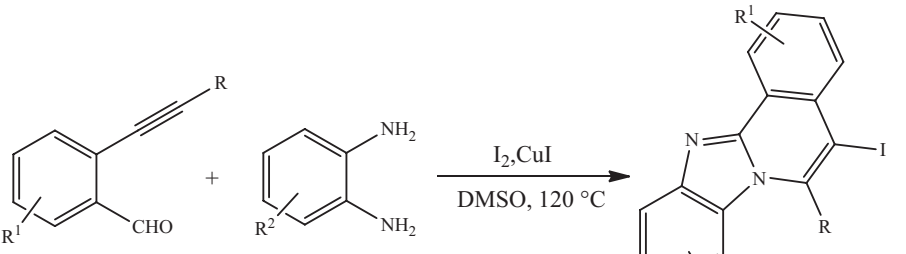
Verma et al. [57] synthesized iodine-catalyzed 4-iodo-pyrano[4,3-*b*]quinoline derivatives **30** and ortho-alkynyl esters selectively from ortho-alkynyl aldehydes by solvent-controlled reaction (Scheme 10.23).



Scheme 10.23

This is the first report of the iodine-catalyzed selective synthesis of iodo-pyrano[4,3-*b*]-quinolines and ortho-alkynyl esters from ortho-alkynyl aldehydes. The developed novel oxidative esterification process provides a powerful tool for the preparation of a wide range of functionalized pyranoquinolinones as well as isocoumarins.

Zhang et al. [58] developed an efficient tandem route for the synthesis of iodoisoquinoline-fused benzimidazole derivatives **31** including an iodocyclization strategy. In the presence of CuI, a variety of 2-ethynylbenzaldehydes underwent the tandem reaction with benzenediamines and iodine to afford the corresponding iodoisoquinoline-fused benzimidazoles in moderate to good yields (Scheme 10.24).

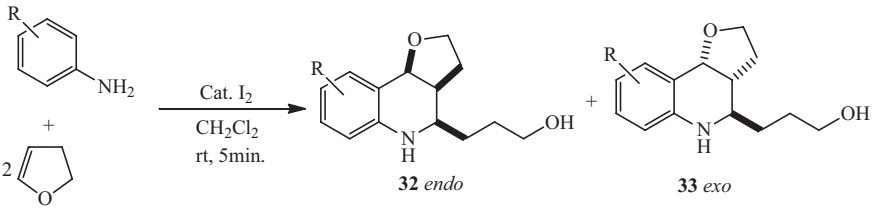


$R = C_6H_5$
R^1 = H, 3-CH_3, 3-OCH_3, 3-Cl
R^2 = 4-CH_3, 4,5-$(CH_3)_2$, 4,5-Cl_2, 4-CF_3

Scheme 10.24

This protocol allows the formation of two heterocyclic rings in a one-pot reaction through the electrophilic annulation. Most importantly, these isoquinoline-fused benzimidazoles with a halo group are important scaffolds for the introduction of various functional groups and significant for drug discovery.

Wang et al. [59] developed a highly efficient method for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives **32** and **33** via a molecular iodine-catalyzed domino reaction of aniline with cyclic enol ethers, such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran. The reaction may proceed through an aza-Diels–Alder process between in situ-generated 2-azadiene and another equivalent of cyclic enol (Scheme 10.25).



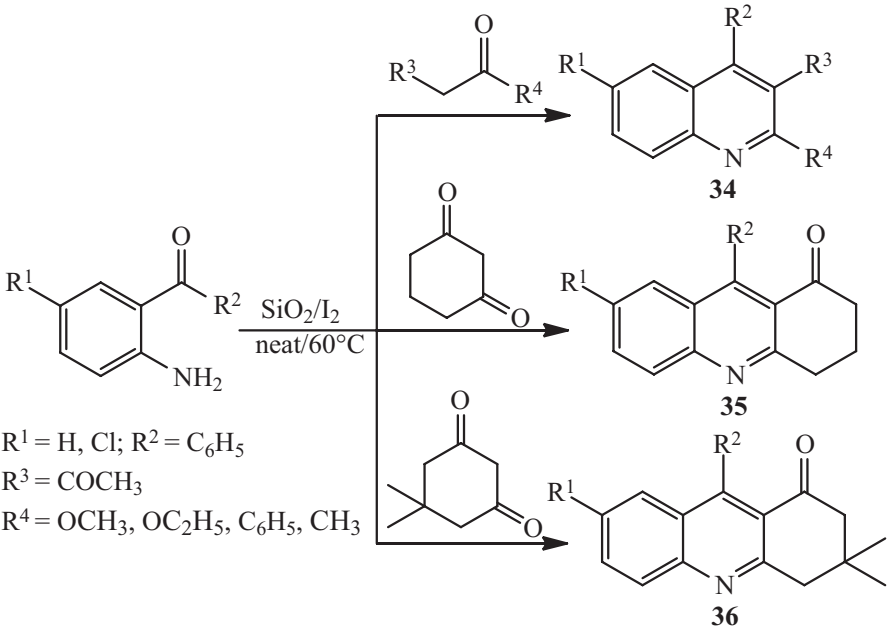
R = H, 4-F, 4-Cl, 4-Br, 4-CH_3, 4-OCH_3, 4-OC_2H_5, 2-CH_3, 4-NO_2, 2,4-$(CH_3)_2$

Scheme 10.25

Different anilines have been used to afford the corresponding products. In all cases, the products were obtained as a mixture of *endo-*/*exo*-isomers. The reaction

using less reactive 3,4-dihydro-2*H*-pyran under the same reaction conditions gave the product in poor yields.

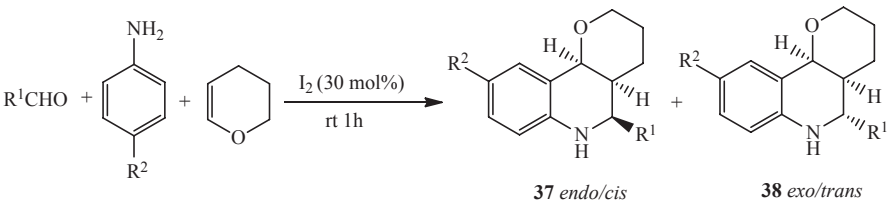
Zolfigol et al. [60] synthesized polyfunctional quinolines **34, 35,** and **36** using Friedlander method catalyzed by molecular iodine in high yields at 60 °C under solvent-free conditions (Scheme 10.26).



Scheme 10.26

They successfully developed an easy and efficient method for the preparation of various quinoline derivatives from different ketones and diketones with 2-aminoarylketones in the presence of catalytic amount of iodine and silica gel at 60 °C under solvent-free conditions. SiO_2 together with molecular iodine is a good catalyst and the reaction proceeded well with moderate to high yields. Under this new condition, 1,3-cyclohexanedione reacted faster than other diketones to produce the corresponding quinolines in high yields.

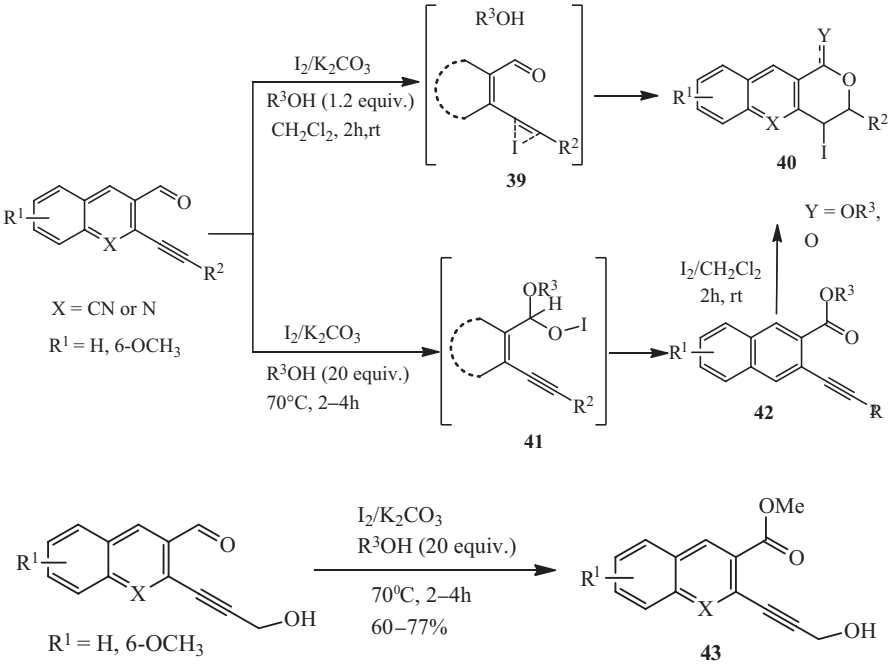
Shashikanth et al. [61] reported iodine-catalyzed aza-Diels–Alder (Povarov) reaction of 3,4-dihydro-2*H*-pyran with in situ-generated *N*-arylimines containing enolizable protons using acetonitrile as a solvent. It is an easy way to introduce C-2 aliphatic substitution in tetrahydroquinolines **37** and **38** (Scheme 10.27). A mixture of *cis* and *trans* products was obtained, but in the case of cyclopropane-substituted compound, the *trans* product is formed selectively in a good amount.



R^1 = 1-ethylpropyl, cyclopropyl
R^2 = H, OCH_3, CF_3, n-C_4H_9, t-C_4H_9

Scheme 10.27

Verma et al. [62] observed a chemoselective behavior of iodine in different solvents in the electrophilic iodocyclization of *o*-alkynyl aldehydes. *o*-Alkynyl aldehydes on reaction with I_2 in CH_2Cl_2 with appropriate nucleophiles provided pyrano[4,3-*b*]quinolines **40** via the formation of cyclic iodonium intermediate **39**. In case of using alcohols as a solvent as well as nucleophile, *o*-alkynyl esters **42** were obtained selectively in good to excellent yields via the formation of hypoiodide intermediate **41**. Subsequently, *o*-alkynyl esters **42** were converted into pyranoquinolinones and isocoumarins by electrophilic iodocyclization. The developed oxidative esterification provides a novel access for the chemoselective synthesis of esters **43** from aldehydes without oxidizing primary alcohol present in the substrate (Scheme 10.28).



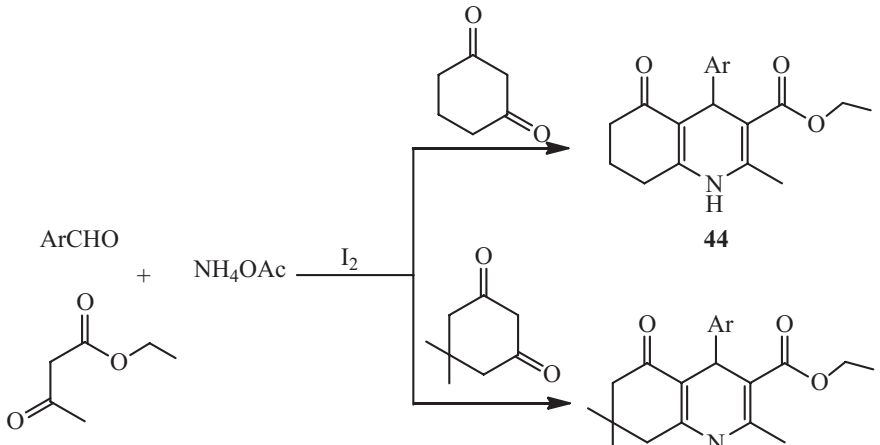
Scheme 10.28

Iodine-catalyzed and solvent-controlled selective method for the synthesis of iodopyrano[4,3-*b*]quinolines and *o*-alkynyl esters from *o*-alkynyl aldehydes in mild reaction conditions is developed for the first time by Verma et al. This novel oxidative esterification provides a powerful tool for the preparation of a wide range of functionalized pyranoquinolinones as well as isocoumarins, and it is applicable for a variety of functional groups including primary alcohol, carboxyl, and methoxy groups.

3.2 Pyridines

Dihydropyridine (DHP) drugs such as nifedipine, nicardipine, amlodipine, and others are effective cardiovascular agents for the treatment of hypertension [63]. DHPs have been explored for their calcium channel activity and are found as a constituent in a variety of bioactive compounds which show many biological activities such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, antidiabetic, geroprotective, heptaprotective [64], etc.

Yao et al. [65] developed a simple, inexpensive, and efficient one-pot synthesis of 1,4-DHP derivatives **44** and **45** at room temperature using catalytic amount of iodine with excellent product yields (Scheme 10.29). This method offers several advantages such as shorter reaction times, milder conditions, simplicity of the reaction, and excellent product yields. The easy procedure to carry out the reaction using inexpensive and commercially available iodine made it a powerful catalyst for the synthesis of 1,4-DHPs.

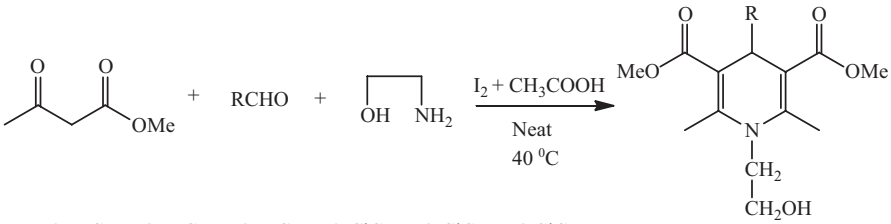


Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$,
4-FC_6H_4, 4-ClC_6H_4, 4-OHC_6H_4,
2,$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$,
Iso-C_3H_7

Scheme 10.29

In this reaction, significant improvement in the yield of the product **44** (Ar = C_6H_5) was observed when iodine (15 mol%) was employed as a catalyst (56–99 %). The increase in the quantity of iodine from 15 to 30 mol% not only reduced the reaction time from 4 to 2.5 h but also enhanced the product yield from 56 to 99 %. Similarly, the use of 50 mol% of iodine as the catalyst further reduced the reaction time to 1.5 h along with a decrease in the yield of the product **44** (70 %).

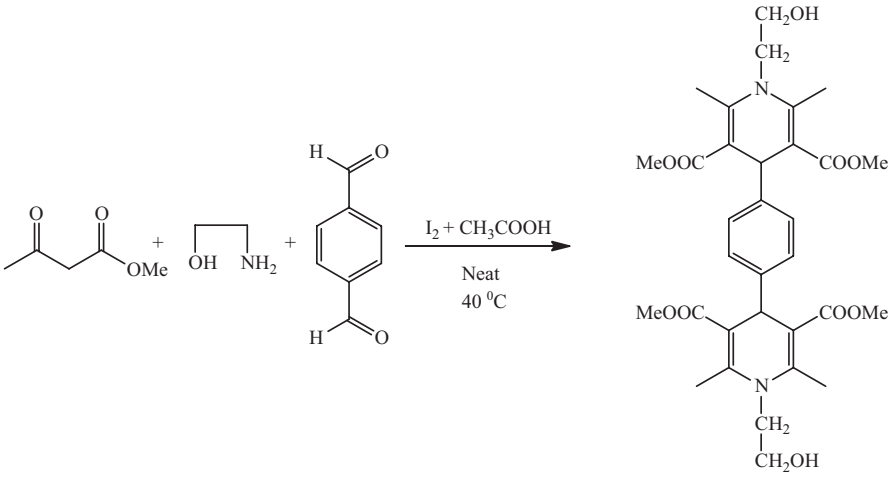
Zolfigol et al. [66] reported the synthesis of 1,4-DHP derivatives **46** and **47** under mild and solvent-free conditions using a mixture of ethanolamine, aldehydes, and methyl acetoacetate in the presence of acetic acid and iodine as a catalyst for the synthesis of 1,4-DHPs (Schemes 10.30 and 10.31).



R = 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-Furyl ,2-Thienyl

46

Scheme 10.30



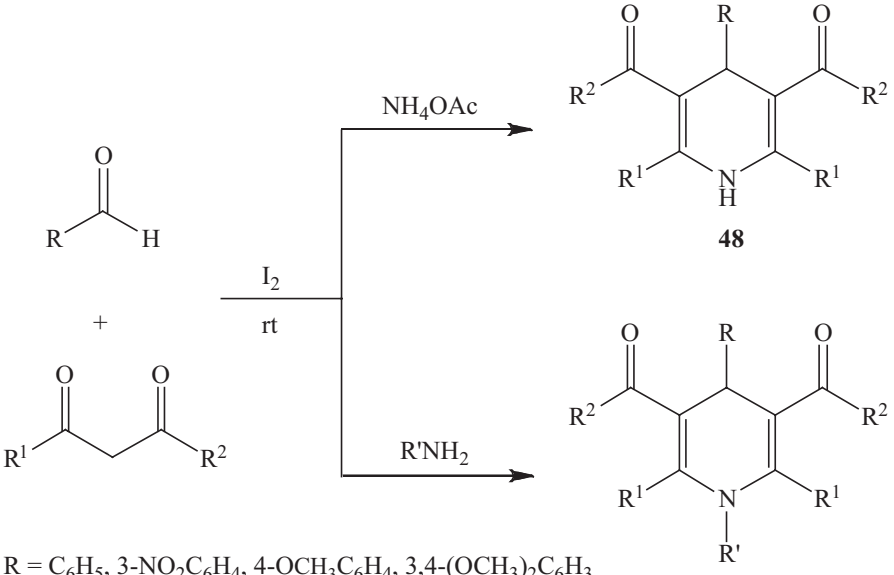
47

Scheme 10.31

Although reactions occurred both in the presence and absence of molecular iodine, I_2 catalyzed the reaction efficiently and also improved the reaction yields. Showing the catalytic role of iodine, two reactions were run solely in the presence

of I_2 and in acetic acid without iodine. Reaction did not occur in the absence of acetic acid and I_2. Therefore, one of them is necessary for this reaction.

Joshi et al. [67] developed an efficient and simple one-pot synthesis of some new symmetrical, unsymmetrical, and *N*-substituted Hantzsch 1,4-DHPs **48** and **49** using molecular iodine as catalyst by the reaction of aldehydes, 1,3-dicarbonyl compound, and ammonium acetate/aromatic amine in EtOH. This new method has the advantage of good to excellent product yields and shorter reaction times at ambient temperature (Scheme 10.32).

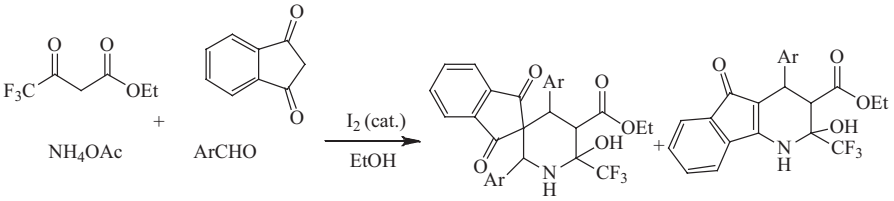


R = C_6H_5, 3-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$, 3,4-$(OCH_3)_2C_6H_3$
R^1 = $CH(CH_3)_2$, CH_3; R^2 = $OCH(CH_3)_2$, OCH_3
R' = 4-$OCH_3C_6H_4$, C_6H_5

Scheme 10.32

For the synthesis of the desired product, 30 mol% of catalyst was sufficient, and a small amount of EtOH afforded the corresponding 1,4-DHPs in 88–95 % yield at room temperature. This methodology offers very attractive features such as shorter reaction times, milder conditions with simplicity of the reaction, good to excellent product yields, and commercially available iodine as a powerful catalyst for the synthesis of 1,4-DHPs.

Liping et al. [68] reported the iodine-catalyzed one-pot multicomponent reaction of ethyl trifluoroacetoacetate, indan-1,3-dione, ammonium acetate, and aromatic aldehyde which gave ethyl-6′-hydroxy-1,3-dioxo-2′,4′-diaryl-6′-(trifluoromethyl)-1,3-dihydrospiro[indene-2,3′-piperidine]-5′-carboxylate derivatives **50** as the major product and 2-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-b]pyridine derivative **51** as the minor product (Scheme 10.33).

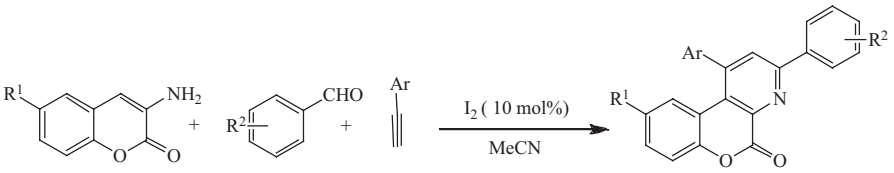


Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 2-$CH_3OC_6H_4$, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 3-$C_6H_5OC_6H_4$

Scheme 10.33

In the absence of catalytic amount of molecular iodine, the reaction did not occur even after reflux for 12 h in EtOH. The 0.05 equimolar amount of molecular iodine was insufficient to push the reaction forward and higher catalyst loading (from 0.2 to 0.4 equivmolar amount of molecular iodine) neither shortened the reaction time, nor increased the products yields. The reactions gave better yield in polar protic solvents such as EtOH and MeOH as compared to aprotic solvents.

Khan et al. [69] synthesized pyrido[2,3-*c*]coumarin derivatives **52** from 3-aminocoumarins, aromatic aldehydes, and alkynes in the presence of 10 mol% of molecular iodine in acetonitrile under reflux conditions through one-pot Povarov reactions (Scheme 10.34).



R^1 = H, Br, OCH_3
R^2 = H, Cl, Br, F, CH_3, CH_3O, CN, NO_2
Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-tert-Bu-C_6H_4
3,4-$(CH_3)_2C_6H_3$, 3,5-$(CH_3)_2C_6H_3$, 1-$C_{10}H_7$

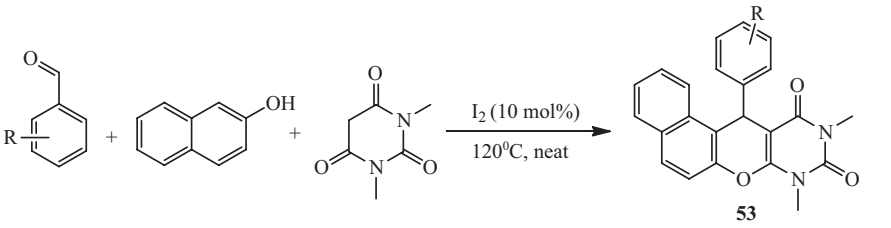
Scheme 10.34

3.3 Pyrans

Pyrans and fused pyrans are biologically interesting compounds with antibacterial [70], antifungal [71], and antitumor activities [72]; hypotensive effects [73]; and spasmolytic, hypnotic, diuretic, and insecticidal properties [74, 75]. Further, multisubstituted 4*H*-pyrans also constitute a structural unit of a series of natural products [76, 77].

Subba Reddy et al. [78] developed a highly efficient iodine-catalyzed methodology for the three-component coupling (3CC) of aldehydes, β-naphthol, and 1,3-dimethylbarbituric acid under solvent-free conditions affording the corresponding

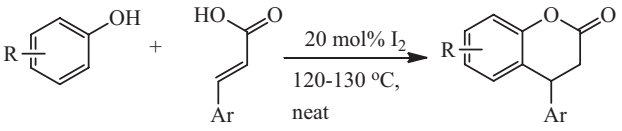
8,10-dimethyl-12-aryl-12*H*-naphtho[1′,2′5,6]pyrano[2,3-*d*]pyrimidine-9,11-diones **53** with high selectivity (Scheme 10.35).



R=H, 4-Cl, 4-Br, 4-F, 4-CH_3, 3-Cl, 4-NO_2, 4-CN, 2-Br, 2,4-Cl_2, 3-OC_6H_5

Scheme 10.35

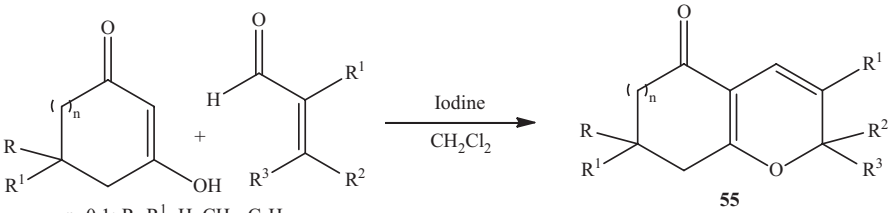
Tilve et al. [79] developed a molecular iodine-catalyzed synthesis of substituted 4-aryl-3,4-dihydrobenzopyran-2-ones **54** by [3 + 3] cyclocoupling of phenols and cinnamic acids which proceeds via a tandem esterification–hydroarylation process at 120–130 °C under solvent-free conditions (Scheme 10.36).



R = 3-CH_3, 4-CH_3, 2-CH_3, 2,3-$(CH_3)_2$, 2,5-$(CH_3)_2$, 3,5-$(CH_3)_2$, 3,4-$(CH_3)_2$, 4-OH, 4-Cl, 4-NO_2, 4-F,3-NO_2

Scheme 10.36

Lee et al. [80] synthesized 2*H*-pyrans **55** by the reaction of cyclic 1,3-dicarbonyl compound with 3-methyl-2-butenal or 1-cyclohexene-1-carboxaldehyde in methylene chloride using iodine as a catalyst. Mechanistically, iodine first activated carbonyl oxygen atom of 3-methyl-2-butenal to give iodine–aldehyde complex and thus increased the electrophilicity of carbonyl carbon of aldehydes (Scheme 10.37).



n=0,1; R=R^1=H, CH_3, C_6H_5
R^2=R^3=H, CH_3

Scheme 10.37

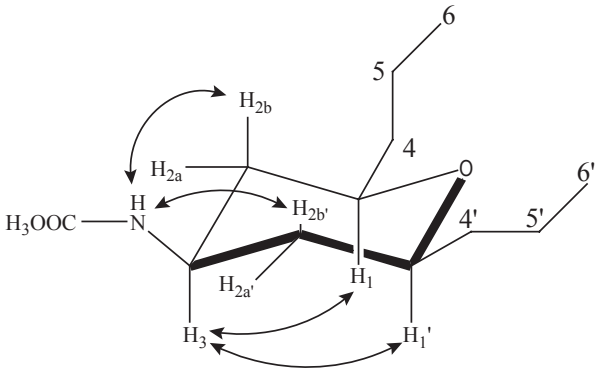
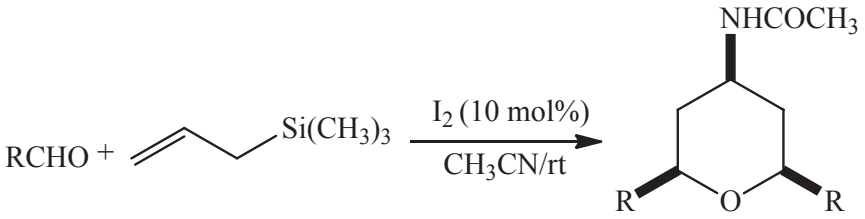


Fig. 10.2 Schematic NOE diagram of **56** (R = $CH_2CH_2CH_3$)

Sabitha et al. [81] developed a simple and efficient one-pot synthetic strategy for the synthesis of symmetrical 4-amido tetrahydropyrans **56** via the Sakurai–Prins–Ritter reaction sequence using molecular iodine as the catalyst by the reaction of aldehyde and allyltrimethylsilane in acetonitrile at room temperature (Scheme 10.38).



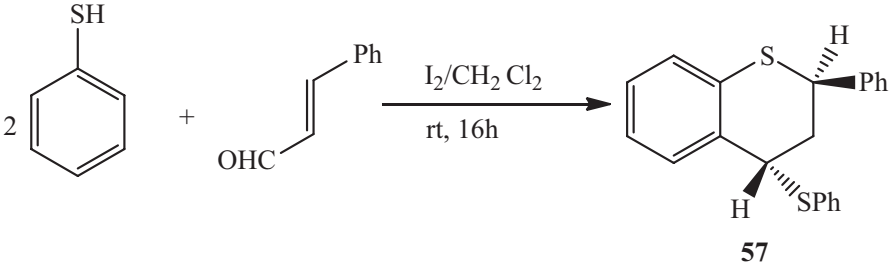
R = C_6H_5, 4-$CH_3C_6H_4$, 4-FC_6H_4, 4-$NO_2C_6H_4$, 2-ClC_6H_4, 3-$NO_2C_6H_4$, 2,6-$(OCH_3)_2C_6H_3$, CH_3CH_2, $CH_3(CH_2)_2$, $CH_3(CH_2)_4$, $CH(CH_3)_2$ **56**

Scheme 10.38

The structure of the 2,6-disubstituted-4-acetamido tetrahydropyran was established by nuclear Overhauser effect (NOE) experiments. From NOE studies, it was confirmed that all three substituents occupy equatorial positions on the tetrahydropyranyl ring (Fig. 10.2).

They noticed that $\delta H_1 = \delta H_{1'}$, $\delta H_{2a} = \delta H_{2a'}$, and $\delta H_{2b} = \delta H_{2b'}$. NOE cross peak $CH_1 = CH_3$ ($CH_{1'} = CH_3$) reveals that $H_1(H_{1'})$ and H_3 are on the same side of the ring and take a diaxial orientation. The proposed structure of **56** was further supported by the coupling constants $^3J_{CH1/CH2a} = 1.8$, $^3J_{CH1/CH2b} = 11.7$, $^3J_{CH2a=CH3} = 4.3$, and $^3J_{CH2b/CH3} = 11.7$ Hz. Thus, CH2b(CH2b′) is antiperiplanar to both $CH_1(CH_{1'})$ and CH_3. Interestingly, they also observed a ω coupling of ~2 Hz between H_{2a} and $H_{2a'}$, further supporting their equatorial orientation. All the findings confirm that the pyran ring takes a chair conformation, where substituents at C_1, $C_{1'}$, and C_3 are present in equatorial positions.

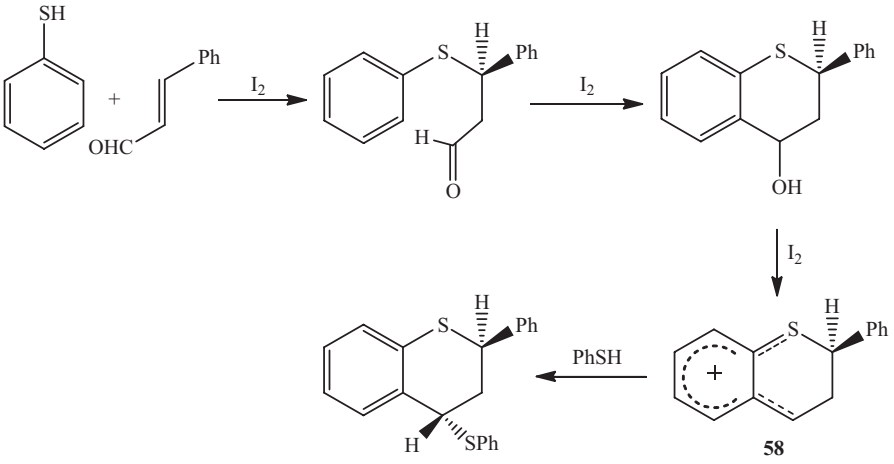
Mallik et al. [82] described a rapid iodine-catalyzed cyclocondensation of cinnamaldehyde and thiophenol to synthesize trans-2-phenyl-4-thiophenoxy-3,4-dihydro-2*H*-1-benzothiopyran **57** in excellent yields with high diastereoselectivity (Scheme 10.39).



57

Scheme 10.39

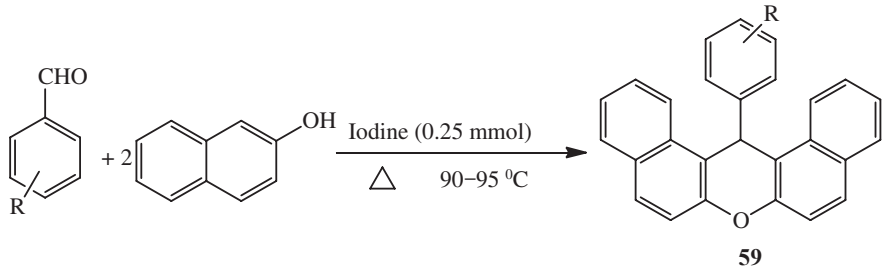
High diastereoselectivity of the iodine-catalyzed reaction may be accounted by the consideration that the stable cation **58** (generated by the initial combination of the two reactants followed by cyclization) was formed selectively from the side opposite of the existing phenyl group (Scheme 10.40).



Scheme 10.40

3.4 Xanthenes

Pasha et al. [83] reported the molecular iodine-catalyzed reaction of β-naphthol and araldehydes on a preheated hot plate at 90–95 °C to give aryl-14*H*-dibenzo[*a, j*] xanthene derivatives **59** under solvent-free conditions (Scheme 10.41).

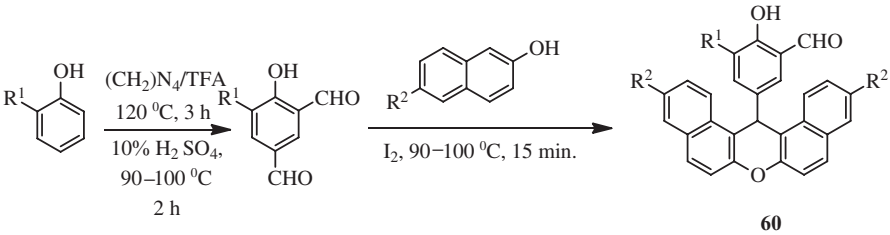


59

R = H, CH_3, NO_2, OCH_3, Cl, Br, F

Scheme 10.41

Sashidhara et al. [84] reported the iodine-catalyzed one-pot regioselective synthesis of *p*-condensed xanthenes **60.** The developed method provides an efficient access to five skeletally diverse scaffolds in excellent yields (Scheme 10.42).



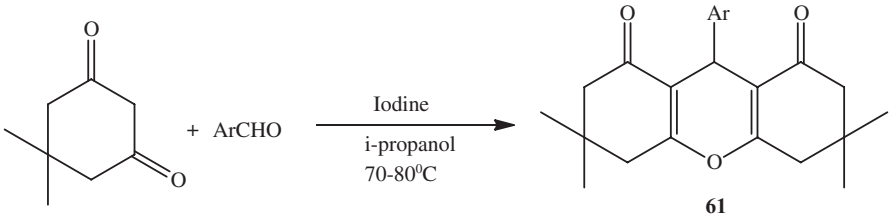
60

R^1 = $^sC_4H_9$, $^tC_4H_9$, $^iC_3H_7$, C_2H_5
R^2 = H, Br

Scheme 10.42

The advantages of this method are the ease of modification of each unit and their combination with other pharmacophores as potential pharmacological agents. This transformation could be of immense importance to medicinal chemists using appropriate templates to generate a library of substituted xanthenes. It is proved to be a diversity-oriented protocol for the synthesis of pharmaceutically important molecules like coumarins, chalcones, Schiff base, arylcoumarins, and dioxocine analogs.

Rao et al. [85] reported the molecular iodine-catalyzed reaction of 5,5-dimethyl-1,3-cyclohexanedione with aromatic aldehydes in iso-propanol affording a variety of 1,8-dioxo-octahydroxanthenes **61** (Scheme 10.43). Synthesized compounds were tested for in vitro antiproliferative properties against three cancer cell lines and 9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione possessing a 2-hydroxy phenyl group at C-9 position. Antiproliferative properties of these compounds were also evaluated in vitro against a number of cancer cell lines, for example, human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), and human neuroblastoma cells (IMR32).

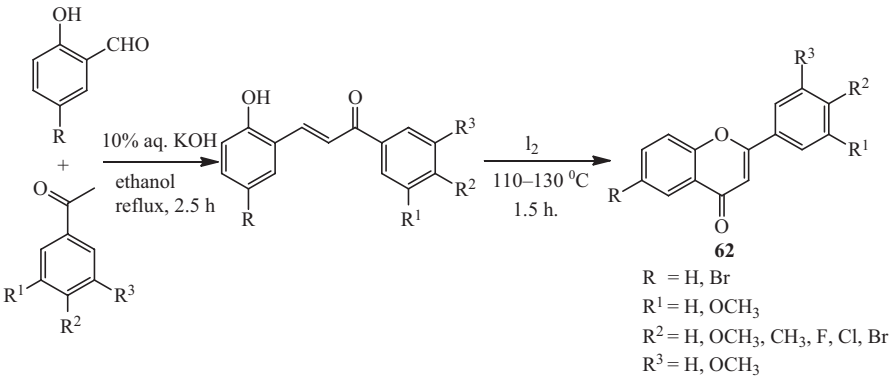


Scheme 10.43

3.5 Flavanones

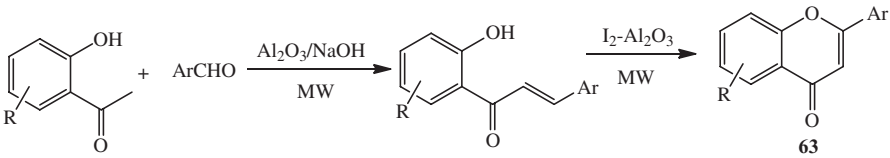
The flavanone skeleton is present in a wide range of synthetic or naturally occurring products exhibiting various interesting pharmacological activities [86] such as antioxidant [87], antitumoral [88], and antiproliferative [89], etc.

Sashidhara et al. [90] developed a convenient, facile, and alternate method for the synthesis of medicinally important flavanones. The 2-hydroxychalcones derived from the condensation of acetophenones and salicylaldehyde underwent oxidative cyclization on heating in the presence of catalytic iodine, generating diversified flavanones **62** under solvent-free conditions. This methodology involves the use of salicylaldehydes instead of 2-hydroxyacetophenone, in which formation of chalcone is quite easier with high isolated yields. The advantages of this method comprised good substrate generality, the use of inexpensive reagents and catalyst, and experimental operational ease (Scheme 10.44).



Scheme 10.44

Pawar et al. [91] reported a simple method for the synthesis of flavanones **63** using the heterogeneous catalyst molecular iodine loaded on neutral alumina under microwave irradiation (Scheme 10.45). Combination of iodine with alumina showed an excellent heterogeneous catalyst for the synthesis of flavanone derivatives in excellent yield. α, β-Unsaturated carbonyl compounds were prepared by well-known Claisen–Schimdt condensation process using NaOH–Al_2O_3 under microwave irradiation.

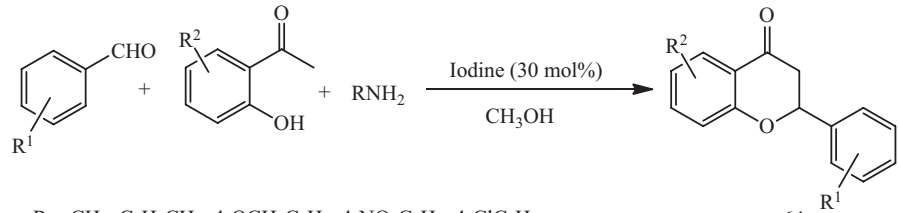


R= 2-OH, 2-OH-3-CH_3
Ar= C_6H_5, 4-ClC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4,5-$(OCH_3)_2C_6H_4$, 4-$NO_2C_6H_4$, 2-Furyl

Scheme 10.45

However, in the absence of iodine, the reaction did not proceed even after a long time. It indicates that the oxidation of 2-hydroxy chalcone into flavones is only due to molecular iodine and not because of air O_2. The reaction proceeded smoothly at 400 W and no undesirable side products were formed. At higher power level, decrease in yield was observed due to product decomposition.

Yao et al. [92] reported one-pot synthesis of flavanone **64** via Mannich type reaction catalyzed by molecular iodine. A simple workup and the high compatibility of functional groups made this an attractive synthetic approach to access flavanone derivatives (Scheme 10.46). The three-component Mannich reaction of aldehyde, amine, and enolizable ketone to obtain the β-aminocarbonyl compounds has been known, but when the Mannich reaction of benzaldehyde, aniline, and 2-hydroxyacetophenone had been explored in the presence of iodine, no trace of β-aminocarbonyl compound is observed and flavanone was formed as the sole product in moderate yield.

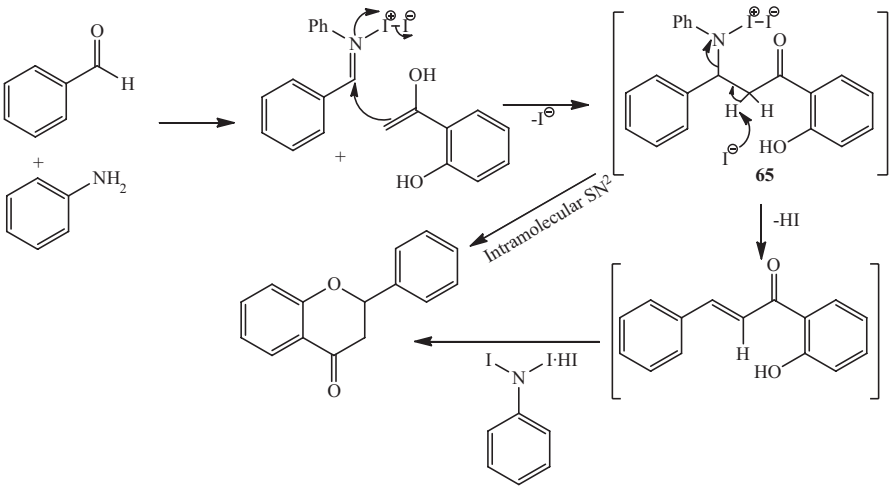


R = CH_3, $C_6H_5CH_2$, 4-$OCH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4
R^1 = H, 4-Cl, 2-F,4-NO_2, 3-NO_2, 2-NO_2, 4-CH_3O, 3-CH_3O, 2-CH_3O, 4-CH_3, 1-naphthalyl, 2-thiophene
R^2 = 3-Cl, 3-OCH_3, 3, 4-$(OCH_3)_2$, 2,4-$(OCH_3)_2$, 1-naphthalyl

Scheme 10.46

In the absence of iodine, reaction was decelerated after the formation of imine. Aliphatic amines were less effective than aromatic amines. The reaction trend suggests that the formation of imine as well as the elimination of amine are the key steps which are involved in the formation of flavanone derivatives. Michael addition is probably catalyzed by the in situ-formed *N*-iodoaniline–HI complex. Alternatively, the intermediate **65** could give the flavanone directly via an

intramolecular SN_2 reaction. The aniline acted as a leaving group in the possible mechanism (Scheme 10.47).

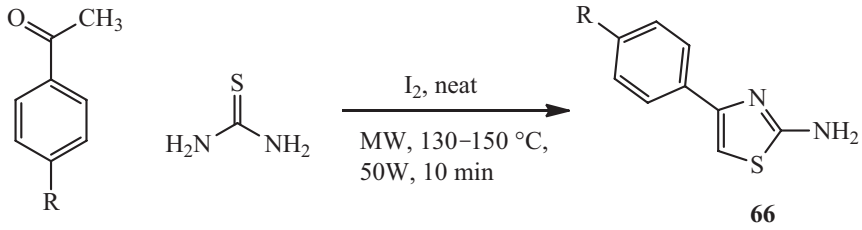


Scheme 10.47

4 Five-Membered Heterocycles with Two Heteroatoms

4.1 Thiazoles

Gonzalo et al. [93] developed a one-pot solvent-free procedure for the synthesis of 2-amino-4-arylthiazoles **66** by the reaction of *p*-substituted acetophenones with thiourea and iodine under microwave irradiation (Scheme 10.48).

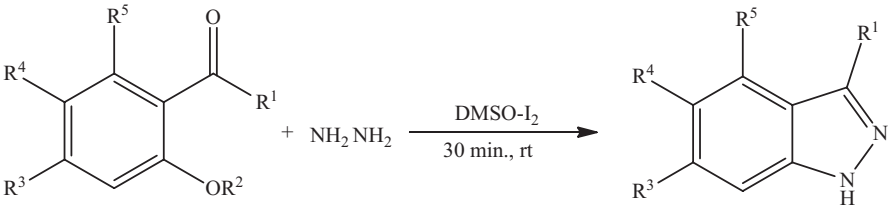


R = H, CH_3, OCH_3, OH, NH_2,
Cl, Br, NO_2

Scheme 10.48

4.2 Indazoles

The indazole derivatives are pharmacologically important compounds as their ring system forms a large number of drug molecules, such as granisetron, $5HT_3$ receptor antagonist, which are used as an antiemetic in cancer chemotherapy [94]. Gaikwad et al. [95] developed an efficient approach for the synthesis of indazoles **67** from ortho-alkoxyacetophenone and hydrazine hydrate using DMSO as a solvent and molecular iodine as a catalyst. In the absence of iodine, the reaction did not proceed even after 24 h (Scheme 10.49).



67

R^1= R^2=H, CH_3
R^3= R^4=H, NH_2, OCH_3, Cl
R^5= H, OH, OCH_3, CH_3

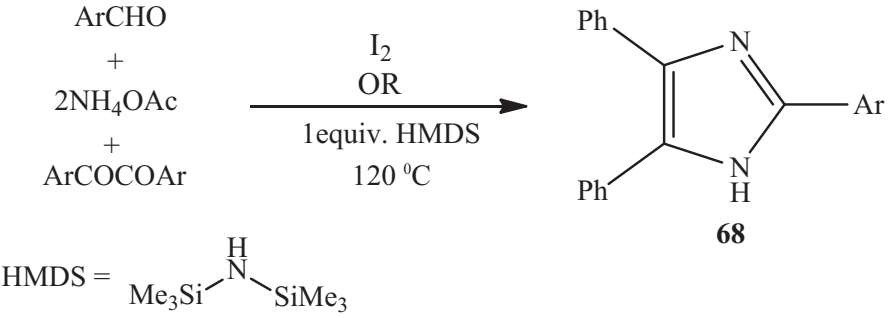
Scheme 10.49

4.3 Imidazoles

Compounds with an imidazole ring system are biologically important due to their role in biochemical processes. Substituted imidazoles are well known as inhibitors of P38MAP kinase [96], fungicides, herbicides [97], plant growth regulators [98], and therapeutic agents [99].

Kidwai et al. [100] reported the synthesis of 2,4,5-triarylimidazoles **68** in excellent yields via the condensation of benzoin, ammonium acetate, and aromatic aldehydes using elemental iodine as an efficient catalyst. Molecular I_2 was capable of binding with the carbonyl oxygen atom and increased the reactivity of the parent carbonyl compound. Iodine facilitates the formation of the diimine intermediate, which under mild catalysis of I_2 was condensed further with the carbonyl carbon of the 1,2-diketone followed by dehydration to afford the iso-imidazole, which was rearranged via a [1,5] sigmatropic shift to the required 2,4,5-triarylimidazole derivatives (Scheme 10.50).

Further, Hemmati et al. [101] developed a one-pot efficient procedure for the synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives **68** by the reaction of hexamethyldisilazane and arylaldehydes in the presence of molecular iodine (Scheme 10.50).

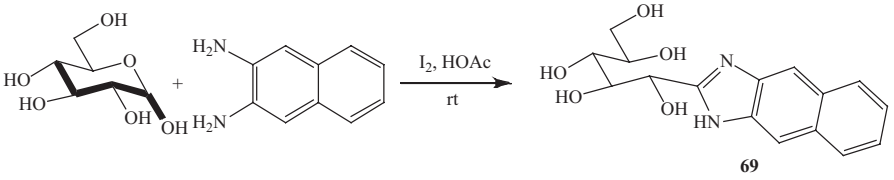


Ar = C_6H_5, 4-$CH_3C_6H_4$, 3-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-OHC_6H_4, 2-thienyl, 3,4-piperonyl

Scheme 10.50

Use of molecular iodine as an inexpensive and effective activator and oxidant for the efficient one-pot synthesis of 2,4,5-triaryl-1*H*-imidazoles in high yields was studied in the present reaction. In this procedure, molecular iodine acted both as a catalyst to activate the HMDS and as an oxidant for the oxidation of imidazoline to imidazole.

Yang et al. [102] developed a novel method for the conversion of unprotected and unmodified aldoses to aldo-imidazoles **69**. Using iodine as a catalyst in acetic acid solution, a series of monosaccharides and oligosaccharides (including those containing carboxyl and acetamido groups) underwent an oxidative condensation reaction with aromatic vicinal diamines at room temperature to give the corresponding aldo-imidazole derivatives in high yields. No cleavage of the glycosidic bond occurred under the mild reaction conditions. The compositional analysis of saccharides is commonly realized by capillary electrophoresis of the corresponding aldo-imidazole derivatives, which were easily synthesized by the reported iodine-promoted oxidative condensation (Scheme 10.51).

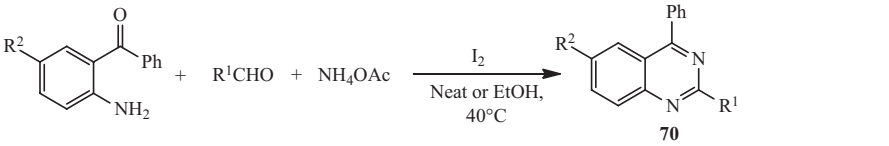


Scheme 10.51

5 Six-Membered Heterocycles with Two Heteroatoms

5.1 Quinazolines

Saha et al. [103] developed an efficient and one-pot three-component strategy for synthesizing highly functionalized quinazoline derivatives **70**. A mixture of 2-aminobenzophenone, aromatic aldehyde, and ammonium acetate in the presence of I_2 provides desired products in excellent yields even at moderate temperature (40 °C), with no need of chromatographic purification (Scheme 10.52).



R^1=*o*-pyridyl, *o*-OH-*m*-$OC_2H_5C_6H_3$, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *o*-$NO_2C_6H_4$, *p*-$NO_2C_6H_5$, 1-Naphthyl

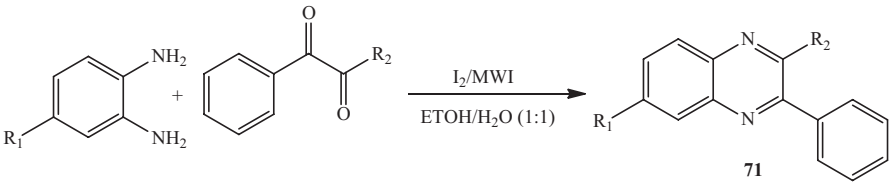
R^2 = H, Cl, NO_2

Scheme 10.52

5.2 Quinoxalines

Quinoxaline moiety possesses several biological activities such as antitumor [104], antimycobacterial [105], antidepressant [106], etc. Some antibiotics, such as levomycin, actinoleutin, and echinomycin, also contain a quinoxaline scaffold.

Banik et al. [107] developed a microwave-induced iodine-catalyzed simple, rapid, and convenient method for the synthesis of different types of quinoxaline derivatives **71** via condensation of 1,2-diamines with 1,2-dicarbonyl compounds (Scheme 10.53). The model reaction between *o*-phenylenediamine and phenylglyoxal monohydrate in the presence of iodine as a catalyst using microwave irradiation has been performed in different solvent systems and the best results were obtained when EtOH/H_2O (1:1) was used as a solvent.



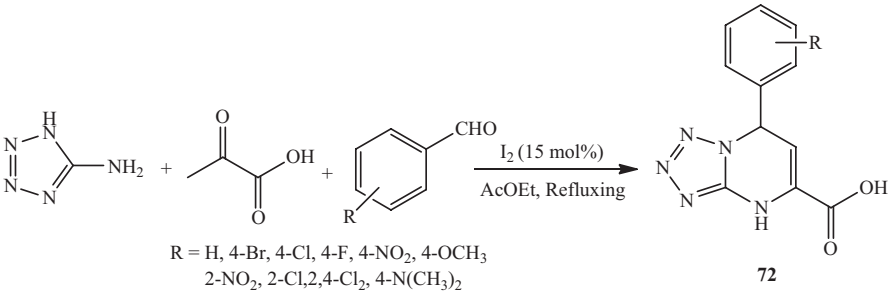
R_1 = H, Cl, OCH_3, NO_2

R_2 = H, CH_3, C_6H_5

Scheme 10.53

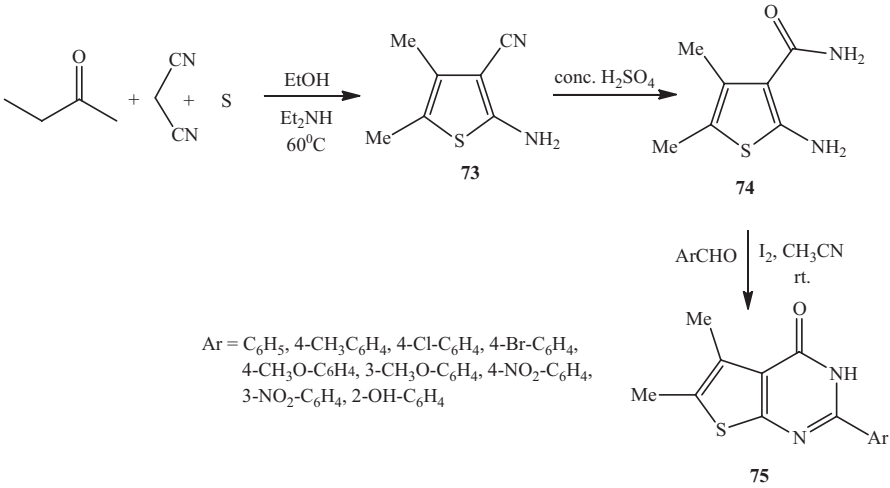
5.3 Pyrimidines

Organic compounds containing pyrimidine as a core unit were known to exhibit various biological and pharmaceutical activities [108]. Chun et al. [109, 110] developed a one-pot synthesis of a series of 5-aryl-5,8-dihydrotetrazolo[1,5-*a*]pyrimidine-7-carboxylic acids **72** from 5-aminotetrazole, pyruvic acid, and aromatic aldehydes in the presence of I_2 as a catalyst. Operational simplicity, mild reaction conditions, and eco-friendly procedure made this novel protocol a promising alternative for the fusion of tetrazolopyrimidines (Scheme 10.54).



Scheme 10.54

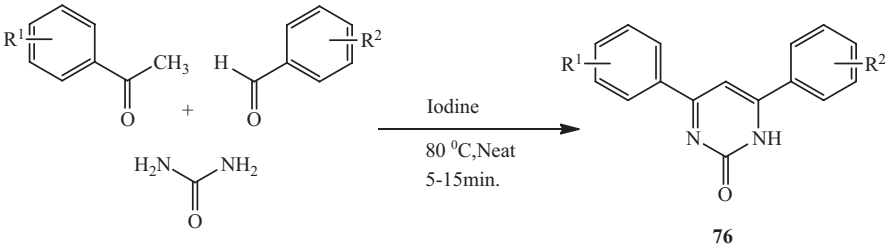
Various biological activities such as antimicrobial [111−113], antiviral [114], antidepressant [115], analgesic, and anti-inflammatory [116] have been recently reported for thienopyrimidine compounds. Mehdi et al. [117] developed a new iodine-catalyzed route for the synthesis of thieno[2,3-*d*]pyrimidine derivatives **75** via heterocyclization of 2-amino-4,5-dimethylthiophene-3-carboxamide **74** with aromatic aldehydes (Scheme 10.55).



Scheme 10.55

The intermediate 2-amino-4,5-dimethylthiophene-3-carbonitrile **73** was prepared according to Gewald procedure [118]. The subsequent hydrolysis of this compound in acidic media afforded the 2-amino-4,5-dimethylthiophene-3-carboxamide **74**. This compound was used as the precursor for the synthesis of various derivatives of thieno[2,3-*d*]pyrimidine **75**. Synthesized compounds were screened for the in vitro antibacterial activity against several pathogenic representatives, e.g., Gram-positive bacteria (*Staphylococcus aureus* PTCC 1074 and *Bacillus subtilis* PTCC 1365); Gram-negative bacteria (*Escherichia coli* HB101 BA 7601C and *Pseudomonas aeruginosa* PTCC 1431) using disk diffusion sensitivity test [119].

Pasha et al. [120] developed an efficient, solvent-free, one-pot, three-component cyclocondensation reaction between aldehyde, ketone, and urea to synthesize 4,6-diarylpyrimidin-2(1H)-ones (DAPMs) **76** using iodine as a catalyst. This protocol provides a simple and environmentally benign route along with the associated advantages of good to excellent yield of the products (90–96 %) and shorter reaction times (5–15 min) at 80 °C (Scheme 10.56).



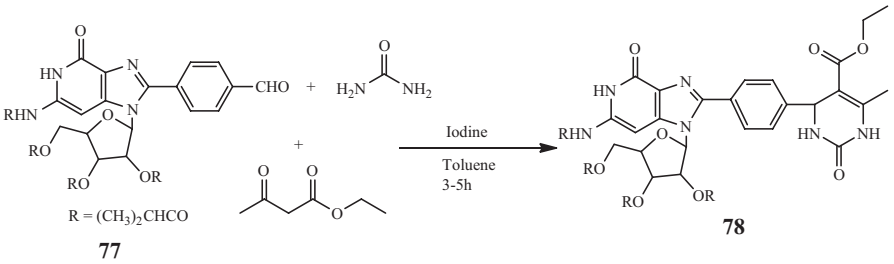
76

R^1 = H, 4-NO_2, 4-OCH_3, 4-Cl
R^2 = H, 4-OCH_3, 4-Cl, 4-CH_3, 4-OH
2,4-$(OCH_3)_2$, 4-$N(CH_3)_2$

Scheme 10.56

The effect of the reaction temperature on the yield of the products was evaluated (70–100 °C). The yield of **77** (R^1 = H, R^2 = 4-OCH_3) reached a maximum of 96 % at 80 °C after 5 min, indicating that ketone reacts rapidly with aldehyde and urea to form diarylpyridinones when the reaction is carried out with 5 mol% of the catalyst. Less than 5 mol% of iodine (1 mol%) led to lesser yields (66 %) after longer reaction times, and more than 2–4 mol% could not improve the yield. In view of the current interest in environmentally benign catalytic processes, development of a protocol involving a lesser amount of iodine would be more appreciable.

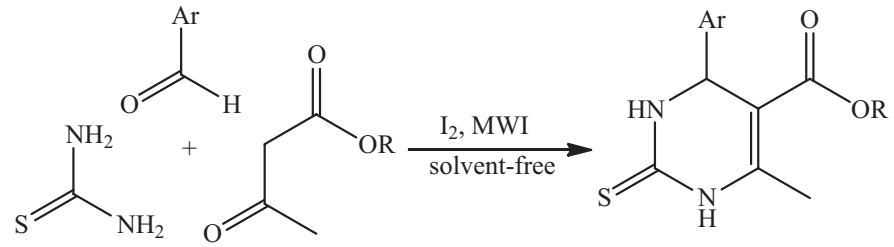
Zubaidha et al. [121] reported the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **78** using iodine as a catalyst (Scheme 10.57). Aldehyde **77** was synthesized by a known method [122] and subjected to cyclocondensation with ethyl acetoacetate and urea.



Scheme 10.57

This one-pot protocol had given excellent yields with substituted aromatic aldehydes but the cyclocondensation with aliphatic aldehydes such as *n*-butanal and *n*-hexanal under the present reaction conditions afforded the corresponding dihydropyrimidin-2(1*H*)-ones in 76 and 69 % yields, respectively. The reaction proceeds via an acyl imine intermediate formed from the condensation of aldehyde and urea. Subsequent addition of the β-keto ester enolate, followed by cyclization and dehydration afforded the dihydropyrimidinone derivatives. Iodine played a crucial role in accelerating the dehydrative steps and enolization of the β-keto ester.

Liu et al. [123] reported the synthesis of 3,4-dihydropyrimidin-2-thiones **79** via Biginelli reaction of aldehydes, acetoacetates, and thiourea in the presence of iodine under solvent-free conditions using microwave irradiation as the energy source. This environmentally benign protocol had the advantages of shorter reaction times, good yields, and simple and easy workup without chromatographic separation (Scheme 10.58).



R = CH_3, C_2H_5

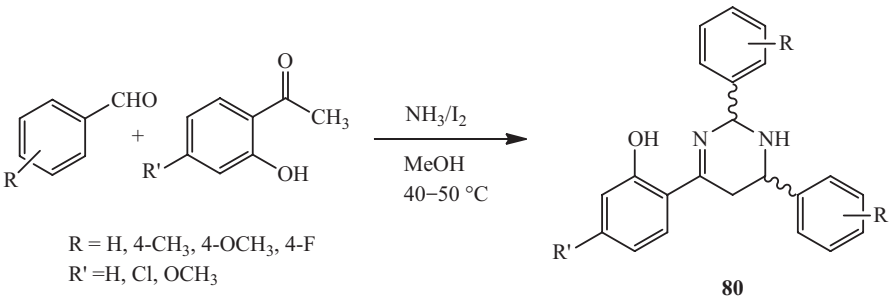
Ar = C_6H_5, 4-ClC_6H_4, 3-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 4-BrC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 4-OHC_6H_4, 3-OHC_6H_4, 4-HO-3-$CH_3OC_6H_3$, 3-$N_3C_6H_4$, 4-$C_6H_5C_6H_4$, 4-IC_6H_4, 2-OH-1-naphthalyl, 4-N$(CH_3)_2C_6H_4$, 2-Furyl

Scheme 10.58

Single-crystal X-ray analysis of the 3,4-dihydropyrimidine ring proved that it had a boat-type conformation, and the phenyl ring is almost perpendicular to the tetrahydropyrimidin-2-thione, which is similar to the structure of monastrol [124].

Yao et al. [92] synthesized pyrimidine derivatives **80** using aldehyde, ammonia (0.5 mL 7 M NH3 in MeOH), and 2-hydroxyacetophenone in methanol in the

presence of 30 mol% iodine. All pyrimidine derivatives were obtained as a mixture of two diastereomers in 3:1 *trans*-to-*cis* ratio (Scheme 10.59).



R = H, 4-CH_3, 4-OCH_3, 4-F
R' =H, Cl, OCH_3

Scheme 10.59

Based on the observations of the coupling constants, all the protons are placed according to the half-chair conformation to obtain the relative configuration. The relative configuration of the major diastereomer was assigned from crystal structure as 4R*6R* (Fig. 10.3) and minor diastereomer was assigned as 4R*6S* (Fig. 10.4).

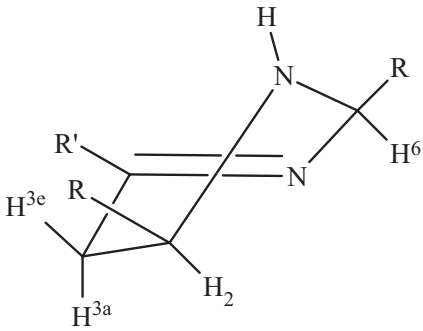


Fig. 10.3 Major diastereomer

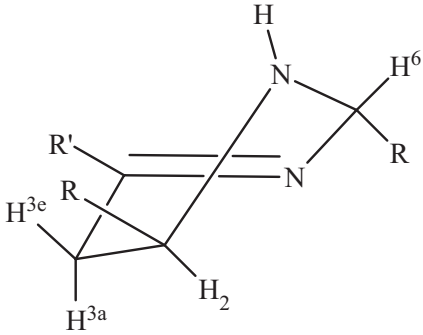
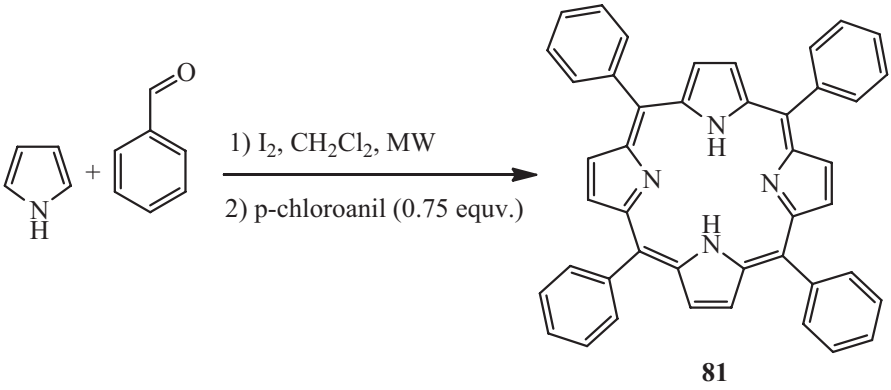


Fig. 10.4 Minor diastereomer

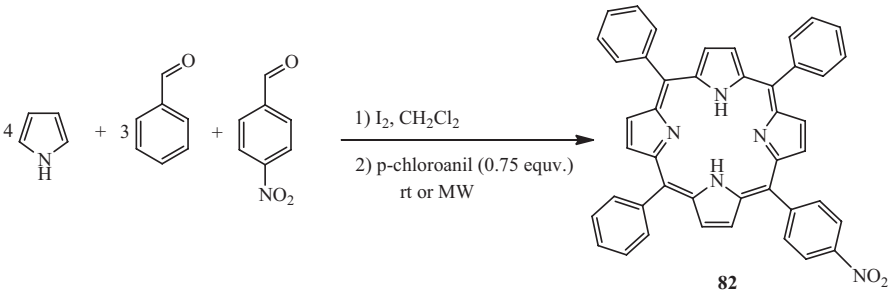
6 Miscellaneous

The widely ranged use of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin was well established, but its synthesis requires two steps and is not very practical. Rachida et al. [125, 126] developed a one-pot iodine-catalyzed synthesis of porphyrins **81** and **82** (Schemes 10.60 and 10.61). Asymmetrical mono-functionalized porphyrins with various functional groups have also been obtained to validate this method (Scheme 10.61).



81

Scheme 10.60



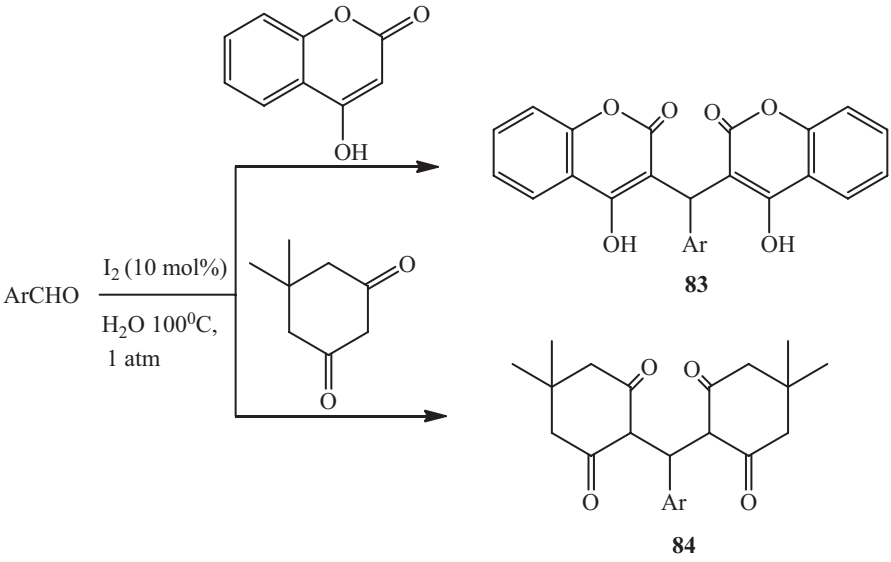
82

Scheme 10.61

A series of mono-functionalized porphyrins have been synthesized by a variation of Little's mixed aldehyde method [127] in which propionic acid was replaced by catalytic amount of molecular iodine. The use of undistilled solvents and reactants are major advantages of this method because it is accomplished in shorter reaction time and avoids drastic conditions. Further, this method allows the use of high reactant concentration compared to the classical Lindsey method. Activation by microwave irradiation has been used to provide final product in short times with a good selectivity ($-NO_2$ and –COOMe). This method has been validated by the synthesis of other mono-functionalized porphyrins of interest,

with yields ranging from 8 to 27%, always higher than reference yields obtained in Little's method.

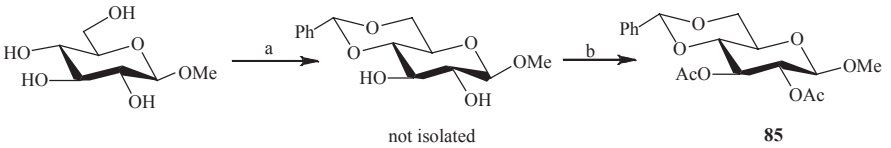
Kidwai et al. [128] used molecular iodine as an efficient catalyst for an improved and rapid one-pot synthesis of 3,3′-arylmethylenebis-(4-hydroxycoumarin) **83** and 2,2′-arylmethylenebis(3-hydroxyl-5,5-dimethyl-2-cyclohexen-1-one) **84** using water as a reaction medium. This aqua-mediated Michael addition of various aromatic and heteroaromatic aldehydes with 4-hydroxycoumarin or dimedone using catalytic amount of molecular iodine prevents the use of any expensive, corrosive reagents and toxic solvents and also provides operational simplicity (Scheme 10.62).



Scheme 10.62

Iodine shows a very strong catalytic activity in aqueous medium, which is much faster than any catalyst reported for the synthesis of 3,3′-arylmethylenebis-(4-hydroxycoumarin). The powerful catalytic activity of iodine is further substantiated by less reaction time as well as high product yields for the desired transformation.

Galan et al. [129] developed an iodine-catalyzed one-pot tandem acetalation–esterification reaction of thioglycosides and *O*-glycosides providing a fast and mild route to orthogonally protected glycosides **85** which can be used as building blocks in glycosylation reactions (Scheme 10.63).

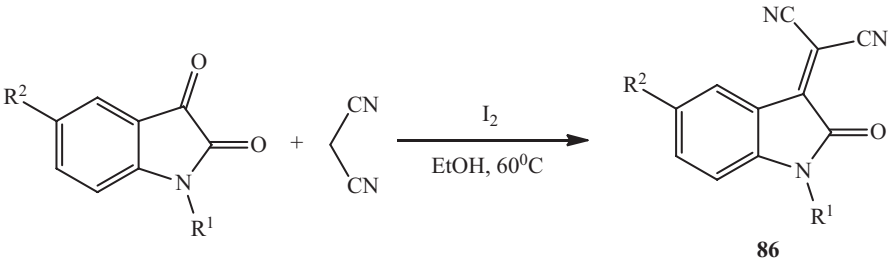


Reagents: (a) $PhCH(OCH_3)_2$ (1.5 equiv), I_2 (0.4 equiv) CH_3CN; (b) Ac_2O (5 equiv), DMAP.

Scheme 10.63

They also demonstrated that inexpensive molecular iodine can be used as a cheap, nontoxic, general, and fast catalyst for one-pot tandem acetalation–esterification reactions of glycosides in good to excellent yields without the need of purification after every reaction step. Further, the addition of catalytic DMAP can be used to accelerate the esterification step and thus shorten the reaction times. The method is mild and compatible with different thioglycosides and *O*-glycosides, applicable to the formation of 4,6-*O*-benzylidene and 4,6-*O*-*p*-methoxybenzylidene acetals in tandem reaction with either 2,3-*O*-di-acetate or 2,3-*O*-di-benzoate esters and also amenable to commonly used amino-protecting groups (e.g., phthalimides and 2,2,2-trichloroethoxycarbonyl chloride).

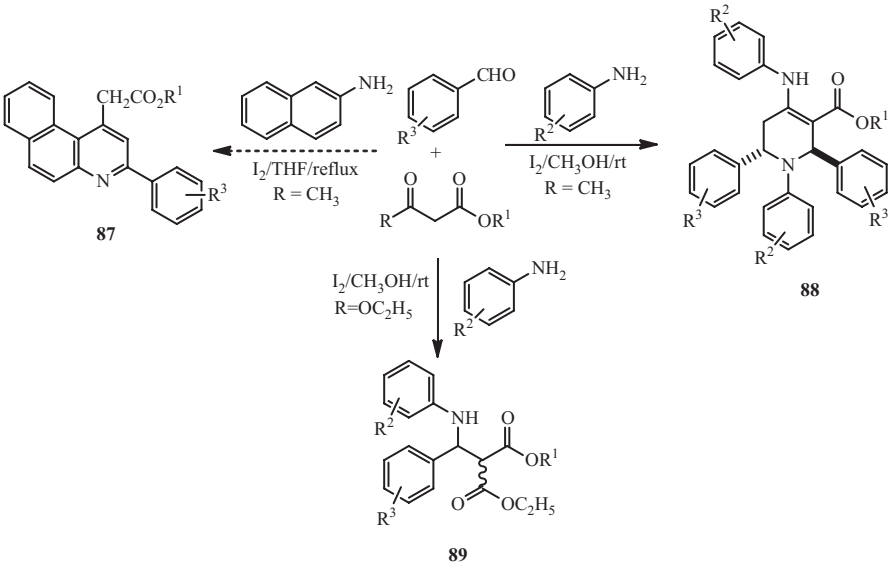
Yang et al. [130] reported an improved and rapid condensation of isatins with malononitrile **86** in the presence of molecular iodine as an efficient catalyst. The significant features of the iodine-catalyzed Knoevengeal condensation were its operational simplicity, inexpensive reagents, high yield of products, and the use of nontoxic reagents (Scheme 10.64).



Scheme 10.64

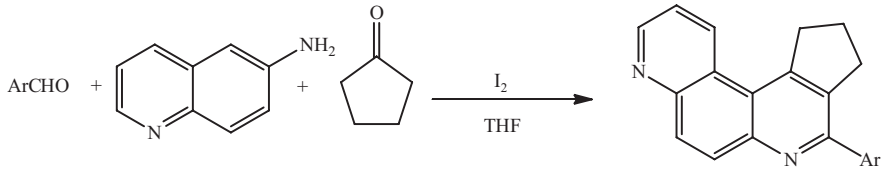
Khan et al. [131] reported a simple and convenient one-pot multicomponent reaction (MCR) for the synthesis of highly functionalized piperidines **87, 88,** and **89** using molecular iodine as a catalyst. This strategy demonstrated the five-component reaction of 1,3-dicarbonyl compounds, amines, and aromatic aldehydes in

methanol using 10 mol% of iodine at room temperature. This methodology provides an alternative approach for an easy access of highly and fully substituted piperidines in moderate to good yields using readily available starting materials. Notably, this method is mild, cheap, straightforward, applicable to a broad range of substrates, and environmentally friendly as compared to the existing methods (Scheme 10.65).



Scheme 10.65

Wang et al. [132] reported a series of 10,11-dihydro-8-aryl-9*H*-cyclopenta[*a*][4,7] phenanthroline derivatives **90** by a three-component reaction of aromatic aldehyde, quinolin-6-amine, and cyclopentanone using iodine as a catalyst (Scheme 10.66).

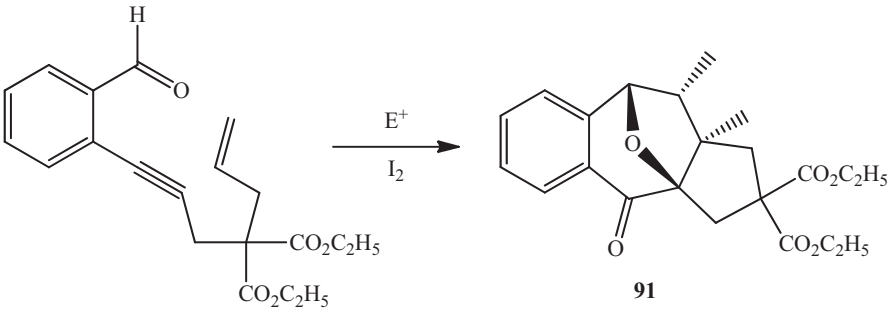


Ar= C_6H_5, 4-ClC_6H_4, 3-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 4-BrC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$

Scheme 10.66

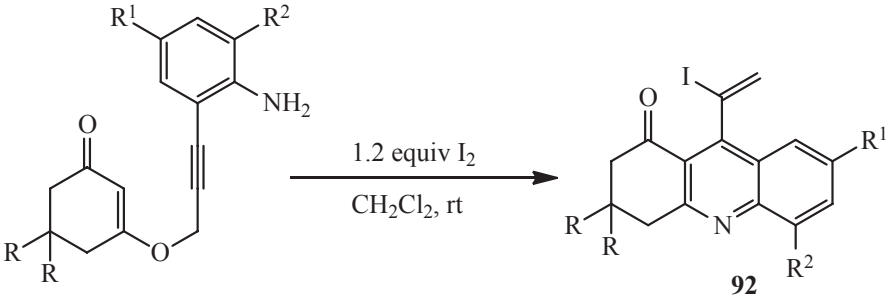
Liang et al. [133] developed an iodine-catalyzed tandem cyclization–cycloaddition reaction of ortho-alkynyl-substituted benzaldehydes leading to polyoxacyclic ring systems, which represents a useful approach towards the synthesis of the oxabi-

cyclo-[3.2.1]octane **91** ring skeleton which is found in a variety of natural products (Scheme 10.67).



Scheme 10.67

Perumal et al. [134] developed an efficient and rapid synthetic strategy for the construction of a pharmaceutically important 9-(1-iodovinyl) acridin-1(2*H*)-one **92** scaffold by a simple and efficient cascade transformation of 2-aminophenyl propynyl oxyenone by employing iodine as a catalyst which promoted 6-endo-dig iodocyclization and intramolecular condensation followed by 3,3-sigmatropic rearrangement. The salient features of this strategy are shorter reaction times, broader substrate scope without the need of inert conditions, and elevated temperature, and it allows the construction of tricyclic heterocycles in a single step (Scheme 10.68).



R= H, CH_3
R^1= H, CH_3, Cl, NO_2
R^2= H, CH_3, Cl, OCH_3

Scheme 10.68

7 Conclusion

Iodine has been a catalyst of substantial applications in recent years. It is a remarkably versatile, flexible, and multipurpose catalyst and has gained substantial significance as a mild and nontoxic Lewis acid catalyst since it catalyzes various organic reactions with high efficiency and selectivity. It has several advantages over the vast majority of the other Lewis acid catalysts, especially the metallic catalysts. Due to the biological activities associated with different heterocyclic nuclei, considerable achievements have been made in their synthesis, especially in the last few years. This chapter focuses on the catalytic role of molecular iodine in heterocyclic synthesis. A variety of iodine-catalyzed reactions have been discussed and classified according to the size of the ring system of the heterocyclic moiety generated. Iodine as a catalyst could be a future perspective in terms of green chemistry and sustainable development. The present chapter would serve the need of organic chemists who are engaged in the study of thorough applications of iodine for heterocyclic synthesis.

We hope and anticipate that this chapter will provide additional stimulus for the further development of chemistry of molecular iodine-catalyzed reactions.

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Chapter 11
Microwave Radiations: A Tool for the Synthesis of Heterocycles in an Ecofriendly Manner

Shipra Bhardwaj and K. L. Ameta

Contents

Abstract In modern aspect, microwave synthesis is an ecofriendly process for the synthesis of heterocyclic compounds. Due to its rapid action to produce products with greater purity and yield, it is now used worldwide. In the present chapter, a survey on the microwave technique and a number of five- and six-membered heterocyclic compounds are reported which are synthesised by scientists under microwave irradiations.

Keywords Ecofriendly · Microwave · Bioactive · Heterocycles

1 Introduction

Microwave radiations are electromagnetic radiations. Their frequencies, wavelengths and energies lie between that of infrared (IR) and radio radiations. Here, radiation means rays and not the radioactive irradiation. Let us compare the three:

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	IR	Microwave	Radio wave
Wavelength	750 nm to 1 mm	1 mm to 1 m	1 m to 100,000 km
Energy	1.7 eV to 1.24 meV	1.24 meV to 1.24 μeV	1.24 meV to 12.4 feV
Frequency	400 to 300 THz	300 GHz to 300 MHz	300 MHz to 3 Hz

Further, microwave radiations are divided into three parts based on their frequencies: ultrahigh, extremely high and superhigh frequencies.

Generally, microwave technology is used in telecommunication, radars, wireless LAN, wireless access radios, satellite communication, navigation, paramagnetic resonance in combination with magnetic field, electron spectroscopy, heating and powered appliances, etc.

'Micro' in microwave stands for wavelength in the micrometre range. Further, the frequencies are divided into groups and the groups are named as: L band (1–2 GHz), S band (2–4 GHz), C band (4–8 GHz), X band (8–12 GHz), Ku band (12–18 GHz), K band (18–26.5 GHz), Ka band (26.5–40 GHz), Q band (33–50 GHz), U band (40–60 GHz), V band (50–75 GHz), E band (60–90 GHz) and W band (75–110 GHz). A microwave oven for heating employs the S band with a frequency range of 2–4 GHz. Microwave frequencies can be measured by a wave meter through mechanical method or by frequency counters through electronic method.

Microwave radiations are not capable of performing ionization due to lower energy and so are not capable of harming the biological system, but long-time exposure is harmful and carcinogenic effects are suggested [1].

Moving on to chemistry, microwave chemistry is the method of applying microwave radiations to chemical reactions [2, 3]. As the reactions were found to have enhanced rates under microwave radiations, due to its heating effect, the technique gained popularity by various names like microwave-enhanced chemistry (MEC), microwave organic reactions enhanced (MORE), etc. The first microwave irradiation to carry out organic transformation was reported by Gedye et al. (1986) [4]. Microwave synthesis is preferred nowadays over the conventional method because of enhanced product yield with greater purity, reduced reaction times and fewer unwanted side reactions. Further, multistep synthesis increased due to the use of microwave radiations [5–7].

In the present era, many other fields have been explored in microwave synthesis like biochemical process [8, 9], medical chemistry [10, 11], polymer synthesis [12, 13], nanotechnology [14, 15], etc.

MEC is based on microwave dielectric heating effects. This is the ability of any solvent or reagent to absorb microwave energy and to convert it into heat. The electric component of an electromagnetic wave produces heat by two methods:

- Dipolar polarisation
- Ionic conduction

On irradiation, a dipole or an ion realigns itself with the electric field thus losing energy in the form of heat. If the dipole or the ion does not have sufficient time to realign, no heating occurs. All commercial systems lie in between these two extremes, i.e. giving a molecule sufficient time to realign but not to follow the alternating field precisely [16, 17]. The heating tendency of any solvent or material depends upon its dielectric constant. The ability of any substance to convert electromagnetic

energy into heat at a given frequency and temperature is determined by loss factor $\tan\delta = \varepsilon''/\varepsilon'$, where ε'' is the dielectric loss and is indicated by the efficiency of any substance to convert electromagnetic radiations into heat. ε' is the dielectric constant describing the ability of a molecule to be polarised by the electric field. A medium with a higher tanδ value is required for rapid heating. Generally, solvents are said to be high microwave absorbing for $\tan\delta > 0.5$, medium microwave absorbing for tanδ between 0.1 and 0.5 and low microwave absorbing for $\tan\delta < 0.1$. Some solvents with optimum tanδ are ethanol with 0.941, water with 0.123, dimethylformamide (DMF) with 0.161, dimethyl sulphoxide (DMSO) with 0.825, ethylene glycol with 1.350, methanol with 0.659, nitrobenzene with 0.589, chlorobenzene with 0.101, etc. [18].

Newly constructed microwave ovens now offer temperature and pressure sensors, built-in magnetic stirrers, power controllers, software operation techniques and safety control measures. Thus, microwave reactors can be named as the 'Bunsen burners of twenty-first century' and may be used in laboratories for the same purpose.

2 Solvents in Microwave Synthesis

Generally, microwave apparatus is set at 2.45 GHz frequency. It is established that the dielectric constant of solvents decrease with increase in temperature. For example, water has a dielectric constant of 78 at 25 °C and this reduces to 20 at 300 °C. Polar solvents are generally used in microwave synthesis and so water can act as a pseudo-organic solvent at higher temperatures. It then becomes beneficial for organic synthesis because nonpolar solvents do not get heated in a microwave oven. A small amount of polar solvent, when added, increases the heating rate for the whole mixture. New developments have reported ionic liquids being used as dipolar aprotic solvents for organic synthesis [19, 20]. These ionic liquids are used as solvents in microwave synthesis probably due to their excellent dielectric properties and due to low vapour pressure. Some ionic liquids are soluble in nonpolar organic solvents, and so are used as coupling agents for microwave-transparent solvents.

Domestic microwave ovens were used widely in earlier stages of microwave synthesis. But risks were associated with such ovens like uncontrolled temperature rising, explosion or any other undesired happenings. To avoid such situations later on, solvent-free synthesis came into existence. Some solid supports like clay, alumina, silica, etc. were also used to perform such reactions [21].

3 Enhancements of the Rate of Chemical Reactions

The rate of any reaction is given by the Arrhenius equation:

$$K = Ae^{-\Delta G/RT}$$

Thus, the rate of any reaction would be enhanced by two ways. First, by increasing the pre-exponential factor A that describes the mobility of molecules and depends

on the frequency of the vibrations of the molecules at the reaction interface [22, 23]. Berlan et al. [24] suggested that rate expedition can be caused by altering the exponential factor ΔG, the free energy of activation. Thus, microwave heating may result in different outcomes even if the end temperature is same as the conventional method. For example, microwave heating may alter the regioselectivity in the sulphonation of naphthalene [25].

4 Significance of Heterocyclic Compounds in Pharmaceutical and Agrochemical Field

Approximately 75% of the chemicals used in the pharmaceutical and medicinal fields comprise heterocyclic rings in one or the other form. Some heterocyclic compounds are used in treating diseases in crops. For example, the broad-spectrum fungicide azoxystrobin [26] shown in Fig. 11.1 is used in treating hundreds of crops.

Besides monocyclic heterocycles, annelated bicyclic ring systems are also used in pharmaceutical fields. For example, the tetrahydroimidazothiazole levamisole (Fig. 11.2) is used as anthelmintic and immunomodulator [27]. A compound known as talipexole (Fig. 11.3) consists of five- and seven-membered rings and is used as an antiparkinsonian agent [28].

Compounds containing two or more heterocyclic rings in entirely different positions are also known to be used in this field. For example, a nonsteroidal anti-inflammatory drug meloxicam (Fig. 11.4) consists of an amide with benzothiazine-dione acid and a thiazole amine component [29].

Sometimes, heterocyclic compounds are finely tuned to give more active analogues or analogues with similar activities and some beneficial properties. Aromatic compounds are found to be more polar than their isocyclic analogues and are found to be more efficient. For example, antiulcerious ranitidine (Fig. 11.5) can be tuned

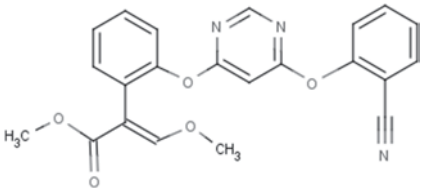


Fig. 11.1 Azoxystrobin fungicidal

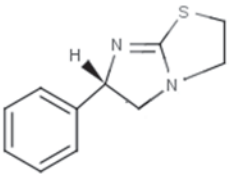


Fig. 11.2 Levamisole (anthelminthic)

Fig. 11.3 Talipexole (antiparkinsonian)

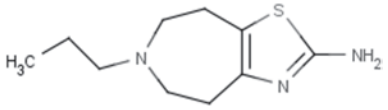


Fig. 11.4 Meloxicam (anti-inflammatory)

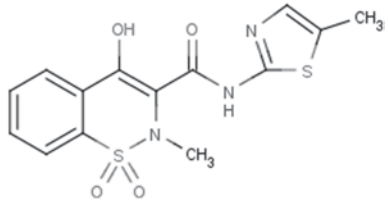


Fig. 11.5 Ranitidine (antiulcerious)

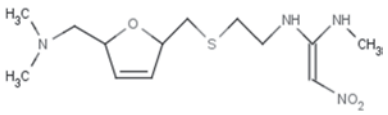
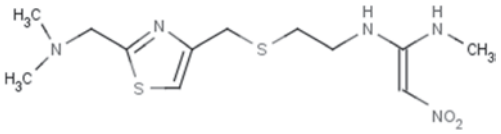


Fig. 11.6 Nizatidine (antiulcerious)



finely by replacing its furane scaffold with thiazole resulting in nizatidine (Fig. 11.6). Nizatidine possesses a lower logP value, i.e. higher human oral bioavailability [30].

Some heterocycles are used as prodrugs because they directly are not able to act upon any enzyme or organism, rather they furnish intrinsically active compound. This transformation may be achieved by heat, light, moisture or metabolic activities. For example, leflunomide [31] (Fig. 11.7a) is prodrug and is used against transplant rejection. Ring opening occurs quantitatively in the cellular system to generate hydroxyl propanamide (Fig. 11.7b). This new hydroxy compound is responsible for the immunosuppressive efficiency of the drug.

Fig. 11.7 **a** Leflunomide **b** Hydroxypropenamide (immunomodulatory)

Fig. 11.8 Saquinavir Anti HIV

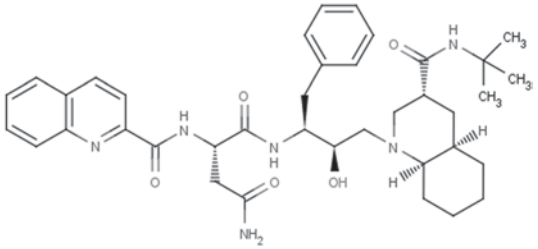


Fig. 11.9 Saquinavir Anti HIV

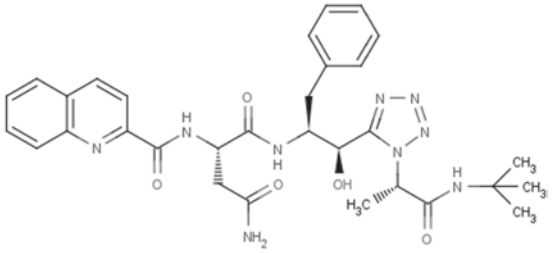
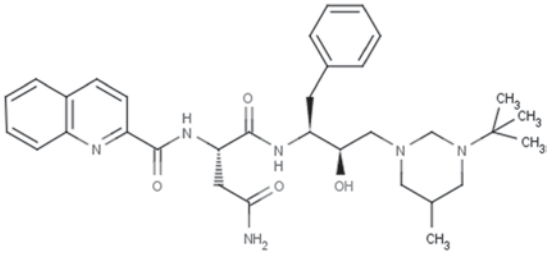


Fig. 11.10 Telinavir Anti HIV



Many heterocyclic rings can replace an amide function in peptide linkages and so can be named as perfect isosteric replacements [32]. These are designed to replace a peptic linkage so are also termed as peptidomimetic, as they mimic the original structure. For example, two saquinavir (Figs. 11.8 and 11.9) are highly active HIV-1 protease inhibitors and are analogues of telinavir (Fig. 11.10) [33, 34]. Generally, these mimicked structures are found to be more efficient than their original ones. Some other heterocycles used as amide isosteres are pyrroles [35], benzimidazoles [36], oxadiazoles [37], triazoles [38], oxazoles [39], imidazolines [40], isoxazolines [41], thiazolidines [42], etc.

Other groups besides amide may also be replaced by heterocycles providing much promising results. For example, carboxylic acid group (Fig. 11.11) is replaced by 5-substituted 1 H-tetrazole (Fig. 11.12). Both have equivalent pKa value but the tetrazole derivative, i.e. losartan has higher lipophilicity and so has improved bioavailability [43]. Other reported carboxylic group exchangers that offer greater bioactivities are thiazolidines diones [44], oxadiazolones [45], triazoles [46], hydroxychomones [47], hydroxythiadiazoles [48], etc.

Fig. 11.11 Antihypertensive

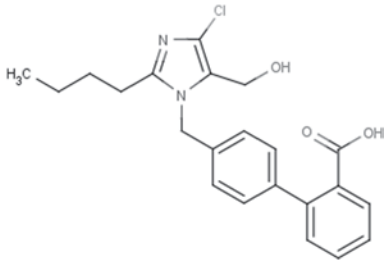


Fig. 11.12 Losartan antihypertensive

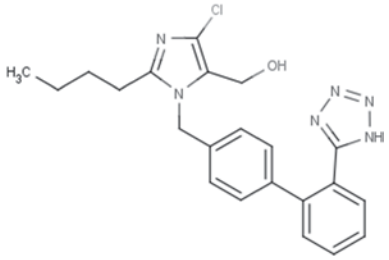


Fig. 11.13 Pilocarpine cholinergic

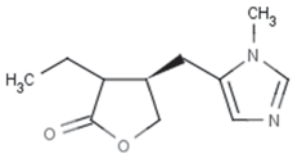


Fig. 11.14 Pilocarpine cholinergic

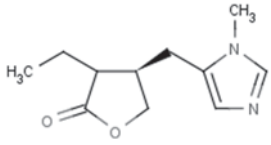
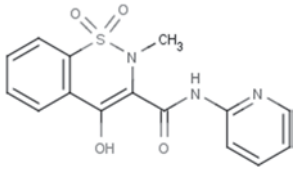


Fig. 11.15 Piroxicam anti-inflammatory



Many heterocyclic rings can be replaced by other heterocyclic rings with similar biological activities. For example, the structures given in Figs. 11.13 and 11.14 are pilocarpine and are used in lowering the elevated intraocular pressure associated with glaucoma, but cyclic carbamate is less susceptible to hydrolysis [49].

Sometimes benzene or other rings are replaced by heterocyclic rings with the retention of properties or enhanced bioactivities. For example, piroxicam (Fig. 11.15)

Fig. 11.16 Tenoxicam anti-inflammatory

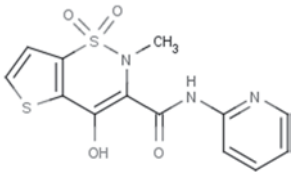


Fig. 11.17 Fentayl analgetic

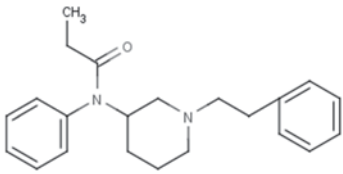
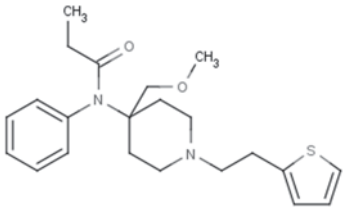


Fig. 11.18 Sufentanil analgetic



gets converted to tenoxicam (Fig. 11.16) by the exchange of a benzene ring with a thiophene ring [50]. Both possess the same inflammatory effect. Monk et al. [51] showed that thiophene derivative sufentanil (Fig. 11.17) is five times more potent than the phenyl ring-containing fentanyl (Fig. 11.18).

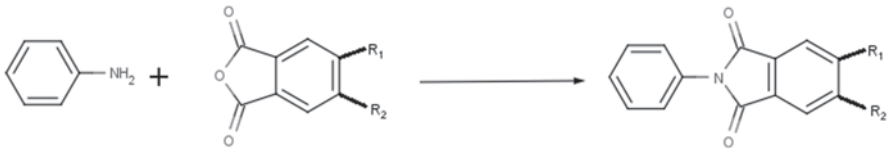
5 Synthesis of Bioactive Heterocycles Under Microwave Irradiations

Due to a number of advantages offered by microwave heating and irradiation, it was also employed in the synthesis of bioactive heterocycles. Although numerous literature is available on heterocyclic chemistry [52], heterocyclic name reactions [53], catalysed heterocyclic reactions [54], fluorinated heterocyclic compounds [55], heterocyclic carbene complexes [56], etc., green chemical pathways such as microwave synthesis has been found to be the superior one.

5.1 Microwave-Assisted Synthesis of Five-Membered Heterocycles

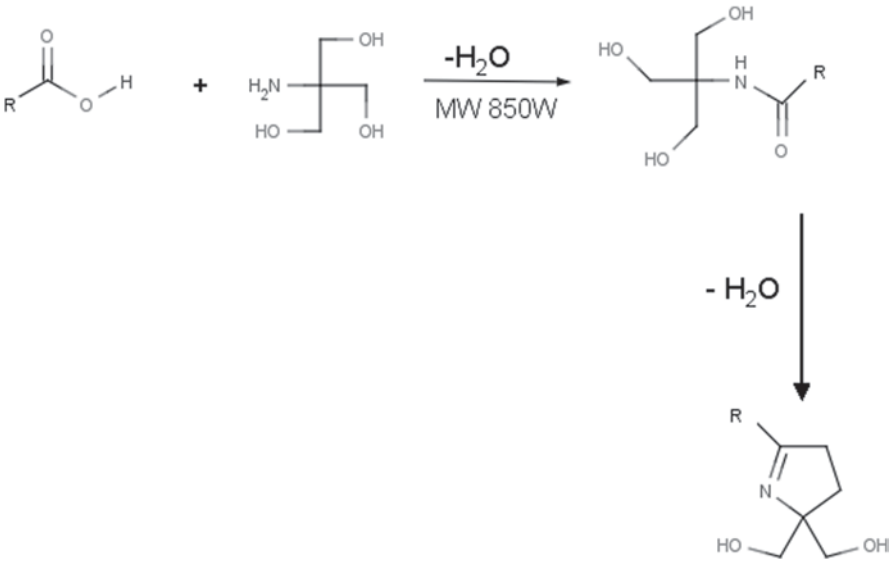
A number of heterocyclic compounds are synthesised under microwave irradiations nowadays. *N*-Acylation was carried out by Borah et al. [57] under microwave

irradiation. It was found that energy of activation reduces with a corresponding decrease in lnA, the pre-exponential factor in the Arrhenius equation. The value of lnA was 254 under thermal conditions which reduces to 131 in the microwave method. Similarly, ΔG was 105 KJ/mol under the thermal process and reduces to 575 KJ/mol under microwave irradiation. The reaction is given in Scheme 11.1. The reaction was carried out under solvent-free conditions.



Scheme 11.1

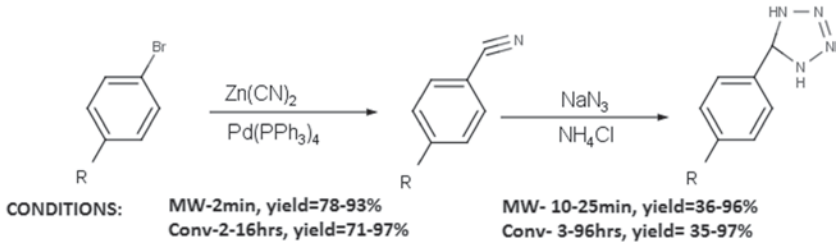
Preparation of oxazolines under microwave irradiation was carried out by Marrero-Terrero et al. [58]. The product was obtained by irradiating for 5 min at 200 °C under solvent-free conditions. The same process when carried out under the conventional method took 15–16 h (Scheme 11.2).



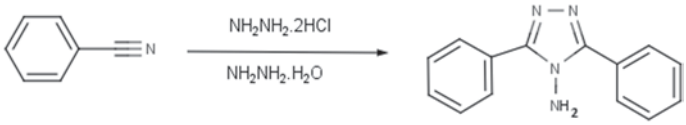
Scheme 11.2

Tetrazoles are prepared under microwave irradiation and is compared with the conventional method [59]. The results are reported in Scheme 11.3. R is taken as $–OCH_3$, $–NO_2$, $–CH_3$, etc. 1,2,4-Triazole is synthesised under microwave conditions by using reactant aryl cyanide in presence of hydrazine chloride. A number

of compounds were synthesised by taking different aryl groups like 4-$CH_3C_6H_4$, 4-$NH_2C_6H_4$, 4-HOC_6H_4, 4-$CH_3OC_6H_4$, etc. [60] (Scheme 11.4).

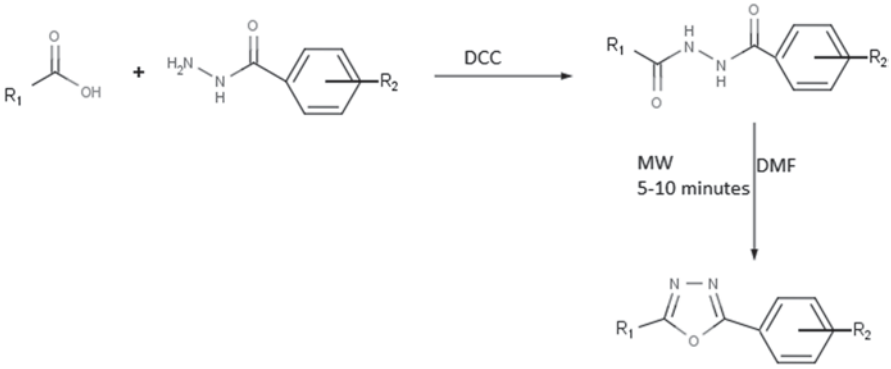


Scheme 11.3



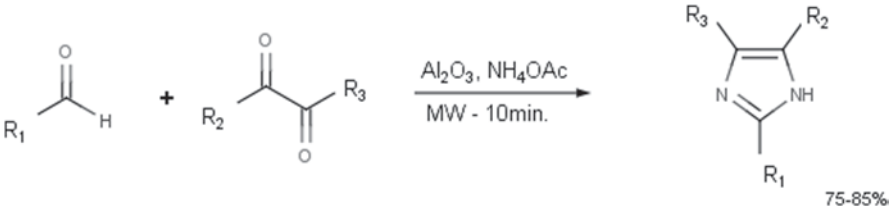
Scheme 11.4

Microwave irradiations require 10 min at 130 °C to get the product whereas the conventional method needs 60 min at 130 °C for the same process. The yield through the microwave method is 63–96 % whereas the conventional method gives 45–60 % yield. 1,3,4-Oxadiazoles were prepared under microwave conditions by Burgess's reagent through the dehydration of unsymmetrical diarylhydroazines [58]. The product was obtained in two steps in the presence of DMF and DCC in 5–10 min. The yield was 100 %. The same reaction under conventional conditions required 90 min to form the product (Scheme 11.5). R_1 was taken as alkyl or aryl and R_2 was taken as –Cl or $–OCH_3$.



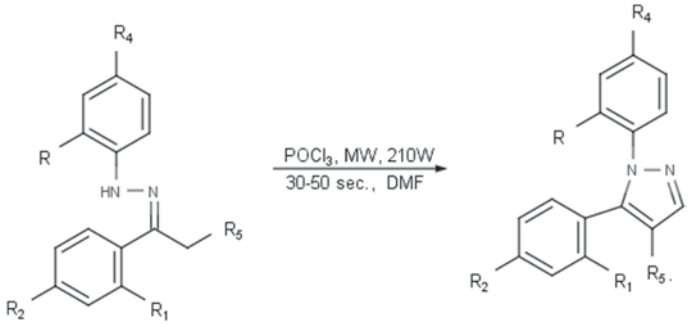
Scheme 11.5

Imidazoles were prepared from α-diketones, aldehyde and ammonia [61]. The reaction (Scheme 11.6) requires 4 h for completion under the conventional heating method and requires only 10 min of irradiation under microwave conditions. By varying R_1, R_2 and R_3 in the reaction, the number of products were obtained with a yield of 75–85 %. The reaction was carried out under solvent-free conditions. R_1 taken was $–C_6H_5$, 4-ClC_6H_4, 2-thiophenyl, etc. $R_2 = R_3$ were taken as $–C_6H_5$, 4-$CH_3C_6H_4$, etc.



Scheme 11.6

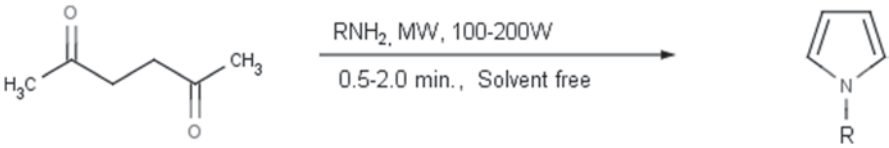
Preparation of pyrazoles from hydrazones using the Vilsmeier cyclisation method was carried out by reaction with $POCl_3$ in the presence of DMF. The reaction was found speeded up by factors of several hundredfold under microwave irradiation [62]. The reaction is given in Scheme 11.7. It was observed that the conventional method needs 4–5 h and the yield is 41–76 % whereas the microwave method requires only 30–50 s to complete the reaction with 45–78 % yield of the product. A number of compounds were prepared by taking different alkyl groups as given R = –H or NO_2, R_1 = –H or -OH, R_2 = –H or $–CH_3$, R_4 = $–NO_2$, and R_5 = $–CH_3$ or $–C_2H_5$.



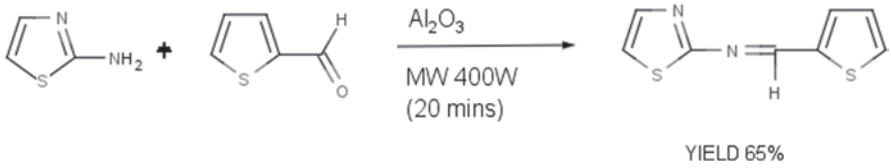
Scheme 11.7

Paal and Knorr cyclisation [63] of 1, 4-diketone to give pyrroles was speeded up by microwave irradiation. The reaction was carried out under microwave solvent-free conditions and was completed within 2 min (Scheme 11.8). R was taken as $–CH_2C_6H_4$, 4-$CH_3COC_6H_4$, 2-ClC_6H_4, etc.

Imine was synthesised under microwave irradiation at 400 W in the presence of Al_2O_3 [64]. The yield was 65 % in a due span of 20 min (Scheme 11.9).

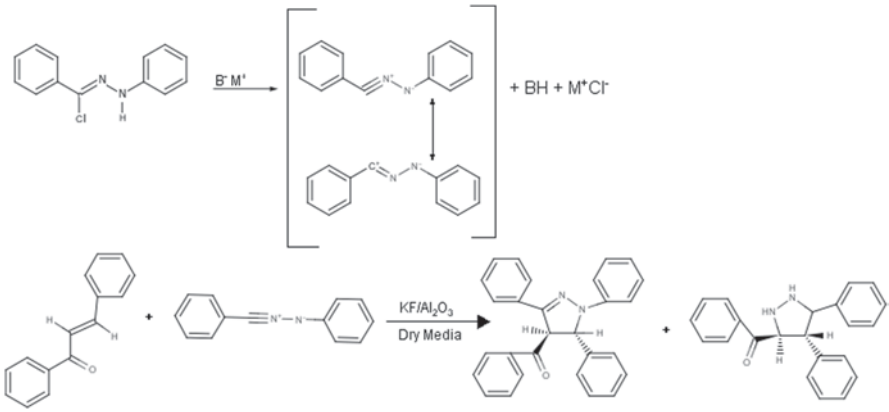


Scheme 11.8



Scheme 11.9

1, 3-dipolar cycloaddition of diphenyl nitrilimine (DPNI) was studied by Bougrin et al. [65]. This DPNI adds to the electrophilic double bond in KF/Al_2O_3 dry media giving rise to bioactive heterocyclic compounds (Scheme 11.10).



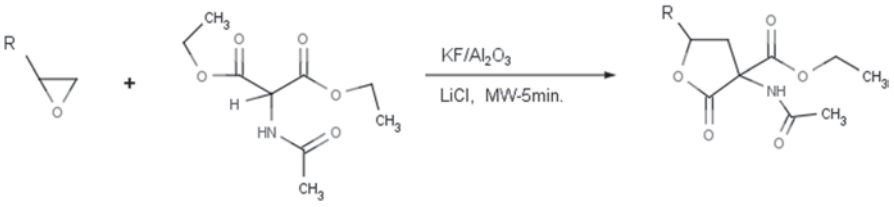
Scheme 11.10

Table 11.1 Al_2O_3/KF-catalysed 1, 3-dipolar cycloaddition of diphenyl nitrilimine (DPNI)

Heating	Type	Time	Temp (°C)	Yield %
MW	Domestic oven	12 min	123	90
MW	Monomode reactor	6 min	170	90
Δ	Oil bath	6 min	170	<2
Δ	Oil bath	24 h	170	90

The rate of reaction, percentage yield and temperature, etc. were compared for conventional and microwave methods. The data are given in Table 11.1. The reaction carried out in a monomode reactor under microwave conditions was found the most efficient one.

The formation of reaction by ring opening of a fatty epoxide was carried out in a microwave oven [66]. Tetradecyloxirane reacts with diethylacetamidomelonate in basic medium and the presence of LiCl to assure electrophile availability for the ring-opening structure (Scheme 11.11).



Scheme 11.11

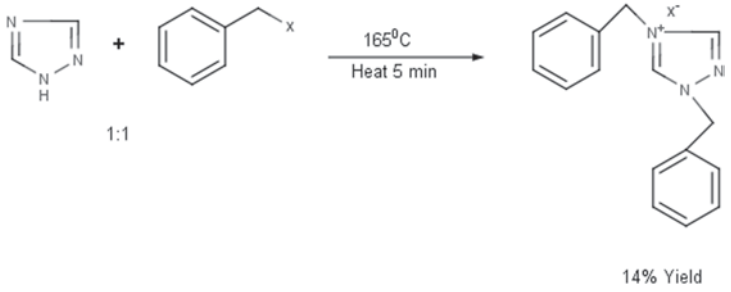
N-Alkylation of phthalimide [67] is compared with different alkyl halides and results are reported in Table 11.2 (Scheme 11.12). TBAB stands for tetrabutyl ammonium bromide.

Scheme 11.12

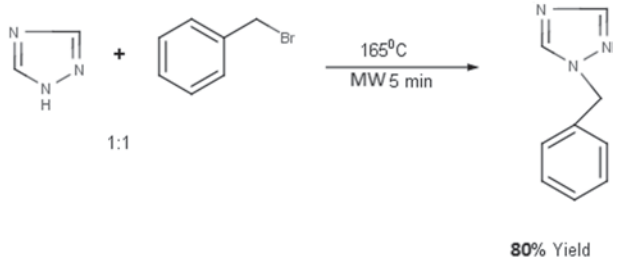
N-Alkylation of 1,2,4-triazole under microwave conditions yields an entirely different product as suggested by Diaz-Barra et al. [68] (Schemes 11.13 and 11.14).

Table 11.2 *N*-Alkylation of phthalimide with different alkyl halides

RX	Time (min)	Yield %
$C_6H_5CH_2Cl$	4.0	93.0
n-C_4H_9Br	4.0	73.0
n-$C_{10}H_{12}Cl$	4.0	51.0

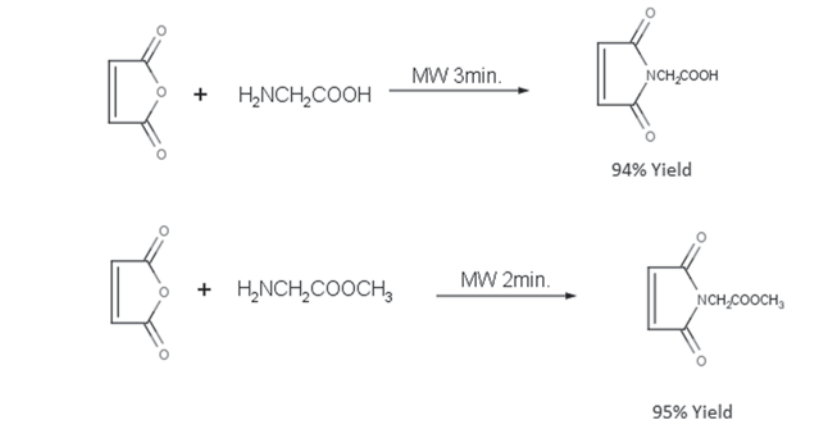


Scheme 11.13



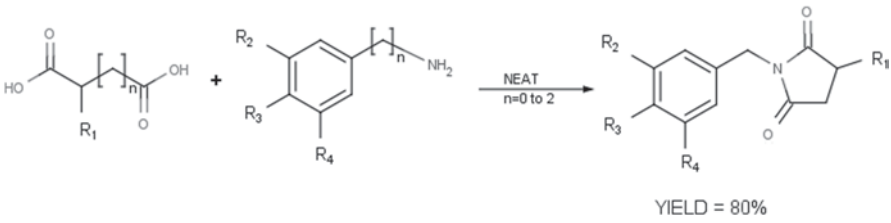
Scheme 11.14

Synthesis of *N*-carboxyalkyl maleimide and phthalimides is carried out under microwave irradiations to give nearly 95% yield. The reactants taken are maleic and phthalic anhydrides and are condensed with amino acids for 2–3 min to give the products [57]. The reactions are given in Scheme 11.15.



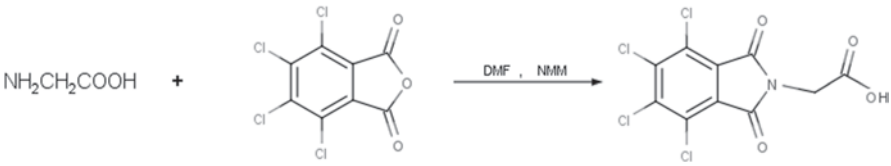
Scheme 11.15

N-Acylation to form maleimide with approximately 80% yield was given by Seijas et al. [69]. The reaction was carried out without a solvent (Scheme 11.16).



Scheme 11.16

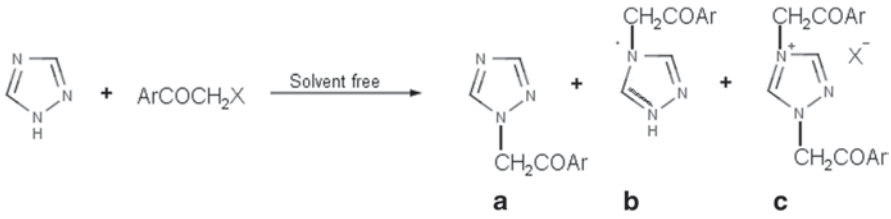
N-Acylation with 94% yield of the product was proposed by Bose et al. [70]. The reaction was carried out under microwave irradiation with DMF and *N*-methylmorpholine (NMM). The reaction is given in Scheme 11.17. In many reactions, microwave irradiation is preferred as it reduces the formation of side products because of the speedy process and was observed in the following example [71] (Scheme 11.18) of phenylacylation of 1,2,4-triazoles (Table 11.3).



Scheme 11.17

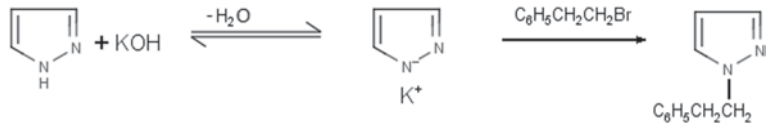
Table 11.3 Phenylacylation of 1,2,4-triazoles

Ar	X	Time (min)	Temp (°C)	Mode	Total yield %	Yield % of A	Yield % of B	Yield % of C
	Cl	20.0	140	MW	90.0	100	–	–
				Δ	98.0	33	29	38
	Cl	25.0	140	MW	95.0	100	–	–
				Δ	98.0	38	27	35
	Br	25.0	170	MW	90.0	100	–	–
				Δ	98.0	38	28	34



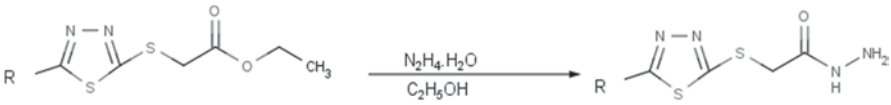
Scheme 11.18

The reaction of pyrazole with phenethyl bromide [72] (Scheme 11.19) gave the product in the absence of base, and the time consumed in microwave irradiation was 8 min as compared to conventional heating that took 48 h, but for the same reaction the presence of base KOH overruled the microwave effect. The yield with KOH was 64% in microwave irradiation and 61% with conventional heating at 145 °C for 8 min. This was because of the availability of a loose ion pair at the reactive species and weak evolution of polarity between transition state and reactant molecules.



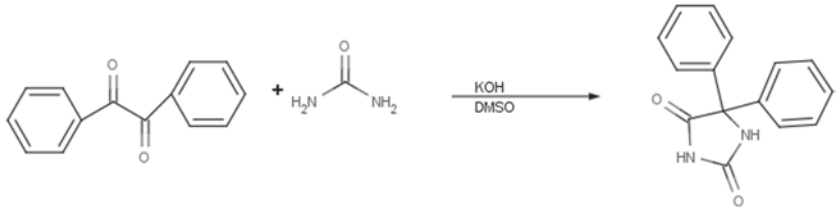
Scheme 11.19

Lidstrom et al. [73] reported, in a review, hydrazide formation with 77–85% yield under microwave irradiation and ethanol was used as the solvent in this reaction (Scheme 11.20).



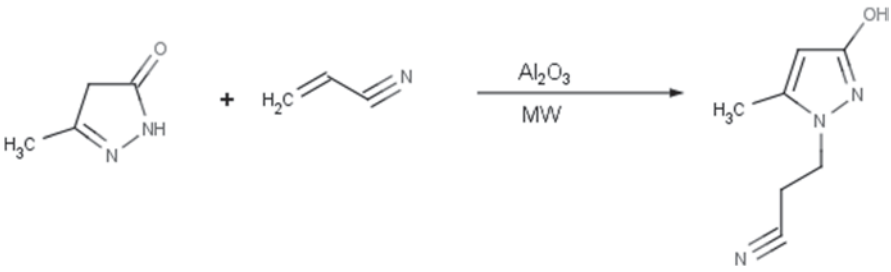
Scheme 11.20

A rapid and efficient microwave-assisted synthesis of hydantoins and thiohydantoins was reported by Muccioli et al. [74]. The reaction is known as Biltz synthesis and is the base-catalysed condensation of benzil and urea. It was observed that microwave irradiation reduced the reaction time as well as increased the yield of the product as compared to the conventional method. The reason behind this is the involvement of polar transition state, i.e. nucleophilic addition of a neutral NH_2 group to a carbonyl site (Scheme 11.21). The yield via the conventional method was 36 % when heated for 2 h whereas the yield via microwave irradiation was 80 % when heated only for 30 min.



Scheme 11.21

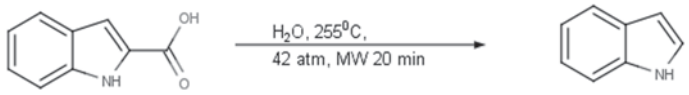
Sviridove et al. [75] proposed microwave-assisted Michael addition in the presence of Al_2O_3 (Scheme 11.22). *o*-Alkylation under microwave irradiation is reported by Majidoule et al. [76] (Scheme 11.23). The reaction was carried out in the presence of KOH and the yield of product was 74–94 %.



Scheme 11.22

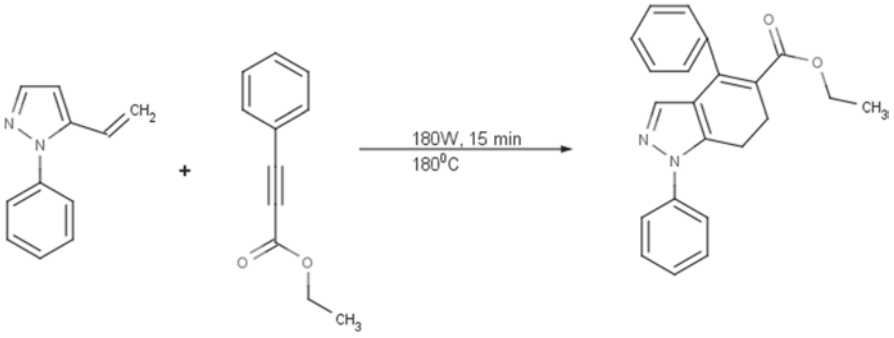
Scheme 11.23

Strauss et al. [3] used water as solvent for the decarboxylation of indole-2-carboxylic acid. The reaction conditions were: temperature 255 °C and pressure 42 atm. The yield was 100 % when treated under microwave irradiation for 20 min (Scheme 11.24).



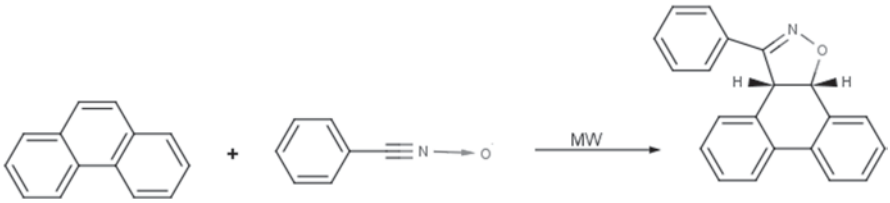
Scheme 11.24

Solvent-free conditions were preferable [77] due to several benefits. The reaction runs safely at atmospheric pressures with increased yield percentage. Here, the radiations are directly absorbed by the reactants thus increasing the yield as well as the purity of the product. The Diels–Alder cycloaddition of vinylpyrazoles under microwave irradiation was carried out by Diaz-Ortiz et al. [78]. It was observed that poor reactive dienophiles like phenyl propiolate do not react when heated conventionally but were found to react under microwave heating (Scheme 11.25).



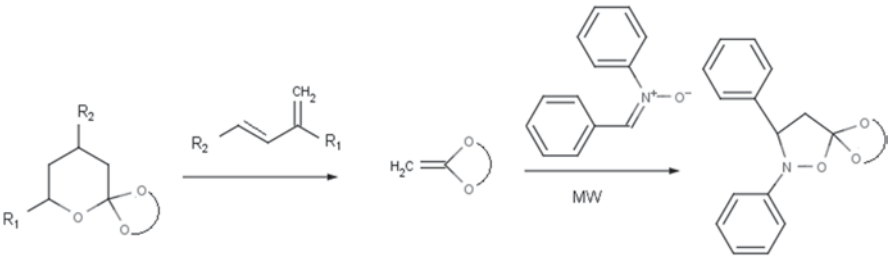
Scheme 11.25

Corsaro et al. [79] reported a solvent-free cycloaddition reaction of polycyclic aromatic hydrocarbon with nitrile oxide. The reaction was completed under microwave irradiation in 3–10 min. It was observed that conventional heating is not capable to perform this reaction because of the dehydration of 1,3-dipole (Scheme 11.26). Yet, the yield 18–21 % is low under microwave irradiation.



Scheme 11.26

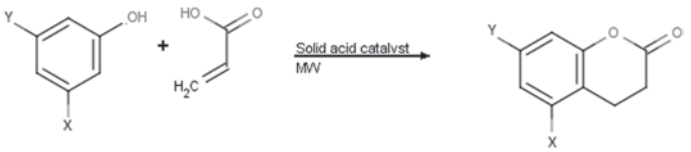
A common problem occurring with ketenes is their polymerization. Diaz-Ortiz et al. [80] reported hetero-Diels–Alder reaction and 1,3-dipolar cycloaddition of ketone acetals under microwave irradiation which was completed in 3 min. The product was isolated directly through crude reaction mixture without the polymerization of ketene (Scheme 11.27).



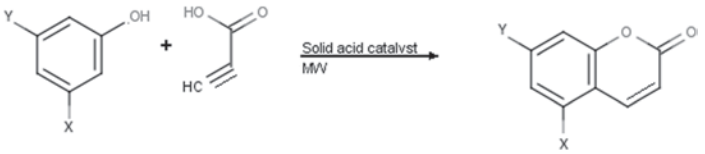
Scheme 11.27

The same scheme is used to follow the Diels–Alder reaction of 3-styrylchromones [81] and intramolecular 1, 3-dipolar cycloaddition of azomethine ylides [82]. The yield of the product was about 80 % in 15 min of microwave irradiation. These reactions were found to take much longer time through conventional heating method.

De la Hoz A et. al carried out the coumarin synthesis under microwave irradiation and it was observed that the use of heterogeneous catalysts like Amberlyst, dowex or KSF eliminates the product of acid waste, which are formed in conventional synthesis, and also overruled the substitution at position 4 of the ring [83]. The reaction is given in Schemes 11.28 and 11.29 and is said to be a difficult preparation.

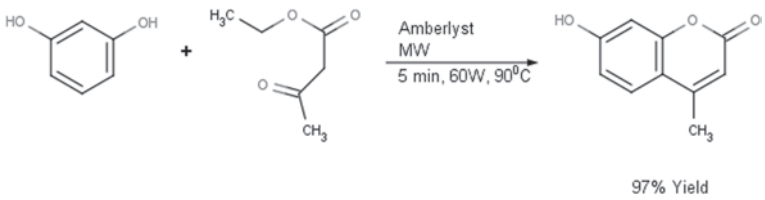


Scheme 11.28



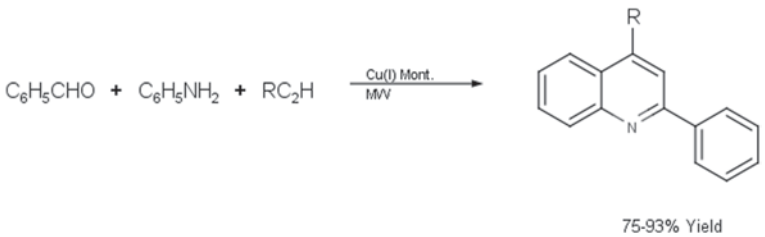
Scheme 11.29

The use of Amberlyst-15 catalyst in the preparation of 7-hydroxy-4-methyl coumarin is found effective quantitatively with 97% yield. This 7-hydroxy-4-methyl coumarin is the starting material for the preparation of an insecticide Hymerocromone. The reactants are heated at 90 °C under microwave irradiation at 60 W for 5 min to yield 97% of the product (Scheme 11.30).



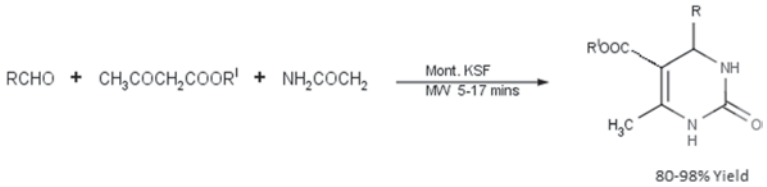
Scheme 11.30

A solvent-free catalysed microwave synthesis of quinolones was proposed by Yadav et al. [84]. The reaction was carried out with reactants aldehydes, amines and alkynes over montmorillonite clay impregnated with Cu(I)bromide. The yield of the product was 75–93% (Scheme 11.31).



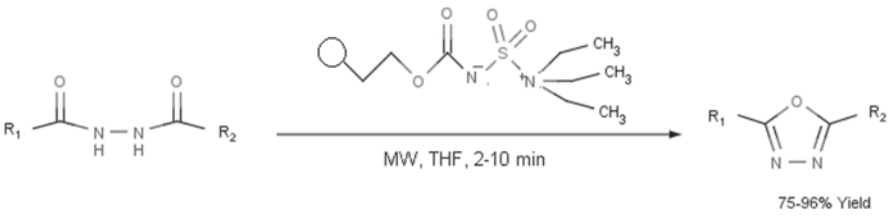
Scheme 11.31

Using montmorillonite KSF clay as the catalyst, Mitra et al. [85] prepared dihydropyrimidinone derivatives. The reactants taken were β-keto esters, urea and different aliphatic and aromatic aldehydes. Depending upon the irradiation time, the yield varies from 80 to 98% (Scheme 11.32).

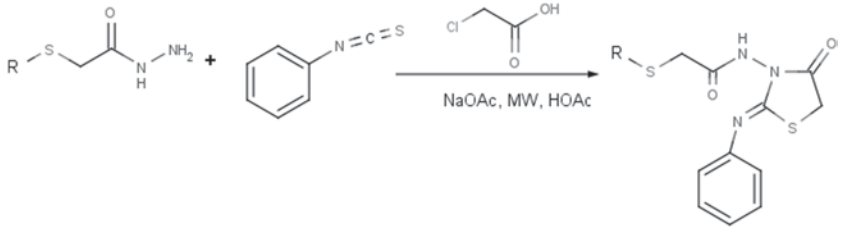


Scheme 11.32

Brain et al. [86] suggested the synthesis of 1,3,4-oxadiazoles using a polymer-supported Burgess reagent (Scheme 11.33). Reactant 1,2-diacylhydrazines were taken and the product was purified by filtration through silica gel. The product was obtained with up to 96% yield under microwave irradiation within 2–10 min. Kidwai et al. [87] reported *N*-alkylation with 71–79% yield of the product under microwave irradiation (Scheme 11.34).

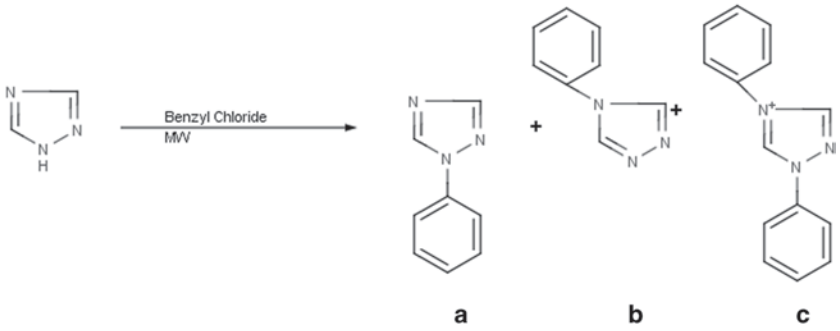


Scheme 11.33



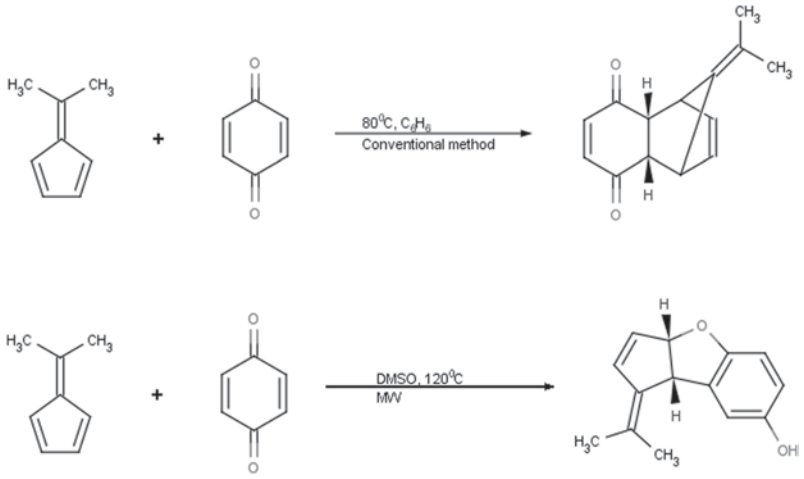
Scheme 11.34

The alkylation of 1,2,4-triazole was carried out by Abenhaim et al. [88] (Scheme 11.35). It was observed that the classical method leads to quaternization or decomposition of triazole whereas microwave irradiation generates pure *N*-1-alkyated product with benzyl chloride. It was found out that in the classical route, in absence of base and solvent, heating up to 165 °C for 5 min generates only 13 % of 1,4-added product C and on further heating for 1 h at 120 °C decomposes the reactant. On the other hand, microwave irradiation at 450 W for 5 min at 165 °C forms only 1-alkylated product with 70 % yield.



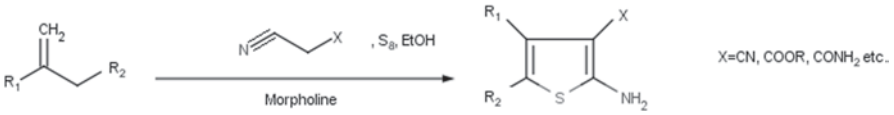
Scheme 11.35

Hong et al. [89] showed that the reaction of 6, 6-dimethylfulvene with *p*-benzoquinone produced [4+2] cycloaddition product under conventional heating method whereas it produced [6+2] cycloaddition product under microwave irradiation (Scheme 11.36).



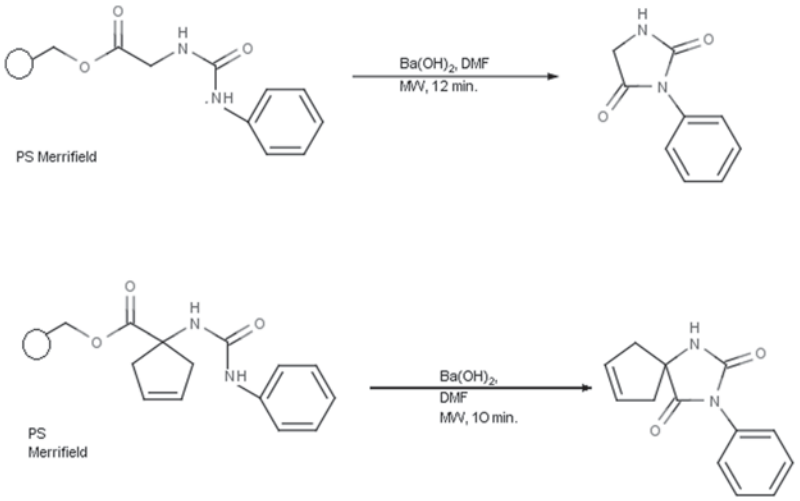
Scheme 11.36

Hoener et al. [90] investigated a one-pot reaction for Gewald synthesis on solid support (Scheme 11.37). The products 2-amino-3 acyl thiophenes are used commercially as dyes.



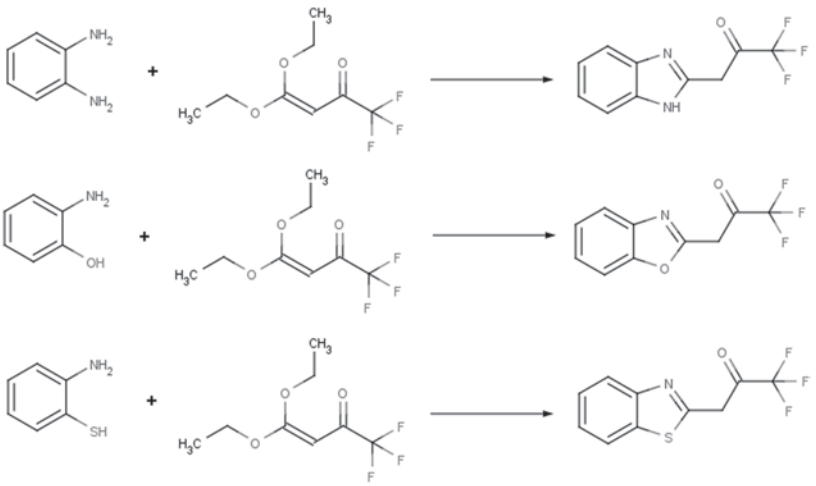
Scheme 11.37

Microwave-mediated intramolecular carbanilide cyclisation to hydantoins was described by Gong et al. [91] (Scheme 11.38). Hydantoins are used as bioactive compounds widely. The reaction was carried out on solid PS Merrifield support. The reaction under the conventional technique requires 8–48 h for completion whereas only 10 min are taken under microwave irradiation.



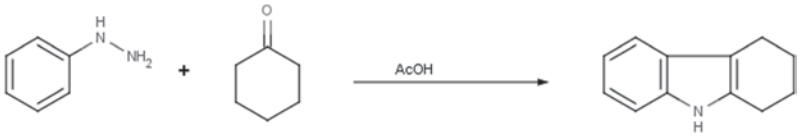
Scheme 11.38

Benzimidazoles, benzoxazoles and benzthiazoles are prepared by ring closure of *o*-substituted anilines and the yield of product was found much higher under microwave conditions [92] as compared to the conventional method [93] (Scheme 11.39).



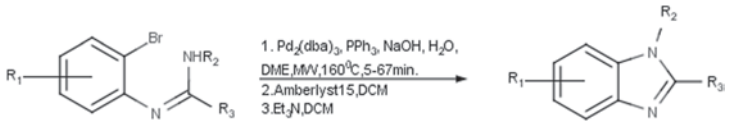
Scheme 11.39

Under microwave conditions at 980 W and in the solvent toluene, the reactants were heated for 9–11 min to yield the product up to 89–96% whereas the same reaction was completed in 3.5 h via the conventional technique and the yield was 40–80%. Fischer indole synthesis [94] under microwave irradiation was found to be much faster than in the conventional method (Scheme 11.40) where the reactants were refluxed in ethanol for the completion of the reaction.



Scheme 11.40

Scheme 11.41 shows microwave-assisted intramolecular amination of arylbromides to benzimidazole.



Scheme 11.41

The reaction is known as Buchwald–Hartwig amination. A number of compounds have been synthesised with enhanced rates, greater purity, reduced reaction times and lesser amount of side reactions and side products [95].

Here, R_1 = 3-CH_3, 5-H, 5-OCH_3, 5-NO_2

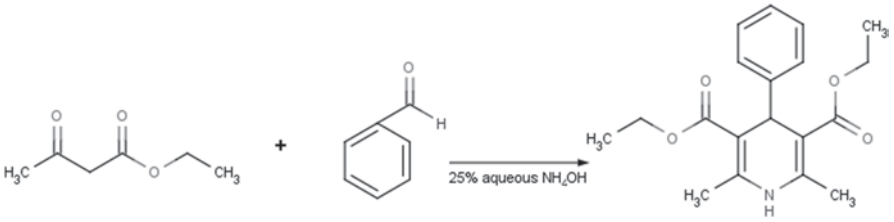
R_2 = –CH_3, –C_6H_5

R_3 = –CH_3, –C_6H_5

The yield of the product was 66–98 % at 160 °C.

5.2 *Microwave-Assisted Synthesis of Six-Membered Heterocycles*

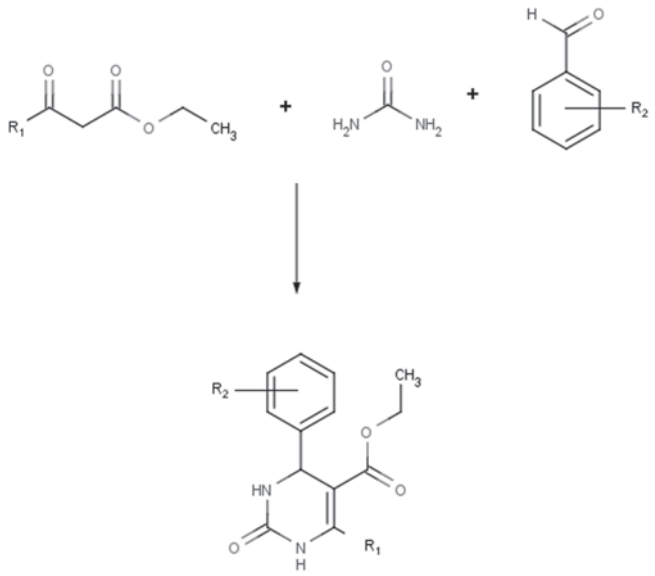
Numerous studies have been carried out on microwave-assisted organic synthesis, and chemists have observed that the chemical reaction rates can be enhanced by 1,000 fold [96–98]. Various six-membered heterocyclic compounds are synthesised under microwave conditions with greater yield, enhanced purity and lesser amount of side products. Hantzsch dihydropyridine synthesis is the most common method for the synthesis of a six-membered pyridine ring. The reaction is given in Scheme 11.42 [99].



Scheme 11.42

The yield under microwave conditions was 51–92 % in 10–15 min whereas under conventional conditions, it took 12 h of heating to give 15–61 % yield. The heating was done at 140 °C under microwave irradiation and solvent-free conditions. A number of compounds are synthesised by taking different aryl groups like –C_6H_5, -2-NO_2, –C_6H_4, -2-$CH_3OC_6H_4$, -2-ClC_6H_4, etc.

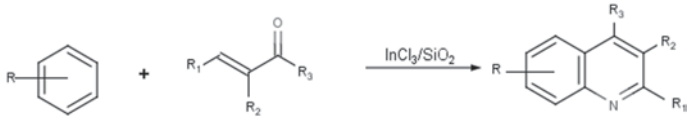
The Biginelli reaction is used to prepare dihydropyrimidine derivatives. Under microwave irradiation, the yield was much greater as compared to the conventional method. The reactants when heated under microwave irradiation for 5 min gave 60–90 % yield whereas it took 12–24 h under conventional conditions to give 15–60 % yield of the product [18] (Scheme 11.43).



Scheme 11.43

Different products can be prepared by taking different groups for R_1 and R_2. For example, R_1 =–H, $–CH_3$ can be taken. R_2 =–H, –Cl, OCH_3 groups are taken.

Skraup's synthesis is found to give very low yield of the product under very drastic conditions in conventional synthesis process. Recently, under microwave irradiation, quinolines have been synthesised through Skraup's synthesis [100] and higher yield was obtained within lesser time of irradiation. A number of products were synthesised by taking the following alkyl groups (Scheme 11.44):



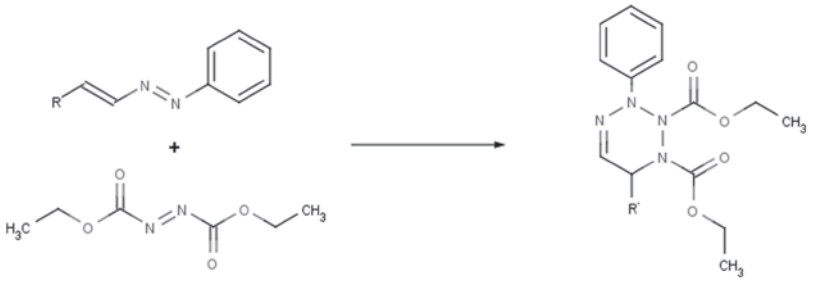
Scheme 11.44

R =–H, *o*-CH_3, m-CH_3, *p*-CH_3, *o*-OCH_3, *p*-OCH_3, *m*-OH, *m*-Cl, etc.
R_1 =–H, $–CH_3$, *n*-C_3H_7, etc.
R_2 =–H, $–C_2H_5$ and
R_3 =$–CH_3$, *p*-$CH_3OC_6H_4$.

It was observed that in the conventional heating process, the reactants were taken in H_2SO_4 and heated at 150 °C, but very low yield of products was obtained. On the

other hand, on microwave irradiation by 600 W in solvent-free conditions, 80–87% yield was obtained within 5–12 min.

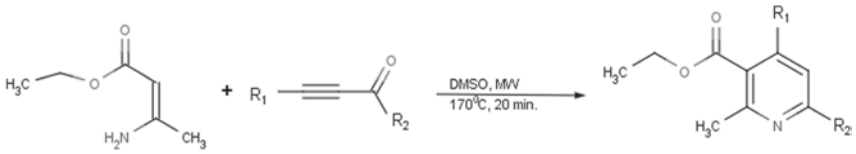
A 1,000-fold-enhanced rate was observed in the Diels–Alder reaction of azaolefins and azadicarboxylic ester to give tetrazines [101] (Scheme 11.45).



Scheme 11.45

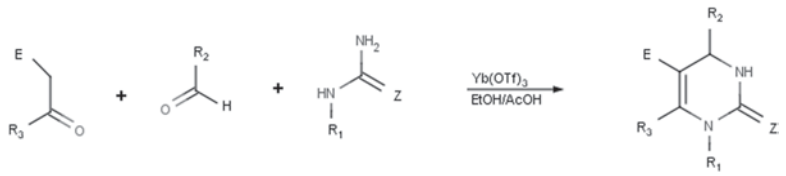
The conventional process required 30 days for the completion of the reaction whereas under microwave irradiation it reached completion, with 300 W and solvent-free condition, in 15 min with a yield of 80–96%. R here is taken as carbohydrate.

Bagley et al. [102] synthesised pyridine derivatives under microwave irradiation at 170 °C and in the presence of DMSO to give 24–94% yield in 20 min. Different products were synthesised by taking R_1 = –H, $–C_2H_5$, $–C_6H_5$ and R_2 = alkyl or aryl group (Scheme 11.46).



Scheme 11.46

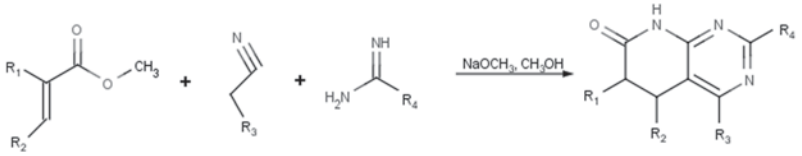
Biginelli synthesis [103] was also carried out by Kappe et al. [104] to get about 48 different products. The reactions were carried out under microwave irradiation to get nearly 52% average yield of products (Scheme 11.47).



Scheme 11.47

The conventional method for these syntheses took several hours treatment at 80 °C in solvents such as ethanol, etc. The reactions were carried out at 100 °C for 10–20 min to give the products. The groups taken for R_1 were –H, -alkyl or aryl, R_2 were alkyl, aryl or heterocycles, R_3 were alkyl or aryl, Z was O or S, and E was –COOR, –C(O)R, C(O)NR_2 or NO_2. Tf stands for trifluoromethanesulphonyl.

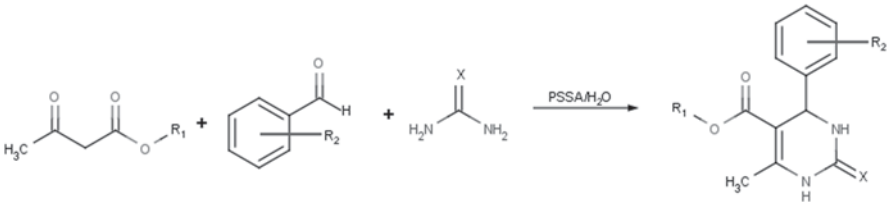
The Victory reaction for the synthesis of heterocycles was carried out by Mont et al. [105]. The reaction was carried out under microwave irradiation at 100–140 °C for 10 min to give nearly 98 % yield of the product (Scheme 11.48).



Scheme 11.48

Here, R_1 may be –CN or –$COOCH_3$, R_1,R_2 and R_4 may be alkyl or aryl groups, and R_3 may be NH_2 or OH groups.

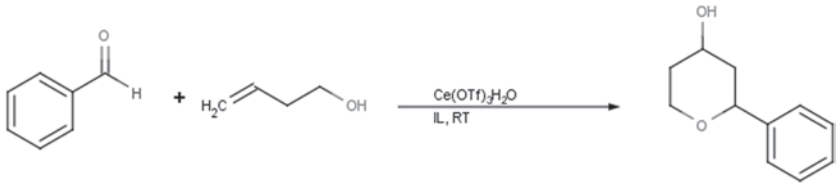
Dihydropyrimidinones were synthesised by benign aqueous Biginelli reaction using polystyrenesulphonic acid (PSSA) as the catalyst [106]. The reactants were heated at 80 °C under microwave irradiation to give the products. A number of compounds may be synthesised by taking R_1 and R_2 group varieties. The reaction is given in Scheme 11.49.



Scheme 11.49

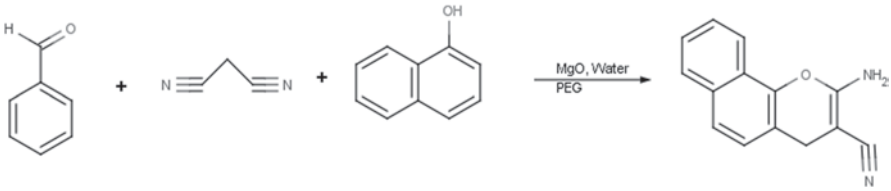
The same reaction was carried out under solvent-free conditions by Kappe et al. [107]. The products were filtered directly to remove the aqueous medium.

Tetrahydropyranol derivatives in ionic liquid were prepared by the reaction of homoallyl alcohols and an aldehyde (Scheme 11.50) in the presence of the catalyst cerium triflate [108].



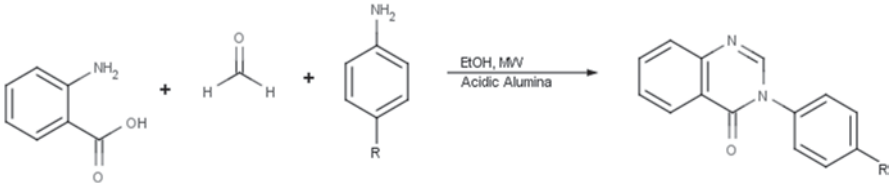
Scheme 11.50

The reaction of aldehyde, malononitrile and α-naphthol was carried out under microwave irradiation in the presence of the water–polyethylene glycol system and nanosized MgO as the catalyst. The product 2-amino-2 chromene was obtained in high yield. The reaction is given in Scheme 11.51 [109].



Scheme 11.51

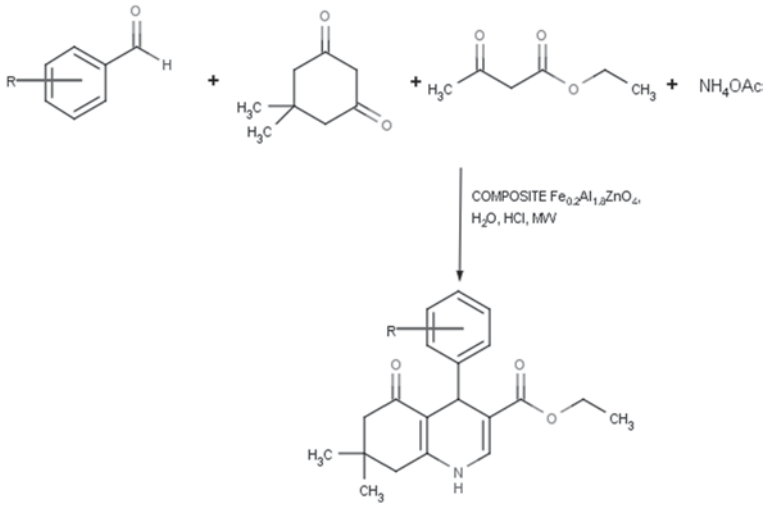
The synthesis of quinazolinones under microwave irradiation was carried out by Mishra et al. [110] (Scheme 11.52).



Scheme 11.52

A series of compounds was prepared by varying the R groups. It was taken as –H, 4-CH_3, 4-CH_2CH_3, 4-OCH_3, 4-Cl, 4-Br or NO_2. It was observed that the reaction reached completion within 5–7 h through the conventional process whereas it was completed in 2–4 min under microwave irradiations. The yield was 56–68% through the conventional method and was 82–94% under microwave irradiation.

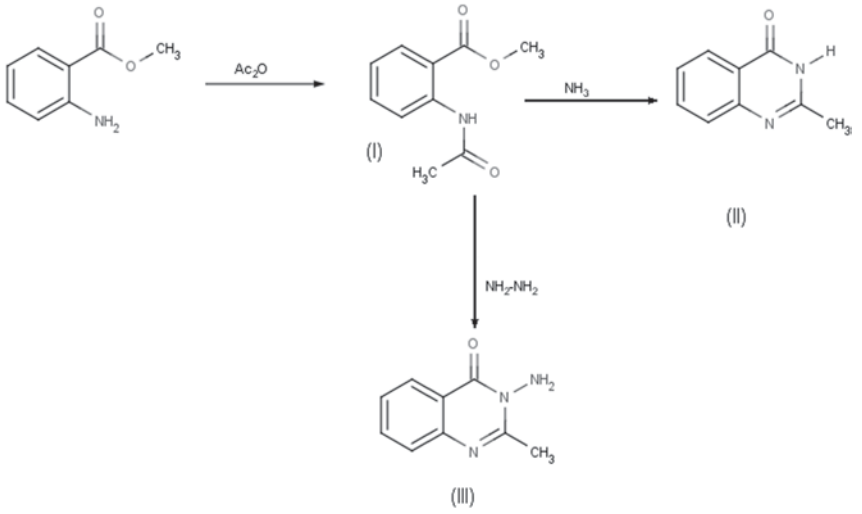
Microwave-assisted synthesis of bioactive polyhydroquinoline derivatives was carried out by Joshi et al. [111] (Scheme 11.53).



Scheme 11.53

The yield of products was 90–95 % under microwave irradiation for 3–5 min. A number of products were synthesised by varying R as –H, 4-CH_3, 2-Cl, 3-Cl, 4-Cl, 4-OH, 4-OCH_3, 4-NO_2, 2-OCH_3, 4-Br or 4-F.

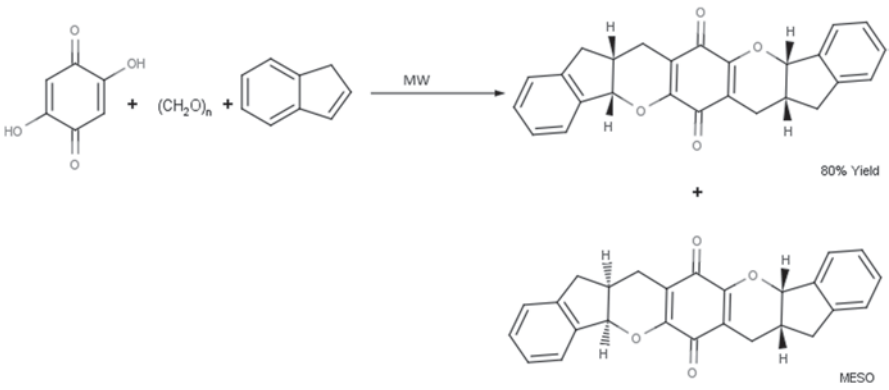
Microwave-assisted synthesis of quinazolinone using different bases was carried out by Patil et al. [112] (Scheme 11.54).



Scheme 11.54

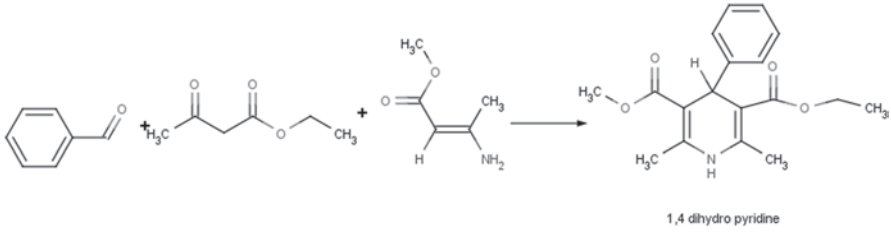
Product I was obtained on 15 min of microwave irradiation with 73.7% yield. This, on treatment with ammonia at 140 W for 15 min, gave product II with 84–86% yield. Product III was obtained by treating compound I with hydrazine under microwave irradiation for 3 min. The yield was 77.93%.

The regioselective multicomponent construction of bis-pyrano-1,4-benzoquinone derivatives IV and V from the reaction of 2,5-dihydoxy-1,4-benzoquinone, para-formaldehyde and an alkene was carried out by Jimenez-Alonso et al. [113]. Depending on the alkene, the products obtained were linear tricyclic, pentacyclic or heptacyclic diastereomers (Scheme 11.55). The reactants were irradiated under microwave irradiation for 20 min at 200 °C to give the products.



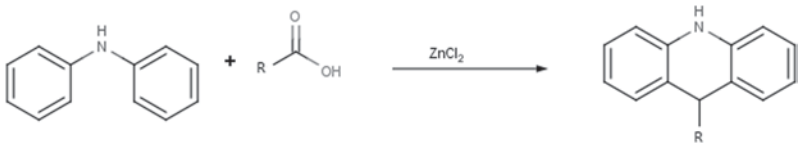
Scheme 11.55

Suarez et al. [114] also reported Hantzsch synthesis under microwave irradiations. It was observed that in the conventional method the reaction mixture in the presence of ethanol was refluxed for 8 h to give 55% yield of the product. The same reactants heated at 120 °C in the presence of alumina and DMF for 6 min gave 5% yield and when heated for 1 h gave 30% yield. The reaction mixture when taken in dry media with alumina and heated at 80–85 °C for 6 min, gave 40% yield. The same reactants under microwave irradiation in the presence of alumina and DMF at 120 °C gave 95% of the product within 6 min of irradiation (Scheme 11.56). In this case, a small amount of polar DMF allows the temperature to reach up to 120 °C. This technique was also used for the synthesis of various substituted pyridines [21].



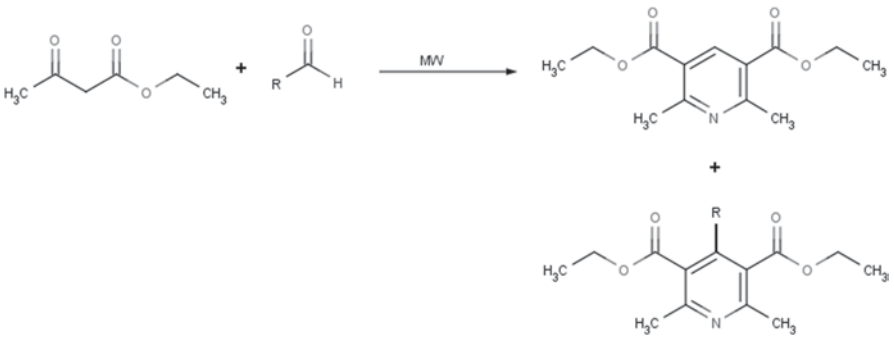
Scheme 11.56

Seijas et al. [115] suggested microwave-assisted synthesis of Bernthsen reaction in the presence of Lewis acid catalyst $ZnCl_2$ with shortened reaction time and increased yield (Scheme 11.57). The yield was 57–98 % within 2.5–11 min. R was taken as alkyl or aryl group.



Scheme 11.57

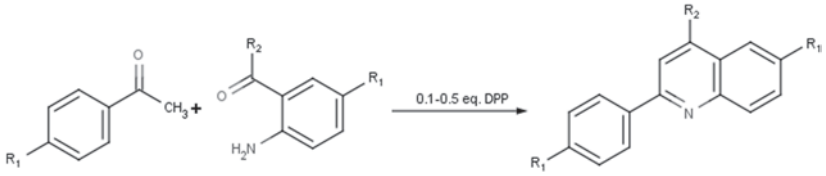
Cotterill et al. [21] also reported the first parallel microwave-assisted synthesis of functionalized pyridine (Scheme 11.58).



Scheme 11.58

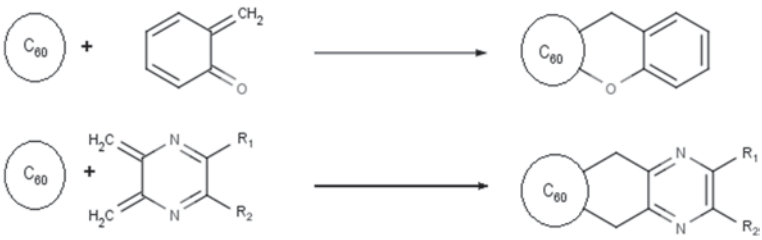
The reaction is carried out in the presence of NH_4NO_3 and bentonite.

Synthesis of quinoline derivatives via the Friedlander coupling condensation reaction [116] was carried out under microwave irradiation. The reactants were different acetophenones and 2-aminoacetophenones or benzophenones. The product was obtained in 4 min of irradiation (Scheme 11.59).



Scheme 11.59

Fullerenes derivatives are prepared by Diels–Alder and 1,3-dipolar cycloadditions under microwave irradiation [117] (Scheme 11.60).



Scheme 11.60

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Chapter 12
Green Chemistry Approach Using Heterogeneous Catalysts in the Heterocyclic Synthesis

Sudesh Kumar, Prachi Rathi, K. L. Ameta and Dharma Kishore

Contents

Abstract The present chapter deals with the recent developments in green chemistry approach using heterogeneous catalysts in heterocyclic synthesis. The process of heterogeneously catalysed reactions of furan, oxazoline, pyrazole, piperidine, piperazine, pyridine and their derivatives are discussed.

Keywords Biocatalysis · Diastereoselective · Microwave-assisted reaction

1 Introduction

Chemical developments bring new environmental problems and harmful, unexpected side effects [1]. The present economy remains utterly dependent on a massive inward flow of natural resources that include vast amounts of nonrenewable [2] reverse flow of economically spent matter back to the ecosphere [3]. Chemical sustainability problems are determined largely by these economy–ecosphere materials flows [4]. It has become imperative to the development of the technological dimension of a sustainable civilization [5]. In the 1980s and 1990s, several envi-

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ronmentally conscious terms entered the chemical arena, e.g. clean chemistry, environmental chemistry, green chemistry, benign chemistry and sustainable chemistry. These terms are not well defined and are subject to a debate among chemists [6–7].

Modern organic synthesis eagerly demands methods that allow the preparation of target-relevant products from simple and readily available precursors in a rapid and economical fashion [8–10]. The use of hazardous catalysts and reagents is one of the most important aspects of eco-friendly chemistry. Reagent chemists are working towards the development of more benign and selective reagents that require ambient conditions. The elimination of hazardous solvents is one of the prime concerns among them. In recent years, microwave-assisted organic synthesis (MAOS) has developed into a popular branch of synthetic organic chemistry [11–12]. One of the most fundamental obstacles in developing technologies is to minimize the energy consumption and to eliminate/minimize the use of hazardous solvents.

Green chemistry provides the design and development of sequential processes that use a set of principles that eliminates or reduces hazardous substances in the manufacture, design and application of chemical products. It is a highly effective approach to pollution prevention [13–14]. Organic compounds that contain heterocyclic moieties are quite significant because of their interesting biological properties [15–16]. Heterocyclic compounds form important building blocks for naturally occurring and biologically active compounds. The application of catalytic methods can have highly efficient catalytic efficiency and substrate generality [17]. Heterocyclic compounds have been extensively studied for their biological applications like antiviral, antibacterial, antifungal, antimalarial [18], antileukemic agents [19], antifertility activity, antitubercular, antipyretic, antitumor and anticancer [20].

Conventional methods of organic synthesis usually need longer heating time and elaborate and tedious procedures which result in higher cost of process, and the excessive use of solvents and reagents leads to environmental pollution [21–22]. Microwave-induced organic reactions have emerged as a new ‘lead’ in organic synthesis [23]. Microwave reactions under solvent-free conditions are attractive in reducing pollution, lowering the cost and offering high yields together with simplicity in processing and handling [24]. The salient features of the microwave approach are shorter reaction times, simple reaction conditions and enhancements in yields [25]. The microwave-enhanced chemical reactions are gaining importance due to the advantages and environmentally friendly processes they offer, as compared to conventional reactions [15].

Organic reactions focus on the number of atoms being transformed during the specific synthetic transformation from one phase to another. The intention of green chemistry is to present an illustrative approach as to how one evaluates a synthesis with regard to its environmental consequences. The precise nature of the specific starting organic material and the by-products has an overriding importance when evaluating the environmental aspects of a given synthetic sequence. The green chemistry approach minimizes the use of cumbersome separation, recrystallization, distillation, chromatography and other techniques which minimize the formation of undesired by-products. Toxicity of organic chemicals has a direct or indirect effect on global environmental problems, i.e. acute lethality, algal blooming, neurotoxicity, ozone depletion, endocrine disruptions and global warming. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment. Analytical methodologies need to be further developed to allow for real-time, in-process monitor-

ing and control prior to the formation of hazardous substances. Substances used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

Heterocycles are important structural motifs of a wide range of natural substances, compounds of pharmaceutical interest and commodity chemicals. Because of this, a large number of methods have been developed to provide access to almost every type of heterocyclic derivative. In this context, transition metal catalysis has played a remarkable and ever-growing role. Heterocyclic chemistry is no exception to this trend. Transition metal-catalysed reactions have been widely employed in the construction of heterocyclic rings providing increased functional group tolerance, simplified procedures and improved yields.

Six-membered nitrogen-containing heterocycles (e.g., pyridines, piperidines and piperazines) are privileged structures that occupy a central role in bioorganic and medicinal chemistry [26–28]. Consequently, developing efficient regioselective and stereoselective methods to obtain these structures has attracted considerable attention during the past decades. These types of heterocycles have been successfully synthesised by using a range of cycloaddition reactions [29–34]. However, the obtained structural diversity is often limited as a result of the partial access of commercially available starting materials.

2 Synthesis of Heterocyclic Compounds

Compounds classified as heterocyclic probably constitute the largest and the most varied family of organic compounds. Carbocyclic compounds, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogues by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulphur, the permutations and combinations of such a replacement are numerous.

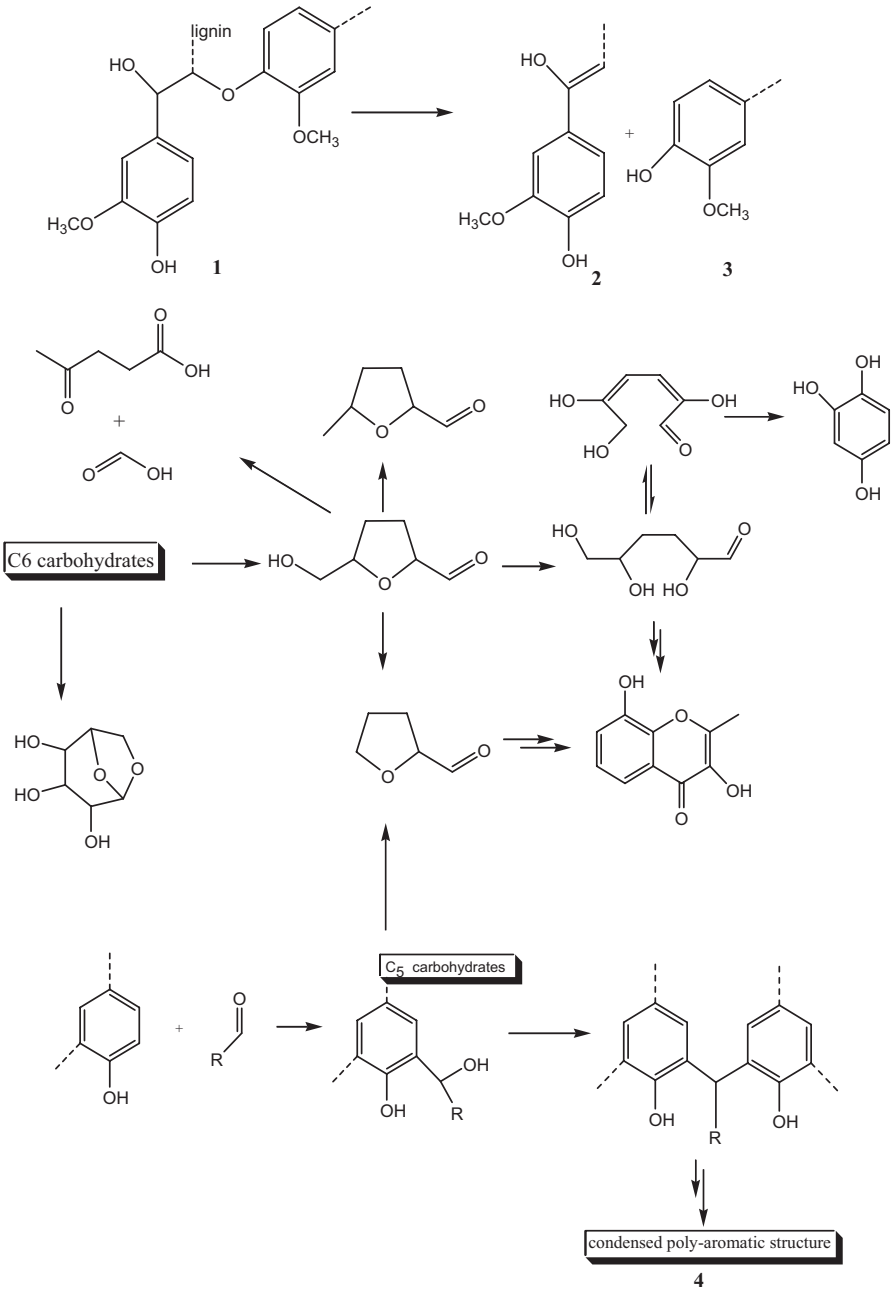
3 Catalytic Applications in Heterocyclic Synthesis

Biological activities of heterocyclic compounds play a crucial role in human life. The aim of this chapter is to design new, safer and environmentally benign methods for the synthesis of heterocyclic compounds for biological applications. All procedures were carried out considering green chemistry principles such as reducing waste generation, increasing atom economy, etc. In all attempts, commercially available and inexpensive starting materials, catalysts and reagents were used in order to make the processes more cost effective.

3.1 Synthesis of Five-Membered Heterocycles

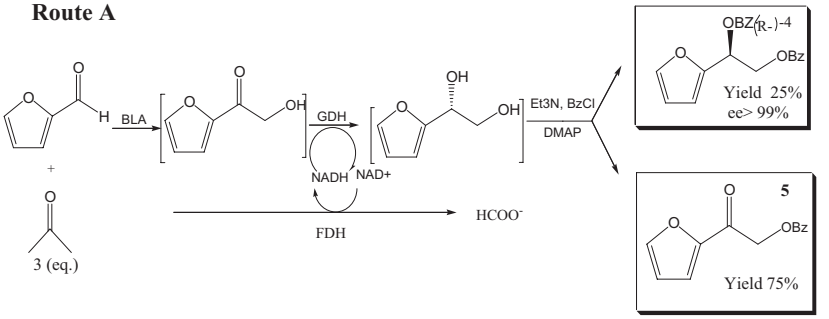
3.1.1 Furan

Formation of an aromatic ring: Reported pathways of decomposition of major wood components and the formation of new functional groups and condensed aromatic units during the torrefaction [35–45] (Scheme 12.1).

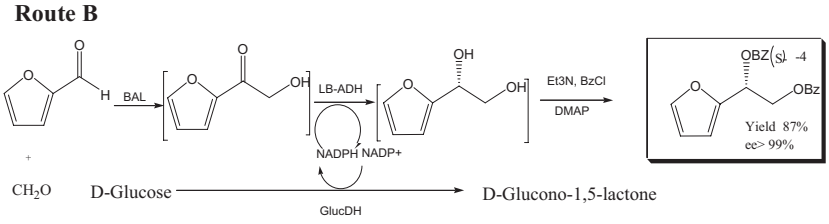

lignin
HO
O
OCH3
H3CO
OH
1
HO
H3CO
OH
2
+
HO
OCH3
3
O
OH
O
+
O
OH
O
HO
OH
HO
O
HO
OH
C6 carbohydrates
HO
O
O
HO
OH HO
HO
O
O
HO
O
O
OH
O
OH
O
HO
O
O
OH
C5 carbohydrates
+
O
R
OH
OH
R
OH
OH
R
condensed poly-aromatic structure
4

Scheme 12.1

Biocatalyzed formation of chiral furane diols: Sufficient amount of **5** as an intermediate despite the higher amount of GDH applied via route **A**, the bottleneck was supposed to be at low activity of GDH towards furan compounds. In fact, in route **B** when *Lb*ADH was applied, with glucose dehydrogenase (GlucDH) for cofactor regeneration, this resulted in excellent isolated yields (87%) and enantioselectivity (>99% ee, (*S*)) [46–49] (Scheme 12.2).



Biocatalytic formation of chiral furane-diols via route A. 40 mL phosphate buffer 50 mmol L-1, pH 8.0, 5% v/v 2-MeTHF, 1.6 mmol furaldehyde, 4.8 mmol formaldehyde, 2.5mmol L-1 MgSO4, 0.15 mmol L-1 ThDP, 168 U BAL, 1500 U GDH, 95 U FDH, NADH/NAD+ 1 mmol L-1 each

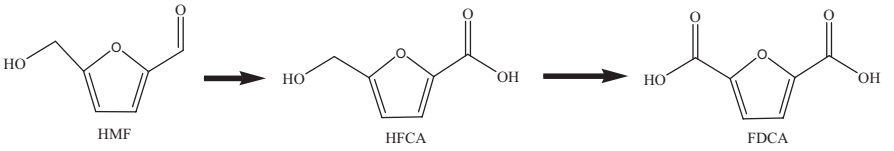


Biocatalytic formation of chiral furan-diols. 40 mL phosphate buffer 50 mM, pH 8.0, 5% v/v 2-MeTHF, 1.6 mmol furaldehyde, 3.6 mmol glucose, 4.4 mmol CaCO3, 4.8 mmol formaldehyde, 2.5 mmol L-1 MgSO4, 0.15 mmol L-1 ThDP, 168 U BAL, 50 U Lb-ADH, 2800 U GlucDH, 0.5 mmol L-1 NADPH

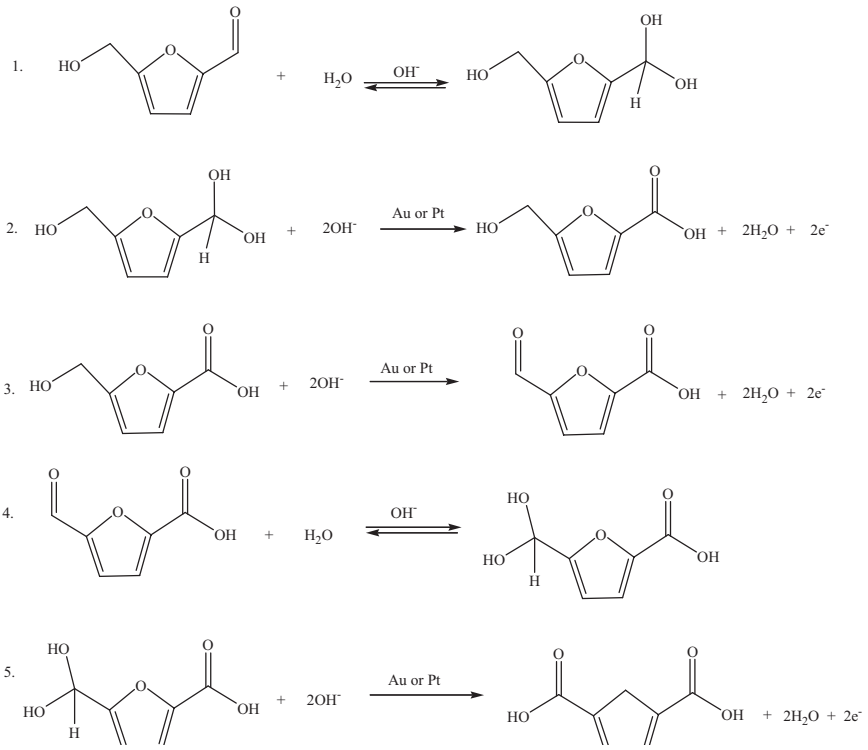
Scheme 12.2

HMF oxidation reaction and mechanism: Hydroxymethylfurfural (HMF) oxidizes in the presence of a base (OH−) and a catalyst, either Pt or Au into HFCA, which on oxidation gives FDCA [50–53] (Scheme 12.3).

HMF oxidation scheme



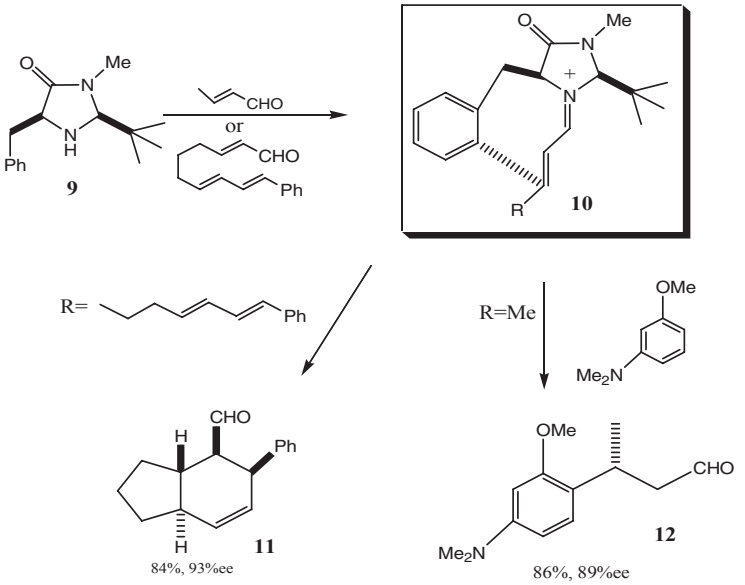
HMF oxidation mechanism



Scheme 12.3

Iminium–π interactions reaction: The enantioselective organocatalytic 1,4-addition reaction of an electron-rich benzene to an α, β-unsaturated aldehyde and an intramolecular Diels–Alder reaction of a trienal has been reported to take place through the sequence of reactions shown in Scheme 12.4. The first step of this reaction is the formation of the intermediary iminium ion **10** from reaction of the

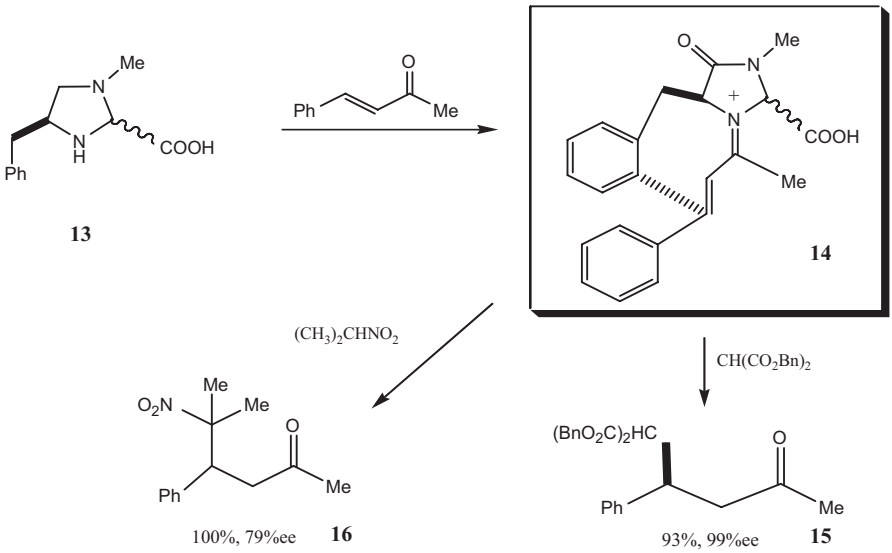
catalyst **9** with α, β-unsaturated aldehydes, followed by face-selective addition of the electron-rich benzene derivative to the iminium ion. The subsequent intramolecular Diels–Alder reaction proceeds to give a bicyclic aldehyde **11** bearing four stereogenic centres in 84 % yield and 93 % ee [54–64] (Scheme 12.4).



Enantioselective organocatalytic 1,4-addition reaction to an α,β-unsaturated aldehyde and an intermolecular Diels–Alder reaction.

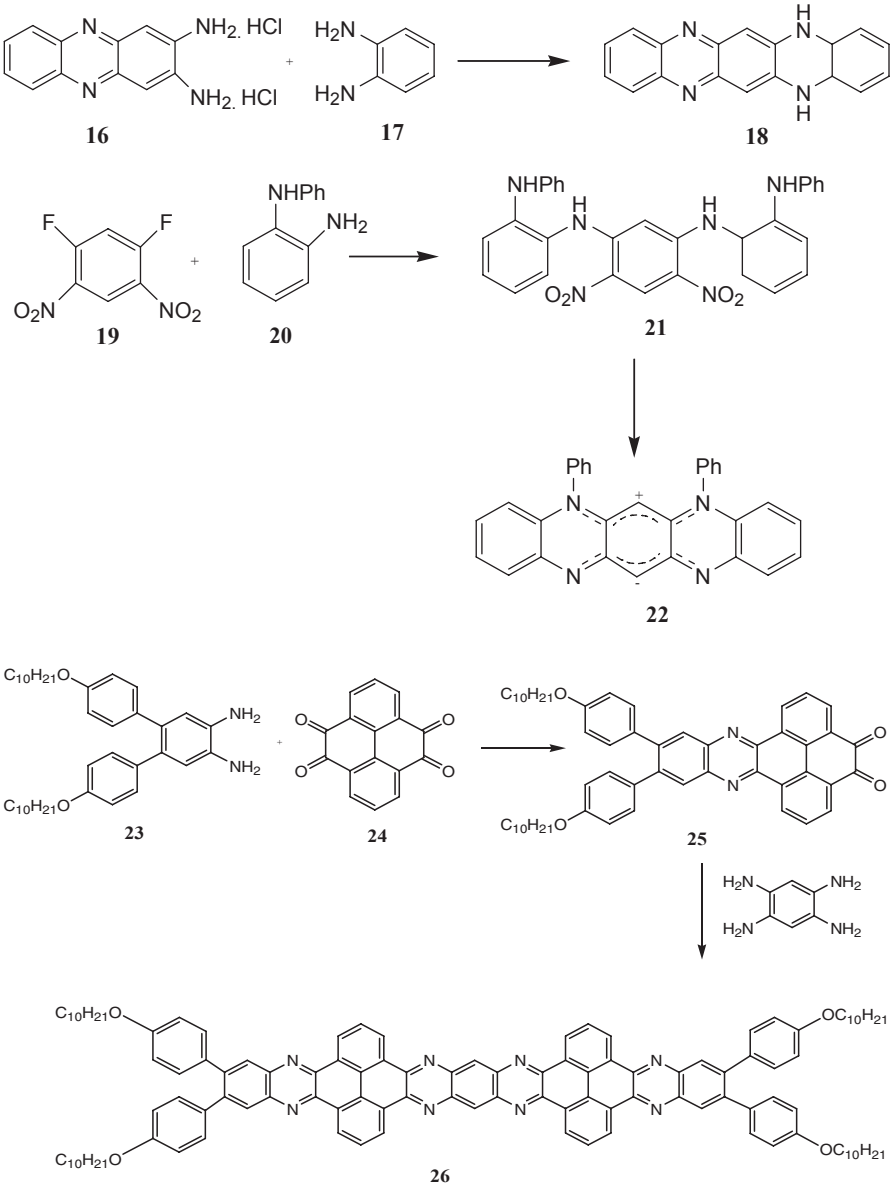
Scheme 12.4

Formation of enones: Jørgensen reported conjugate additions of nitroalkanes and malonates to α, β-unsaturated enones using amine catalyst **13** to give the corresponding adducts **14** with good stereoselectivities [65–67] (Scheme 12.5).



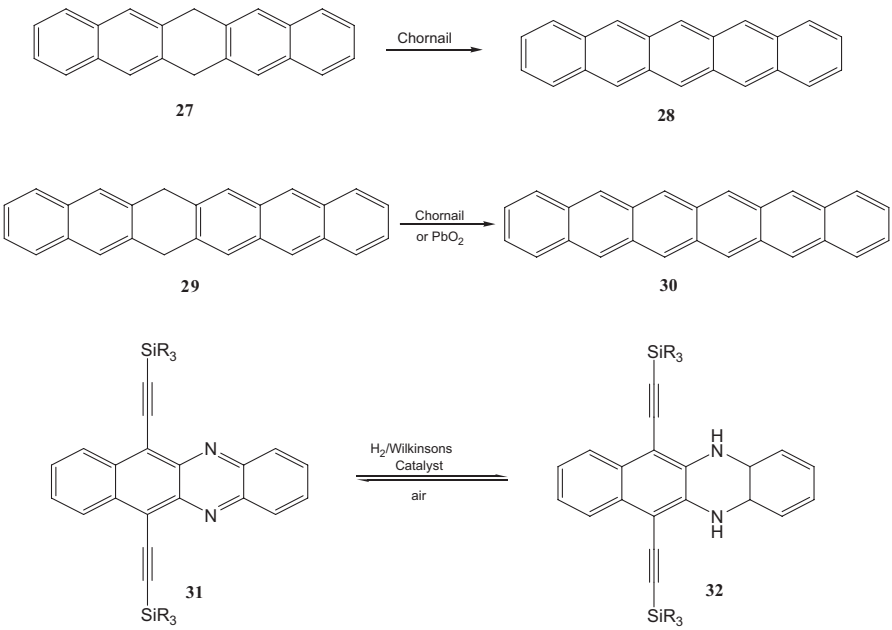
Scheme 12.5

Synthesis of pyrazinacenes: Hepp and Fischer first prepared 5,14-dihydro-5,7,12,14-tetraazapentacene **18** by direct condensation of 2,3-diaminophenazine hydrochloride **16** with *o*-Phenylenediamine **17**. Wudl and co-workers developed a strategy for the synthesis of *syn*-substituted zwitterionic tetraazapentacenes. The preparation involved a double nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene **19** with N-substituted-1,2-phenylenediamines **20** to give 2,4-dinitrobenzene-1,5-diamines **21** in good yield. Hydrogenation of compounds **21** followed by heating in ethanol in air gave the zwitterionic tetraazapentacenes **22**. Pyrazinacenes based on the pyrene moiety have also been prepared. Wang and co-workers developed a series of molecular ribbons with up to linearly fused aromatic rings. Phenylenediamine **23** was condensed with pyrene-4,5,9,10-tetrone **24** to give **25**. A double condensation reaction between benzene tetramine and **25** gave **26** containing linearly fused rings [68–71] (Scheme 12.6).


NH2. HCl
NH2. HCl
H2N
H2N
16
17
18
F
F
O2N
NO2
19
NHPh
NH2
20
NHPh
NHPh
O2N
NO2
21
Ph
Ph
22
C10H21O
C10H21O
NH2
NH2
23
24
C10H21O
C10H21O
25
H2N
NH2
H2N
NH2
C10H21O
C10H21O
OC10H21
OC10H21
26

Scheme 12.6

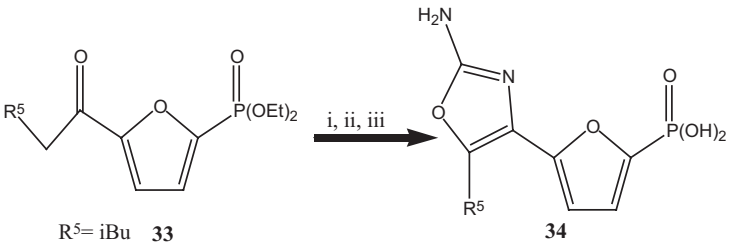
Synthesis of aromatic/antiaromatic compounds: 6,13-Dihydro-6,13-diazapentacene **27** can be oxidized to the fully aromatic form **28** using *p*-Chloranil. As the length of the pyrazinacene is increased, the fully oxidized form becomes even less favoured; for example, the reduced dihydrodiazahexacene **29** cannot be oxidized either with *p*-Chloranil or with lead (IV) oxide. Also, as the number of fused pyrazine rings increases, the reduced form is increasingly favoured. The somewhat unusual stability of the antiaromatic compounds compared to their fully aromatic counterparts was investigated using computational techniques by Bunz and Schleyer. They synthesised two dialkynylated diazatetracenes (**31**, **32**), which could be reversibly reduced/oxidized between the antiaromatic and aromatic forms [72–76] (Scheme 12.7).



Scheme 12.7

3.1.2 Oxazoles

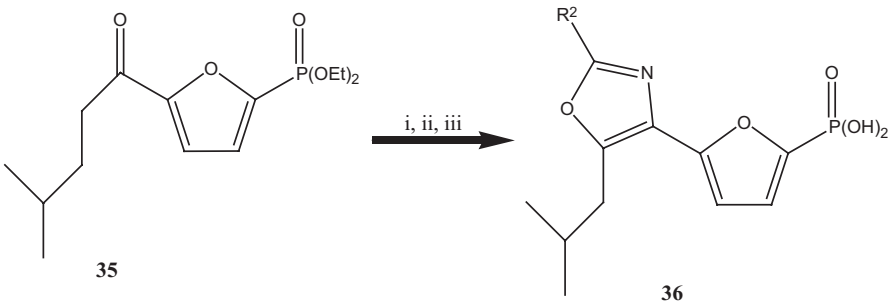
Synthesis of 2-amino oxazole analogues (Method I): α-Bromination of ketones **33** using copper (II) bromide followed by the treatment with excess urea in *tert*-butanol, and finally trimethylsilyl bromide (TMSBr)-mediated removal of the phosphonate diethyl ester produced oxazole phosphonic acids 34 [77] (Scheme 12.8).



R5= iBu **33** **34**

Reagents and conditions: i. $CuBr_2$, EtOAc-$CHCl_3$; ii. Urea, tBuOH, 80°C; iii. TMSBr, CH_2Cl_2.

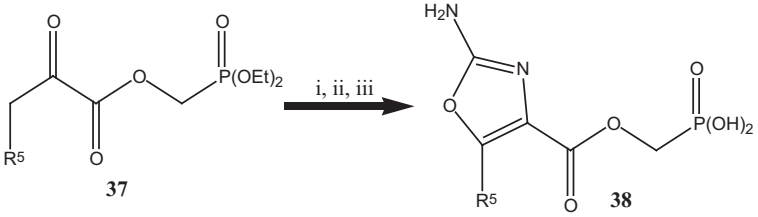
(Method II): α Bromination of ketones **35** using copper (II) bromide and cyclisation of the resulting bromide with excess R_2CONH_2 in *tert*-butanol followed by TMSBr-mediated removal of the diethyl ester gave oxazoles **36** [77].



35 **36**

Reagents and conditions: i. $CuBr_2$, EtOAc-$CHCl_3$; ii. Urea, tBuOH, 80 °C; iii. TMSBr, CH_2Cl_2.

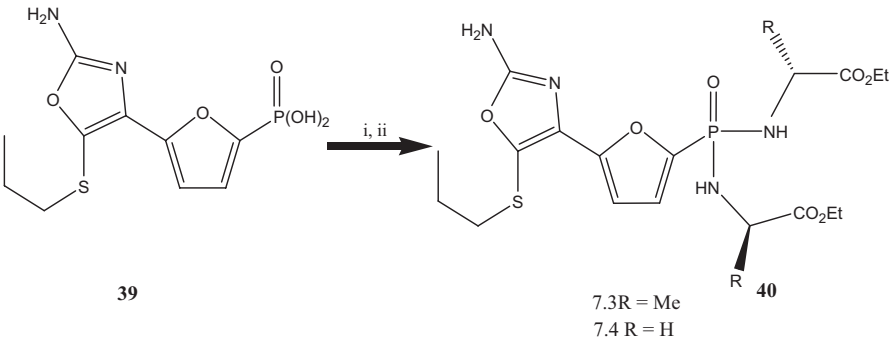
(Method III): Oxazoles with ester-linked phosphonic acids **38** that were prepared from pyruvate esters **37**, which were obtained via Fischer esterification as previously reported, were brominated using copper (II) bromide and subsequently cyclised with urea followed by TMSBr-mediated deprotection of phosphonate diester gave oxazoles **38** [77].



37 **38**

Reagents and conditions: i. $CuBr_2$, EtOAc-$CHCl_3$; ii. Urea, tBuOH, 80 °C; iii. TMSBr, CH_2Cl_2

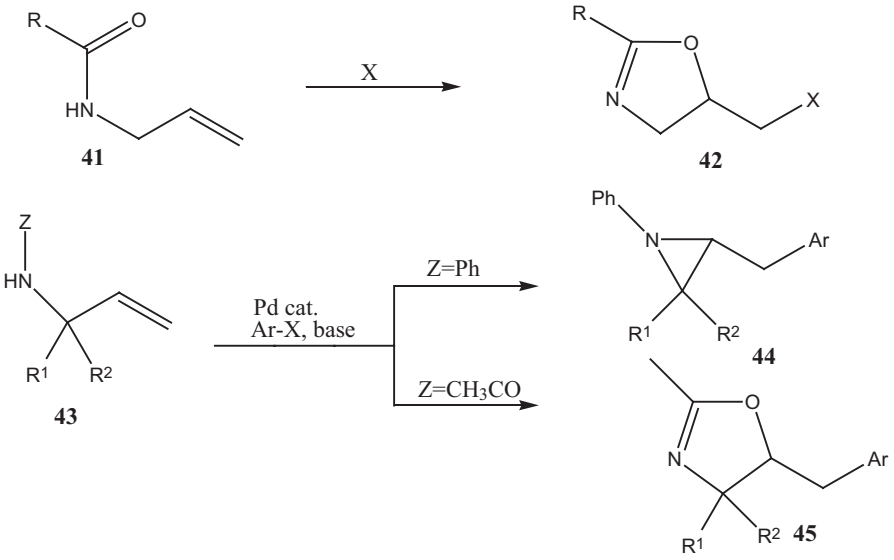
(Method IV): The phosphonic diamide prodrugs of the oxazole phosphonate FBPase inhibitor **39** were prepared using the dichloridate method [78].



Reagents and conditions: i. SO_2Cl_2; ii. amine, Hunig's base, CH_2Cl_2

Scheme 12.8

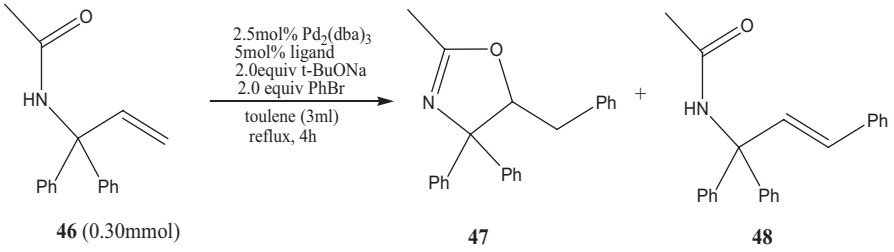
Palladium-catalysed reactions of allylamine derivatives with aryl halides: Palladium-catalysed intramolecular arylative cyclisation reactions of *N*-Allylanilines with aryl halides to yield aziridines **44** (Z = Ph) and a similar reaction of *N*-Allylacetamides resulted in the selective formation of 5-benzyl-substituted oxazolines **45** without contamination by the corresponding aziridines **44** (Z = CH_3CO) [79–82] (Scheme 12.9).



Scheme 12.9

Effect of ligands on palladium-catalysed phenylative cyclisation reaction and competitive Mizoroki–Heck reaction: Palladium-catalysed intramolecular arylative cyclisation reactions of *N*-Allylacetamide **46** with bromobenzene afforded

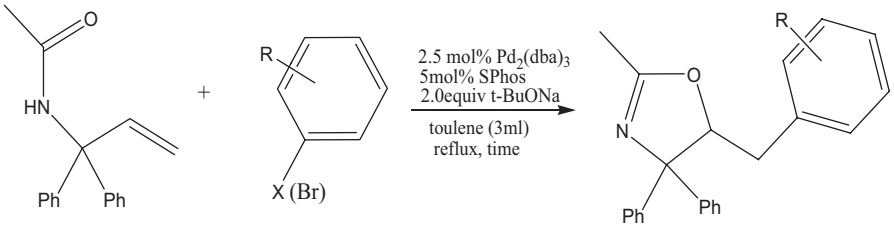
benzyl-substituted oxazoline **47** in 75% yield. The cyclisation reaction inevitably competed with the Mizoroki–Heck reaction, which yielded **48** as the only identifiable by-product. Several ligands were screened, and bulky ligands are generally effective for the cyclisation (Scheme 12.10).



46 (0.30mmol) **47** **48**

Scheme 12.10

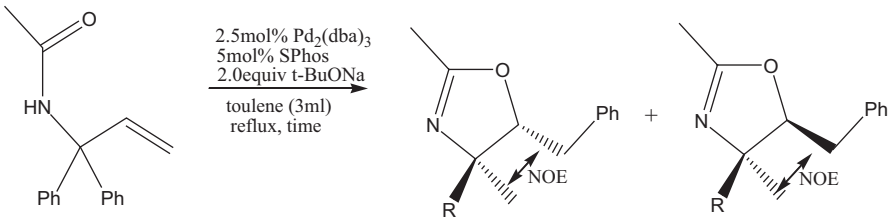
Scope of aryl halides: Aryl chlorides as well as aryl bromides participated in the reaction. Sterically demanding aryl bromides reacted smoothly. Electron-deficient fluorinated aryl bromides were also reactive. Aryl halides bearing a t-butoxycarbonyl, diethylaminocarbonyl or a cyano group underwent the arylative cyclisation to yield the corresponding products in good yields. The reaction of **46** with electron-rich 4-bromoanisole **49** resulted in a modest yield of **50** and formation of a significant amount of Mizoroki–Heck by-product (Scheme 12.11).



46 (0.30mmol) **49** 1.2(equiv) **50**

Scheme 12.11

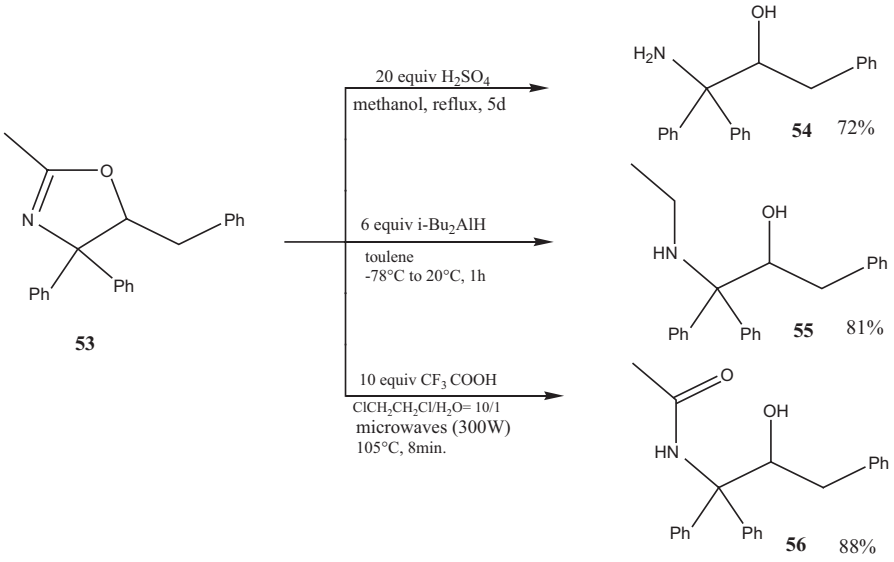
Diastereoselective cyclisation: *N*-Allylacetamides **46** that bear a stereogenic centre at the allylic position were prepared and subjected to the arylative cyclisation reaction. The reactions proceeded smoothly with good diastereoselectivity. The major isomers have the larger R group and the newly formed benzyl group is in a *trans* relationship. The relative stereochemistries of **51** and **52** were determined by NOE analysis (Scheme 12.12).



46 (0.30mmol) **51** (major) **52** (minor)

Scheme 12.12

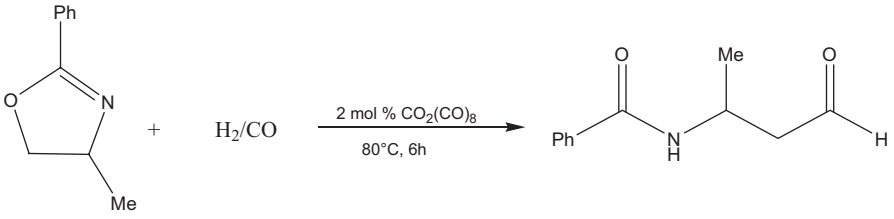
Transformation of oxazoline: **53** formed the amino alcohol derivatives **54** on opening of the ring with H_2SO_4. Reduction of **53** with diisobutylaluminium hydride provided *N*-Ethyl amino alcohol **55**. Oxazoline was converted to acetamide **56** by acidic hydrolysis with trifluoroacetic acid. The overall transformation of **53** to **56** represents the regioselective carbohydroxylation of *N*-Allylacetamide [83–84] (Scheme 12.13).



Transformation of oxazoline

Scheme 12.13

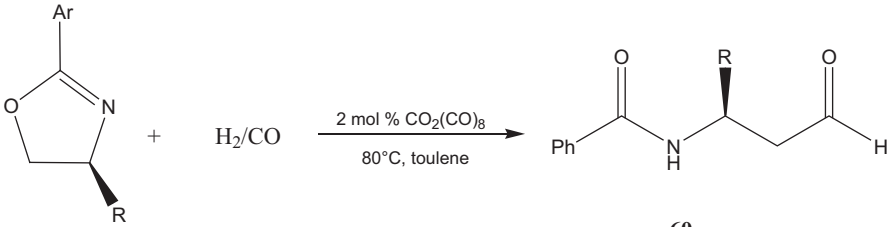
Solvent effect on oxazoline hydroformylation: Solvent choice is important for achieving optimal rates and product selectivities in epoxide carbonylation and began by screening the hydroformylation of 4-methyl-2-phenyloxazoline in solvents of varying polarity and donicity. Solvents of moderate donicity such as tetrahydrofuran, diethyl ether and 1,4-dioxane also provided only modest yields of the desired product, while the strongly coordinating solvent acetonitrile completely inhibited the reaction; of the solvents screened, toluene proved to be the highest yielding (Scheme 12.14).



57 **58**

Scheme 12.14

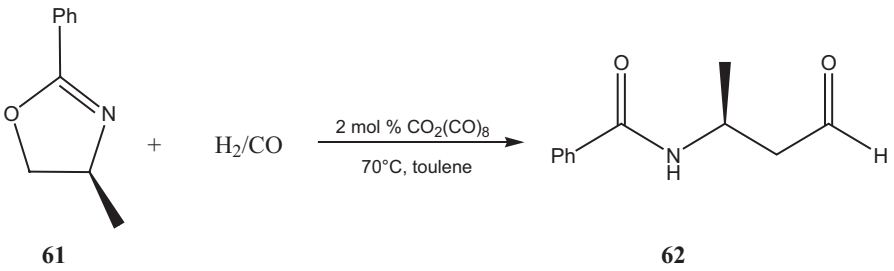
Hydroformylation of oxazolines to β-amidoaldehydes: Oxazoline **59** undergoes carbonylation to form oxazinones which under the pressure of hydrogen and carbon monoxide gives a complicated mixture of products and only a small amount of the desired β-amidoaldehyde **60** (Scheme 12.15).



59 **60**

Scheme 12.15

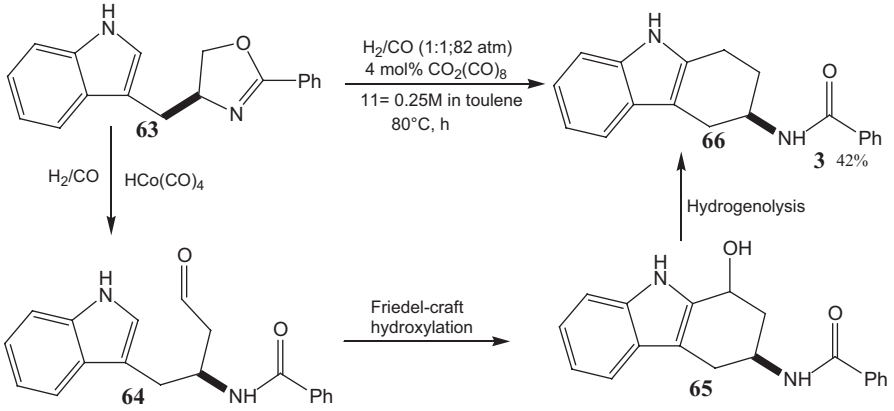
Effect of temperature on the hydroformylation of oxazoline: Oxazoline hydroformylation is also impacted by temperature and pressure. As the reaction temperature is lowered, an increase in the enantiomeric excess of β-amidoaldehyde **62** was observed. Also, an increase in % ee was observed when the total pressure of H_2/CO was increased. Hydroformylation at temperatures below 70°C led to the formation of significant amounts of oxazinone (Scheme 12.16).



61 **62**

Scheme 12.16

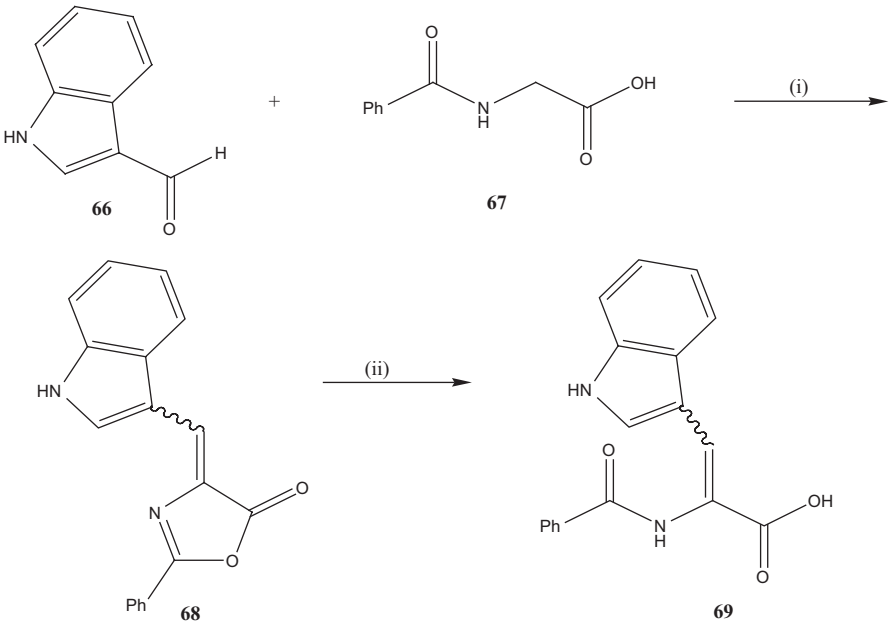
Hydroformylation: Hydroformylation of the tryptophan-derived oxazoline **63** led to the formation of tetrahydrocarbazole product **66**. In the reaction pathway, β-amidoaldehyde product **64** is initially formed, which is followed by intramolecular Friedel–Crafts hydroxyalkylation to give **65** (Scheme 12.17).



Scheme 12.17

3.1.3 Indole

Synthesis of dehydrotryptophan: The amino acid tryptophan was first synthesised by Erlenmeyer's method via the dehydrotryptophan intermediate. Ellinger et al. reacted indole-3-carbaldehyde **66** with the glycine derivative hippuric acid **67**, after which hydrolysis of the azlactone intermediate **68** afforded the dehydrotryptophan intermediate **69** [85] (Scheme 12.18).



i) Ac_2O, NaOAc

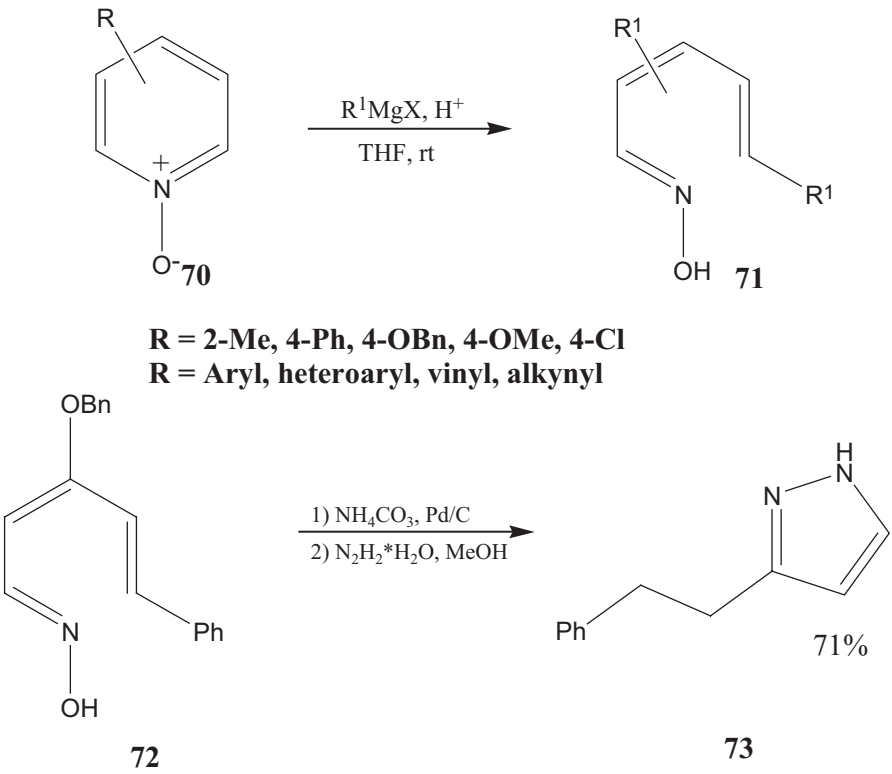
ii) NaOH, H_2O

Scheme 12.18

(i) Ac_2O, NaOAc
(ii) NaOH, H_2O

3.1.4 Pyrazole

Synthesis of different substituted dienal-oximes and pyrazole: Addition of an activating group (e.g., chlorine, methoxy, etc.) at the 2 position of pyridine *N*-oxide **70** gives a diverse set of functionalized dienal-oximes **71**, which were used as starting materials in the synthesis of conjugated nitriles, aliphatic primary and secondary amines, enaminones and the substituted pyrazole **73** [86–88] (Scheme 12.19).



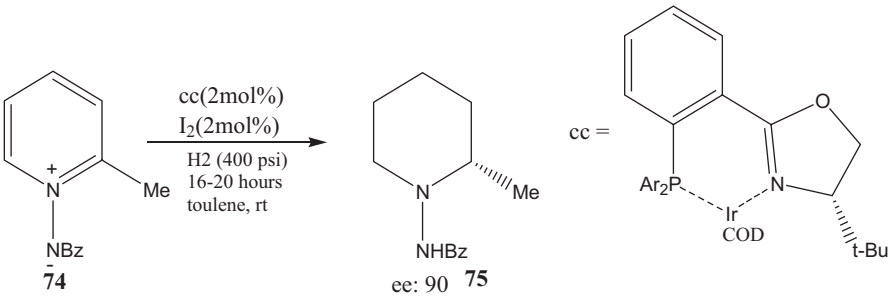
Scheme 12.19

3.2 Synthesis of Six-Membered Heterocycles

3.2.1 Piperidines

Piperidine is a widely used building block and chemical reagent in the synthesis of organic compounds, including pharmaceuticals.

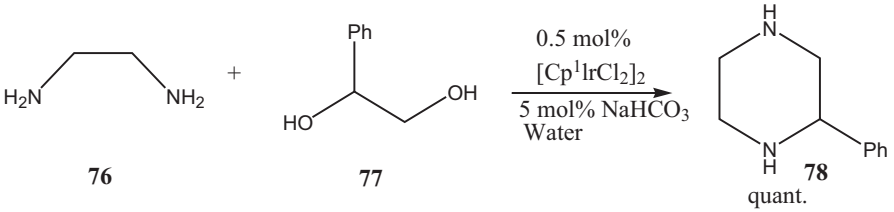
Synthesis of substituted piperidines: Charette and co-workers recently reported a method for the preparation of substituted piperidines from activated pyridines. The method is based on an iridium-catalysed asymmetric hydrogenation of *N*-Iminopyridinium ylides **74** for the synthesis of enantiomerically enriched piperidines **75** [89] (Scheme 12.20).



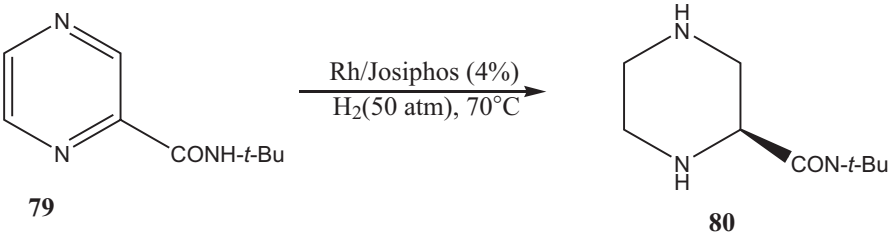
Scheme 12.20

3.2.2 Piperazines

Synthesis of piperazines: Madsen and co-workers recently reported an iridium-catalysed synthesis of piperazines from diamines **76** and diols **77**. Another procedure is the hydrogenation of pyrazines which gives piperazine [90–91] (Scheme 12.21).

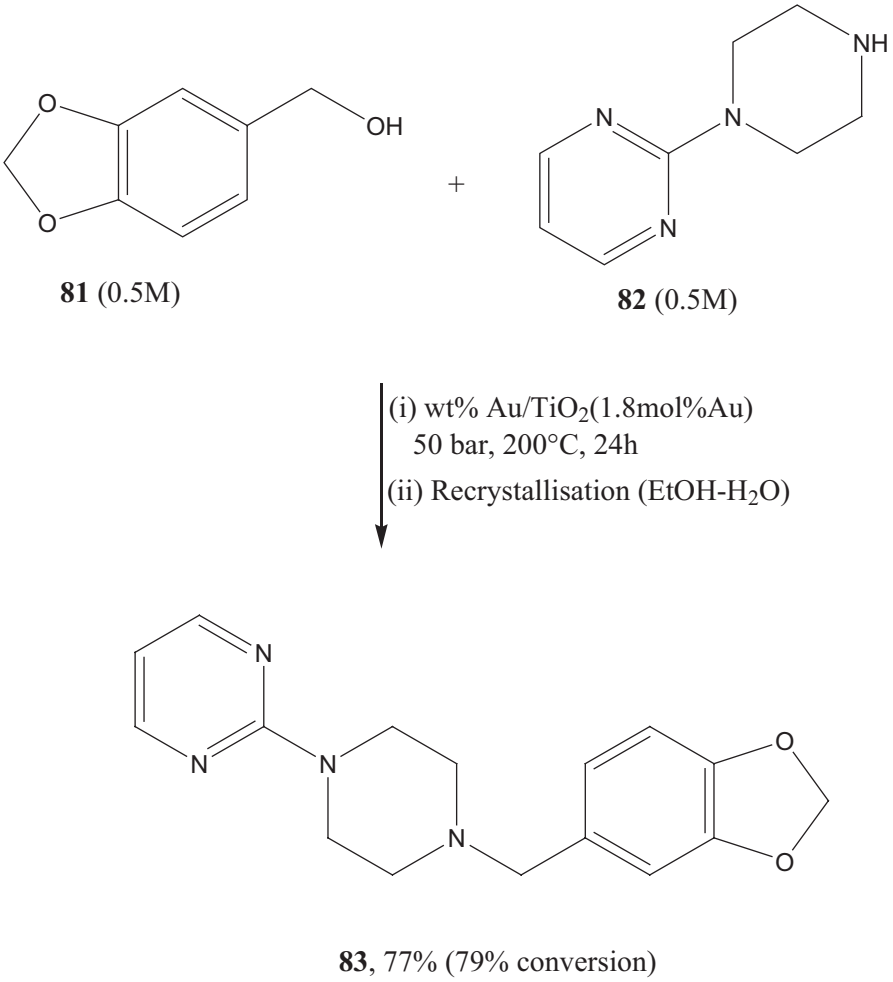


Another procedure is the hydrogenation of pyrazines **79** which gives piperazine **80**.



Scheme 12.21

Synthesis of piribedil: Direct alkylation of piperazine-substituted pyrimidine derivative **82** and benzyl alcohol derivative **81** in a 2:1 ratio gives piribedil **83** (Scheme 12.22).

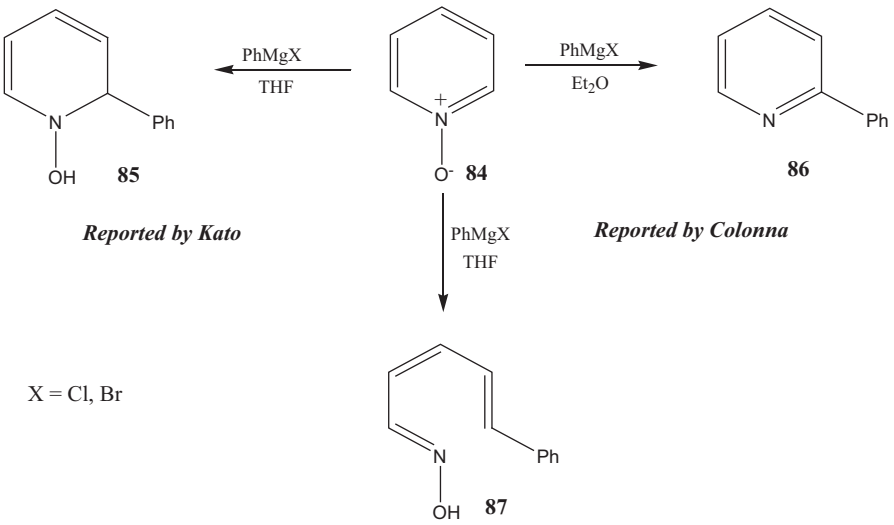


Scheme 12.22

3.2.3 Pyridine

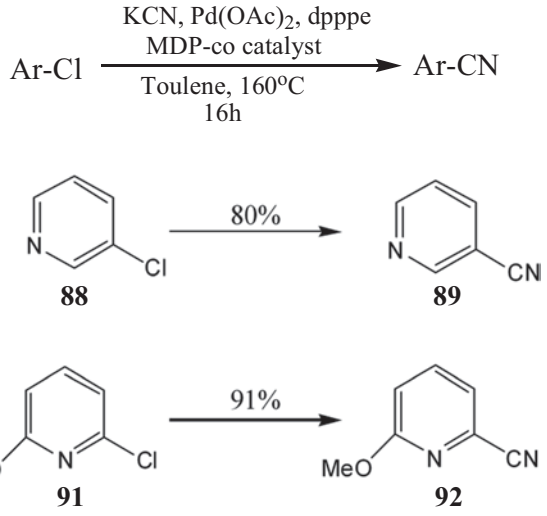
Pyridine has a conjugated system of six π-electrons that are delocalized over the ring. The molecule is planar and, thus, follows the Hückel criteria for aromatic systems.

Grignard additions to pyridine N-oxides: Colonna and co-workers published the first report on the reaction between Grignard reagents and pyridine *N*-oxide **84**. They isolated 1,2-dihydropyridine **85** in 60–80 % yield. The ring-opened dienal-oxime **87** was isolated in a low 28 % yield (Scheme 12.23).



Scheme 12.23

MDP-catalysed cyanation: Heteroaryl substrates converted to their corresponding nitriles under MDP (1–1′-methylenediperidine)-catalysed cyanation with best yields, such as **89** and **92** form **88** and **91**, respectively (Scheme 12.24).



Scheme 12.24

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Chapter 13
Synthesis and Biological Evaluation of Some Quinazoline Heterocyclic Derivatives

R. R. Dangi, N. S. Chundawat and K. L. Ameta

Contents

Abstract Owing to the significant biological activities, quinazoline derivatives have drawn more and more attention in the synthesis and bioactivities research. This chapter summarizes the recent advances in the investigations of synthesis and biological activities of quinazoline derivatives. According to the main method the authors adopted in their research design, those synthetic methods include microwave-assisted reaction, ultrasound-promoted reaction, metal-mediated reaction, water reaction, and phase-transfer catalysis reaction. The biological activities of the synthesized quinazoline derivatives are also discussed.

Keywords Quinazoline · Biodynamic heterocycles

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Fig. 13.1 Quinazoline

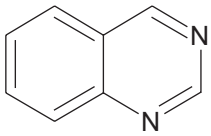
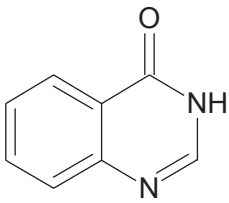


Fig. 13.2 Quinazolinone



1 Introduction

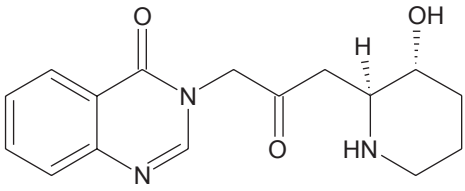
Quinazoline is a compound made up of a fused benzene ring and a pyrimidine ring (Figs. 13.1 and 13.2). Its chemical formula is $C_8H_6N_2$. Quinazoline appears as a yellow crystalline substance. Any derivative of quinazoline may be described as a quinazoline compound.

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their wide and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anticancer [1–4], anti-inflammatory [5, 6], antibacterial [7–10], analgesic [5, 9], antiviral [11], anti-cytotoxic [12], antispasmodic [9, 13], antituberculosis [14], antioxidant [15], antimalarial [16], antihypertensive [17], antiobesity [18], antipsychotic [19], antidiabetic [20], etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. Potential applications of the quinazoline derivatives in fields of biology, pesticides, and medicine have also been explored. This chapter summarizes the representative synthetic methods, either traditional or novel, and categorized them as microwave-assisted reaction, metal-catalyzed reaction, ultrasound-promoted reaction, and phase-transfer catalysis. In addition, the bioactivity researches of quinazoline derivatives are also discussed in order to provide valuable reference for future synthesis and biological investigation of these compounds.

2 Naturally Occurring Quinazoline-Based Compounds

The quinazoline alkaloids form a small but important group of naturally occurring bases, which were isolated from a number of different families in the plant kingdom. Witt and Bergman [21] review the chemistry of quinazoline alkaloids, viz. chrysogine, luotonine A, tryptanthrin, febrifugine, and rutaecarpine. The only non-alkaloid naturally

Fig. 13.3 Febrifugine



occurring quinazoline is the potent neurotoxin called tetrodotoxin, which was isolated from the Japanese puffer fish and from the *California newt.* Arborine was isolated by two Indian groups from *Glycosmis arborea* [22]. Vasicine was discovered in *Adhatoda vasica* [23] and was found to show bronchodilator activity. The bronchodilator activity of vasicine, vasicinone, and 3,4-dihydro-4-oxoquinazoline was studied in detail but was in no way comparable with known bronchodilator drugs [24].

Experiments in the USA and China during World War II led to the isolation of two compounds called febrifugine (Fig. 13.3) and isofebrifugine from *Dichroa febrifuga* with known antimalarial activity (a Chinese herb). Further studies suggested that it must be the diastereoisomers of febrifugine that posses the antimalarial properties. Baker and co-workers [25] studied the antimalarial activities of synthesized samples of dl-febrifugine and found only one-half activity than the naturally occurring compound. Further, they discovered that it was actually the isofebrifugine that possessed the antimalarial properties, but was highly toxic in isolation to the other compounds found in the naturally occurring alkaloid [26]. Finally, the antimalarial activity of febrifugine and many of its synthetic derivatives were confirmed by Hewitt and collaborators [27].

A hypotensive red alkaloid isolated from the Brazilian plant *Hortia arborea* England was called hortiamine. One of the most potent nonprotein neurotoxin tetrodotoxin was isolated from certain varieties of the Japanese puffer fish. Several quinazoline derivates show antimalarial properties against *Plasmodium gallinaceum*. The most effective was 6-chloro-2-ethyl-3,4-dihydro-4-oxo-3-*p*-pyrimidin-2′-ylsulfa-moylphenylquinazoline [28].

Cytotoxic alkaloids of the fumiquinazoline (Fig. 13.4) family have been isolated from different fungi including a strain of the fungus *Aspergillus fumigatus, Acremonium* sp.*, Ecteinascidia turbinata,* and *Neosartorya fischeri*. The first total synthesis of fumiquinazolines has been described by Snider and Zheng [29].

3 Microwave Methodology of Quinazolines Synthesis

3.1 Microwave-Assisted Synthesis of Quinazoline Compounds

Microwave-assisted organic synthesis is becoming popular with organic chemists, and comprehensive chapters have become available in recent years. Microwave

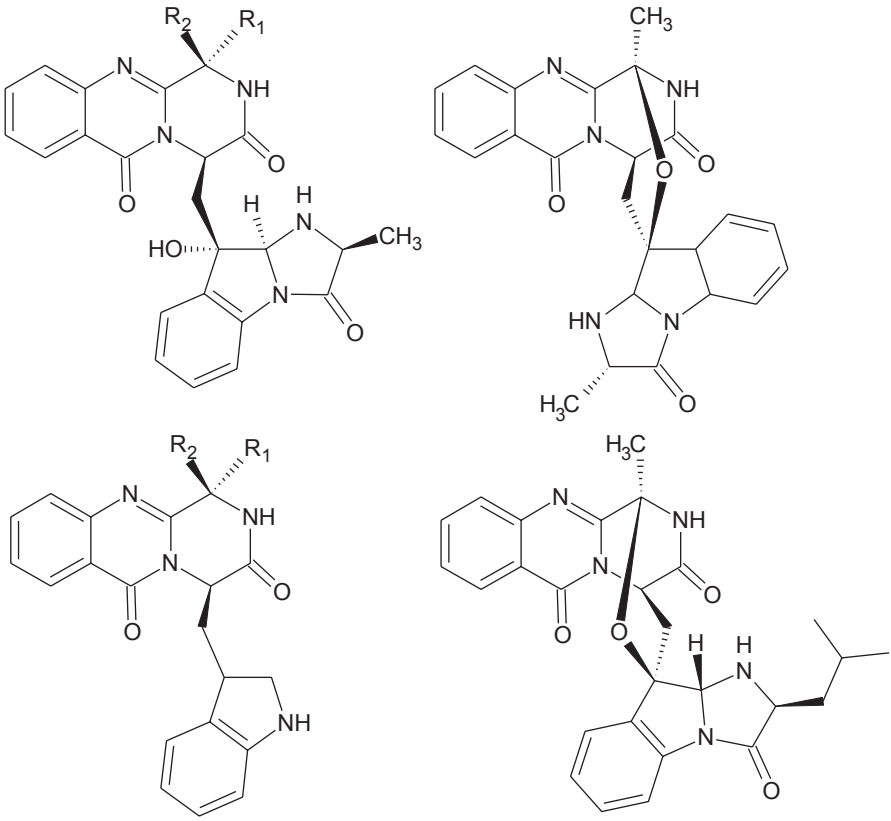


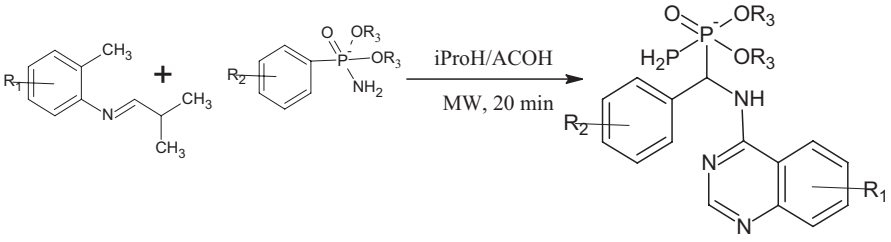
Fig. 13.4 Fumiquinazoline

heating is very convenient to use in organic synthesis. The heating is instantaneous, very specific, and there is no contact required between the energy source and the reaction vessel. Recent interest has been focused on "dry media" synthesis and particularly on solvent-free procedures using various mineral oxides and solvent-less reactions with neat reactants in the absence of a catalyst or solid support. Furthermore, the diversity-generating potential of multicomponent reactions (MCRs) has been recognized and their utility in preparing libraries to screen for functional molecules is well appreciated. Consequently, the design of novel MCRs is an important field of research. In this section, some selected literature examples of quinazoline synthesis by these methodologies are discussed.

Compared to traditional heating methods, microwave heating could expand the reaction range as well as shorten the reaction time from a few days or hours to a few minutes. Thus, when applied in fields of organic synthesis, pharmaceutical chemistry, and high-throughput chemistry, microwave heating shows greater advantage than traditional heating methods [30–33].

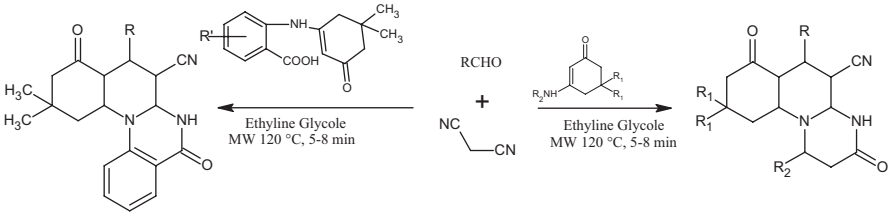
Luo et al. reported the first microwave-assisted synthesis of new quinazoline derivates containing α-aminophosphonate [34]. In their method, N′-(substituted-2-

cyanophenyl)-N, N-dimethyl-formamidine derivatives, and dialkyl amino(phenyl) were adopted as the raw materials to react in 4:1 volume ratio of isopropanol to acetic acid solvent for 20 min under microwave irradiation (100 psi) and obtained 24 quinazoline compounds, two of which had similar activity as commercial reagent ningnanmycin (Scheme 13.1).



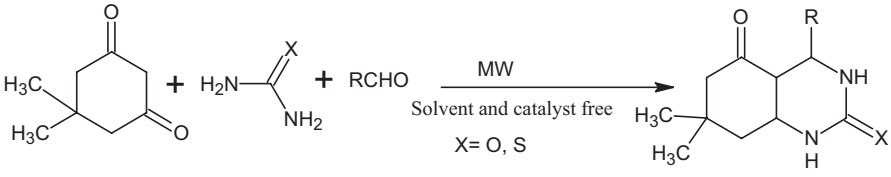
Scheme 13.1

Tu et al. reported a fast one-pot, microwave-assisted synthesis of polysubstituent imidazo[1,2-a]quinoline, pyrimido [1,2-a]quinoline, and quinolino[1,2-a]quinazoline derivatives [35]. They explored the optimal reagent, volume, and heating temperature by testing different reagents under different reaction times and temperatures. Then, under optimal conditions (2.0 ml glycol), several aldehydes were separately made to react with various enaminones and malononitrile to obtain different products (Scheme 13.2).



Scheme 13.2

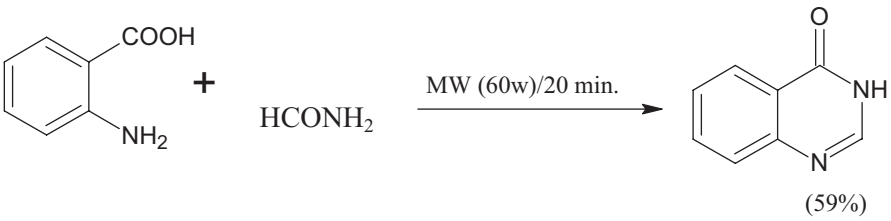
In the synthetic research conducted by Kidwai et al. [36], the target compounds quinazoline derivatives were obtained by heating an equimolar amount of aldehyde, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and urea/thiourea under microwave irradiation in the absence of solvent and catalyst (Scheme 13.3).



Scheme 13.3

3.2 Niementowski Quinazoline Synthesis

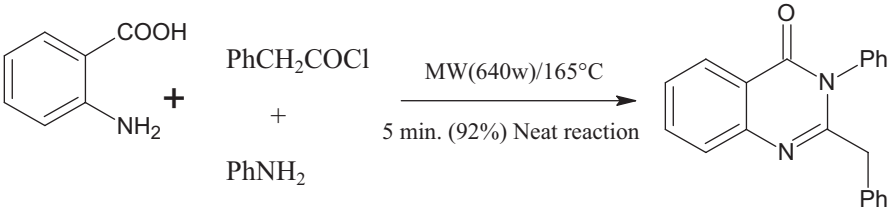
The striking improvement in the Niementowski quinazoline synthesis has been fulfilled using microwave irradiation (Scheme 13.4). Using microwave irradiation and/or Appel's salt, new efficient routes to various substituted and fused quinazolines have been developed by Besson et al. [37, 38].



Scheme 13.4

3.3 MultiComponent One-Pot Synthesis of Quinazolines

One-pot synthesis of 4(3*H*)-quinazolinones from amines and formic acid (or orthoesters) was developed, and recently, more detailed procedures using inorganic solid support and neat one-pot procedures under microwave irradiation have been developed by Dandia et al. [39] (Scheme 13.5) and Liu et al. [40]. Also facile one-pot synthesis of 2,4(1*H*,3*H*)-quinazolinediones has been developed recently as a green chemical procedure.



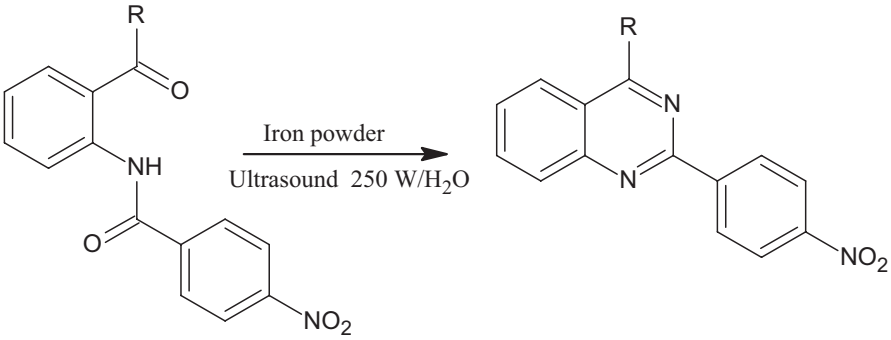
Scheme 13.5

4 Ultrasound-Promoted Synthesis of Quinazoline

In critical synthesis, ultrasonic assistance is needed to meet the high requirements for temperature and pressure. For instance, in Bischler cyclization, the most traditional synthetic methods for quinazoline derivatives, high temperature

(above 120 °C) and high pressure are needed for at least 5 h in saturated ammonia alcohol solution. Various syntheses applying this method contain the passage of ammonia through a mixed melt of the amino compound and sodium acetate at a temperature higher than 160 °C in which ultrasonic promotion is demanded.

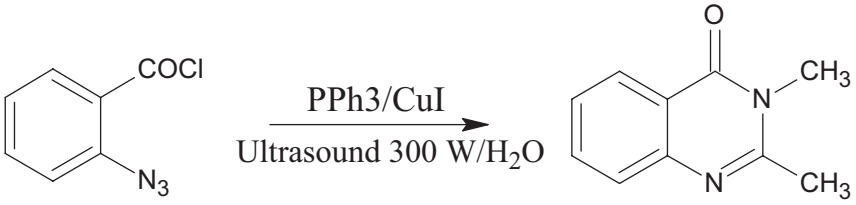
Zhang et al. [41] reported an ultrasound-assisted synthesis of novel quinazoline derivatives (Scheme 13.6), including a four-step synthesis of quinazoline core and the optimization of the Bischler cyclization [42].



Scheme 13.6

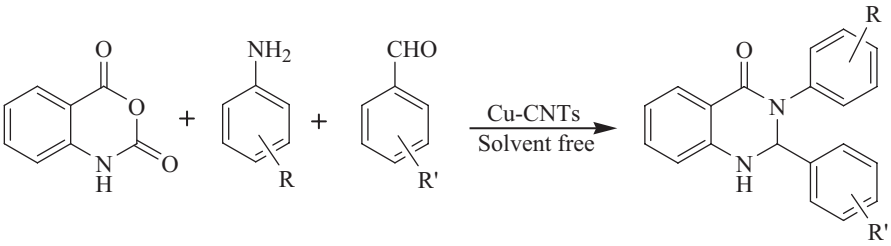
We had an interest in utilizing 2-phosphoranylideneamino-benzoyl derivatives as building blocks, particularly in view of anthranilic acids as important biological precursors of various alkaloids such as glomerine, vascine, and microbial products like tryptanthrin and anthramycine.

Thus, acylation of *N*-methylamides with 2-azidobenzoyl chloride (readily available from 2-azidobenzoic acid [43]) forms imides which upon treatment with triphenylphosphine (TPP) in the course of consecutive Staudinger reaction/intramolecular aza-Wittig reaction yields exclusively 3-methylquinazolin-4(3*H*)-ones quantitatively (Scheme 13.7) [44, 45]. This procedure provides simple and efficient quinazolinone annelation of amides and lactams.



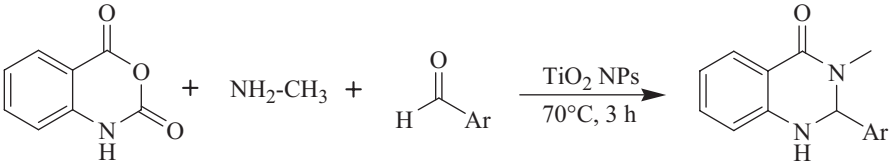
Scheme 13.7

Safari et al. [45] successfully demonstrated for the first time that Cu powder and ultrasound 300 w/H_2O could be used as an excellent and efficient catalyst for convenient synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives under solvent-free conditions and microwave irradiation (Scheme 13.8). The protocol proves to be efficient and environmentally benign in terms of easy workup, high yields, and ease of recovery of catalyst. In addition, the present method is superior in terms of green media, the amount of catalyst, and reaction time.



Scheme 13.8

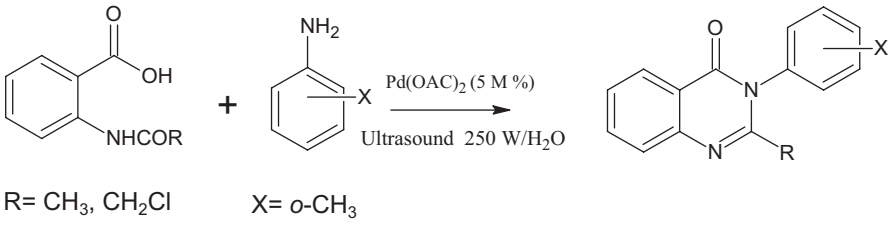
Bharathi et al. [46] successfully synthesized the TiO_2 nanoparticles using aqueous *Annona squamosa* peel extract (Scheme 13.9). These synthesized TiO_2 nanoparticles were characterized using UV, XRD, and TEM and used as a catalyst for 2,3-dihydro-3-methyl-2-phenylquinazolin-4(1*H*)-one analogue synthesis.



Scheme 13.9

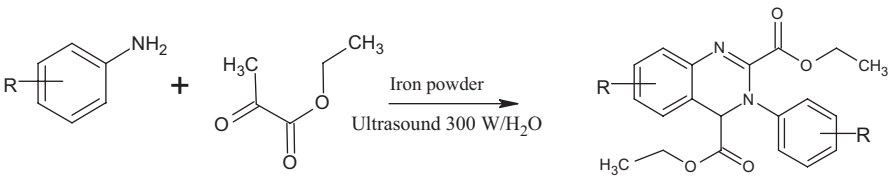
Muthukrishnan et al. [47] discovered that the EtOAc fraction of *Glycosmis pentaphylla* leaf extract inhibits the juvenile hormone III biosynthesis in vitro of corpora allata from 3-day-old females of the field cricket *Gryllus bimaculatus*. The bioactive compound responsible for this activity was identified as the quinazolone alkaloid arborine. This alkaloid also exhibited larvicidal activity against the mosquito.

Derivatives of 2-methyl-3-(o-tolyl)-4(3H)-quinazolone (Scheme 13.10) bearing new substituents on the 2-methyl group have been synthesized. It was established that most substitutions at this position reduce or remove the CNS-depressant activity of methaqualone [48].



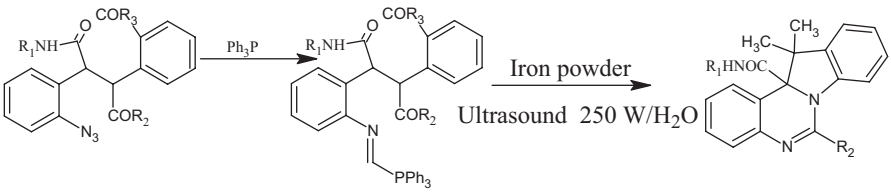
Scheme 13.10 Aza-Diels–Alder reaction

Imino-Diels–Alder reaction [49] containing the coupling of imine and electron-rich alkene gradually became a powerful tool for the synthesis of quinazoline derivatives [50]. In Povarov imino-Diels–Alder reaction, aniline and ethyl glyoxalate were chosen as substrates. And two molecules of α-iminoesters, which were obtained from the condensation of aniline and ethyl glyoxalate, were hypothesized to form the direct additive product. Cascade imino-Diels–Alder reaction conducted by Chen et al. [51] (Scheme 13.11) was extended from the Povarov imino-Diels–Alder reaction. In this research, researchers chose the same substrates as in the Povarov imino-Diels–Alder reaction, adopted various kinds of Lewis acids as catalysts, and finally produced quinazoline derivatives. Iron powder was determined as the optimized catalyst with highest yields.



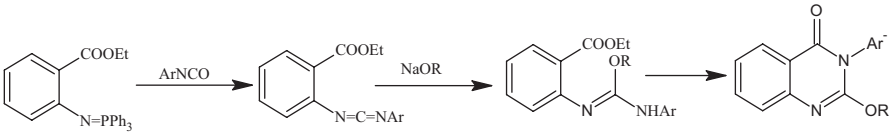
Scheme 13.11 Aza-Wittig reaction

Aza-Wittig reaction, which generally precedes in cascade with easy operation under mild reaction conditions, is widely used in the synthesis of N-heterocycles [52]. He et al. reported a kind of tandem Staudinger–Aza-Wittig–nucleophilic addition reaction to synthesize indolo[1,2-c]quinazolines recently [53]. Results showed that the nitrogen evolution through the Staudinger reaction halted during the initial 2 h and surprisingly produced the final product indolo[1,2- c]quinazolines directly from the reaction mixture (Scheme 13.12).



Scheme 13.12

A synthetic method for 2-alkoxy-3H-quinazolin-4-ones was reported by Ding et al. in 2004 [54]. In this study, 12 novel 2-alkoxy-3H-quinazolin-4-ones were synthesized from carbodiimide, which was obtained from aza-Wittig reaction of iminophosphorane with aromatic isocynate (Scheme 13.13).

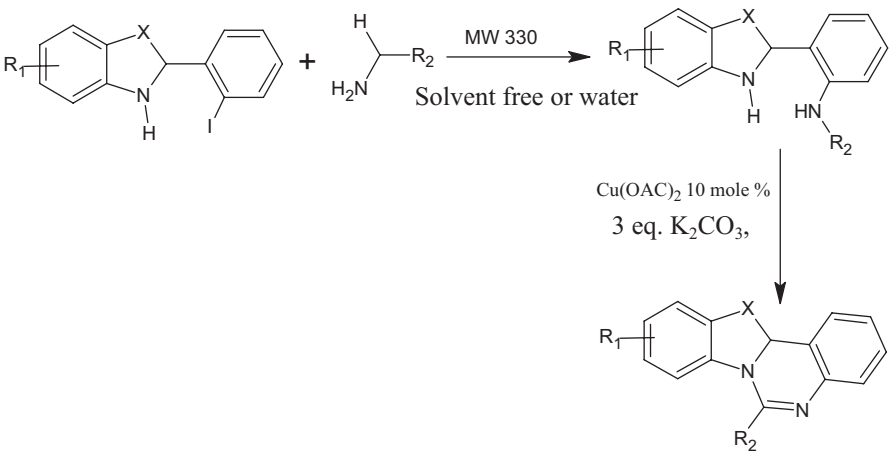


Scheme 13.13

5 Water-Mediated Quinazoline Synthesis

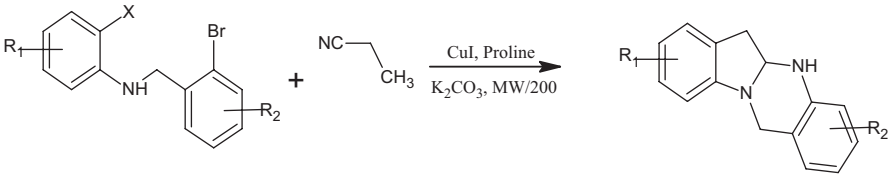
Organic reactions in water, without the use of any harmful organic solvents, are of great interest because water is nontoxic, nonflammable, abundantly available, and inexpensive. Thus, water as the reaction medium is generally considered a cheap, safe, and environmentally benign alternative to synthetic solvents. Furthermore, because of the low solubility of common organic compounds in water, the use of water as a solvent often makes the purification of products very easy by simple filtration or extraction.

A convenient and clean water-mediated synthesis of a series of indolo[1,2-c] quinazoline derivatives was reported using alternative nonconventional energy sources. The products are obtained in shorter times with excellent yields (78–89 %) from the MCR of 2-aminobenzimidazole, malononitrile, and carbonyl compounds [55]. In their research, 2-(2-halophenyl)-1H-indoles and (aryl)methanamines were adopted as raw materials to generate corresponding Schiff base via the Ullmann reaction. Then, gas as oxidant, 3 equiv K_2CO_3 as base, and 10 mol% $Cu(OAc)_2$ as catalyst were revealed as the optimum conditions to conduct aerobic oxidative C–H amination under solvent-free conditions or water (Scheme 13.14).



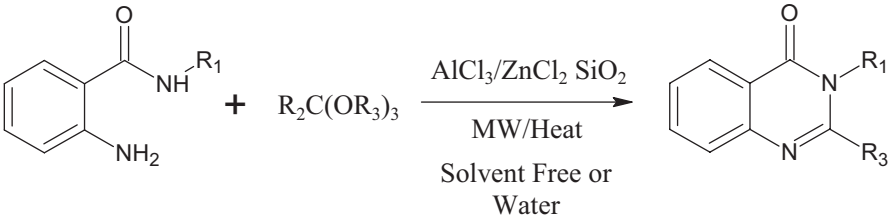
Scheme 13.14

Jiang et al. also reported a one-pot synthesis of 5,12-dihydroindolo[2,1-b]quinazolines [56]. N-(2-bromobenzyl)-2-iodoani-line and malononitrile were adopted as the raw materials to afford the desired compound through copper-catalyzed intramolecular C–N coupling reaction (Scheme 13.15).



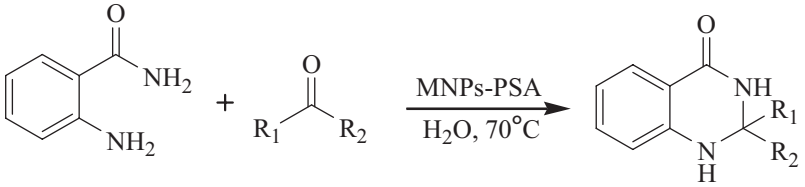
Scheme 13.15

Dabiri and Mostafa reported [57] a rapid, efficient, and one-pot procedure for the synthesis of mono- and di-substituted (3H)-quinazolin-4-ones in the presence of an $AlCl_3/ZnCl_2$ mixture supported on silica gel, under solvent-free conditions or water.



Scheme 13.16

An efficient and eco-friendly method is reported for the synthesis of 2-substituted-2,3-dihydroquinazolin- 4(1*H*)-ones from direct cyclocondensation of anthranilamide with aldehydes and ketones using N-propylsulfamic acid supported on magnetic Fe_3O_4 as a recoverable and recyclable nanocatalyst in good to excellent yields in water (Scheme 13.17). The characteristic advantages of this catalyst are rapid, simple, and efficient separation using an appropriate external magnet, which minimizes the loss of catalyst during separation and is reusable without significant loss of activity up to ten cycles.



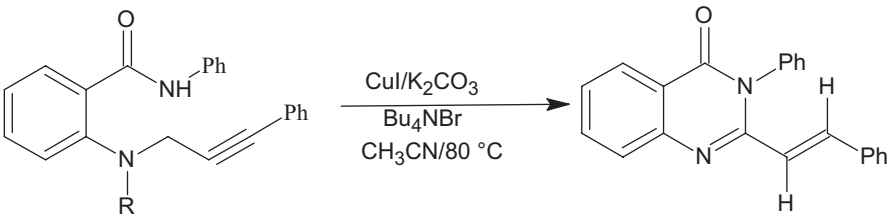
R_1, R_2 = Alkyl, aryl, H

Scheme 13.17

The procedure does not involve the use of any additional reagent/catalyst, produces no waste, and represents a green synthetic protocol with high atom economy. The combination of microwave irradiation, ultrasonic irradiation, and aqueous-mediated conditions using MCRs lead to enhanced reaction rates, higher yields of pure products, easier workup, and sometimes selective conversions. Consequently, this protocol should be welcome in these environmentally aware days.

6 Metal-Catalyzed Synthesis of Quinazoline Derivatives

In 1993, several catalytic methods have been developed for the synthesis of 4(3*H*)-quinazolinones via transition-metal catalyzed reductive *N*-heterocyclization. For example, palladium-catalyzed cyclocarbonylations of halides with appropriate reactants provided regioselective synthesis of 4(3*H*)-quinazolinone derivatives and indoloquinazolines [58]. Also, selenium-catalyzed reductive *N*-heterocyclization to quinazolinones has been developed. Copper-catalyzed heteroannulation with alkynes has been developed as highly region- and stereoselective route to 2-(2-arylvinyl)-1,2,3,4-tetrahydroquinazolin-4-ones by Kundu et al. [59] (Scheme 13.18). Recently, condensation of anthranylamide with various aldehydes to 4-quinazolinones has been found to give excellent yields in the presence of cupric chloride. For synthesis of quinazoline derivatives, various coupling reactions have been utilized after synthesis of quinazoline-2,4(1*H,3H*)-diones via palladium-catalyzed oxidative coupling. For example, synthesis of diarylquinazolines by iron-catalyzed cross-coupling reaction and diaminoquinazolinones by palladium-catalyzed amination have been developed.

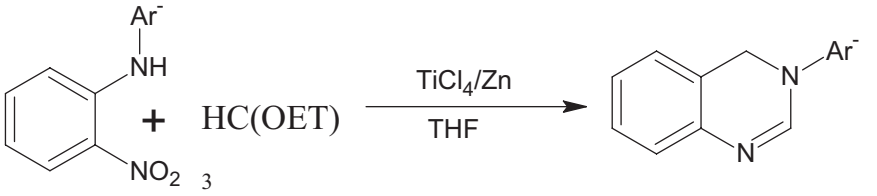


Scheme 13.18

6.1 Titanium-Catalyzed Reaction

A convenient method for the synthesis of 3-substituted quinazolin-4(3H)- ones using the convergent reactions of formic acid, a primary amine, and isatoic anhydride under solvent-free conditions and with brief microwave irradiation is described.

Natural and synthetic molecules with the core of quinazoline ring system show a wide range of biological activities [60–64]. The chemotherapeutic use of quinazoline alkaloids may date back to the ancient Chinese treatment of malaria with the herbal preparations from *Dichroa febrifuja* [65]. At present, some synthetic quinazoline-based drugs such as metolazone, quinethazone, and prazosin have acquired medicinal approval for their unique pharmacological indices and many others are under clinical evaluation [66–71]. In this synthesis, a series of quinazoline derivatives were afforded by adopting anhydrous THF as solvent and the $TiCl_4$–Zn system as reducing agent. Several representative synthetic routes were selected [72, 73]. In many such cases, the role of solvents as heat dispersants are no longer needed. The so-called solvent-free reactions are eco-friendly and, in view of green chemistry's desire for avoiding solvent hazards, are in demand (Scheme 13.19).

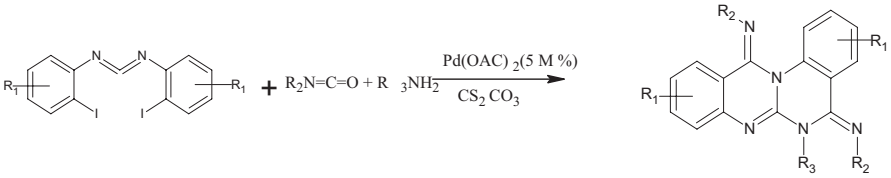


Scheme 13.19

6.2 Palladium-Catalyzed Reaction

Palladium-catalyzed coupling reaction, which plays a vital role in the pharmaceutical industry, is widely applied in the chemical synthesis industry and laboratories as an efficient method for the formation of C–C and C–heteroatom bond. Qiu et al.

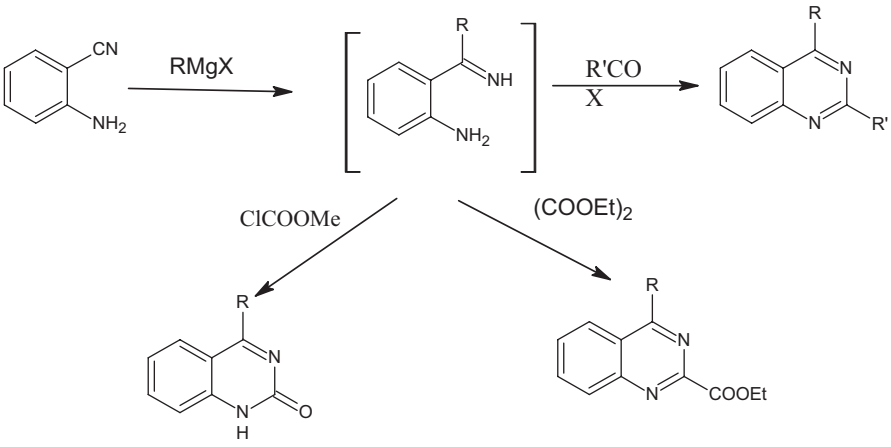
[74] determined the optimum conditions for the palladium-catalyzed three-component synthesis of quinazolino[3,2-a]quinazolines as follows: amine (3.0 equiv), isocyanide (3.0 equiv), carbodiimide (0.2 mmol), $Pd(OAc)_2$ (5 mol%), and Cs_2CO_3 (3.0 equiv) in 3.0 ml toluene (Scheme 13.20).



Scheme 13.20

6.3 Organometallic Reagents

Various quinazolines from 2-aminobenzonitrile using organometallic reagents have been developed by Bergman et al. [75–76]. The topical synthetic methodologies such as iminophosphorane-mediated synthesis (aza-Wittig methodology), microwave-assisted synthesis, solid-phase synthesis, and application of organometallic reagents, etc. will be discussed retrospectively, focusing on the pathways to quinazoline, quinazoline-4-one (Scheme 13.21), and their derivatives.

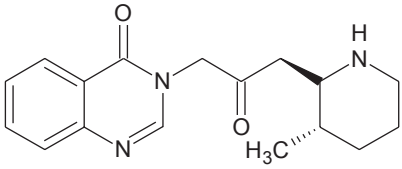


Scheme 13.21

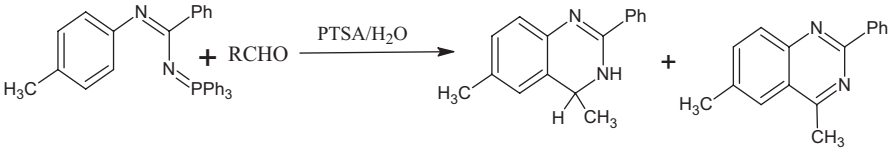
6.4 PTSA-catalyzed Reaction

Rossi et al. have utilized the tandem aza-Wittig/electrocyclization principle for synthesis of quinazoline ring starting from *N*-imidoyl iminophosphorane [77]. Other

Fig. 13.5 (+)-febrifugine

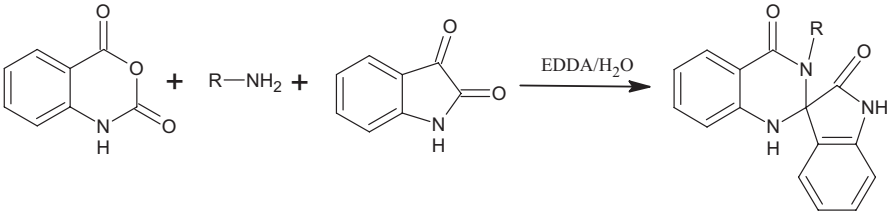


unique synthetic strategies with *N*-vinyliminophosphoranes and benzotriazolyl derivatives (Scheme 13.22) have also been developed demonstrating the maturity and excellent prospects of iminophosphorane-mediated syntheses.



Scheme 13.22

Quinazolines and their spiro derivatives are also available via MCRs in water. The three-component condensation of isatoic anhydride, primary amines, and aromatic aldehydes or isatin to give 2,3-dihydroquinazolin-4(1*H*)-ones or spirooxindole derivatives (Scheme 13.23) was performed in water using ethylenediamine diacetate (EDDA) as catalyst [78].



Scheme 13.23

7 Antimalarial Activity

Several bio-active natural products such as febrifugine (Fig. 13.5) and isofebrifugine (Fig. 13.6) contain quinazolinone moieties with potential antimalarial [79] activity.

Quinazolinone derivatives attract widespread attention due to the diverse biological activities associated with them. Rutaecarpine (Fig. 13.7) and luotonine A [80] (Fig. 13.8) are the two natural quinazoline-fused compounds exhibiting very potent pharmacological values.

Fig. 13.6 (+)-iso febrifugine

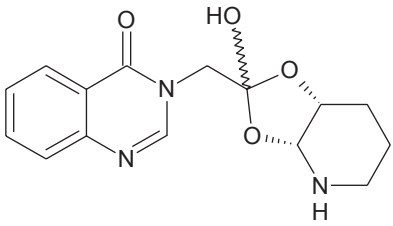


Fig. 13.7 Rutaecarpine

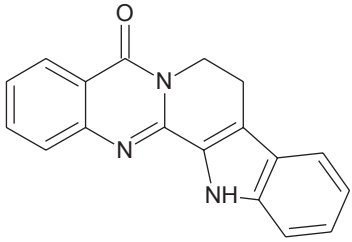
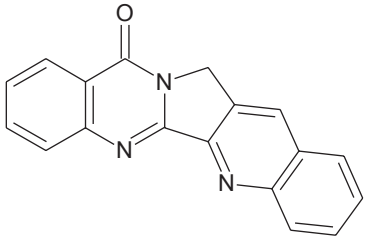


Fig. 13.8 Luotonine



8 Conclusions

Conventional synthetic methods for quinazoline derivatives, still in general use, including microwave-assisted reaction, ultrasound-promoted reaction, metal-mediated reaction, water reaction, and phase-transfer catalysis reaction for the synthesis of this important heterocyclic compounds are discussed. It could be seen from the examples compiled above that some novel synthetic methods are in constant development and different methods are adopted in the synthesis of different quinazoline analogues. On the other hand, it is known that substituents at different positions affect the activity differently. By careful observation of the recent researches, substituted quinazoline analogues remain a majority among the products. However, with the deepening and development of researches, substituent groups at other positions are also achieved and studied increasingly, such as the construction of N-heterocyclic quinazolines by introduction of active groups into the 3-position of the quinazoline core. It is worth mentioning that N-heterocyclic quinazolines

with more rigid and complicated structures were synthesized successively, some of which showed excellent biodynamic derivatives. In addition, it could be drawn from the research progress discussed above that enhancement of activity by the splicing method of installing various active groups is and will still be the main method for drug design and reconstruction of quinazoline derivatives. We hope that the information contained here encourages the readers to make use of these green protocols for the efficient and eco-friendly construction of novel heterocyclic frameworks.

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