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REVIEW PAPER

One-pot access to a privileged library of six membered nitrogenous heterocycles through multi-component cascade approach

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Abstract The presence of heterocycles and heteroaromatics as ubiquitous components in a diverse variety of synthetic drugs, biologically active molecules, and natural products has inspired the researchers to develop new strategies and technologies for their easy accessibility. Among them, six membered nitrogenous heterocycles gained immense interest, and significant efforts have been made to the development of synthetic strategies which could lead to the discovery of architecturally complex and diverse molecules with high efficiency, low cost, less organic waste and shorter reaction time. Access to such systems by one-pot multi-component approach with inherent advantages of step-economy, operational simplicity, synthetic efficiency, and environmental compatibility is particularly attractive. The current review article highlights the recent developments in the synthesis of six membered nitrogen-containing heterocyclic scaffolds through one-pot multi-component assembly approach.

Keywords Nitrogen heterocycles · Synthetic methods · Diversity · Multi-component reactions

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Introduction

Heterocycles are ubiquitously imperative structural units and major building blocks of a diverse variety of natural products [1]. They also find useful applications in pharmaceutical and agrochemical industry, and functional materials. The conventional multistep synthetic approach to access such complex molecules generally involves several functional groups interconversions and each synthetic operation includes extraction and purification processes. This whole procedure leads to not only synthetic inefficiency but also adds to the amount of the waste produced. In recent times, multi-component reactions (MCRs) earned eminence as a powerful synthetic tool for the generation of structurally complex molecular frameworks with attractive biological features. The whole process generally relies upon the formation and breakage of several carbon–carbon and carbon–heteroatom bonds in one-pot [2–8].

MCRs offer remarkable advantages including convergence, operational simplicity, higher chemical yields, shorter reaction times, facile automation, minimization of the requisite reagents, reduction in the number of extraction and purification steps, hence minimizing the quantity of waste generation, rendering the chemical transformations green and environment friendly [9–12]. Multi-component reactions are also useful for the expedient generation of chemical libraries of bioactive compounds with great diversity and high levels of molecular complexity, thereby contributing towards the identification and optimization of potential molecules in drug discovery programmes [13–17]. Therefore, designing new MCRs toward the synthesis of novel heterocycles from simple and readily available feedstock with green procedures has gained immense importance, especially in the areas of drug discovery and organic synthesis [18–21].

While there is much review literature [22–28] explaining the main MCR strategies applied to the synthesis of a large variety of heterocycles like indoles, pyrroles, etc., the use of multi-component reactions in the synthesis of six membered monocyclic nitrogen-containing heterocycles has hardly been touched recently in the review literature. The current review article is aimed at presenting recent (2014) MCR approaches to access these heterocycles in one-pot.

Progress in synthetic methods

The rapid and easy access to biologically active compounds by MCRs and the scaffold diversity of MCRs has been recognized by the synthetic community in industry and academia as a preferred method to design and discover biologically active compounds. All these transformations provide expeditious access to new bioactive heterocycles, with increased structural diversity in a straightforward fashion starting from readily approachable, simple and common substrates. The main theme of the present review is to highlight comprehensively the recent (2014) developments in the synthesis of six membered monocyclic nitrogen-containing heterocyclic scaffolds like pyridines, dihydropyridines, tetrahydropyridines,

piperidines, pyridazinones, dihydropyrimidine, pyrimidin(thi)one derivatives and fused six membered heterocycles like quinoline. In addition, some recent examples depicting elegant developments in the catalytic asymmetric construction of six membered nitrogenous heterocycles have also been discussed.

Synthesis of pyridines

The pyridine ring system is of imperative significance and an important structural unit prevalent in a large variety of natural products and also in clinically functional molecules. In the pharmaceutical and agrochemical arena, pyridine derivatives have attracted significant attention due to their diverse spectrum of biological applications such as antimicrobial [29], anti-hyperglycemic properties [30], Ca^{2+}-channel blockers [31], and anti-diabetic agents [32]. In addition, they have been screened as protein kinase B (PKB/Akt) [33], protein kinase Cq (PKCq) [34], carbonic anhydrase [35], dipeptidyl peptidase-IV (DPP-IV), cholinesterase [36], C-Jun NH_2 terminal kinase (JNKs) [37], and RET tyrosine kinase inhibitors [38]. Moreover, molecular entities like lavendamycin, streptonigrin and streptonigrone incorporating a pyridine core are reported as anticancer drugs, and cerivastatin is considered as HMG-CoA enzyme inhibitor [39]. Furthermore, π-stacking ability of the pyridine ring makes it a key synthon in supramolecular chemistry [40], and in the development of non-linear optical (NLO) materials [41], and nondoped organic light-emitting devices (OLEDs) [42]. Some 2-amino-3-cyanopyridine derivatives (Fig. 1) have raised considerable attention as antifungal agents and potent inhibitors of HIV-1.

In this part, we summarize examples dealing with the synthesis of pyridine skeleton from readily available feedstock through multi-component approach.

Ammonium salts as nitrogen source

Moosavi-Zare et al. [43] developed a facile and efficient one-pot four-component procedure for the synthesis of 2,4,6-triarylpyridines **4** by involving aldehydes **1** (1.0

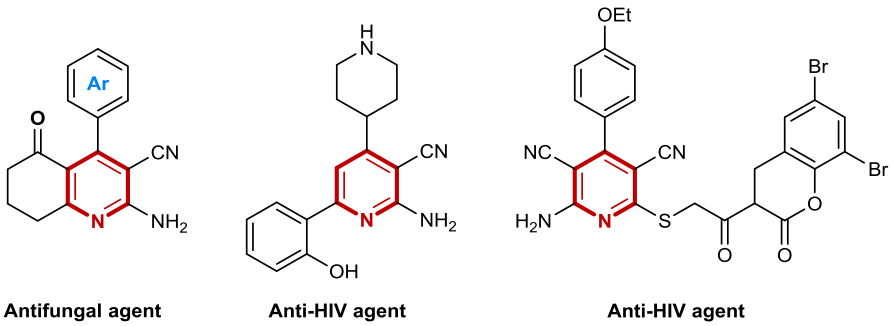


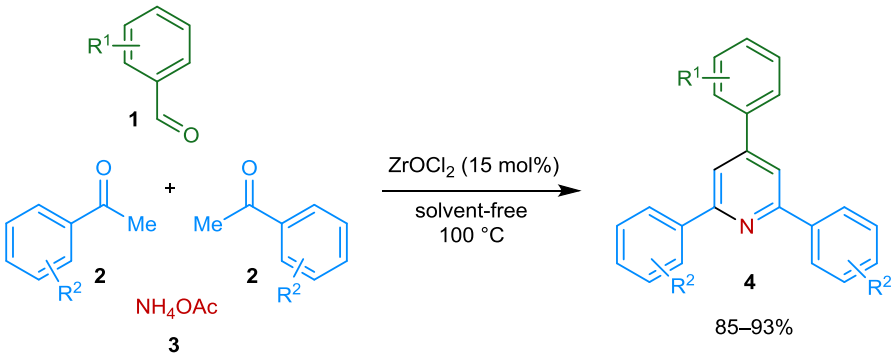
Fig. 1 Bioactive polysubstituted pyridines with adjacent amino and nitrile functionalities

equiv), acetophenones **2** (2.0 equiv) and ammonium acetate **3** (1.2 equiv) under solvent-free conditions. Oxozirconium(IV) chloride ($ZrOCl_2$) was used as a catalyst (Scheme 1). Under optimized reaction conditions, this strategy allowed exploring the scope of reaction by utilizing a diverse range of substituted aldehydes (electron-rich, electron-poor and halogen substituents), and various acetophenones and ammonium acetate. The corresponding products were furnished in high chemical yields and short reaction times. This simple methodology possesses several advantages including easy purification step, clean reaction and reusability of the catalyst.

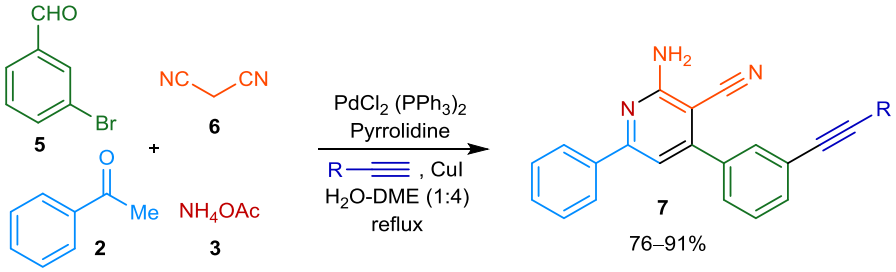
Bodireddy et al. [44] developed structurally diverse alkynyl/alkenyl-substituted pyridine derivatives **7/8**. This process involves the heterocyclization and subsequent Pd-mediated Sonogashira and Heck coupling reactions. This multi-component reaction involves bromobenzaldehyde **5**, malononitrile **6**, acetophenone **2**, and ammonium acetate **3**. Several terminal alkynes/alkenes were also employed in the presence of pyrrolidine and Pd-catalyst under reflux conditions (Scheme 2). Under optimal reaction conditions, the substrate scope and generality of this reaction was investigated using various terminal alkynes. A range of functional groups on alkynes were compatible affording the desired densely decorated pyridines in good yields.

Furthermore, a series of terminal alkenes were also tolerated. This time alkenyl-substituted pyridine derivatives **8** were accessed. The process was largely found to be insensitive for various functional groups on terminal alkenes providing the desired compounds in good yields (Scheme 3). In general, this MCR procedure offers several advantages including easy purification of products, straightforward construction of diversity oriented pyridine derivatives with high substitution.

Bharkavi et al. [45] reported an elegant one-pot domino procedure for the synthesis of a series of novel 2,6-diaryl-4-(1*H*-indol-3-yl)-3-cyanopyridines **11** by involving 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **9**, 4,4,4-trifluoro-1-phenylbutane-1,3-dione **10**, and aromatic aldehydes **1** in the presence of ammonium acetate **3**,

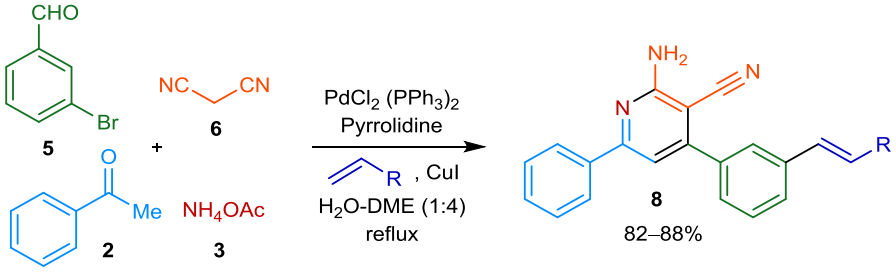


Scheme 1 Synthesis of 2,4,6-triarylpyridines catalyzed by $ZrOCl_2$



R = CH_2OH, CH_2CH_2OH, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2Cl$, *n*-Bu, *n*-Pent, *n*-Hex

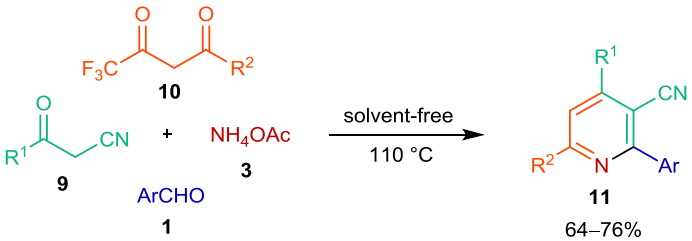
Scheme 2 Synthesis of polysubstituted pyridines



R = CO_2Me, CO_2Et, CO_2t-Bu, COMe, $CONH_2$, CN

Scheme 3 Synthesis of multisubstituted pyridines

under solvent-free conditions (Scheme 4). This transformation generates two new carbon–carbon and two carbon–nitrogen bonds leading to the construction of a six-membered ring in a one-pot operation. The scope of this methodology was examined by tolerating a range of functional groups (electron-rich and electron-



R^1 = Ph, 3-indolyl
R^2 = Ph, 2-thienyl
Ar = 2-Br-Ph, 4-Br-Ph, 4-Me-Ph, 4-Cl-Ph, 4-OMe-Ph, 3-NO_2-Ph

Scheme 4 Synthesis of poly substituted pyridines

poor) on the aromatic ring of aldehydes apart from dicarbonyl and nitrile substrates. The desired pyridine compounds were obtained in 64–76 % yields.

A plausible mechanism for the formation of pyridines **11** is depicted in Fig. 2. Presumably, the reaction initiates with the condensation of aldehyde with ammonium acetate to form imine which on reaction with 3-(1*H*-indol-3-yl)-3-oxopropanenitrile furnished the intermediate **12**. Then, intermediate **12** reacts with 4,4,4-trifluoro-1-phenylbutane-1,3-dione **10** in a chemoselective fashion to afford intermediate **13**, which undergoes annulation and concomitant dehydration leading to **14**. This intermediate **14** upon reaction with ammonia leads to dihydropyridine via fragmentation, which ultimately undergoes air oxidation affording the final product **11**.

Pagadala et al. [46] described an elegant, effective and simple one-pot methodology for the preparation of highly substituted pyridines **16** in excellent yields. They studied the reaction among simple starting materials which include aromatic aldehydes **1**, ketone **15**, malononitrile **6**, and ammonium acetate **3** using Au loaded on MgO as a catalyst (Scheme 5). Under the optimal reaction parameters, the generality of this one-pot transformation was investigated by employing several aromatic aldehydes. The results revealed that the electronic nature of the substituents on the benzene ring had no significant influence on the reactivity. It is also evident that spatially hindered aldehydes (2-methoxy, 2-bromo, and 2-chloro substituted) also worked efficiently affording the desired products. In general, the present protocol offers several advantages in terms of higher chemical yields, short reaction times, catalyst recyclability, and no column chromatography is needed.

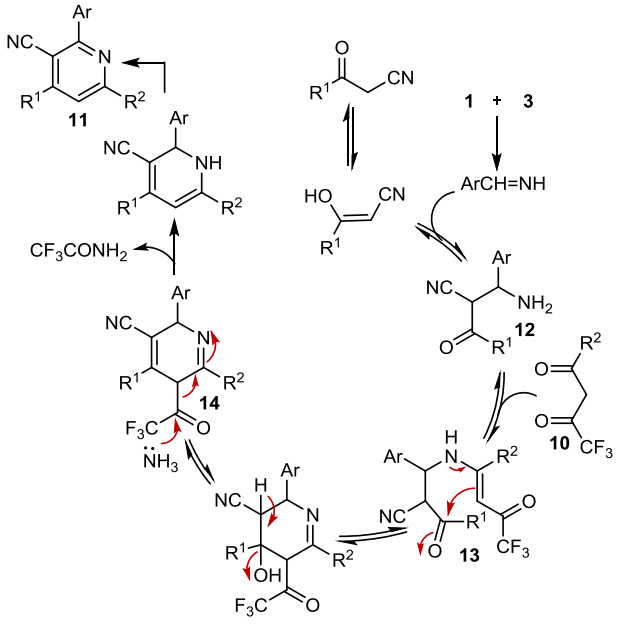
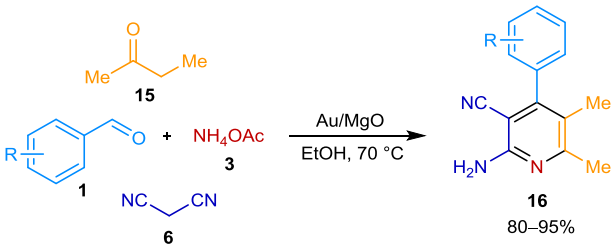


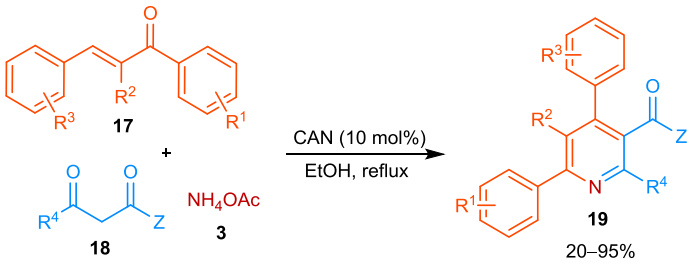
Fig. 2 Possible mechanism for the synthesis of 2-aryl-4-(1*H*-indol-3-yl)-6-phenyl-3-cyanopyridines



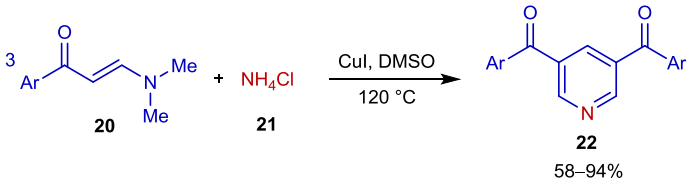
Scheme 5 Synthesis of penta-substituted pyridines

Tenti et al. [47] disclosed the development of a simple, versatile and efficient three-component aza-annulation between chalcones **17**, *β*-ketoamides **18**, and ammonium acetate **3**. The Lewis acid like CAN was used to promote the reaction affording highly substituted nicotinamides **19** in good to excellent yields (Scheme 6). This transformation creates one carbon–carbon and two carbon–nitrogen bonds in a single synthetic operation. Having recognized the optimized conditions for this multi-component reaction, an exploration of the scope of the substrates was investigated by tolerating electron-deficient and electron-rich chalcones affording the desired products in good yields.

Wan et al. [48] developed a copper-catalyzed domino strategy for the unprecedented synthesis of 4-unsubstituted pyridines **22** with both symmetrical and unsymmetrical structures (Scheme 7). The reaction proceeds under aerobic conditions involving enaminones **20** and ammonium chloride **21** leading to pyridine skeleton. On the basis of the optimized results, the synthesis of different symmetrical pyridines using different enaminone substrates was then conducted. According to the acquired data, the present protocol was generally applicable for the synthesis of symmetrical pyridines using aryl functionalized enaminones via their



Scheme 6 Three-component synthesis of nicotinamide derivatives



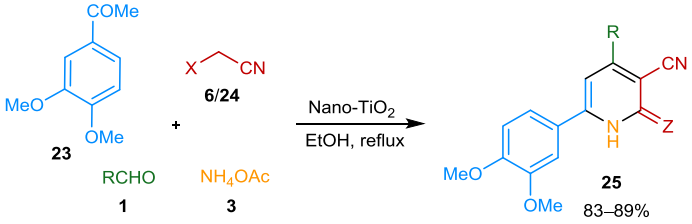
Ar = Ph, 4-Me-Ph, 2-Br-Ph, 3-OMe-Ph, 4-OMe-Ph, 4-Me_2N-Ph, 4-Cl-Ph, 4-NC-Ph, 4-CF_3-Ph, 2-Me-Ph, 3,4-Cl_2-Ph, 3-NO_2-Ph, naphthyl, thienyl

Scheme 7 Synthesis of different symmetrical pyridines

branched transformations. A range of enaminones containing a variety of different functional groups, such as alkyl, alkoxyl, halide, nitro, amino, cyano, as well as heteroaryl, were tolerated leading to the corresponding pyridines with good to excellent yields. Among these reactions, the halogenated aryl-based substrates gave excellent yields of related pyridines. However, with the other enaminones (electron-deficient or electron-rich), the electronic property showed no deducible impact on the reaction results.

Another notable point in the results was the synthesis of thiophene-functionalized pyridine, which proved the good tolerance of the present method to heteroaryl functionalized enaminones. However, when the Ar fragment in enaminones was alternated with an alkyl such as methyl, the target transformation was not observed under the standard conditions. On the other hand, the scope of this process was further expanded using two different enaminones resulting in a diverse library of unsymmetrical pyridine structures with fair yields.

A one-pot four-component procedure for the preparation of 3-cyano-2(1*H*)-pyridinones and their 2-imino derivatives **25** was developed by Baghernejad [49]. The reaction used simple starting materials like 3,4-dimethoxyacetophenone **23**, malononitrile **6** or ethylcyanoacetate **24**, ammonium acetate **3** and various aldehydes **1** catalyzed by Nano-TiO_2 in ethanol (Scheme 8). This procedure tolerates a range of aldehydes affording title products in ample yields.



R = Me, Ph, 4-Cl-Ph, 4-OMe-Ph, 4-OH-Ph
X = CN, COOEt
Z = NH, O

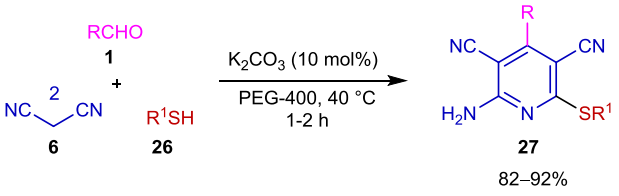
Scheme 8 Nano-TiO_2-catalyzed synthesis of 3-cyanopyridines

Nitrile as nitrogen source

Kidwai and Chauhan [50] demonstrated a facile, clean, simple and one-pot three-component procedure for the synthesis of a series of 2-amino-3,5-dicarbonitrile-6-thiopyridine derivatives **27** involving aromatic aldehydes **1**, malononitrile **6**, and substituted thiophenols **26** using potassium carbonate as a base and polyethylene glycol (PEG-400) as a reusable solvent (Scheme 9). The versatility of this protocol was explored with a wide range of structurally diverse aldehydes by reacting with malononitrile and different thiophenols under the optimized reaction parameters. Apart from aromatic, heteroaromatic aldehydes like thiophene-2-carbaldehyde and furan-2-carbaldehyde were equally tolerable to these conditions. However, aliphatic aldehydes were not effective reaction partners.

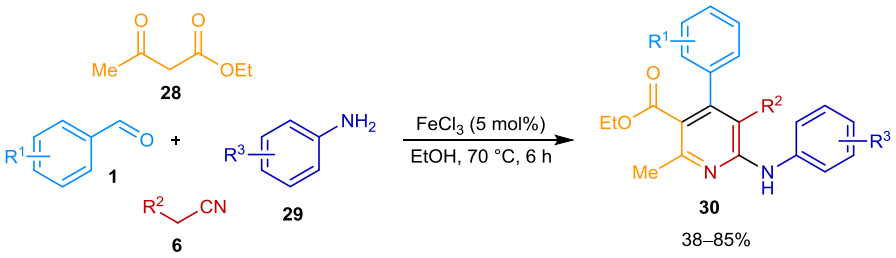
He et al. [51] developed an efficient and straightforward route to polysubstituted pyridine derivatives **30**. This four-component process involves an $FeCl_3$-catalyzed nucleophilic addition/intermolecular cyclization sequence, providing access to a range of pyridine derivatives from simple and readily accessible starting materials under mild conditions (Scheme 10). After identifying suitable reaction conditions, the substrate scope was tested with various aromatic aldehydes **1**, activated methylene compounds **6/24/28**, and aromatic amines **29**. Among the tested substrates, electron-withdrawing (NO_2, Cl, Br) functional groups were more compatible as compared to electron-donating (OMe, Me) groups and resulted in higher yields of the products irrespective of the substitution position. *ortho*-Substituted electron-withdrawing groups were less productive in terms of yield. When ethyl α-cyanoacetate **24** was used as a substrate, the reaction appeared to be quite general with respect to malononitrile **6**. On the other hand, aromatic amines bearing electron-donating groups gave higher yields than electron-withdrawing groups.

Furthermore, the scope of this reaction was extended to various nucleophiles such as ethanol **32** under the optimized conditions. The desired products were obtained in good yield (Scheme 11). This methodology works best without base and ligand under air, which is the advantage of this reaction.

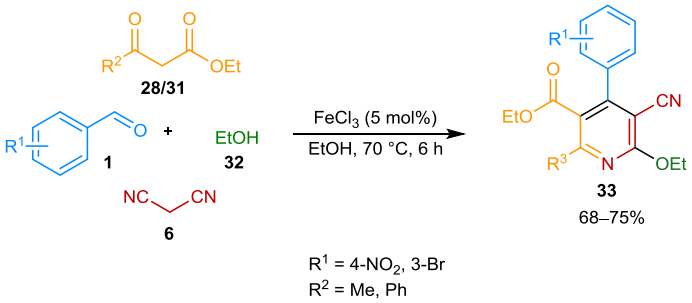


R = Ph, 4-OMe-Ph, 4-Br-Ph, 4-Cl-Ph, 4-Me-Ph, 2-thienyl, 2-furanyl
R^1 = Ph, 4-OMe-Ph, 4-Br-Ph, 2-NH_2-Ph

Scheme 9 Synthesis of a library of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives



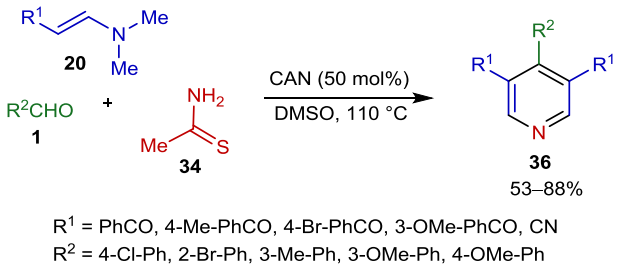
Scheme 10 $FeCl_3$-catalyzed synthesis of polysubstituted pyridine derivatives



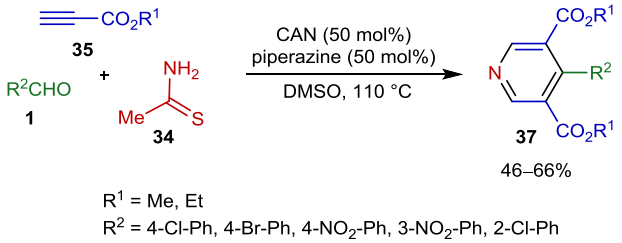
Scheme 11 $FeCl_3$-catalyzed synthesis of pyridine derivatives using ethanol as a nucleophile

Thioacetamide as nitrogen source

Wan et al. [52] developed a generally applicable multi-component method for the synthesis of pyridines by involving aldehydes **1**, electron-deficient enamines **20** or thioacetamide **34** and alkynes **35** as a cheap and efficient ammonium source (Schemes 12, 13). This one-pot process provided a diverse variety of 2,4,5-trisubstitutd pyridines **36**,**37** in generally good yields. By using the optimized



Scheme 12 Electron-deficient enamine-based multi-component synthesis of pyridines

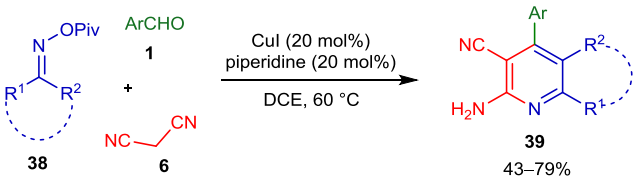


Scheme 13 Electron-deficient alkyne-based synthesis of pyridines

protocol, the scope of the reaction towards the product formation was assessed. A large variety of substrates bearing diverse functional groups including alkyl, alkoxy, cyano, halo and hetaryl were tolerated. The reaction efficiency and the obtained chemical yields were not influenced by the electronic properties of the enamines or aldehydes. However, some aldehydes possessing an electron-deficient group were more favorable and gave smooth cyclization and the corresponding pyridine products in relatively higher yields. On the other hand, to further expand the general applicability of the protocol, electron-deficient alkynes were used as alternative building units for the synthesis of pyridines.

Oxime ester as nitrogen source

Wu et al. [53] developed a copper-catalyzed domino cyclization strategy by involving an oxime ester **38** leading to the synthesis of pyridines **39**. In this process, oxime ester is utilized as an enamine precursor which on cyclization with malononitrile **6** and aldehydes **1** furnishes the 2-aminonicotinonitriles in one-pot fashion (Scheme 14). With the optimized conditions, the scope of this reaction was explored. Various oxime esters and aldehydes were tested. Several electron-rich (methyl, methoxy) and electron-poor (trifluoromethyl, bromo, cyano, chloro) groups on the aromatic ring were examined, and the products were obtained in moderate to good yield (45–79 %). In addition, heteroaromatic aldehydes like thiophene-3-aldehyde, furan-2-aldehyde, and pyridine-3-aldehyde also worked efficiently producing title products in good yields (62–77 %). Several oxime esters, with variable substitution pattern on the aromatic ring afforded the



Scheme 14 Synthesis of 2-aminonicotinonitriles

2-aminonicotinonitriles in moderate yield (44–56 %), whereas heterocyclic oxime esters with thiophene indole and furan also pertinent in this transformation, delivering the corresponding products in moderate yield (43–68 %). Moreover, oxime esters bearing a cyclic skeleton were used to generate polycyclic products.

Synthesis of dihydropyridines

1,4-Dihydropyridines (DHPs) are considered as one of the most vibrant classes of heterocyclic compounds as privileged pharmacophores. The key examples of 1,4-DHPs pharmaceuticals include Nimodipine, Felodipine, Nifedipine and Nicardipine (Fig. 3), used as calcium channel blockers. In addition, 1,4-dihydropyridines (1,4-DHPs) is an important class of pharmaceutically privileged moieties [54–59] with a versatile biological profile such as anticonvulsant activity [60], selective adenosine-A3 receptor antagonism [61], sirtuin activation and inhibition [62] and radioprotective activity [63]. The compounds of this class also exhibit various therapeutic properties such as platelet antiaggregatory, neuroprotectant, and cerebral antischemic activity in the treatment of Alzheimer's disease and chemosensitizing activity in tumor therapy [64]. They are therefore striking synthetic targets of organic chemistry and the researchers are highly interested in the synthesis of 1,4-DHPs by multi-component reactions (MCRs), the most efficient strategies in terms of providing both sufficient structural diversity and generating compound libraries for drug discovery.

In this section, we highlight the recent developments for the construction of dihydropyridine compounds through one-pot multi-component strategy using cheap and easily available substrates.

Ammonium salts as nitrogen source

A very efficient and green approach for the rapid synthesis of biologically active substituted Hantzsch 1,4-dihydropyridine derivatives **40** was developed by Nasr-Esfahani et al. [65]. A mixture of dicarbonyl compounds **28**, aldehydes **1** and ammonium acetate **3** was used to construct this core using magnetic Fe_3O_4 nanoparticles (Fe_3O_4 MNPs) as a recyclable catalyst under solvent-free conditions (Scheme 15). In order to show the generality of the method, this reaction was developed with different aldehydes **1**. By using this heterogeneous nanocatalyst, the aromatic aldehydes, incorporating electron-donating substituents such as methyl,

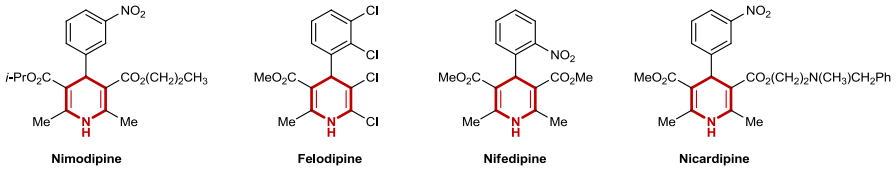
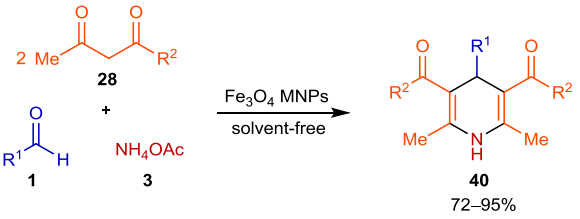


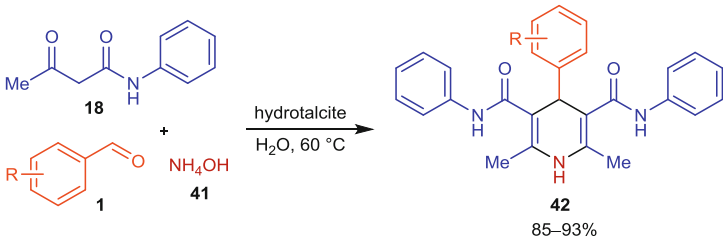
Fig. 3 1,4-DHPs used as clinical drugs



Scheme 15 Synthesis of 1,4-DHPs in presence of Fe_3O_4 NPs as catalyst

methoxy, and hydroxy and electron-withdrawing groups such as nitro and halide, gave high yields. The procedure worked well for cyclohexyl as well as heterocyclic aldehydes in addition to aromatic aldehydes. In general, low catalyst loading, facile catalyst separations, nonhygroscopic and inexpensive catalyst system for this transformation are advantages of this procedure.

Pagadala et al. [66] reported an efficient catalyst (Zn-VCO_3 hydrotalcite) for the one-pot synthesis of triphenylpyridine-3,5-dicarboxamide **42** via Hantzsch reaction of acetoacetanilide **18**, ammonium hydroxide **41** and various aromatic aldehydes **1** (Scheme 16). The catalyst was active for the Hantzsch reaction in water at 60 °C. The products were isolated in good yields (85–93 %) with short reaction times (2–3 h). The scope of the reaction was investigated by reusing the hydrotalcite catalyst. The catalyst showed good recovery and reusability profile affording the product in 93 % yield. This process could be repeated up to four times, delivering the desired product in good yield, with undiminishing efficiency. Using five different substrates, the formation of dihydropyridines has occurred in good yields spontaneously and exclusively. Notably, even sterically hindered substrate also participated effectively to afford the dihydropyridine derivative. In general, solvent-free conditions and non-toxic reusable heterogeneous catalyst make this method simple, convenient, cost-effective and environment friendly in character, which will have an advantage over other existing methodologies.



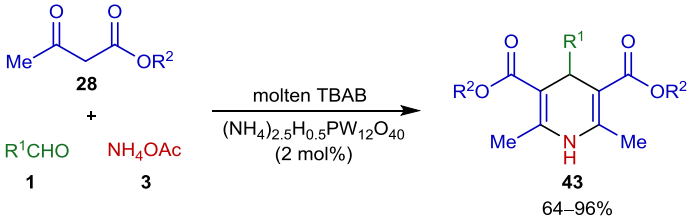
Scheme 16 Hydrotalcite-catalyzed synthesis of 1,4-DHPs

Ghattali et al. [67] developed a novel and highly effective one-pot multi-component approach for the synthesis of dihydropyridines **43** catalyzed by $(NH_4)_{2.5}H_{0.5}PW_{12}O_{40}$ under solvent-free conditions (Scheme 17). Several types of aldehyde with electron-rich or electron-deficient substituents were reacted under the optimized conditions to establish the scope and generality of the process.

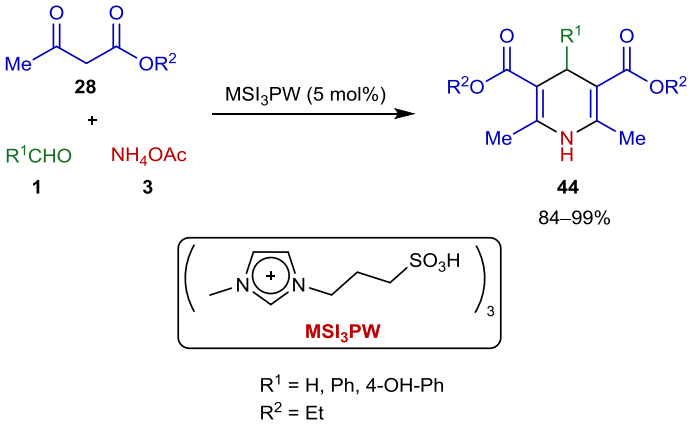
In all cases good yields of the expected 1,4-DHP derivatives were obtained without any electronic influence. Overall, this method has several attractive features like short reaction times, higher chemical yields, use of a molten salt instead of organic solvents, and economic reusability of the catalyst, The simple reaction procedure combined with ease of recovery and reuse of the catalyst makes this an atom-economic and environmentally benign chemical process to access 1,4-DHPs. Simple filtration affords the catalyst which could be further used without any loss of catalytic activity.

A similar procedure was introduced by Alvim et al. [68] who demonstrated that the TSIL MSI_3PW functions as a very efficient catalyst for the Hantzsch MCR to obtain bioactive compounds in excellent yields. A range of different aldehydes were tolerated to obtain dihydropyridine products **44** (Scheme 18). Ammonium acetate could be replaced with ammonium chloride at the sacrifice of some yield (5–8 %).

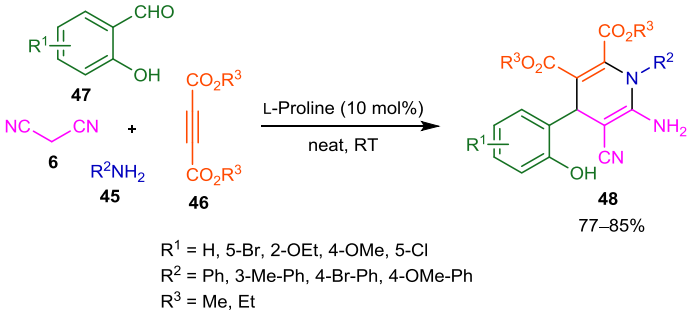
Kiruthika and Perumal [69] developed an efficient, greener and environment friendly approach for the one-pot four-component synthesis of dihydropyridines **48** under solvent-free conditions. L-proline was used as a catalyst (Scheme 19). This process involves Huisgen dipolar additions using amines **45** and alkynes **46** delivering the new dihydropyridine derivatives. Using the optimized reaction protocol, various aromatic aldehydes **47** were readily applied to this protocol to investigate the substrate scope which afforded the desired products in high to excellent yields. Stereoelectronic nature of the aldehydes had not any profound effect on the product formation. In addition, several amines were also tolerated in this protocol with both electron-rich and electron-deficient substituents present on aryl ring. Two different types of alkynyl esters were also examined. In general, this new protocol features operational simplicity, easy reaction and purification procedure, high atom economy, broad substrate scope, excellent yields of title products, and relatively cheap solid catalysts. The reaction also avoids the use of harmful solvents.



Scheme 17 $(NH_4)_{2.5}H_{0.5}PW_{12}O_{40}$ catalyzed synthesis of 1,4-DHP derivatives



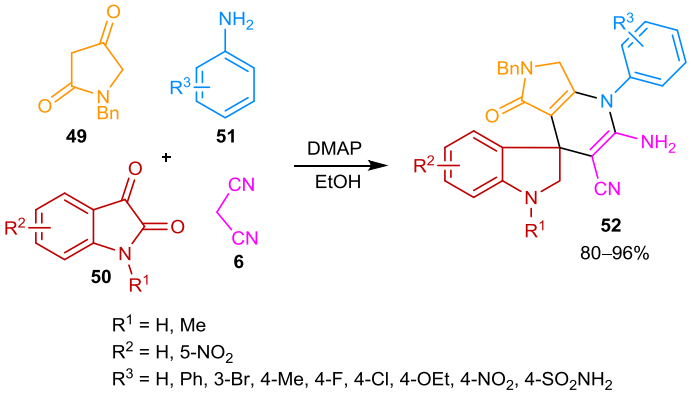
Scheme 18 MSI_3PW-catalyzed synthesis of 1,4-DHPs



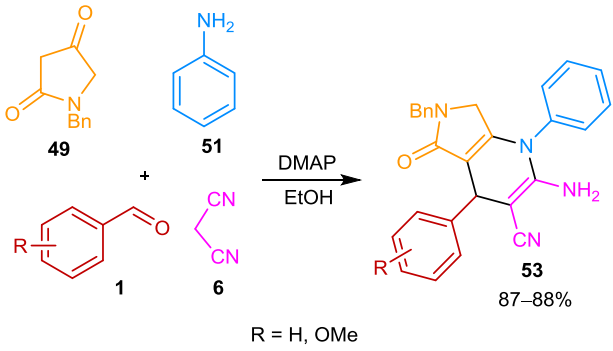
Scheme 19 L-Proline-catalyzed synthesis of dihydropyridines

Han et al. [70] developed an efficient, clean, and environment friendly one-pot four-component protocol for the generation of a new type of spirooxindole derivatives containing dihydropyridine **52** using DMAP as a catalyst in aqueous ethanol (Scheme 20). The reaction involves *N*-benzylpyrrolidine-2,4-dione **49**, isatin/aldehyde **50/1**, aniline **51**, and malononitrile **6**. With an aim to construct a library of spirooxindoles containing DHP, this methodology was evaluated by using *N*-benzylpyrrolidine-2,4-dione, different substituted aromatic amines including either electron-deficient or electron-rich groups, different isatin derivatives and malononitrile as easily available starting materials.

The reaction was found to be facilitated with electron-donating groups, such as 4-Me and 4-OEt on the aniline ring as compared to electron-withdrawing groups, e.g., 4-NO_2 on the same position. It was also notable that the presence of two methyl groups (R^1/R^3, or R^2/R^3) produced desired compounds in highest yields, whereas the reaction partners containing nitro groups gave worst yields. The scope of this methodology was further extended by using a range of aromatic aldehydes affording similar products **53** in good yields and shorter reaction times (Scheme 21).



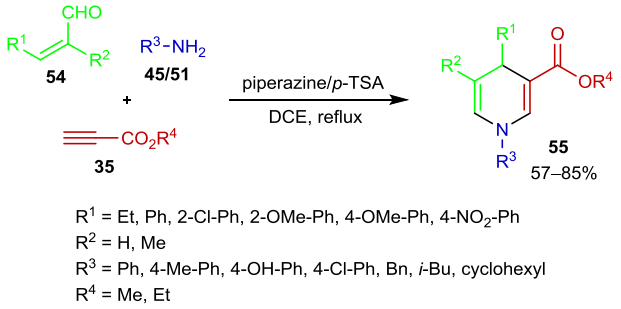
Scheme 20 DMAP-catalyzed synthesis of 1,4-DHP derivatives



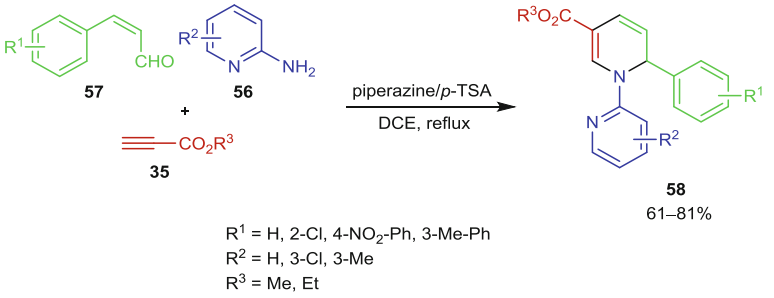
Scheme 21 DMAP-catalyzed synthesis of 1,4-DHP derivatives

A three-component one-pot reaction between electron deficient alkynes **35**, enals **54** and primary amines **45/51** was reported by Wan et al. [71] that leads to a tunable synthesis of various 1,4- and 1,2-dihydropyridines **55**, **58** using piperazine/*p*-TSA as a catalyst (Scheme 22). Based on the initial results, the scope and diversity of this one-pot regioselective methodology was evaluated with various enals, primary amines and alkyl propiolates. Both the enal and amine components bearing aromatic and aliphatic backbones reacted smoothly under optimized reaction conditions to give 1,4-DHPs **55** with moderate to excellent yields.

By changing the relative nucleophilicity of the amino group by using 2-aminopyridines **56**, the regioselective formation of 1,2-DHPs **58** was successfully achieved. Different cinnamaldehydes **57**, alkyl propiolates and 2-amino pyridines readily incorporated to provide products **58** with moderate to good yields (Scheme 23). While different types of functional groups such as aryl, alkyl, halide as well as nitro were compatible for the synthesis. In general, the selectivity, product diversity and the facility of the present method make it a useful option in the synthesis of important heterocyclic compounds.

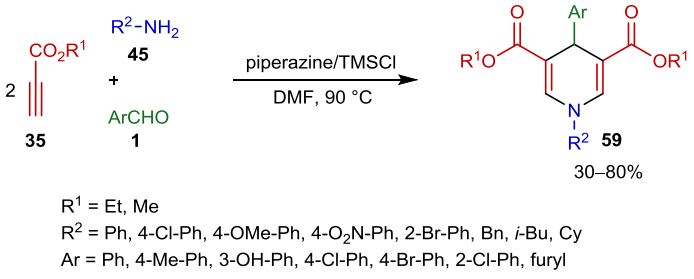


Scheme 22 Three-component synthesis of different 1,4-DHPs



Scheme 23 Regioselective synthesis of 1,2-DHPs

In another study, Wan et al. [72] successfully developed a multi-component reaction of aldehydes **1**, electron-deficient alkynes **35** and amines **45** to afford several symmetrical 2,6-unsubstituted 1,4-dihydropyridines **59** (Scheme 24). The key factor initiating the reaction was the activation of secondary amine to the electron-deficient alkynes. Under the standard conditions, the broad applicability of this multi-component method was explored. A diverse number of aldehydes, alkynes and amines were used. Benzaldehydes incorporating several substitution



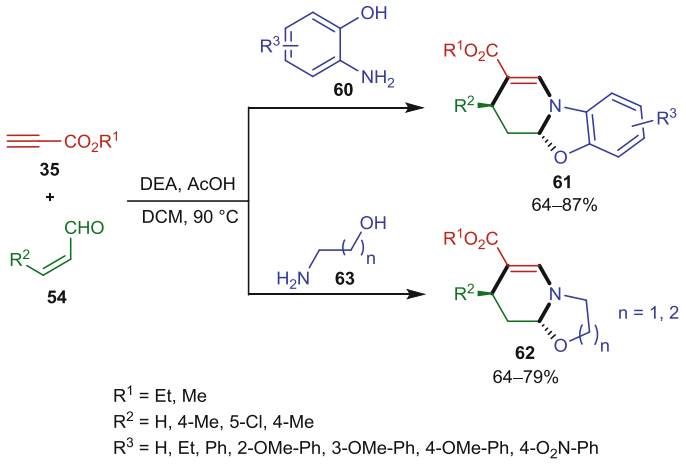
Scheme 24 Multicomponent synthesis of different *N*-substituted 1,4-DHPs

groups such as alkyl, alkoxy, halides, at variable positions were tested. Apart from aryl, heteroaryl aldehydes were also tolerated. Interestingly, this protocol was also tolerant of alkyl amines and the corresponding 1,4-DHPs were accessed with ample yields. Methyl propiolate was also found as efficient coupling partner in addition to the ethyl propiolate, and the corresponding 1,4-DHPs were obtained efficiently with acceptable yields. However, aliphatic aldehydes were not successful under present conditions. The use of ammonium acetate instead of amines as *N*-source was also investigated and provided the desired products in moderate yields.

Synthesis of tetrahydropyridines

Amines as nitrogen source

Wan et al. [73] developed a one-pot three-component reaction of enals **54**, electron-deficient alkynes **35**, and hydroxyl-functionalized primary amines **60** for the highly diastereoselective construction of dihydro-3*H*-benzo[4,5]oxazolo-[3,2-*a*]pyridines **61**, hexahydropyrido[2,1-*b*][1,3]oxazines, and tetrahydro-2*H*-oxazolo[3,2-*a*]pyridines **62** (Scheme 25). The scope of this catalytic method was investigated which revealed the broad tolerance of a range of functional groups such as alkyl, alkoxyl, halide, and nitro providing the corresponding ring-fused products. The property of functional groups in alkyne and *o*-aminophenol components did not show evident impact on the results, and most fused heterocyclic products were provided in good to excellent yields. However, for the enal component, an alkyl-substituted enal such



Scheme 25 Synthesis of tetrahydropyridine fused bicyclic structures

as pent-2-enal gave relatively lower yield of corresponding products than those entries using aryl functionalized and nonsubstituted enals. On the other hand, the reactions using linear amino alcohols of type **63** would also undergo similar transformation to give fused heterocyclic products **62** with different ring sizes in good yields.

Synthesis of piperidines

Synthesis of six-membered nitrogen heterocyclic compounds such as piperidine rings is very important because of their pharmacological and biological properties. The piperidines and their analogues exhibit diverse biological activities such as antihypertensive [74], antibacterial [75], anticonvulsant, anti-inflammatory [76], antidepressant [77], farnesyltransferase inhibition [78], norepinephrine reuptake inhibitor (CTDP 31,446) [79], antipsychotic agent (MDL-100907) [80]. Furthermore, several substituted piperidines have been recognized as remarkable therapeutic agents in the treatment of Parkinson's disease [81, 82], prolactinoma [83], schizophrenia [84, 85], influenza infection [86], cancer metastasis [87], obesity, and diabetes [88]. Moreover, functionalized piperidines have been identified as valuable therapeutic agents [89–91]. Several piperidine derivatives like Palinavir [92, 93], Risperdal [94], Aricept [95, 96], and 3-nitro piperidine derivatives [97], have been employed to treat a range of disorders. Given their enormous medicinal practicality, the development of effective and competent synthetic strategies to access these bioactive functionalized piperidines has thus attracted synthetic and medicinal chemists over the decades. Some representative bioactive compounds with piperidine core are shown in Fig. 4.

This section highlights the one-pot multi-component reactions providing access to a library of functionalized piperidine derivatives from cheap and readily accessible starting precursors in a straightforward fashion.

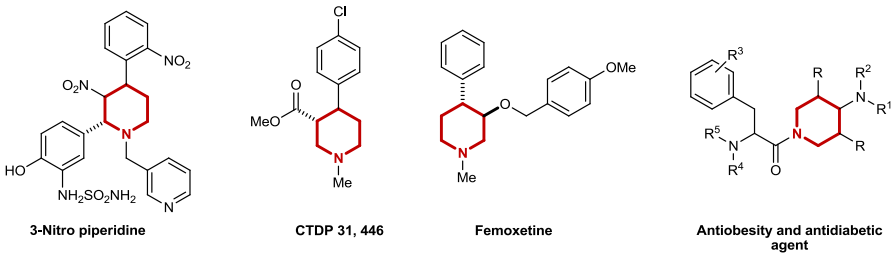


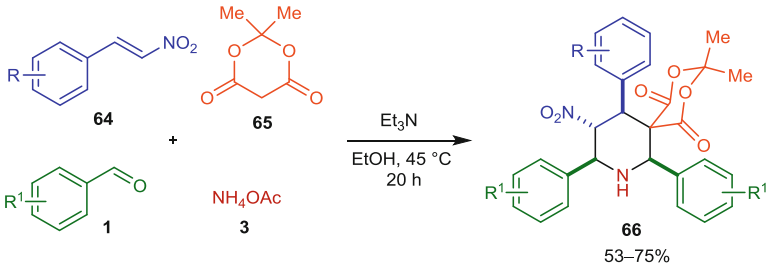
Fig. 4 Pharmaceutically active compounds containing piperidine framework

Ammonium salts as nitrogen source

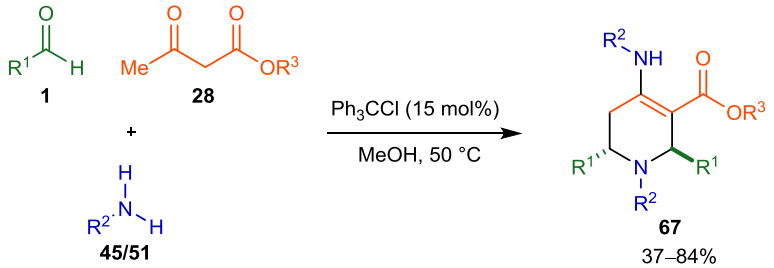
Li et al. [98] developed an efficient and direct procedure for the diversity-oriented synthesis of highly functionalized piperidines **66**. This process involves a Meldrum's acid moiety **65**, aromatic aldehydes **1**, ammonium acetate **3**, and substituted β-nitrostyrenes **64** for the easy accessibility of a diverse library of structurally exciting and pharmacologically useful products (Scheme 26). With an optimized set of reaction parameters, the scope of this MCR protocol was explored. A number of readily available aldehydes, and substituted nitrostyrenes were employed affording the desired structures in good yields. Aldehydes with *p*-chloro and bromo substituents proved to be good substrates. Aliphatic aldehydes were found to be incompatible in this reaction. Similarly, a range of substituents were also tolerated on the aromatic ring of nitrostyrenes showing diverse compatibility of different functional groups.

Amine as nitrogen source

Sajadikhah et al. [99] succeeded to develop an efficient and facile one-pot, five-component diastereoselective synthesis of diversely decorated piperidines **67** involving aromatic aldehydes **1**, amines **45/51** and β-ketoesters **28**. Trityl chloride was employed as an effective organic catalyst (Scheme 27). The structural diversity was ensured by using a range of benzaldehydes with electron-deficient and/or electron-releasing group delivering piperidines in good to high yields. The product obtained with low yield by the reaction of benzyl amine, 4-methyl benzaldehyde and methyl acetoacetate is suggested to be because of the higher basicity of aliphatic amine compared to anilines. The aliphatic aldehydes like propanal were not compatible in this protocol. This homogeneous catalytic procedure includes some important aspects like the easy work-up, diastereoselectivity, simple and readily available precursors, inexpensive catalyst, relatively short reaction time, and good to high yields.



Scheme 26 Synthesis of highly functionalized piperidines

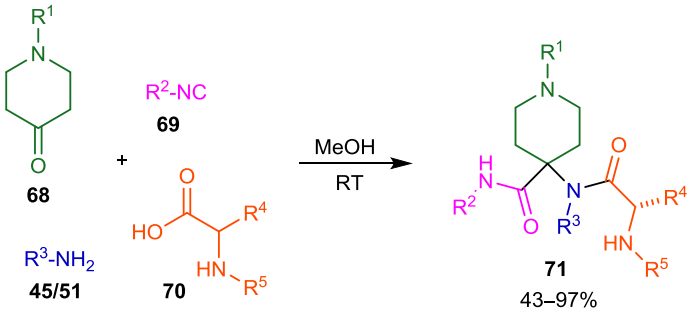


R^1 = Et, Ph, 3-Me-Ph, 3-Cl-Ph, 4-Me-Ph, 3-NO_2-Ph, 4-OMe-Ph, 4-F-Ph
R^2 = Ph, 4-Cl-Ph, 4-Br-Ph, 4-OMe-Ph, 4-Me-Ph, 4-F-Ph, 3,4-Cl_2-Ph, Bn
R^3 = Me, Et

Scheme 27 Synthesis of highly substituted piperidines

1,4-Disubstituted piperidines

A straightforward route to pharmacologically attractive 1,4-disubstituted piperidines **62** was developed by de Castro et al. [100] and is based on one-pot four-component reaction of *N*-substituted 4-piperidone **68**, anilines **45/51**, isocyanide **69** and amino acids **70** in MeOH at room temperature. This procedure produced a structurally diverse library of piperidine-based analogues with five points of diversity as potential anticancer agents (Scheme 28). A range of functional groups were tolerated on all the four-components of this reaction delivering the desired compounds in good yields.



R^1 = Bn, Boc, Alloc
R^2 = Bn, *t*-Bu, CH_2CO_2Me
R^3 = H, Me, Bn, 4-F-Bn, 3,4,5-tri-OMe-Bn, cyclopropyl
R^4 = H, Bn, CH(Me)Et, CH_2CO_2Me
R^5 = Boc, Cbz, Fmoc

Scheme 28 Synthesis of the 1,4-disubstituted piperidine library via Ugi four-component reaction

Synthesis of pyridazinones

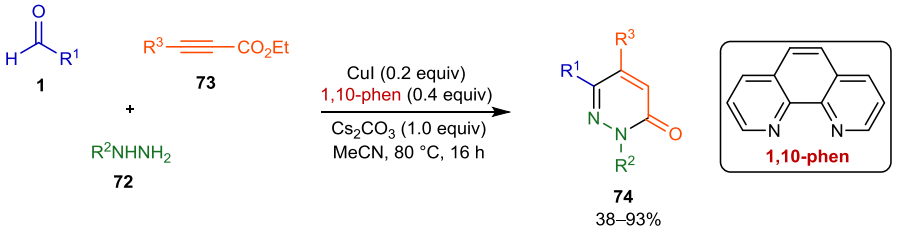
Six-membered nitrogenous heterocycles are key structural motif of particular interest in synthetic and pharmaceutical chemistry. These are prevalent in a diverse range of bioactive natural products [101]. In this part, we cover the synthesis of pyridazinone derivatives.

Hydrazine as nitrogen source

Mantovani et al. [102] developed an elegant one-pot, three-component intermolecular cyclization strategy for the synthesis of decorated pyridazinones **74** involving aldehydes **1**, hydrazines **72**, and alkynylesters **73** under inexpensive copper catalysis. This process results an array of nitrogenous compounds in good yields (Scheme 29). The optimization of the reaction conditions clearly demonstrated the critical role of the ligand and the nature of the base on the cyclization to proceed and the best results were obtained when Cs_2CO_3 was used as the base and 1,10-phenanthroline as the ligand.

Thus, under an optimized set of reaction conditions, this procedure was applied to a variety of different aldehydes, hydrazines, and alkynylesters; resulting in the synthesis of pyridazinones in good yields, irrespective of the substituents (electron-deficient or electron-rich groups) present on the aromatic part of the aldehydes. The structural reactivity of aryl alkynylester was also investigated. Both aryl alkynylesters substituted either with electron-withdrawing and electron-donating groups provided efficient access to pyridazinones in variable yields (40–85 %). Alkynylester bearing an alkyl chain directly linked to the triple bond was found to be unreactive. Next, two different hydrazines were also explored in this multicomponent reaction leading to the desired pyridazinones in acceptable yields. However, the unsubstituted or aliphatic hydrazines were failed to show any reactivity.

The mechanism for this cyclization was proposed involving the initial formation of hydrazone **75** from aldehyde and hydrazine. Base assisted deprotonation of NH from hydrazones **75** affords intermediate **76**, which on reaction with CuI to form



R^1 = Ph, 2-Cl-Ph, 4-Cl-Ph, 4-NO_2-Ph, 4-Me-Ph, 2,5-diOMePh, 3,4,5-tri-OMe-Ph
R^2 = Ph, 4-Cl-Ph, 2,5-diMe-Ph
R^3 = Ph, 4-Cl-Ph, 4-OMe-Ph, 4-Me-Ph, 2,5-diOMe-Ph

Scheme 29 Synthesis of pyridazinones

cuprate **77**. The Michael addition of **77** into the carbon–carbon triple bond of the alkynylester gives Michael adduct **78**, which on isomerization delivers **79**. The pyridazinone **74** is released by the intramolecular 1,2-addition of nitrogen to the ester carbonyl functionality (Fig. 5).

Synthesis of pyrimidinone (thione) derivatives

2-Oxo (thioxo)-1,2,3,4-tetrahydropyrimidines are structurally significant heterocyclic moieties prevalent in a diverse range of natural, synthetic, and medicinal chemistry [103]. This chemical functionality is also named as 3,4-dihydropyrimidine-2(1*H*)-one (thione), Biginelli compounds and DHPMs. The literature is highly enriched with significant amount of data showing their bioorganic expediency. Some key representative pharmaceutical applications include antiviral activity [104], adrenoceptor blocking potential [105], anti-inflammatory efficiency [106], antihypertensive effect [107], antitumor efficacy [108], anticarcinogenic [109], antimicrobial [110], and antibiotic activities [111]. In addition, these core structures are represented in some natural anti-HIV marine alkaloids like batzelladine A and B [112, 113]. In synthetic chemistry, 3,4-DHPM skeletons have also been investigated

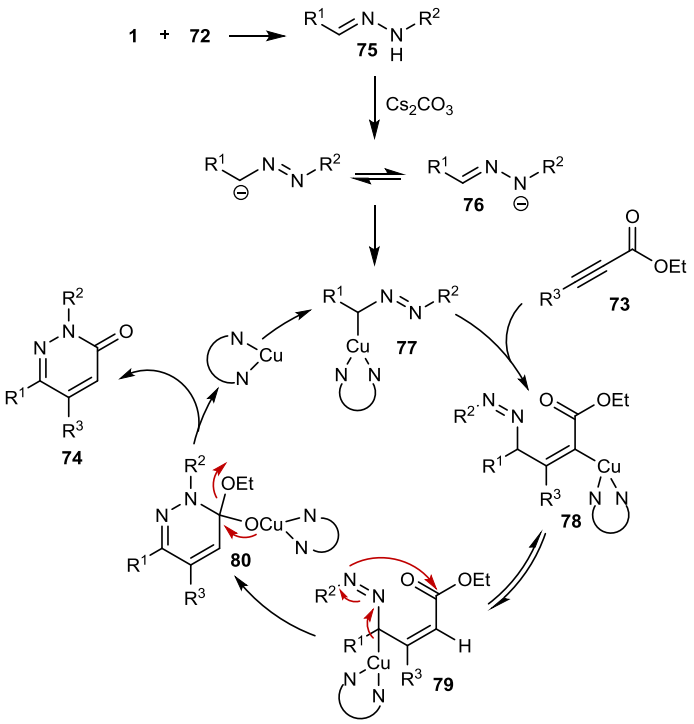


Fig. 5 Proposed mechanism for the preparation of **74** through the multi-component reaction

as key building units to access a diverse range of heterocyclic compounds [114–116].

On the other hand, dihydropyrimidinones (DHPMs) have also been widely discovered as potential scaffolds exhibiting adrenergic receptor antagonist, kinesin inhibition and antibacterial activities [117–120]. As an independent fragment, the urea and thiourea moieties present in 2-pyrimidinones and 2-pyrimidinethiones are also the essential building blocks of various natural products, synthetic drugs and lead compounds such as Nitractin [121], SQ32926 [122], (*S*)-Monastrol [123, 124], (*S*)-L-771688 [125], (*R*)-Fluorastrol [126], and (*S*)-Enastron [127, 128] (Fig. 6). Recent research has disclosed the potent inhibition potential of MAL3-101 as prepro-α-factor translocation and Hsp40-stimulated Hsp70 ATPase [129, 130] (Fig. 6).

With a proven broad synthetic utility and potential applicability profile, numerous attractive synthetic strategies have been disclosed to access this privileged class of compounds. Among them, development of procedures that allow the simple isolation and purification of products from complex reaction mixture remained challenging. In this regard, multi-component reactions (MCRs) have provided a practical platform for the simple and diversity-oriented synthesis of pharmaceutically interesting compounds in an atom- and step-economic and environmentally benign fashion. In this section, we highlight recent approaches made towards the synthesis of THPMs and DHPMs derivatives through one-pot multi-component condensation.

Urea/thiourea as nitrogen source

Guo et al. [131] developed a photo-assisted multi-component dehydrogenative protocol without using any metal to access several novel tetrahydropyrimidines

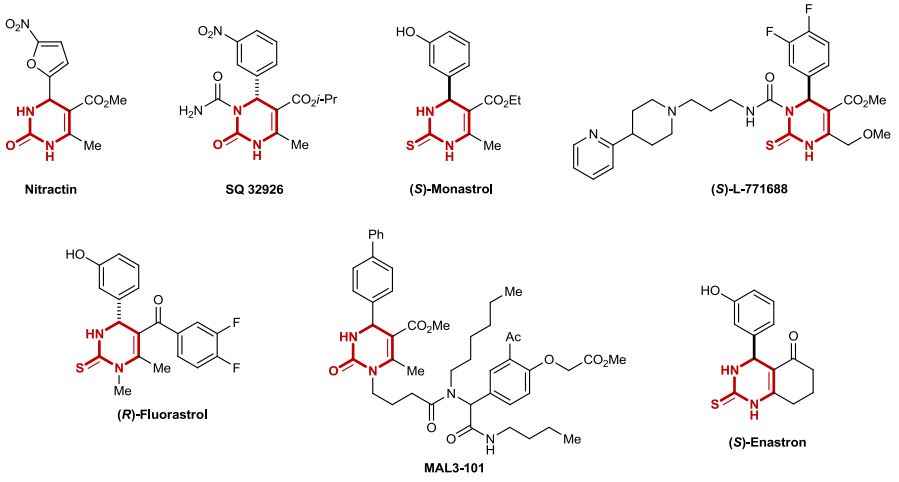
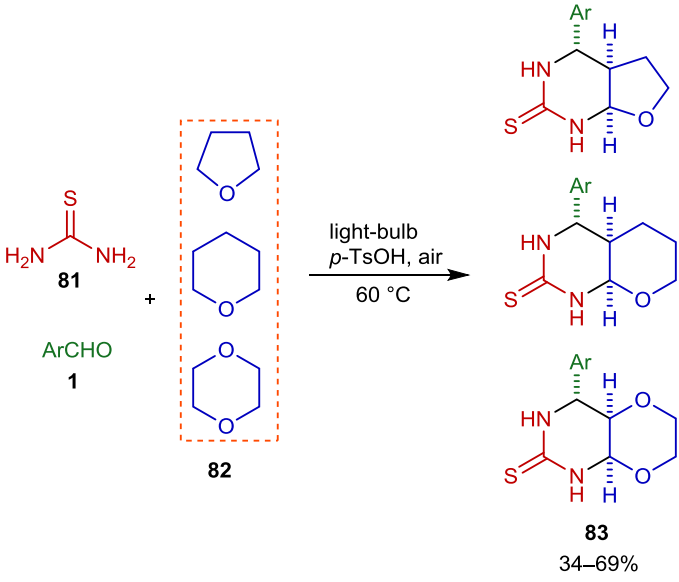


Fig. 6 Representative compounds containing the 2-pyrimidin(thi)one motif

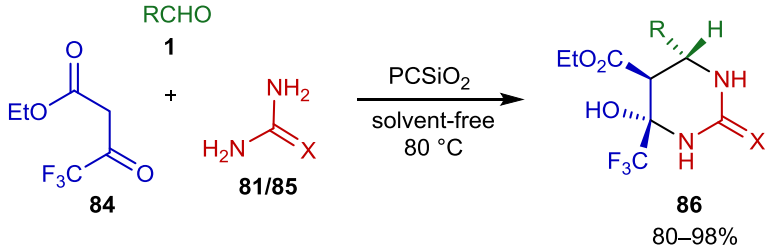
(THPMs) derivatives **83** under mild reaction conditions in moderate yields and stereoselectivities (Scheme 30). Under the optimized conditions, several aromatic aldehydes and thioureas were investigated to explore the scope of this MCR process. A range of electron-rich and electron-poor functional groups such as methyl, methoxy, hydroxy, *tert*-butyl, NMe_2, chloro, fluoro and bromo were applied and the target products were obtained in good yields and excellent stereoselectivities. Aldehydes with electron-releasing substituents demonstrated enhanced reactivity than the aldehydes bearing electron-withdrawing substituents. Moreover, heteroaromatic aldehydes like picolinaldehyde and 2-furaldehyde gave title compounds in moderate yields. Moreover, the approach demonstrated a simple and facile construction of numerous 2-pyrimidinethione derivatives using common cyclic ethers.

Sathicq et al. [132] developed a simple and expedient catalytic one-pot three-component procedure for the synthesis of fluorinated hexahydropyrimidine derivatives **86** from readily available starting materials under solvent-free conditions (Scheme 31). The scope and generality of this catalytic method was explored using a range of aldehydes. The reaction progressed smoothly with aldehydes bearing both electron-rich and electron-deficient substituents. The functional groups tolerated gave smooth and facile conversion with good yields of the desired hexahydropyrimidines. Similarly, replacing thiourea with urea also led to the corresponding hexahydropyrimidines in good yields. In general, this one-pot procedure demonstrated several advantages such as high environmental



Ar = *t*-Bu-Ph, 4-Me-Ph, 4-OMe-Ph, 4-Cl-Ph, 2-OMe-Ph, 2-Cl-Ph, furyl, pyridyl, thienyl

Scheme 30 Photo-assisted cyclic ether involved MCR

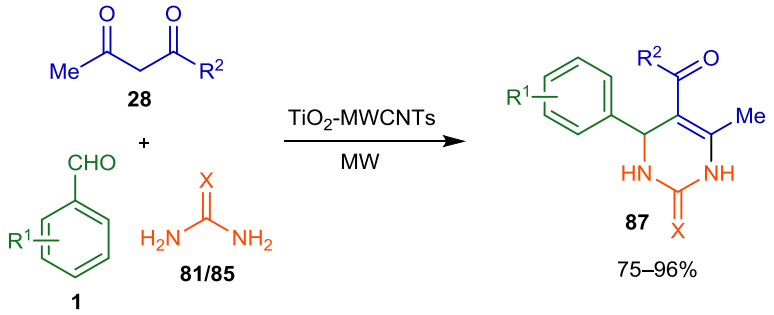


R = Ph, 4-MeO-Ph, 4-Cl-Ph, 4-Br-Ph, 4-NO_2-Ph, 2-thienyl, 2-pyrrolyl, 2-furanyl, 3-furanyl
X = S, O

Scheme 31 Synthesis of fluorinated hexahydropyrimidinones

compatibility, good yields of products, high selectivity, reduced reaction time, and the recyclability of the catalyst.

Safari and Gandomi-Ravandi [133] established a one-pot three-component Biginelli reaction involving aldehydes **1**, *β*-dicarbonyl compounds **28** and urea (thiourea) **81/85** under solvent-free conditions. Titanium dioxide supported on MWCNTs served as an efficient eco-friendly catalyst under microwave irradiation conditions (Scheme 32). After establishing the optimal conditions, the scope of this novel method was expanded. A diverse range of aromatic aldehydes incorporating electron-donating and electron-withdrawing substituents were tested. Both types of functional groups on the aromatic ring of the aldehydes showed successful and comparable reactivity leading to the corresponding heterocyclic products in good yields. This fact revealed the non-influential nature of electronics on the yield of the desired products.



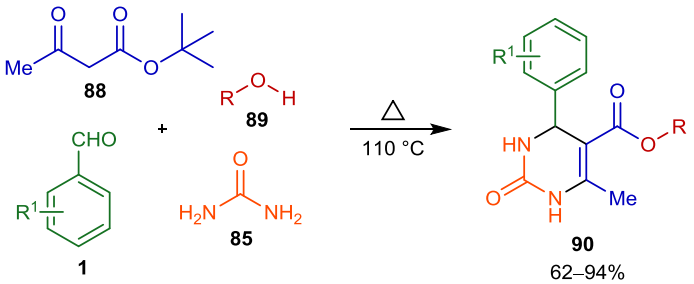
R^1 = H, 4-Cl, 4-Me, 4-Br, 4-OMe, 3-NO_2, 2,4-Cl_2, 4-F, 2-OMe, 3-Br
R^2 = OMe, OEt
X = O, S

Scheme 32 Microwave mediated synthesis of pyrimidinones/thiones using TiO_2-MWCNTs

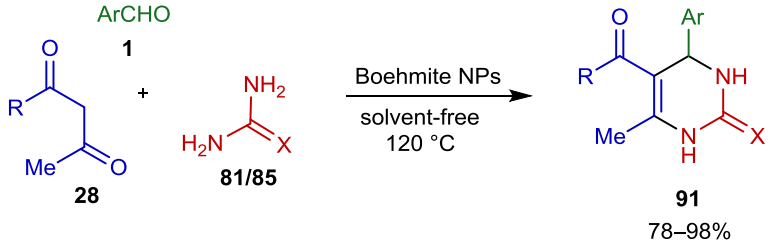
Next, the urea component was varied and the potentially bioactive 3,4-dihydropyrimidin-2(1*H*)-thiones derivatives were successfully obtained using thiourea. Moreover, various alkyl esters were also tested and gave successfully the expected 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones in good yields. In general, the environment friendly nature, sustainable and atom-economic features make this protocol an acceptable synthetic tool which leads to the production of heterocyclic skeletons with high chemical efficiency under solvent-free conditions. The reusability of the nanocomposites is an additional advantage.

Rao et al. [134] described an efficient, environment friendly and straightforward one-pot synthesis of dihydropyrimidin-2(1*H*)-one derivatives **90** through in situ generation of new *β*-ketoester **88** (transesterification) followed by Biginelli reaction. The readily available starting materials were employed under catalyst and solvent free conditions at 110 °C to afford the target compounds (Scheme 33). The applicability of this protocol under optimized reaction conditions was extended to diversified arylaldehydes and alcohols. Numerous functional groups with both electron-donating and electron-withdrawing substituents on aromatic aldehydes were tolerated in this protocol. A range of different alcohols were also utilized to expand the scope of dihydropyrimidin-2(1*H*)-one derivatives. In general, several outstanding features such as operational simplicity, mild conditions, easy purification procedure, and reduced reaction time make this protocol environmentally benign and commercially viable.

Keivanloo et al. [135] developed a simple, green, and effective one-pot three-component procedure for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones **91**. Boehmite nanoparticles were applied as an efficient catalyst (Scheme 34). The scope of this method was investigated with a range of aldehydes along with other coupling partners such as ethyl acetoacetate and urea leading to the construction of decorated DHPMs. Both electron-rich (Me, OMe,) and electron-poor (NO_2, F, Cl) functional groups on the aromatic aldehyde participated efficiently. The substituents on variable positions were evaluated and found to impart no significant effect on the chemical yield of the products. Generally, this one-pot methodology provided



Scheme 33 Synthesis of dihydropyrimidin-2(1*H*)-one derivatives



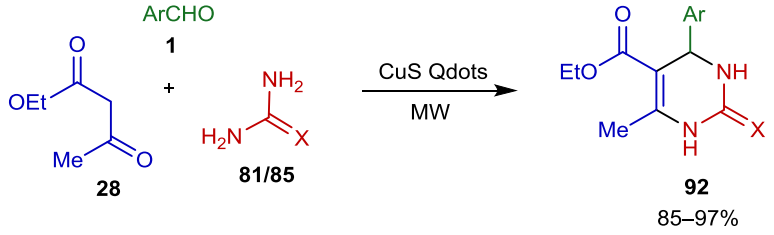
Ar = Ph, 4-MeO-Ph, 4-Cl-Ph, 4-F-Ph, 4-Me-Ph, 4-NO_2-Ph, 2-Cl-Ph
R = Me, OEt
X = S, O

Scheme 34 Synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones or thiones

DHPMs in good yields within short reaction time and operational simplicity. The nanoparticle catalyst was also recycled several times.

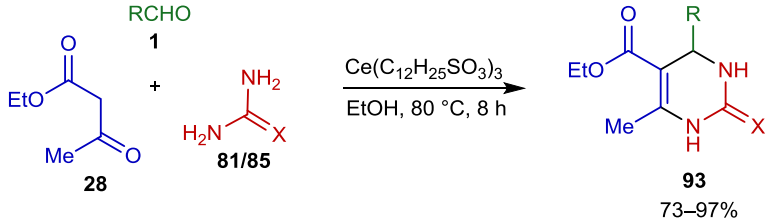
A variation of this method was developed by Chaudhary et al. [136] who used a catalyst system based on CuS QDs for the synthesis of dihydropyrimidine(thi)ones **92** under solvent-free conditions (Scheme 35). Several substitutions were tolerated on aldehydes and it has proved that this system is much more effective compared to other catalysts that deliver the Biginelli products. In addition, this protocol possesses several sustainable features such as short reaction time, higher chemical yields, easy purification steps, economic accessibility of the catalyst. An easy recovery and recyclability without any loss of catalytic activity are also additional compelling features of this catalyst to be used for Biginelli reaction.

Qiu et al. [137] successfully developed an air stable cerium(III) trislaurylsulfonate ($Ce(LS)_3$), a Lewis acid and surfactant combined catalyst, for one-pot synthesis of dihydropyrimidinones or thiones **93** (Scheme 36). Under optimized reaction conditions, the scope of this MCR method was investigated by changing the aldehydes, in addition to 1,3-dicarbonyl compounds and urea or thiourea. A range of structurally diverse DHPMs were obtained in good yields (73–97 %). This catalytic system shows general compatibility towards all three components.



Ar = Ph, 4-MeO-Ph, 4-Cl-Ph, 2-OMe-Ph, 4-NO_2-Ph, 2-NO_2-Ph
X = S, O

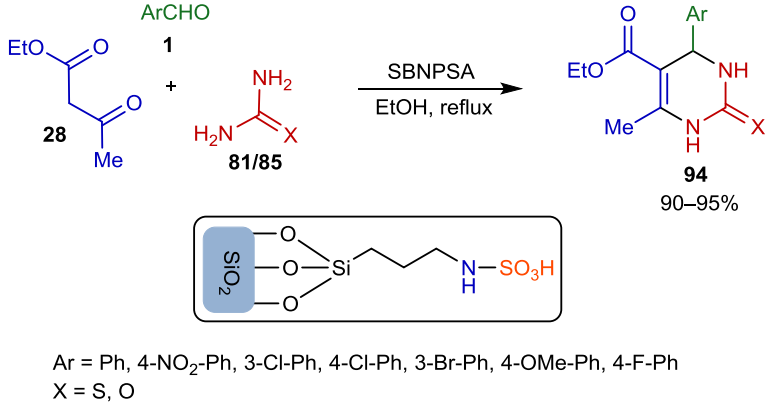
Scheme 35 Biginelli reaction with CuS QDs as a catalyst



Scheme 36 Ce[LS]$_3$-catalyzed synthesis of DHPMs

Aromatic aldehydes featuring electron-rich groups and electron-poor groups in the *ortho*-, *meta*- and *para*-positions are well tolerated in reaction. The position of the substituents was non-influential on the reaction reactivity and product yield. More importantly, sterically encumbered aldehydes also gave the corresponding product in 76 % yield. In addition, methyl acetoacetate, ethyl acetoacetate, and ethyl benzoylacetate, were also compatible under the standard reaction conditions.

Jetti et al. [138] developed a silica-bonded *N*-propyl sulfamic acid (SBNPSA) catalyzed one-pot three-component Biginelli reaction. A range of substituted arylaldehydes with coupled with ethyl acetoacetate and urea/thiourea to deliver the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones and thiones **94** in environment friendly conditions (Scheme 37). The current protocol tolerates a range of variations in all three components. Most importantly, this protocol could easily install several bioactivity relevant substitution patterns on the aromatic ring. Aromatic aldehydes incorporating electron-rich and electron-poor substituents gave promising yields of the products. In addition, thiourea has also been used with comparable reactivity to deliver the corresponding dihydropyrimidin-2(1*H*)-thiones. In general, the facile



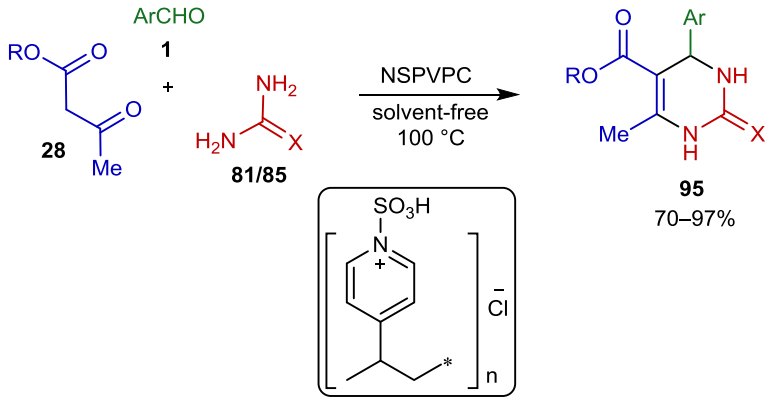
Scheme 37 SBNPSA-catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and -thiones

reaction conditions, easy access to products through this method could be a good choice for the synthesis of dihydropyrimidine(thi)ones.

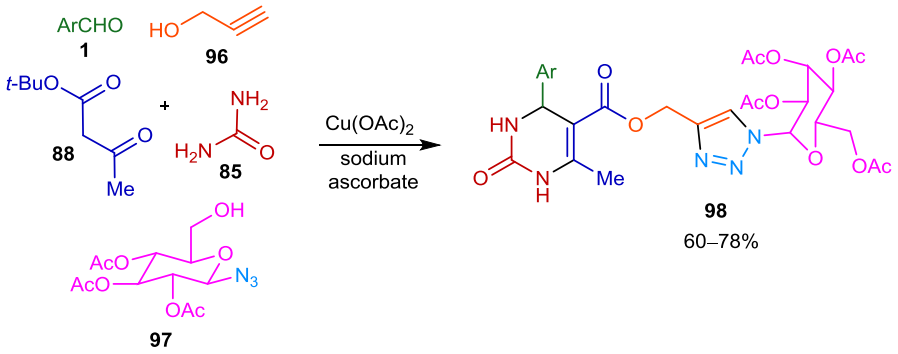
Shirini et al. [139] described a mild, simple and efficient one-pot three component method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones **95**. *N*-sulfonic acid poly(4-vinylpyridinium) chloride (NSPVPC) was used as an efficient catalyst under solvent-free conditions (Scheme 38).

A Cu-catalyzed protocol for the simple and efficient synthesis of a library of glycoside annulated dihydropyrimidinones **98** with 1,2,3-triazole linkage was developed by Rao et al. [140]. This method involves transesterification, Biginelli, and click reactions in one-pot using water as a green solvent (Scheme 39). Under optimal reaction conditions, a wide range of aromatic aldehydes with electron-donating and electron-withdrawing substituents were tolerated to explore the scope of the functionalized DHPM analogues. All substituents were found to be equally reactive with smooth conversion to the products in efficient yields. In addition, a range of sugar moieties such as glucose and galactose were also tested to afford the title products in good yield.

Kolvari et al. [141] were able to synthesize a new, powerful and reusable nanomagnetic-supported sulfonic acid catalyst for the rapid generation of 3,4-dihydropyrimidin-2-(1*H*)-ones **99**. The synthesis was carried out under both conventional heating and microwave irradiation methods (Scheme 40). Using the optimized reaction conditions, the versatility of this method was explored with a series of different aldehydes to prepare a library of DHPMs. In most cases, the reactions proceeded smoothly. When the results of both conventional heating and MW irradiation methods were compared, the desired compounds showed better outcome in terms of yield and reactivity. Also, with both methods, the nature and position of the substituents on the aryl ring has not much influential effect on the formation of the DHPMs.

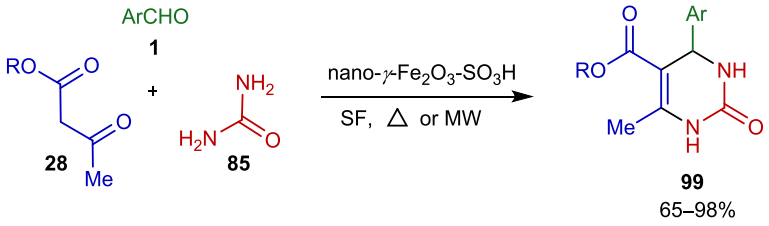


Scheme 38 NSPVPC-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones



Ar = Ph, 4-OEt-Ph, 4-Et-Ph, 4-Cl-Ph, 4-NO_2-Ph, 4-F-Ph, 4-CF_3-Ph, 3-Cl-Ph

Scheme 39 Synthesis of glycoside annulated dihydropyrimidinone derivatives with 1,2,3-triazol linkage

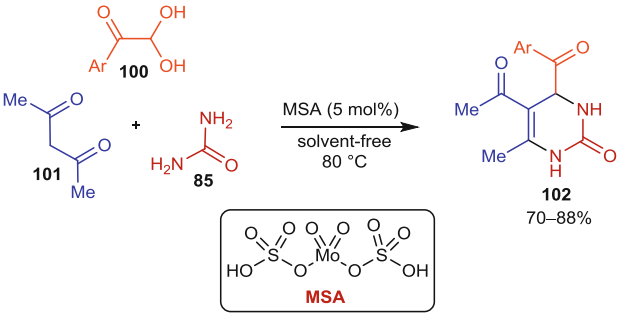


Ar = Ph, 4-OH-Ph, 4-NO_2-Ph, 4-Cl-Ph, 4-Me-Ph, 3,4-diMe-Ph, 2-OH-Ph
R = Me, Et

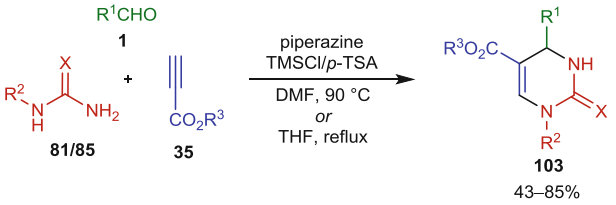
Scheme 40 Nano-γ-Fe_2O_3–SO_3H-catalyzed Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

Karami et al. [142] reported a new one-pot reaction of aryl glyoxals **100** with acetylacetone **101** and urea **85** using molybdate sulfuric acid providing access to a series of 5-acetyl-4-(aryloyl)-3,4-dihydropyrimidinones **102** (Scheme 41). Glyoxals with a range of substitutions including electron-withdrawing substituents and bulky naphthyl group were found to be the efficient partners providing desired products in good yields.

Wan et al. [143] disclosed a one-pot three-component reaction for the synthesis of 3,4-dihydropyrimidinones and thiones **103**. The reaction involves aldehydes **1**, electron-deficient alkynes **35**, and ureas/thioureas **81/85** (Scheme 42). The scope of this one-pot protocol is broad and involves a diverse set of aldehydes (aryl & alkyl), ureas/thioureas (*N*-substituted & unsubstituted) and alkynes to deliver the corresponding DHPMs with specific regioselectivity. The electronic of the functional groups present on the aromatic part of the aldehydes impart a significant impact on the reactivity and yield of the products and in case of electron-poor substituents, the reaction is more facilitated leading to the higher yield of the DHPMs compared to the aldehydes bearing electron-rich functional groups. In addition, benzaldehydes bearing *ortho*- and *meta*-substituents were also productive and gave the



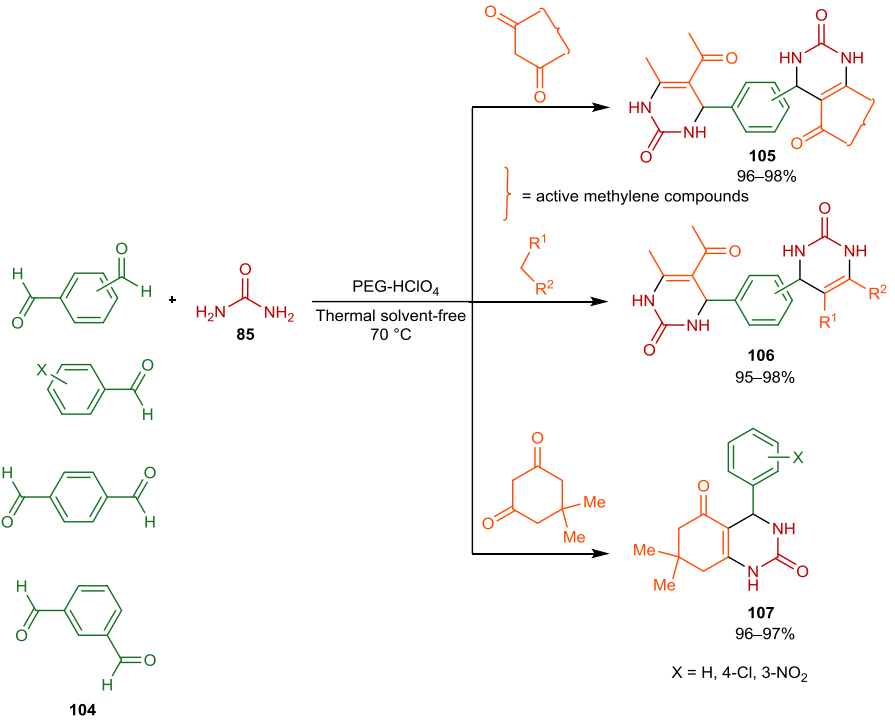
Scheme 41 MSA-catalyzed synthesis of 5-acetyl-4-(aryloyl)-3,4-dihydropyrimidinones



Scheme 42 Multi-component synthesis of different DHPMs

corresponding DHPMs on reaction with thioureas and propiolates. However, in case of urea, the reaction was slow and moderate yields of the final compounds were obtained. compared with thiourea, urea has been found to undergo a similar transformation more toughly, and DHPMs from urea reactions have been obtained with only moderate yields under the conditions of refluxing THF. Apart from aromatic aldehydes, aliphatic aldehydes were also found as efficient reaction partners and the desired 4-alkyl DHPMs were afforded in good yields.

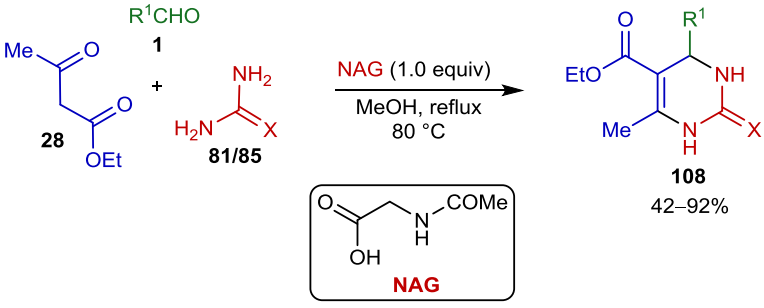
Siddiqui and Khan [144] developed a simple, efficient, solvent-free and environment friendly one-pot synthesis of new bis-3,4-dihydropyrimidin-2(1*H*)-one derivatives **105–107** under solvent-free conditions. The title compounds were obtained in good yields at ambient temperature using perchloric acid-modified PEG-6000 (PEG-$HClO_4$) as a biodegradable and reusable catalyst (Scheme 43). Under optimized reaction conditions, a diverse variety of aldehydes like terephthaldehyde/isophthalaldehyde, aromatic aldehydes, cyclic and acyclic active methylene compounds were utilized to explore the reaction scope. All the reactions proceeded smoothly with short reaction time (3–10 min) to deliver the desired products in



Scheme 43 PEG-$HClO_4$-catalyzed synthesis of bis-dihydropyrimidin-2(1*H*)-one and dihydropyrimidin-2(1*H*)-one derivatives

remarkable yield (95–98 %). On the other hand, the catalyst was recovered and reused further without significant loss of catalytic activity.

Yar et al. [145] developed a convenient and efficient new method for the preparation of dihydropyrimidines **108** catalyzed by inexpensive and non-toxic *N*-acetyl glycine (NAG) using arylaldehydes, ethyl acetoacetate and urea/thiourea (Scheme 44). The synthesized compounds were assayed against α-glucosidase and the results revealed that the majority of tested compounds displayed modest inhibitory activity at low micro-molar concentrations. To demonstrate the scope and generality of this method, a number of pyrimidines bearing different substituents were synthesized in moderate to excellent yields (40–92 %) from urea or thiourea, selected aldehydes and ethyl acetoacetate. It was also found that urea could easily lead to cyclized product relatively in shorter period of time as compared to thiourea which was less effective, producing dihydropyrimidine derivatives in moderate yields. In addition, aldehydes with both electron-donating and electron-withdrawing functional groups were well tolerated.

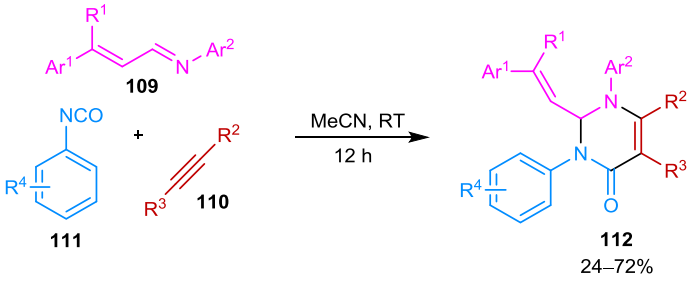


R^1 = Ph, 4-Cl-Ph, 4-OMe-Ph, 4-Me-Ph, 3-OMe,4-OH-Ph
X = O, S

Scheme 44 NAG-catalyzed synthesis of dihydropyrimidine derivatives

Imines and isocyanates as nitrogen source

Lei et al. [146] developed a simple and facile approach to highly functionalized pyrimidone derivatives **112** involving [4 + 2] cycloaddition of α,β-unsaturated imines **109**, dimethyl acetylenedicarboxylate (DMAD) **110** with isocyanates **111** in moderate to good yields (Scheme 45). Under optimized reaction conditions, the scope and limitations of this methodology have been examined using various α,β-unsaturated imines and substituted isocyanates and the results revealed that the imines bearing electron-donating groups tend to result in higher yield than those bearing electron-withdrawing group. However, the electronic effect on cinnamaldehyde part of α,β-unsaturated imines are not significant and resulted 54–67 % yields. Moreover, sterically encumbered imines provided desired compounds in low yields. On the other hand, isocyanates with various functional groups were well tolerated and those bearing electron-deficient groups demonstrated better reactivity than those with electron-releasing groups.



Ar^1 = Ph, 4-OMe-Ph, 4-NO_2-Ph
Ar^2 = Ph, 4-OMe-Ph, 4-NO_2-Ph
R^1 = H, Me
R^2 = H, CO_2Me, CO_2Et
R^3 = CO_2Me, CO_2Et
R^4 = H, 4-Br, 4-F, 4-OMe, 4-Me, 3-Cl, 2-Br, 2-NO_2

Scheme 45 Synthesis of pyrimidone derivatives

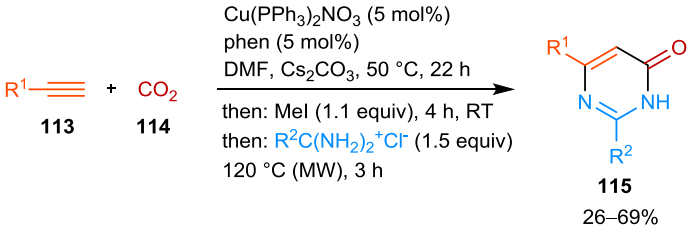
Amidinium chloride as nitrogen source

Schreiner et al. [147] developed a new and efficient one-pot protocol for the preparation of 2,6-disubstituted pyrimid-4(3*H*)-ones **115**. The process is initiated by a copper(I)-catalyzed carboxylation of terminal alkynes **113** followed by a methylation–Michael addition–cyclocondensation sequence (Scheme 46). Several functional groups as well as heterocyclic moieties were tolerated in this protocol. This one-pot procedure is operated under mild reaction conditions and the microwave heating.

Synthesis of quinolines

As an imperative class of nitrogen-containing heterocycles, quinoline is one of the ubiquitous and privileged structural motifs that occur in bioactive natural products and pharmaceutically active therapeutic agents [148]. Quinoline skeleton is also one of the central building unit for a diverse range of natural and synthetic heterocycles which are associated with a variety of biological properties such as antimicrobial [149–151], anticancer [152], antimalarial [153], and antiviral activities [154]. In addition, quinoline scaffold is also prevalent in some natural, semisynthetic and synthetic bioactive compounds which possess MDR reversal activity when combined with anticancer drug [155]. Numerous quinoline derivatives also display anti-HIV, antiasthmatic, antitumor, P-selectin antagonism, and antioxidant potential [156]. Also, these scaffolds are crucial ligands for the preparation of OLED materials [157], and asymmetric catalysts [158]. Some representative quinoline drugs with anticancer potential are shown in Fig. 7.

There have been several efforts on the development of a variety of methods for the synthesis of quinoline skeleton. Some recent review papers [159–161] have also documented a high volume of literature based on the development of synthetic strategies and biological potential of this nucleus. In the current section, we highlight some important examples achieved through multi-component cascade approach.



Scheme 46 One-pot synthesis of pyrimidones initiated by Cu(I)-catalyzed carboxylation of alkynes

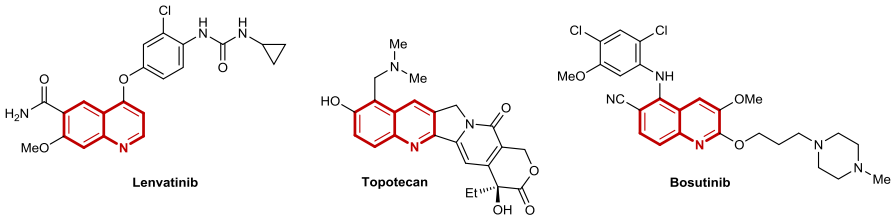
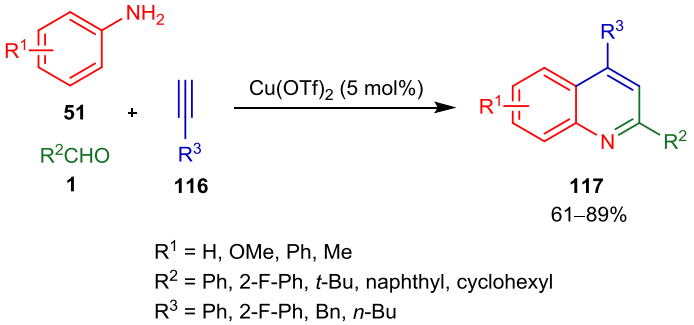


Fig. 7 Quinoline containing anticancer drugs

Anilines as nitrogen source

Meyet and Larsen [162] developed a one-pot three-component methodology for the preparation of alkyl-substituted quinolines **117** from commercially accessible anilines **51**, aldehydes **1**, and alkynes **116**. A variety of substituents were tolerated under copper catalysis (Scheme 47). This method for the multi-component synthesis of quinolines maximizes diversity by the direct use of commercially available starting materials. Simply mixing and heating inexpensive anilines, aldehydes, and alkynes with 5 mol% $Cu(OTf)_2$ provides the first efficient A^3 route to a range of substituted quinolines that includes 2-alkyl quinolines. These robust solvent-free processes complement the many methods for making aryl-substituted quinolines, operate under an ambient atmosphere, and tolerate water. By choosing the appropriate starting aldehyde, aniline, and alkyne, this mode of construction allows maximum variation in the substituents on the quinoline while eliminating the waste generated in multistep syntheses. In addition to the incorporation of alkyl or aryl aldehydes, both electron-rich and electron-poor anilines react efficiently in these three-component couplings.

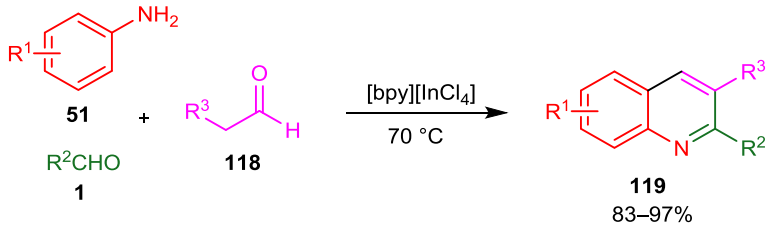
Anvar et al. [163] achieved a novel one-pot protocol for the preparation of a diverse range of 2,3-disubstituted quinolines **119** via a one-pot three-component reaction. Arylamines **51**, arylaldehydes **1** and aliphatic aldehydes **118** were employed as efficient reaction partners using butylpyridinium tetrachloroindate-(III), [bpy][$InCl_4$], ionic liquid as a green catalyst and solvent as well (Scheme 48).



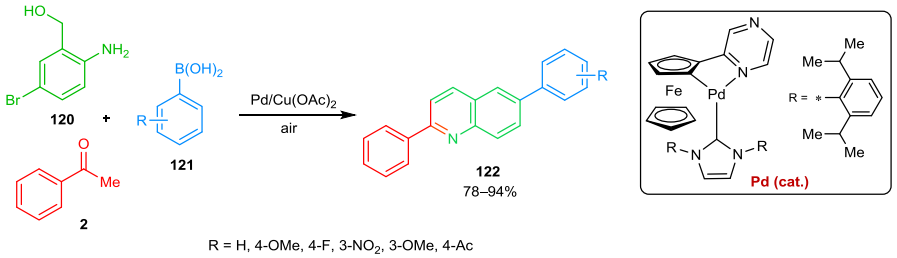
Scheme 47 Three-component synthesis of quinolines

Under an optimized set of reaction conditions, the substrate scope ionic liquid-catalyzed system was then studied which clearly demonstrated a wide utility of this process. A range of arylaldehydes incorporating electron-deficient and electron-rich functional groups at the *para*- or *meta*-positions were selected to couple with anilines bearing *para*- or *meta*-electron-poor substituents and aliphatic aldehydes to afford the corresponding 2,3-disubstituted quinolones in pleasing yields. Notably, the *ortho*-substituted arylaldehydes (2-Br and 2-OMe), and the *ortho*-substituted anilines (2-Cl and 2-Br) were efficiently converted into the desired 2,3-disubstituted quinolines. This process also tolerates the heterocyclic aldehydes (thiophene-2-carbaldehyde and furfural) delivering the title products in good yields. In general, the obtained results clearly demonstrated the wide applicability of [bpy][$InCl_4$] as an efficient catalyst for the preparation of a library of 2,3-disubstituted quinolines. Anilines bearing *p*ara-methoxy and *para*-methyl groups were not effective substrates and retarded the reaction completely. In general, noteworthy advantages like mild reaction conditions with high conversions, catalyst recyclability, and simple product purification procedure make this method environmentally benign and practical.

Xu et al. [164] developed a facile three-component condensation reaction for the preparation of 2,6-diarylquinolines **122** from aminobenzyl alcohols **120**, aryl ketones **2**, and arylboronic acids **121**. This process is catalyzed by NHC-modulated Pd/Cu cocatalytic system under air (Scheme 49). The scope of this process includes the tolerance of a variety of arylboronic acids. The sterically demanding 1-naphthylboronic acid also produced title compound in comparable yield. The electronic nature of the functional groups on the arylboronic acids have an influential effect on the yield of the reaction and electron-rich substrates demonstrated better reactivity and the corresponding products were obtained in slightly higher yields than of electron-withdrawing substrates. Finally, this coupling procedure was also equally effective for the preparation of larger conjugated 6-aryl-2-((1,1′-biaryl)-4-yl)-quinolines via oxidation/double Suzuki coupling of arylboronic acids, 4-bromoacetophenone, and (2-amino-5-bromophenyl)-methanol.



Scheme 48 One-pot three-component synthesis of 2,3-disubstituted quinolines



R = H, 4-OMe, 4-F, 3-NO_2, 3-OMe, 4-Ac

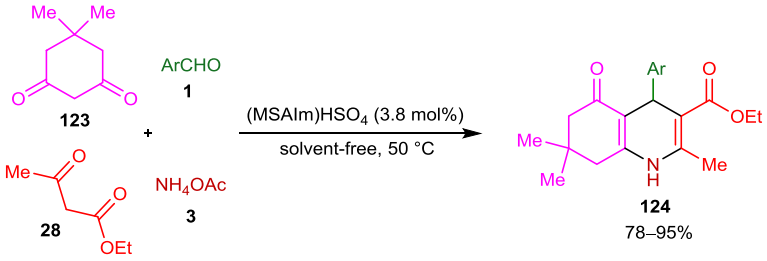
Scheme 49 Synthesis of 2,6-diarylquinolines

Ammonium salts as nitrogen source

Khaligh [165] reported an efficient protocol for the preparation of ethyl-4-aryl/heteryl-hexahydro-trimethyl-5-oxoquinoline-3-carboxylates **124**. This one-pot condensation involves dimedone **123** with aryl/heteryl aldehydes **1**, ethyl acetoacetate **28**, and ammonium acetate **3** under solvent-free conditions (Scheme 50). 3-Methyl-1-sulfonic acid imidazolium hydrogen sulfate served as an efficient Brönsted acidic ionic liquid catalyst with recyclable properties. The scope of this reaction was established by using a diverse range of aryl/heteryl aldehydes bearing electron-rich or electron-poor substituents affording the corresponding polyhydroquinolines in good yields over short reaction time. The variable positions and electronic properties of the functional groups on the arylaldehyde impart a substantial impact on the productivity of the polyhydroquinolines and the reaction time. The sterically hindered aldehydes afforded products with lower yields. However, the aliphatic aldehydes were found as incompatible substrates for this methodology.

Nasr-Esfahani et al. [65] disclosed a green methodology for an efficient and rapid construction of biologically active substituted polyhydroquinoline derivatives **126** using magnetic Fe_3O_4 nanoparticles (Fe_3O_4 MNPs) as a recyclable catalyst under solvent-free conditions (Scheme 51). The generality of this method was based on the use of different aldehydes which polyhydroquinolines in high yields.

Janardhan et al. [166] developed a facile and highly efficient protocol for the synthesis of polyhydroquinolines **127** via Hantzsch multicomponent condensation



Ar = Ph, 4-OMe-Ph, 4-F-Ph, 4-NO_2-Ph, furyl, pyridyl, thienyl

Scheme 50 Synthesis of unsymmetrical polyhydroquinoline derivatives

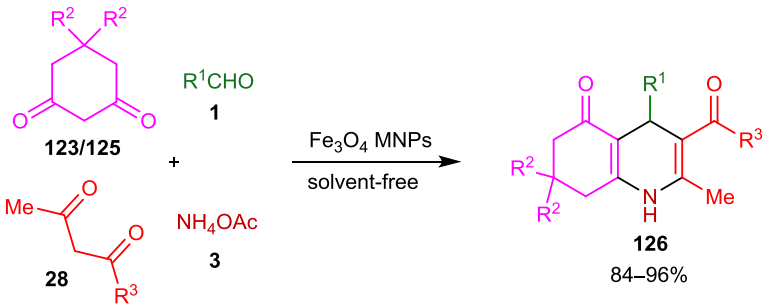
of dimedone **123**, aryl/heteryl aldehydes **1**, ethylacetoacetate **28**, and ammonium acetate **3** utilizing poly(4-vinylpyridinium)hydrogen sulfate as a catalyst in aqueous medium (Scheme 52). A range of aldehydes were used to evaluate the scope of methodology by producing the quinoline compounds in ample yields.

Patil et al. [167] reported an environmentally benign one-pot four-component tandem synthesis of hexahydroquinoline **128** via enaminone intermediate using dimedone **123**, ammonium acetate **3**, aryl aldehydes **1**, and malononitrile **6** in aqueous media without the use of any external catalyst (Scheme 53). The efficiency of this procedure using three representative aryl aldehydes incorporating electron-rich and weak electron-poor and unsubstituted groups was explored. The final compounds were obtained in good yields. The experimental simplicity, excellent yields in small and large scale, reduced reaction time, simple work-up and purification steps, no need of external catalyst, and high atom economy are the captivating features of this protocol.

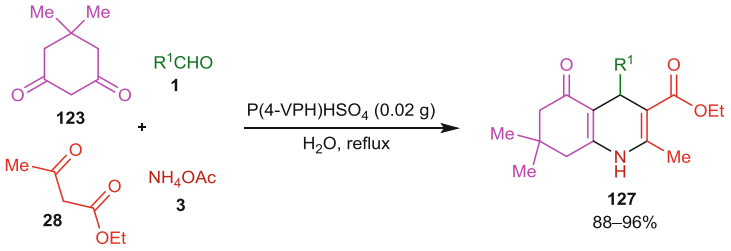
Catalytic asymmetric synthesis of nitrogen heterocycles

Multi-component reactions (MCRs) received significant attention both in terms of diversity and complexity in organic synthesis providing access to diverse sets of relatively complex structures from simple starting materials in a single reaction step. The ever increasing need for enantioriched compounds for pharmaceutical and agricultural applications as well as for catalysis promotes the development of asymmetric multicomponent reactions. Recently, total syntheses of numerous enantiopure natural products and commercial drugs have also been carried out using asymmetric multicomponent reaction methodologies [168].

In this section, we highlight some recent examples of optically pure nitrogen heterocycles accessed through asymmetric MCR approach.

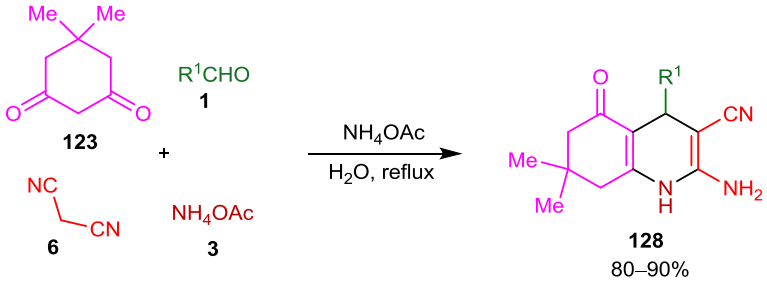


Scheme 51 Fe_3O_4 NPs catalyzed synthesis of polyhydroquinoline derivatives



R^1 = Ph, 4-OMe-Ph, 4-Me-Ph, 4-OH-Ph, 4-Cl-Ph, 2-NO_2-Ph, 4-NO_2-Ph

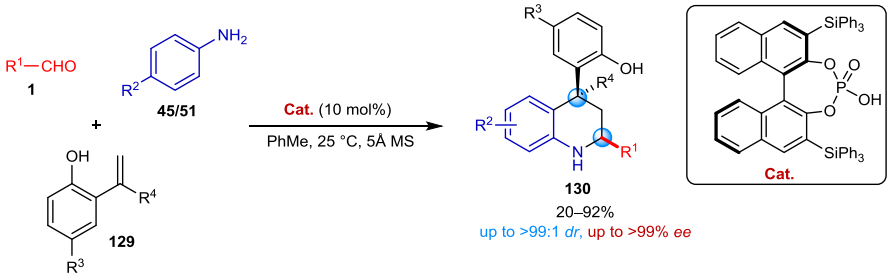
Scheme 52 P(4-VPH)HSO_4 catalyzed synthesis of polyhydroquinolines



R^1 = Ph, 4-OMe-Ph, 4-Me-Ph, 4-OH-Ph, 4-Cl-Ph, 3-NO_2-Ph, 4-NO_2-Ph

Scheme 53 Synthesis of hexahydroquinoline derivatives from tandem reaction

Shi et al. [169] developed an organocatalytic asymmetric three-component Povarov reaction involving 2-hydroxystyrenes **129**, anilines **45/51** and aldehydes **1**. This route provided access to structurally diverse *cis*-disubstituted tetrahydroquinolines **130** in high stereoselectivities (up to >99:1 *dr* and 97 % *ee*; Scheme 54). This

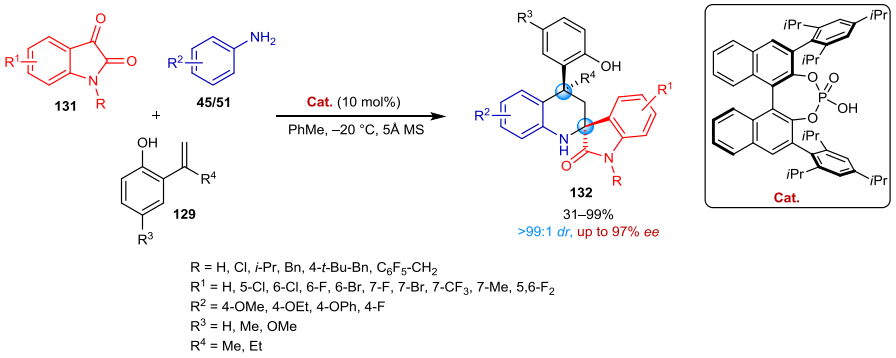


R^1 = Ph, 4-NO_2-Ph, 3-NO_2-Ph, 2-NO_2-Ph, 4-NC-Ph, 4-Cl-Ph, 4-Br-Ph, 4-CF_3-Ph, 3,4-Cl_2-Ph, 3-Me-Ph, 3-OMe-Ph, 2-thienyl
R^2 = OMe, OEt, OPh, Me, F
R^3 = H, Me, OMe
R^4 = H, Me, Et

Scheme 54 Organocatalytic asymmetric Povarov reaction with styrenes

protocol also provided an easy approach to tetrahydroquinolines with chiral quaternary stereocenters using α-alkyl 2-hydroxystyrenes as substrates. Under optimized conditions, this protocol is amenable to a diverse range of aldehydes bearing either of an electronically poor, neutral, or rich substituent, heteroaromatic and aliphatic aldehydes in high enantioselectivities (up to 95 % *ee*) and diastereoselectivities (up to >99:1 *dr*). Next, the substrate scope with respect to anilines was also explored using a variety of anilines bearing both electron-donating or electron-withdrawing groups and the corresponding products were obtained in high yields (70–77 %) and good enantioselectivities (82–95 % *ee*). In addition, the scope was extended to the exploration of styrenes in the reaction. Both 2-hydroxystyrenes and α-alkyl 2-hydroxystyrenes incorporating different substituents on their aromatic rings were examined and led to the generation of desired products in good to excellent stereoselectivities.

In another study, Shi et al. [170] established an unprecedented route to enantioenriched spiro[indolin-3,20-quinoline] derivatives **132** using isatin **131** and electron-rich olefins as starting materials **129**. This method allowed to access compounds **132** with two quaternary stereogenic centers in high yields and excellent stereoselectivities using chiral phosphoric acid as a catalyst (Scheme 55). The scope of the reaction was investigated with a range of isatins. Initially, various *N*-substituted (*N*-benzyl, alkyl, or phenyl) isatins were tested which gave excellent diastereoselectivities (all >99:1 *drs*) and with a high level of enantiomeric excesses (up to 97 % *ee*). Next, the effect of various substituents at different positions of the phenyl moiety of isatins on the reaction was explored. The results obtained demonstrated that a diverse range of electronically different substituents at the C5, C6 and C7 position of isatins tolerated efficiently. The position of the substituent showed some effect on the enantioselectivity and reactivity. Moreover, the substrate scope involving anilines was investigated and the results demonstrated that anilines bearing electron-donating and electron-withdrawing groups served as appropriate substrates, delivering the corresponding products in good yields and excellent stereoselectivities. In addition, the diversity of α-alkyl *o*-hydroxystyrenes was also examined. Several different substituents on the benzene rings or with different α-

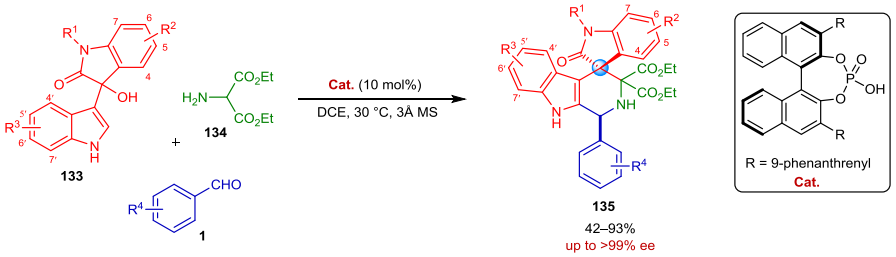


Scheme 55 Enantioselective isatin-involved Povarov reaction

alkyl groups were tolerated in the reaction. The substrates produced an efficient route to the generation of desired products in high yields (86–99 %) and good stereoselectivities (89–91 % *ee*).

Shi et al. [171] reported a catalytic asymmetric formal [3 + 3] cycloaddition of 3-indolylmethanol **133** and an in situ-generated azomethine ylide. This process afforded chiral six-membered piperidine compounds **135** with two stereogenic centers (Scheme 56). Under optimized conditions, the scope and diversity of chiral spiro[indoline-3,4′-pyridoindoles] was expanded using various *N*-substituted isatin-derived 3-indolylmethanols. This protocol tolerates a series of *N*-benzyl isatin-derived 3-indolylmethanols bearing electron-donating and electron-withdrawing substituents delivering the desired spiro-products in good yields and high enantioselectivities (97 to >99 % *ee*). Electron-rich substituents were found to give better results than those of electron-poor substituents in terms of reactivity and enantioselectivity. The reaction scope was also explored in terms of substituents at the phenyl rings of both isatin and indole skeletons, and the corresponding title products were accessed in moderate to good yields (42–90 %) and with good to excellent enantioselectivities (79 to >99 % *ee*). In addition, the substrate scope with respect to aromatic aldehydes was also investigated under the optimized reaction conditions. Various aromatic aldehydes bearing electron-poor, -neutral, or -rich groups tested and the desired chiral spiro[indoline-3,4′-pyridoindoles] was afforded in high yields (73–89 %). However, the electronic nature of aldehydes influenced the stereoselectivity of the reaction where electron-withdrawing groups delivered higher enantioselectivities (80 to >99 % *ee*) than those of electron-donating or neutral groups.

Dai et al. [172] developed the first catalytic asymmetric example of bispirooxindole synthesis containing tetrahydro-*β*-carboline moiety using chiral phosphoric acid as a catalyst. This three-component transformation involves Michael/Pictet–Spengler reactions of isatin-derived 3-indolylmethanols **133**, isatins **131**, and amino-ester **134**, affording structurally complex and diverse bispirooxindoles **136** with one quaternary and one tetra-substituted stereogenic centers in excellent stereoselectivities (all >95:5 *dr* and up to 98:2 *e.r*) (Scheme 57). Under optimal

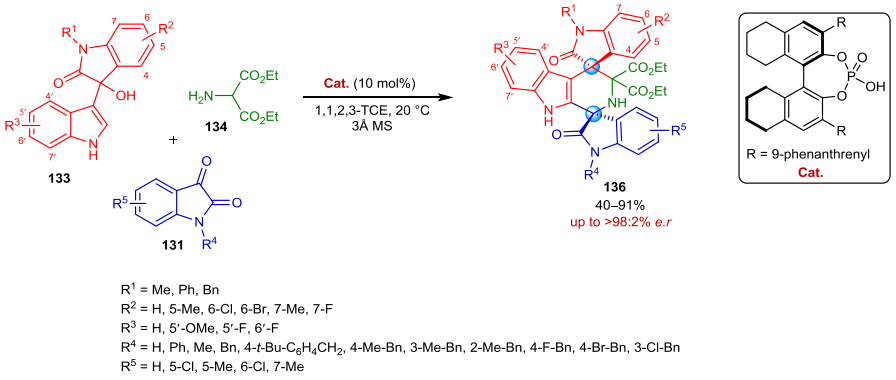


Scheme 56 Enantioselective synthesis of piperidine framework

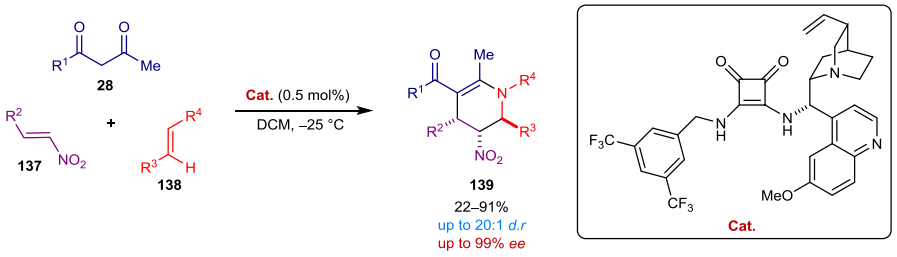
reaction conditions, the scope of isatins was explored. Initially, the effect of *N*-substituents of isatins including *N*-benzyl and *N*-alkyl was tested where *N*-benzyl-substituted isatins showed higher capability in enantioselective control than *N*-alkyl-substituted ones. Then, the impact of the substituents at the phenyl moiety of isatins on the reaction was investigated. A range of electronically different isatins substituted at position C5, C6, and C7 of the phenyl moiety could be utilized to the tandem reaction affording the desired products in excellent stereoselectivities. The position of the substituents had no obvious effect on the enantioselectivity but the electronic nature of the substituents affected the enantioselectivity. Finally, the substrate scope of isatin-derived 3-indolylmethanols was investigated which demonstrated several points of structural diversity in the products.

Blümel et al. [173] developed an efficient triple-domino Michael/aza-Henry/cyclization reaction involving 1,3-dicarbonyl compounds **28**, *β*-nitroolefins **137**, and aldimines **138**. A quinine-derived squaramide catalyzed the reaction to afford a diverse array of tetrahydropyridines **139** bearing three contiguous stereogenic centers in good yields and excellent enantioselectivities (Scheme 58). After extensive screening, suitable reaction conditions were identified and the scope of this organocatalytic cascade transformation was explored. A diverse variation on the aryl ring of *β*-nitroolefin component was investigated first where the corresponding tetrahydropyridines were obtained in 69–88 % yield and high enantioselectivities. Heteroaromatic substituent on the nitroalkene was also tolerated under the standard reaction conditions, delivering the desired product in 91 % yield and 98 % *ee*. An aliphatic nitroalkene also provided tetrahydropyridine in 32 % yield but with excellent *dr* of >20:1 and 93 % *ee*.

Next, various 1,3-dicarbonyl compounds were tested. *β*-Ketoesters gave high yields and enantiomeric excesses of the corresponding tetrahydropyridine products. Moreover, phenyl-substituted diketone gave the desired product in 89 % yield and 99 % *ee*. *β*-Ketoamides and various cyclic dicarbonyl compounds were unreactive in this process. Finally, the scope of aldimines with different substituents was examined. The results depicted that the nature with regard to steric hindrance of the imine carbon and the bulkiness of the R^4 group is crucial for the outcome of the



Scheme 57 Organocatalytic asymmetric synthesis of bispirooxindoles scaffold containing a tetrahydro-*β*-carboline moiety

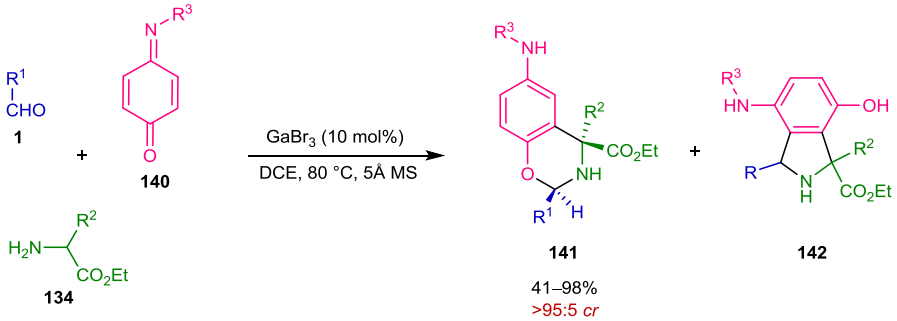


R^1 = Me, Ph, OMe, OEt
R^2 = Ph, 4-Me-Ph, 4-F-Ph, 2-Cl-Ph, cyclohexyl, 2-thienyl
R^3 = Ph, 4-Br-Ph, 4-Me-Ph, 2-furanyl, 2-(*N*-Boc-indolyl), PhC≡C
R^3 = Me, PMB

Scheme 58 Organocatalytic asymmetric synthesis of tetrahydropyridines

reaction. Several *para*-substituted imines furnished the desired tetrahydropyridines, whereas, *ortho*- and *meta*-substituted imines did not react under the standard conditions. In addition, different heterocyclic substituted imines (2-furanyl and 3-Boc-indolyl) were also viable substrates for this transformation. Imines installed an alkyne group also worked well to provide synthetically interesting 6-ethynyl-substituted *N*-heterocycle in 62 % yield and 99 % *ee*.

Recently, Wang et al. [174] developed an elegant chemoselective [3 + 3] cycloaddition of in situ generated azomethine ylides with quinonemonoimides **140**. This process was afforded a range of diverse dihydrobenzoxazine compounds **141** with excellent chemoselectivities and high yields (up to >95:5 *cr* and 98 % yield) (Scheme 59). Having established the optimal reaction conditions, the scope of the reaction was investigated by using a range of substrates. The results demonstrated the general applicability of a wide range of electronically different aromatic, heteroaromatic and aliphatic aldehydes delivering the desired [3 + 3] cycloaddition products **141** in generally high yields and with excellent chemoselectivities.



R^1 = Ph, 4-Me-Ph, 4-NO_2-Ph, 3-NO_2-Ph, 2-NO_2-Ph, 4-NC-Ph, 3-NC-Ph, 4-CF_3-Ph, 4-Cl-Ph, 2-thienyl, 3-thienyl, cyclohexyl, cyclopentanyl
R^2 = CO_2Et, 3-Cl-Ph, 4-Cl-Ph, Ph
R^3 = Ts, 4-Cl-PhSO_2, 4-*t*-Bu-PhSO_2, 4-OMe-PhSO_2, 3-Br-PhSO_2, PhSO_2

Scheme 59 Catalytic chemoselective synthesis of dihydrobenzoxazine compounds

Electronically poor benzaldehydes performed efficiently in the presence of 15 mol% $GaBr_3$. The position of the substituent had slight influence on the reactivity where *para*- or *meta*-substituted nitrobenzaldehydes delivered the desired product with much higher yields than their *ortho*-substituted counterpart. In contrast, electronically neutral and rich aldehydes were unsuccessful under the optimal reaction conditions, however, by increasing the catalyst loading to 20 mol% gave the cycloaddition product on a large scale. Heteroaromatic and aliphatic aldehydes were also among the tested substrates.

Next, the scope of amino-esters was studied. The reaction tolerated several α-aryl amino-esters apart from the commonly used diethyl 2-aminomalonate. In most cases, the tested amino-esters displayed high reactivity, and afforded the [3 + 3] cycloaddition products in good yields (77–87 %) and excellent chemoselectivities (all >95:5 *cr*). Finally, different quinone monoimides were also applied in this reaction which delivered the desired dihydrobenzoxazines with enriched structural diversity.

Concluding remarks

In summary, multi-component reactions (MCRs) provide a most powerful platform for the rapid generation of diverse sets of complex molecules in a sustainable fashion. In this review article, we have introduced readers to a broad range of six membered monocyclic nitrogenous heterocycles (pyridines, dihydropyridines, tetrahydropyridines, piperidines, pyridazinones, dihydropyrimidine, pyrimidin(thi)one derivatives and fused six membered heterocycles like quinoline) which could be generated with diverse structural complexity in one-pot from three or more reactants through multi-component reactions (MCRs) with good convergence, operational simplicity, greater efficiency, atom economy and eco-compatibility. Several reusable catalysts including hydrotalcite, $(NH_4)_{2.5}H_{0.5}PW_{12}O_{40}$, Nano-γ-$Fe_2O_3$–$SO_3H$, Fe_3O_4 NPs, NSPVPC, $PCSiO_2$, CuS Qdots, TiO_2MWCNTs etc. have been developed which worked efficiently for the construction of nitrogen heterocycles under solvent-free conditions or at ambient temperatures, rendering these protocols eco-compatible and in compliance with the green chemistry procedures. Moreover, asymmetric catalytic MCRs demonstrated significant developments in the pharmaceutical industry. In addition, high impact research on multi-component reactions opened exciting opportunities in the field of green chemistry by minimizing waste, cost, and time which are valuable aspects in the chemical and pharmaceutical industries. Thus MCRs represent the cornerstones of both combinatorial chemistry and diversity-oriented synthesis and could be of paramount chemical significance in further streamlining the modern synthetic methodology for pharmaceutical and drug discovery research. We hope that the continued evolution of such methodologies stimulate the synthetic community to develop novel and creative synthetic routes to readily access complex molecules previously thought to inaccessible.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest regarding the publication of this work.

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