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Microwave-assisted Heterocyclic Chemistry

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Abstract Recent developments in the microwave-assisted synthesis of heterocycles are surveyed with the focus on diversity-oriented multi-component and multi-step one-pot procedures. Both solution- and solid-phase as well as polymer-supported methodologies for the preparation of libraries of heterocycles are reviewed. Advantages of microwave dielectric heating are highlighted by comparison with conventional thermal conditions.

Keywords Heterocycles · High-throughput synthesis · Microwaves · Multi-component reactions

Abbreviations

BEMP	2-tert-butylimino-2-dimethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DHP	dihydropyridine
DIEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMF–DMA	*N*,*N*-dimethylformamide dimethyl acetal
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
IL	ionic liquids
MCR	multi-component reaction
MW	microwaves
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidinone
PEG	poly(ethylene glycol)
PPTS	pyridinium *p*-toluenesulfonate
PS	polymer supported
RCM	ring-closing metathesis
SPE	solid-phase extraction
SPOS	solid-phase organic synthesis
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl (*p*-toluenesulfonyl)

1 Introduction

Heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. Because of the drug-like character and considerable range of structural diversity, large collections or libraries of diverse heterocycles are routinely employed in high-throughput screening at early stages of drug discovery programs. Furthermore, a heterocyclic core is propitious for variations of substitution patterns during structure-activity relationship (SAR) studies. Consequently, relatively small (< 300 membered) focused libraries of heterocycles are frequently generated for SAR studies during the development and optimization of lead structures [1]. Among the different synthetic methodologies available for the production of compound libraries, a multi-component synthesis of heterocycles is especially suitable because high structural diversity in the desired scaffolds can be introduced in a single synthetic step simply by proper variation of precursors. One-pot multi-step synthesis constitutes a convenient alternative as it can avoid workup and purification of the intermediates between different reaction steps. Similarly, domino reactions where "two or more bond-forming transformations take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the

previous step" [2] are also perfectly suited for the generation of libraries of heterocyclic compounds.

The competition in the field of drug discovery has helped to identify speed of synthesis as a top priority in drug development. Consequently, technologies that could accelerate and facilitate both synthesis and screening of substances have become highly desirable. The advent of microwave technology enabled organic and medicinal chemists to reduce the time of synthesis of heterocycles from days and hours to minutes and even seconds. In addition, suppressed formation of side-products and improved yields have frequently been observed under microwave heating conditions. Moreover, the extremely fast and efficient dielectric heating mode has sometimes identified unusual reactivities that could not be achieved by conventional heating. The frequently observed acceleration of the reaction speed by microwave heating could be rationalized by considering the Arrhenius law [$k = A \exp(- E_a/RT)$]. Thus, Baghurst and Mingos calculated $t_{9/10}$ lifetimes of a typical first-order reaction for a given activation energy E_a and pre-exponential factor A [3]. Accordingly, 90% completion of the reaction would require 13.4 h in a solvent refluxing at 77 °C, and just 1.61 s (!) if performed in a closed vessel where the temperature is maintained at 227 °C. Thus, a reduction of the reaction time by five orders of magnitude could be achieved by performing reactions 150 °C above the boiling point of the solvent. In the meantime, Strauss and co-workers demonstrated that for the thermally homogeneous reactions at known temperatures the kinetics of microwave-heated and conventionally heated reactions do not differ significantly [4]. Consequently, the authors concluded that "if the microwave conditions can be adequately mimicked, conventional heating will produce a comparable outcome" [5]. On the other hand, reproduction of the dielectric heating conditions is usually a challenging task given the extremely rapid dielectric heating mode originating from the direct coupling of microwave energy with molecules (solvents, reagents, catalysts) that are present in the reaction mixture. Moreover, in-core volumetric heating can suppress the formation of side-products on the hot surface of a reaction vessel, resulting in cleaner reactions. Eventually, mimicking the dielectric heating conditions is virtually impossible in the case of thermally heterogeneous conditions, which operate when inorganic supports such as relatively microwave transparent silica, alumina and clay or strongly absorbing graphite are employed. In this case, selective heating of strongly microwave absorbing reagents or heterogeneous catalysts in a less polar reaction medium (specific microwave effects) presumably accounts for the acceleration of the reaction speed.

Although being essentially reproducible in an oil-bath, thermally homogeneous microwave dielectric heating conditions nevertheless are the preferred methodology for the synthesis of heterocycles on a laboratory scale, especially when high temperatures and long reaction times are necessary

for the reaction to occur. Not surprisingly, microwave-assisted synthesis of heterocycles has been a subject of numerous reviews during the last 5 years [6–10]. The operational simplicity of the microwave technology has led to the design of purpose-built microwave equipment possessing high levels of automation for use in drug development and, particularly, for synthesis of heterocycle libraries. Therefore, the goal of the present review is to demonstrate applications of microwave dielectric heating to facilitate rapid parallel or sequential synthesis of solution- and solid-phase libraries of heterocycles. Consequently, the review focuses preferentially on diversity-oriented (multi-component, multi-step one-pot as well as domino) microwave-assisted synthesis of heterocycles [11]. Generally, procedures are surveyed only where microwave technology is employed in a ring-forming step and examples dealing with modification of pre-existing heterocyclic scaffolds are not discussed.

Last but not least, workup of the reaction mixture and product isolation have frequently been "rate limiting steps" in rapid and automated production of heterocycle libraries. Clearly, acceleration of the reaction speed by microwaves is of little advantage given the subsequent laborious and time-consuming isolation and purification of multi-membered libraries. Therefore, rapid synthesis is to be accompanied by simple and efficient workup-purification sequences, preferentially amenable to automation. In the simplest cases, proper choice of solvents allowed the precipitation of the desired products in acceptable purity directly from the reaction mixture. Routine workup and purification approaches are based on standard phase separation techniques, such as attachment of reagents or catalysts to a solid (or soluble) polymer matrix or the introduction of fluorous tags followed by fluorous-phase extraction. Notably, under microwave flash heating conditions slow heterogeneous solid-phase reactions could be efficiently accelerated without any degradation of the polymer backbone. Consequently, the workup and purification issues are also considered in the review.

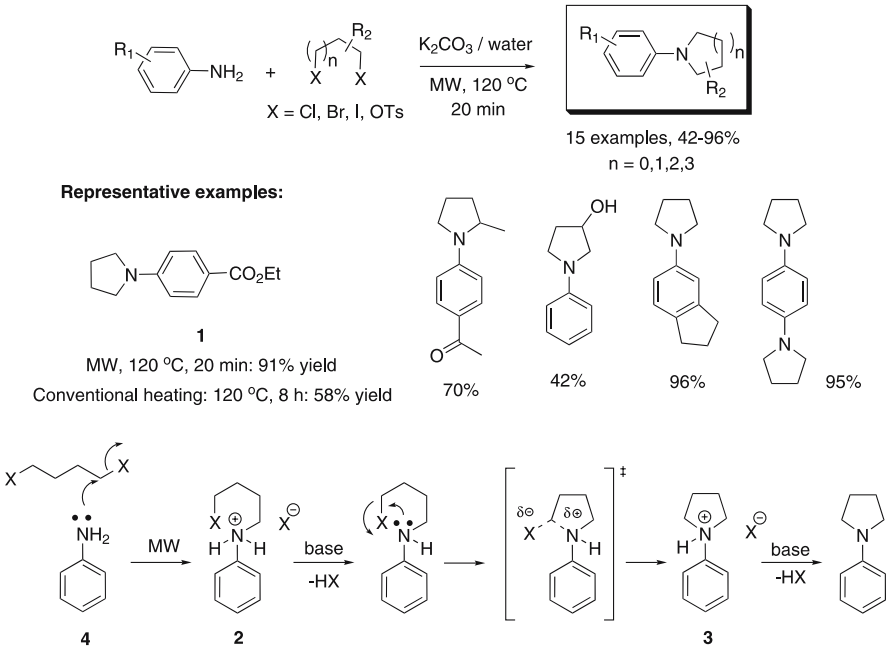
Rather than being comprehensive, this review is aimed at demonstrating tendencies and approaches of diversity oriented synthesis of heterocycles, that appeared in the literature from 2002 through January 2006. Synthesis of heterocycles in dedicated microwave systems is discussed preferentially as this type of equipment renders higher reproducibility and is more amenable to automation than custom-designed or household ovens. The survey of heterocycle synthesis is arranged according to ring-size and number of heteroatoms in the ring.

2
Five-membered Heterocycles

2.1
Pyrrolidines, Pyrrolines and Pyrroles

A series of pyrrolidines was conveniently prepared in a microwave-assisted double alkylation of aniline derivatives with alkyl dihalides in water in the presence of K_2CO_3 as a base (Scheme 1) [12, 13]. Although the reaction mixture could be regarded as a multi-phase system, as neither reactant was soluble in the mildly basic aqueous medium, the microwave-assisted reaction proceeded readily without the use of phase-transfer reagents. The amount of side-reactions such as hydrolysis of bromides to alcohols in an alkaline reaction medium was substantially suppressed compared to the conventional thermal conditions. The reaction conditions were sufficiently mild to tolerate a variety of functional groups in anilines such as hydroxyls, ketones and esters. Alkyl bromides and tosylates were equally efficient as alkylating agents. Notably, isolation and purification comprised simply of phase separations (filtration or decantation) of the desired product from the aqueous media.

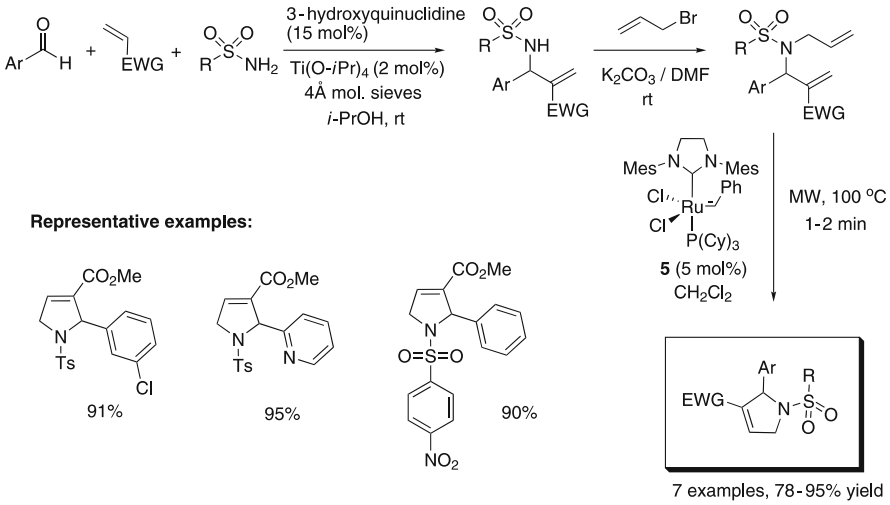
The use of microwave dielectric heating led to the reduction of reaction time from hours to minutes (Scheme 1, pyrrolidine **1**). As the magni-



Scheme 1 Microwave-promoted synthesis of *N*-aryl pyrrolidines in neat water

tude of heating by microwaves depends on the dielectric properties of the molecules, the greater the polarity of the reacting species, the more efficient is the absorbance of the microwave energy. Consequently, acceleration of the reaction by microwaves has been attributed to a greater stabilization of the charged intermediates **2** and **3** by the dipole–dipole interaction with the microwave electric field when compared to the less polar ground state **4** (Scheme 1).

One of the most efficient approaches towards pyrrolines is ring-closing metathesis (RCM) of suitably substituted dienes. The ring closure of *N*,*N*-diallyl *p*-toluensulfonamide, yielding *N*-tosyl-2,5-dihydropyrrole has been often used as a model reaction in the evaluation of novel metathesis catalysts. While in the case of simple dienes the RCM reaction works sufficiently well even at room temperature, tri- and tetrasubstituted olefins carrying electron-withdrawing groups require elevated temperatures (40 °C; refluxing in CH_2Cl_2) to enter the RCM reaction. The advent of the air- and thermally stable Grubbs "2nd generation" ruthenium metathesis catalyst **5** (Scheme 2) enabled the use of microwave heating as a tool to enhance the effectiveness of the RCM method. Subsequently, several groups have reported successful applications of dielectric heating to accelerate the synthesis of different heterocycles, including pyrrolines [14–17]. Starting dienes for the RCM reaction were conveniently synthesized in a three component aza-Baylis–Hillman reaction, followed by *N*-allylation (Scheme 2) [16, 17]. A cyclization reaction in the presence of Grubbs catalyst **5** was completed in 1–2 minutes under dielectric heating conditions at 100 °C [16]. The 2,5-dihydropyrrole products were isolated in high yields after simple filtration of the reaction

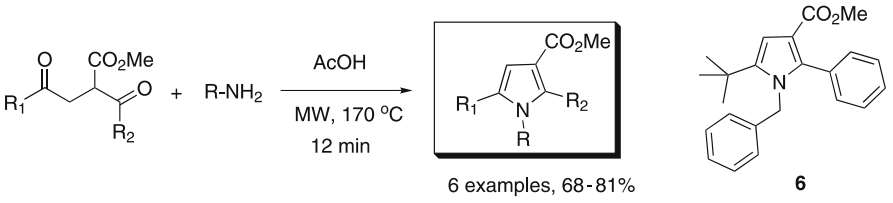


Scheme 2 Rapid preparation of functionalized dihydropyrroles using RCM reaction

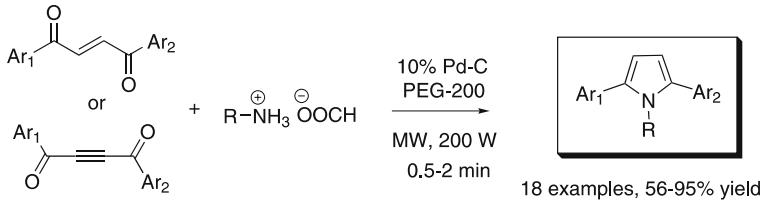
mixture to remove the catalyst, followed by evaporation of the solvent. Overall, the three-step reaction sequence could be conveniently employed for the preparation of a library of trisubstituted pyrroles, with diversity being introduced in the first step (aza-Baylis–Hillman reaction) (Scheme 2). The use of the *N*-2-trimethylsilylethylsulfonyl protecting group instead of the *N*-tosyl moiety (not shown) furnished a straightforward conversion of pyrrolines to pyrroles via a base-promoted dehydrodesulfinylation–aromatization reaction [17].

Selective heating-activation of the polar reagents (catalyst and/or olefin) in a non-polar and microwave transparent reaction medium [18–20] was claimed to be responsible for the observed acceleration of the reaction rate (specific microwave effects) [14, 15]. Accordingly, the heating energy is delivered directly to the reacting species and the bulk reaction medium acts as a thermostat. However, careful comparison studies between microwave and thermal (oil bath) experiments indicated that the reaction proceeded equally well regardless of the type of heating employed. Consequently, the observed rate enhancements can be rationalized solely by thermal effects (the Arrhenius equation) rather than by specific microwave effects [21].

One of the most common approaches to pyrrole synthesis is the Paal–Knorr reaction. The microwave-assisted Paal–Knorr cyclization was successfully carried out on various 1,4-diketoesters in the presence of amines, affording the desired pyrroles in good yields [22]. For example, pyrrole **6** was obtained in 70% yield after dielectric heating at 150 °C for 5 min (Scheme 3). When the reaction was conducted under traditional heating, less than 15% of the pyrrole **6** was formed after 12 h of heating at 110 °C (external oil bath 150 °C). A number of polysubstituted pyrrole derivatives were prepared in a one-pot reaction from 1,4-diaryl but-2-ene-1,4-diones and but-2-yne-1,4-diones via hydrogenation of the carbon–carbon double bond (or triple bond) followed by amination–cyclization. Ammonium formate or aryl/alkyl ammonium formates were employed both as reducing agents in the palladium-catalyzed transfer hydrogenation and also as sources of ammonia. Poly(ethylene glycol)-200 (PEG-200) was identified as the most convenient solvent for the microwave-assisted reaction owing to its high dielectric constant ($\varepsilon = 20$), high boiling point (> 250 °C) and excellent water miscibility (Scheme 4) [23].

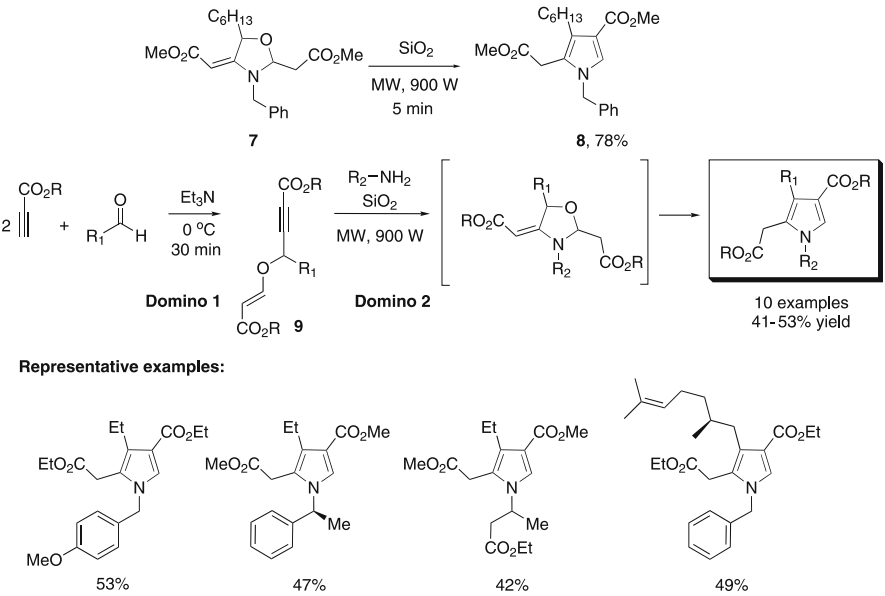


Scheme 3 Paal–Knorr cyclization under microwave irradiation

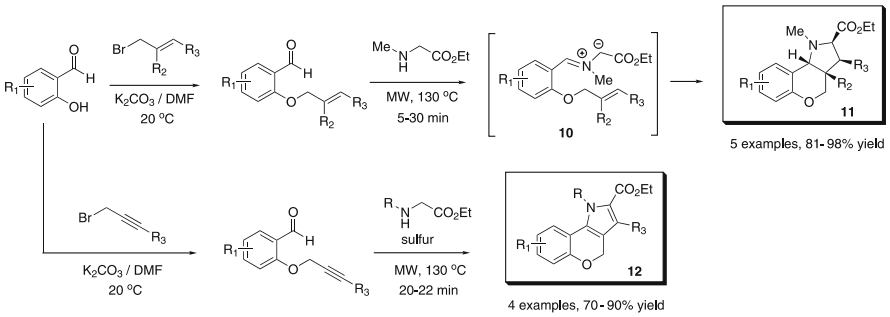


Scheme 4 Preparation of pyrroles in a one-pot hydrogenation–cyclization sequence

Tetrasubstituted pyrroles could be obtained by skeletal rearrangement of 1,3-oxazolidines, a reaction that is substantially accelerated by microwave irradiation. Dielectric heating of a 1,3-oxazolidine **7**, absorbed on silica gel (1 g silica gel/mmol) for 5 min in a household MW oven (900 W power) cleanly afforded the 1,2,3,4-tetrasubstituted pyrrole **8** in 78% yield, thus reducing the reaction time from hours to minutes (Scheme 5) [24]. 1,3-Oxazolidines are accessible in one-pot, two-step, solvent-free domino processes (see also Sect. 2.6). The first domino process, a multi-component reaction (MCR) between 2 equivalents of alkyl propiolate and 1 equivalent of aldehyde furnished enol ethers **9** (Scheme 5). Subsequent microwave-accelerated solvent-free reactions of enol ethers **9** with primary amines on silica support afforded intermediate 1,3-oxazolidines, which in situ rearranged to the tetrasubstituted pyrroles (2nd domino process). Performed in a one-pot format, these



Scheme 5 Sequential domino synthesis of pyrroles



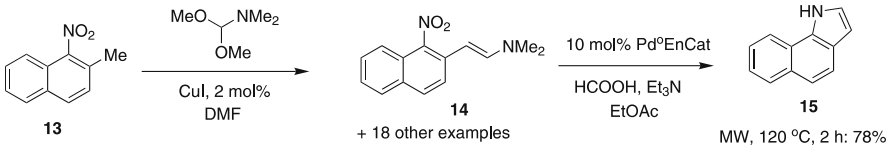
Scheme 6 Microwave accelerated intramolecular [3 + 2] cycloaddition

two sequential domino reactions resulted in an efficient, diversity-oriented synthesis of 1,2,3,4-tetrasubstituted pyrroles from simple and commercially available components [24].

The superiority of microwave dielectric heating was demonstrated in an intramolecular [3 + 2] cycloaddition reaction leading to fused pyrrolidines **11** and complex tricyclic benzopyrano-pyrroles **12** [25]. The reaction evidently proceeded via formation of charged intermediates—for example, the 1,3-dipolar azomethine ylides **10**. As the dielectric heating was proposed to be especially advantageous in the case of polar reaction mechanisms (when the polarity is increased during the reaction from the ground state towards the transition state), acceleration of the reaction speed could be anticipated [26]. Indeed, microwave dielectric heating at 130 °C for 15 minutes afforded the fused pyrrolidine **11** in 93% yield. In contrast, it took 1.5 hours to achieve comparable yields under conventional thermal conditions (130 °C, pre-heated oil bath). Access to fused pyrroles **12** required the [3 + 2] cycloaddition with the *O*-propargyl moiety and subsequent in situ oxidation of the cycloaddition product with sulfur. Both reactions were performed as one-pot procedures, thus establishing a novel one-pot MCR towards complex heterocycles (Scheme 6).

2.2 Indoles, Carbazoles and Phthalimides

The widely employed Leimgruber–Batcho protocol for indole synthesis comprises two consecutive steps—the formation of enamines followed by a reductive cyclization. The formation of enamines (such as **14**, Scheme 7) presumably required an initial deprotonation of the methyl *ortho* to the aromatic nitro-group by methoxide generated from DMF–DMA under elevated temperatures (overnight heating in DMF) [27]. The use of microwave irradiation at 180 °C allowed the reduction of the time of formation of enamines such as **14** from 22 h (at 110 °C) to 4.5 h (and even to 40 min in several



Pd⁰EnCat - encapsulated nanoparticulate Pd catalyst

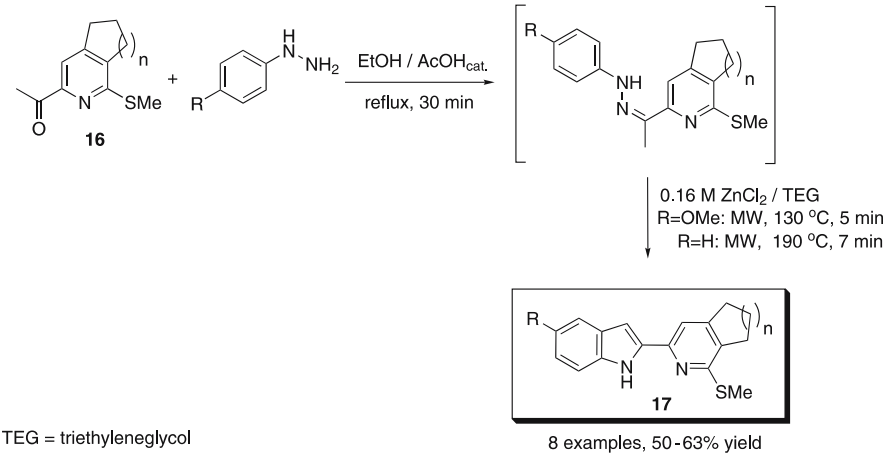
Scheme 7 Leimgruber–Batcho synthesis of indoles

cases) [28]. For example, the enamine **14** was prepared in a microwave-accelerated condensation of 2-methyl-1-nitronaphthalene **13** with DMF–DMA in the presence of catalytic amounts of CuI. A subsequent reductive cyclization of enamine **14** leading to 1*H*-benz[*g*]indole **15** was achieved by transfer hydrogenation in the presence of an encapsulated nanoparticulate Pd catalyst and HCOOH/Et_3N as the reducing agents (Scheme 7). Thus, the combination of microwave-accelerated enamine formation with the use of a recyclable catalyst for reductive cyclization under dielectric heating conditions diminished the reaction times from days to hours.

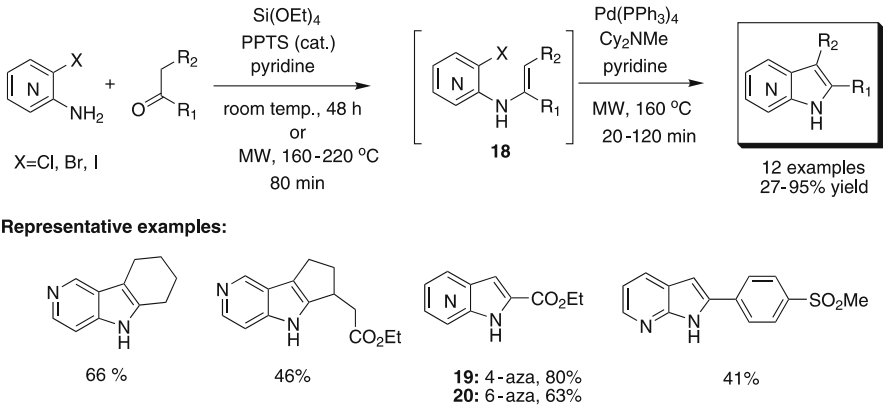
The Fisher indole synthesis (the Lewis or protic acid catalyzed rearrangement of arylhydrazones into indoles) is among the most widely used approaches towards the indole heterocycle. The construction of 2-(2-pyridyl)indoles **17** from 2-acetylpyridines **16** required forced conditions and was consequently regarded as a difficult example of the Fisher indolization and microwave heating was anticipated to be of value for this synthesis. Indeed, several microwave-assisted methods towards indoles **17** have been reported. An initially developed solvent-free protocol employed montmorillonite K10 clay modified with $ZnCl_2$ [29]. Higher yields, however, were obtained by using catalytic amounts (10 mol %) of $ZnCl_2$ in triethylene glycol as a high-boiling, polar solvent [30]. Thus, dielectric heating of a mixture of 2-acetylpyridine **16** ($n = 1$) and phenylhydrazine (R = H) at 180 °C afforded indole **17** in 52% yield after 7 min. Notably, the reaction furnished indole **17** in only 12% yield after 3 hours under otherwise identical conditions in an oil-bath at 180 °C, which clearly demonstrates the advantages of microwave flash heating (Scheme 8).

A two-step, one-pot process has been developed for the synthesis of aza-indoles under dielectric heating conditions [31]. In the first step, aminopyridines and ketones were condensed either at room temperature (in the case of aza-indoles **19–20**) or under dielectric heating at 160–220 °C to yield intermediate enamines **18.** Subsequent microwave-assisted intramolecular Heck reactions furnished the corresponding 4-, 5-, 6- or 7-azaindoles in moderate to good yields (Scheme 9).

Microwave flash heating was successfully employed in another palladium catalyzed two-step process leading to *N*-substituted oxindoles [32]. The



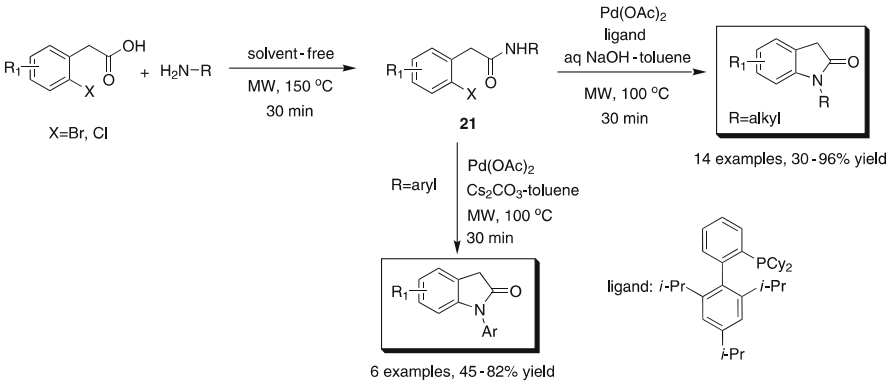
Scheme 8 Microwave-assisted Fisher synthesis



Scheme 9 A two-step, one-pot synthesis of aza-indoles

method involves initial microwave-assisted amide bond formation between 2-halo-arylacetic acids and various alkylamines and anilines. Subsequent palladium-catalyzed intramolecular amidations afforded oxindoles. In the case of alkylamines, the procedure can be carried out under aqueous conditions as a one-pot process without isolation of the intermediate amide **21** (Scheme 10). A number of *N*-substituted oxindoles were also synthesized by microwave-assisted radical cyclization on solid support in DMF as the solvent [33].

A novel microwave-accelerated three-component coupling of α-acyl bromides, pyridine and internal alkynes under solvent-free conditions afforded a collection of indolizines [34]. It was proposed that basic alumina catalyzed the in situ formation of a 1,3-dipole from the *N*-acyl pyridinium salt. Subse-

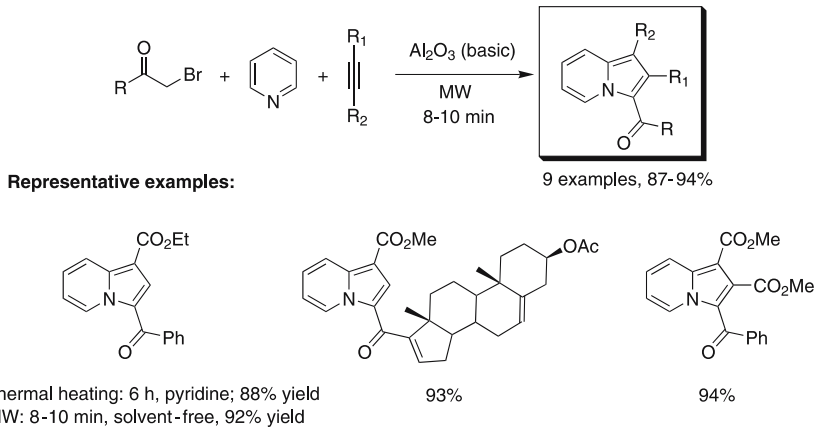


Scheme 10 Preparation of *N*-substituted oxindoles via a condensation–arylation sequence

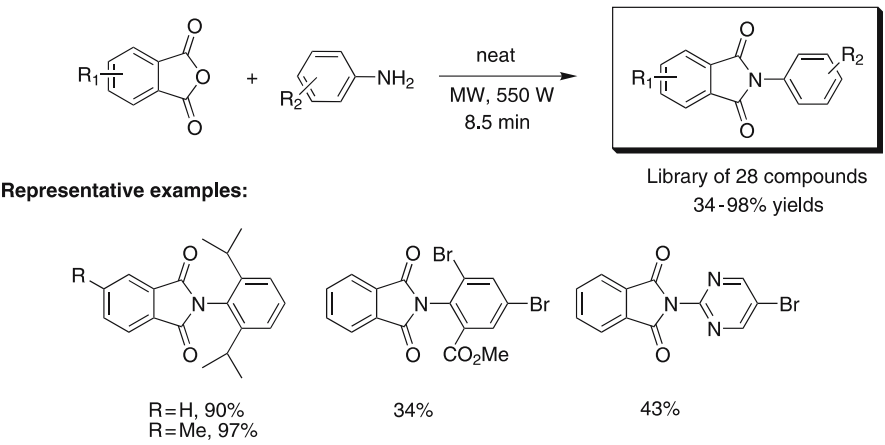
quent [3 + 2] cycloaddition reaction of the 1,3-dipole with alkyne afforded the indolizine core. The reaction products were easily separated from alumina by extraction with dichloromethane or ethyl acetate (Scheme 11).

A rapid parallel solvent-free synthesis of a representative 28-membered library of phthalimides was achieved utilizing a household microwave oven under highly optimized conditions [35]. Thus, the highest irradiation area inside the household microwave oven was determined to ensure better reproducibility of results (Scheme 12).

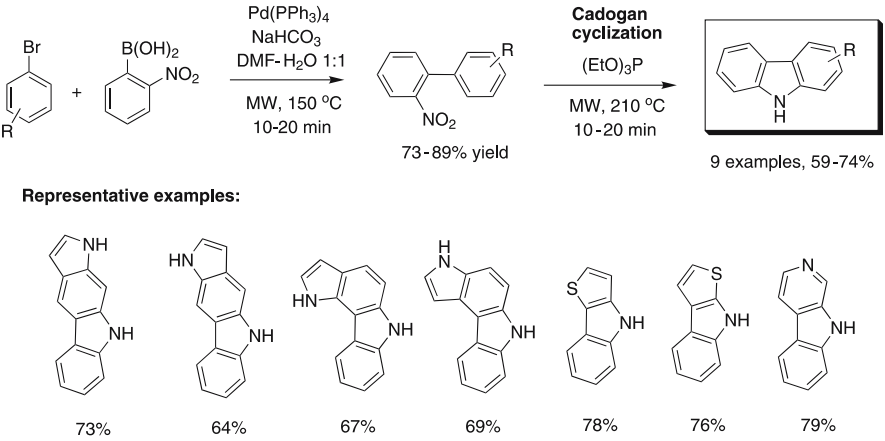
Sequential Suzuki–Miyaura cross-couplings and Cadogan cyclizations were developed under microwave dielectric heating conditions to access a variety of 2-substituted carbazoles and other fused heterocyclic systems (Scheme 13). The use of microwave irradiation not only minimized the proto-



Scheme 11 Microwave-mediated synthesis of indolizines via a three-component cyclocondensation



Scheme 12 A rapid parallel solvent-free synthesis of a library of phthalimides

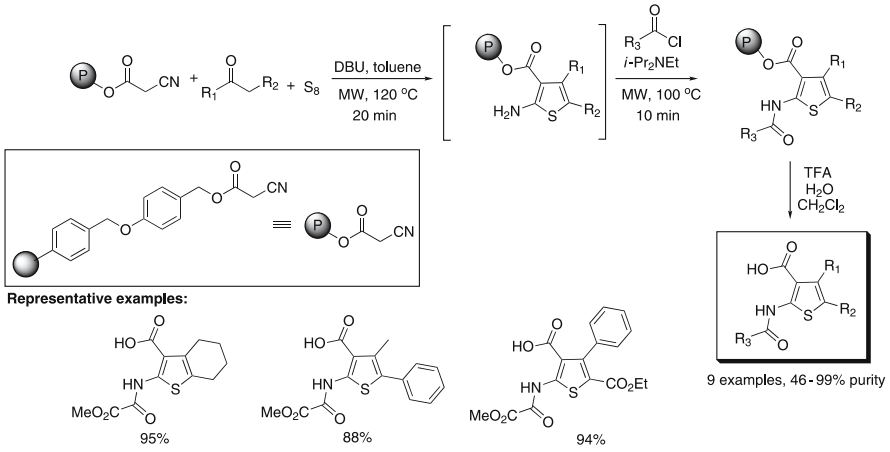


Scheme 13 Preparation of carbazoles via microwave-enhanced Cadogan cyclization

deboronation side reaction in the Suzuki–Miyaura cross-coupling step, but also accelerated the Cadogan cyclization reaction [36]. Thus, carbazoles were formed from 2-nitro-biaryls within 10–20 min of microwave heating at 210 °C. The Cadogan cyclization under conventional thermal heating required up to 24 hours to go to completion [37].

2.3 Thiophenes

Multi-component condensation of ketones (or aldehydes), α-active methylene nitriles and elementary sulfur (the Gewald reaction) is an efficient methodol-



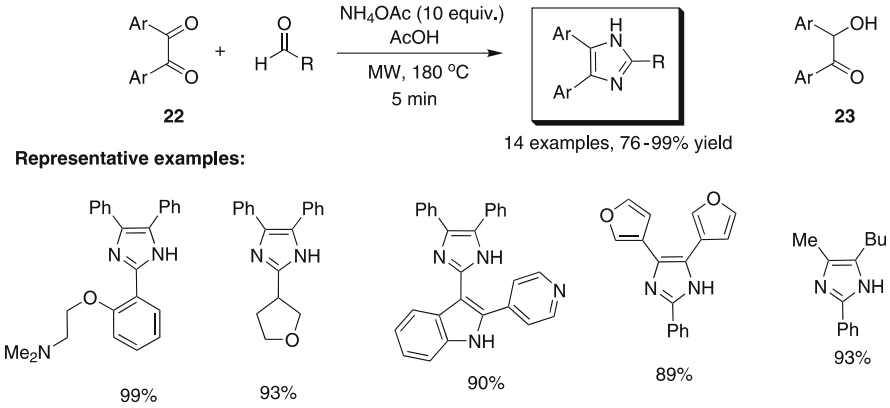
Scheme 14 Microwave-assisted Gewald reaction on solid support

ogy to access diverse 2-aminothiophenes. The Gewald reaction, however, suffers from long reaction times (8–48 hours) and laborious purification of the desired products. To address these disadvantages, the reaction was performed on solid support under microwave dielectric heating conditions, furnishing 2-aminothiophenes within 20 min [38]. Moreover, additional diversity was introduced by a one-pot *N*-acylation of the initially formed 2-aminothiophene within 10 min. The use of a solid support facilitated the workup substantially and the desired heterocycles were obtained after cleavage from the polymer support with 46–99% HPLC purity (Scheme 14).

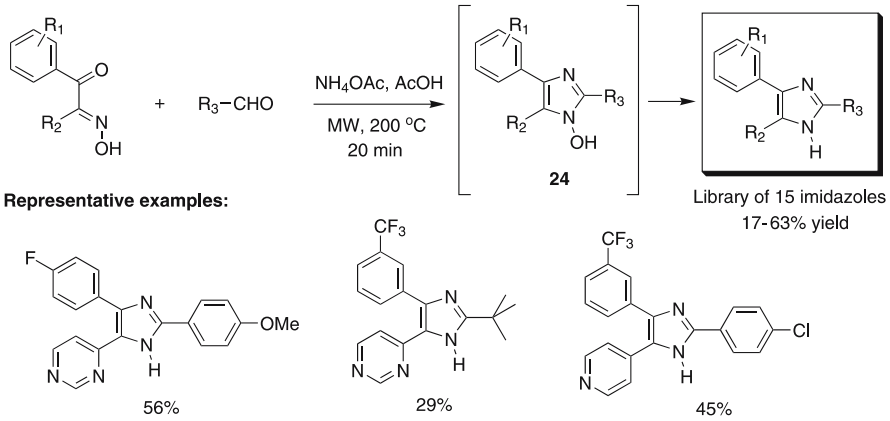
2.4 Imidazoles, Benzimidazoles

Condensation of 1,2-diketones with aldehydes in the presence of NH_4OH constitutes an efficient approach towards trisubstituted imidazoles. Impressively, under dielectric heating conditions (180 °C), the cyclocondensation reaction required merely 5 min to go to completion [39]. Moreover, analytically pure products were easily isolated from the reaction mixture by a neutralization–filtration sequence. The high speed of the reaction combined with the ease of product isolation rendered the cyclocondensation especially suitable for the generation of imidazole libraries (Scheme 15).

Benzoin **23** could be used instead of benzil **22**, provided that the microwave-assisted cyclocondensation is performed on inorganic support (silica gel or alumina) under solvent-free conditions [40]. A related diversity-oriented approach towards imidazoles utilized the cyclocondensation of unsymmetrical keto-oximes with aldehydes in the presence of NH_4OAc [41] (Scheme 16). Hydroxyimidazoles **24** were formed in the cyclization step and



Scheme 15 Fast three-component synthesis of imidazoles

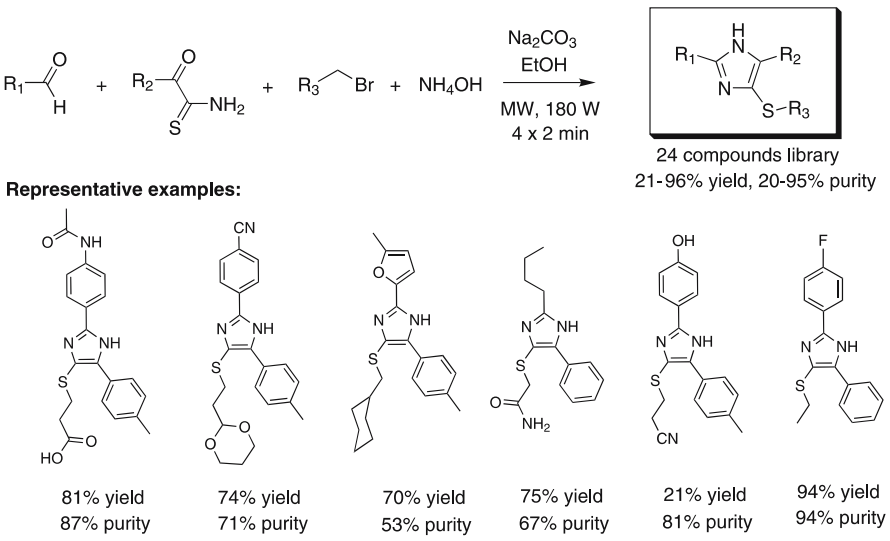


Scheme 16 Preparation of a library of imidazoles under microwave irradiation

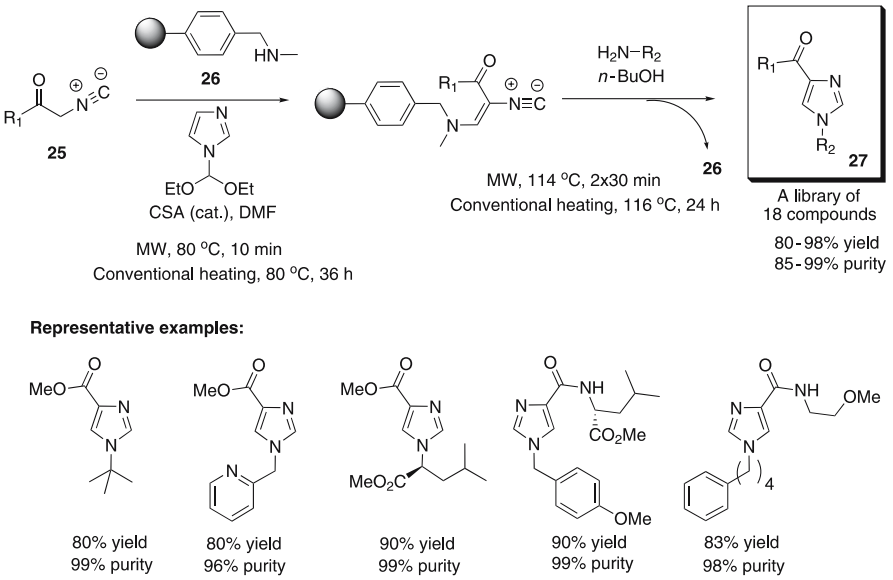
the use of microwave dielectric heating at 160 °C diminished the reaction time from 3 hours (reflux in AcOH) to 20 min. Subsequent reduction of the *N*-hydroxyimidazoles with $TiCl_3$ was also accelerated by microwave irradiation (5 min at 120 °C vs. 16 h at room temperature). It was noteworthy that the use of higher temperatures (200–210 °C) in the cyclocondensation step unexpectedly brought about the concomitant cleavage of the N – O bond, thus leading directly to the desired imidazoles in a one-pot two-step process. The crude products were filtered and purified by injection directly onto a preparative LCMS, thus setting up a high throughput methodology for generation of an imidazole library (Scheme 16). A related one-pot synthesis of tetrasubstituted imidazoles from 1,2-diketones, substituted benzonitriles and primary amines has been achieved in a household microwave oven in the presence of silica gel [42].

A diverse 24-membered library of sulfanyl-imidazoles was prepared in a four-component coupling of 21 different aldehydes, two 2-oxothioacetamides, 12 alkyl bromides and NH_4OAc [43]. Upon completion of the reaction, the products were precipitated from the reaction mixture in an overall average purity of 76% and average yields of 68%. The same representative library was generated under conventional thermal conditions. While purity and yields of the products obtained by the two different methods were comparable, the application of the parallel microwave processing technique reduced the time needed for the library generation dramatically from 12 hours to 16 minutes. Notably, repetitive pulses of microwave heating (2 min, four times) were employed instead of a single prolonged heating profile (8 min; Scheme 17) (the superiority of multiple irradiation cycles compared to prolonged heating for the same time period was also demonstrated by [44]).

To address the purification issue, which frequently is a bottle-neck in the fast microwave chemistry, a solid-phase "catch and release" methodology was utilized in a two-component, two-step synthesis of 1-alkyl-4-imidazolecarboxylates [45]. In the first step, a collection of isonitriles **25** was immobilized onto a solid support by the reaction with the commercially available *N*-methyl aminomethylated polystyrene **26.** Subsequent treatment with various amines brought about simultaneous derivatization and release of the desired imidazoles **27** back into solution. Significantly, only derivatized material was released from the resin, thus ensuring high purity of the desired product. Both steps of the reaction were substantially accelerated by microwave dielectric heating, resulting in the overall reaction time reduction from 60 hours to 70 minutes (Scheme 18).



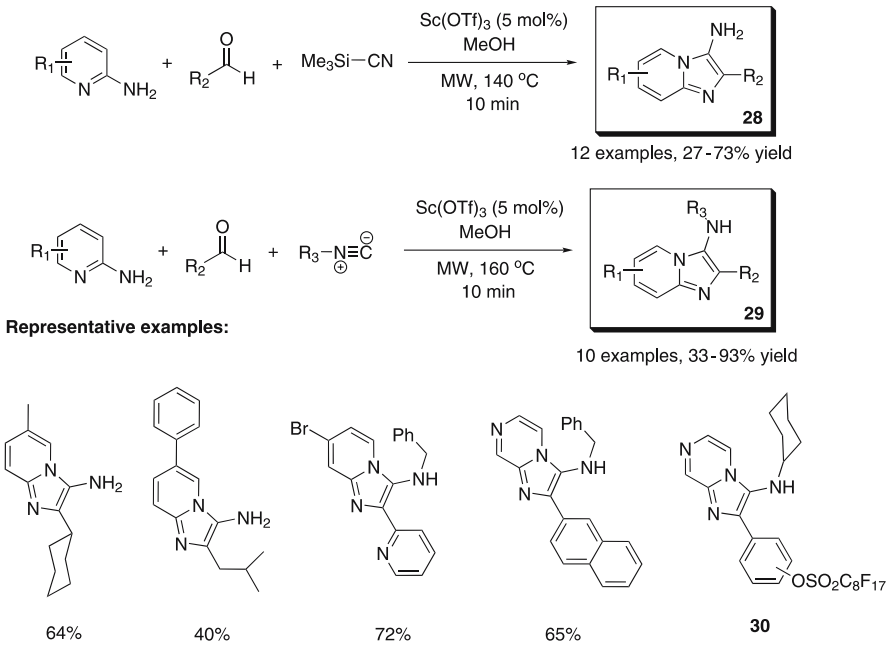
Scheme 17 Microwave-accelerated parallel synthesis of 4(5)-sulfanyl-1*H*-imidazole library



Scheme 18 Solid-phase synthesis of 1-alkyl-4-imidazolecarboxylates using catch and release methodology

A related synthesis of 1-substituted 4-imidazolecarboxylates under microwave dielectric heating conditions employed Wang resin-bound 3-*N*,*N*-(dimethylamino)-isocyanoacrylate [46]. Imidazolidine-2-ones (cyclic ureas) were synthesized by a microwave-accelerated coupling of urea (a cheap and convenient carbonyl source) with aliphatic and aromatic diamines in the presence of ZnO as a catalyst [47]. The use of microwave irradiation in the synthesis of benzimidazoles from *ortho*-phenylenediamine and glycolic acid accelerated the reaction 80 times (from 120 h to 90 min) compared to the standard thermal heating [48]. Other microwave-assisted approaches towards benzimidazoles employed the in situ reduction of *ortho*-nitro anilines to diamines [49] or reaction of dianilines with aldehydes [50]. Purification using a strongly acidic resin was utilized to avoid chromatography in the preparation of *N*-functionalized benzimidazoles via Pd-catalyzed intramolecular arylations of amidines. Notably, the intramolecular aryl-amination was performed under aqueous conditions and the reaction was completed after 20 min of microwave heating at 200 °C [51].

Rapid access to an array of fused 3-aminoimidazoles was conveniently achieved by a $Sc(OTf)_3$ catalyzed three-component cyclocondensation of heterocyclic amidines (such as 2-aminopyridine) and aldehydes with isocyanides (Ugi MCR) [52] or, alternatively, with trimethylsilylcyanide (TMS-CN) [53]. *N*-Unsubstituted 3-aminoimidazo[1,2-*a*]pyridines **28** were formed in the latter case (Scheme 19). Microwave dielectric heating of the methanolic

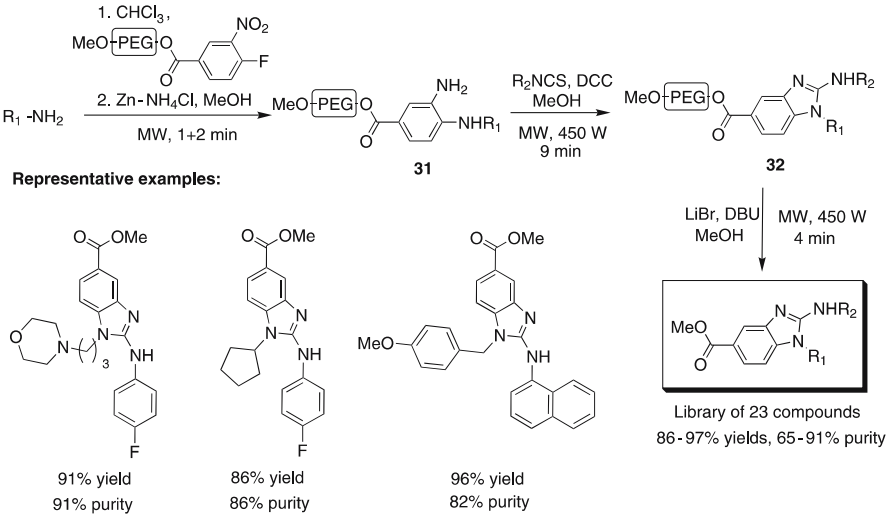


Scheme 19 $Sc(OTf)_3$-catalyzed preparation of fused 3-aminoimidazoles

reaction mixture at 140–160 °C in sealed reaction tubes (75–95 °C above the boiling point) rendered substantial acceleration of the reaction speed. Thus, the desired heterocycles **28** and **29** were formed within merely 10 min. Purification of the target heterocycles was achieved by flash chromatography or supercritical fluid chromatography (Scheme 19).

The time consuming chromatographical purification of heterocycles **28** and **29** slowed down the rate of library production. A phase separation using fluorous chemistry was employed by Zhang and Lu to address the workup and purification of fused 3-aminoimidazo[1,2-*a*]pyridines (such as **30**) [54]. Thus, attachment of a perfluorooctanesulfonyl tag to aldehydes and subsequent Ugi three-component microwave-assisted condensations with 2-aminopyridines and isocyanides furnished the desired heterocycles **30**, which were conveniently isolated by fluorous solid-phase extraction. The fluorous tag could be subsequently used as an activating group in the post-condensation modifications, such as Suzuki–Miyaura cross-coupling reactions.

A library of 2-(arylamino)benzimidazoles was prepared in a microwave-accelerated cyclocondensation of PEG-supported *ortho*-phenylenediamines **31** with isothiocyanates, followed by the product cleavage from polymer support [55, 56]. The quantitative cyclization required either microwave heating (in an open vessel system) for 10 min or reflux in MeOH for 4 hours (Scheme 20). The use of a soluble PEG matrix substantially simplified the



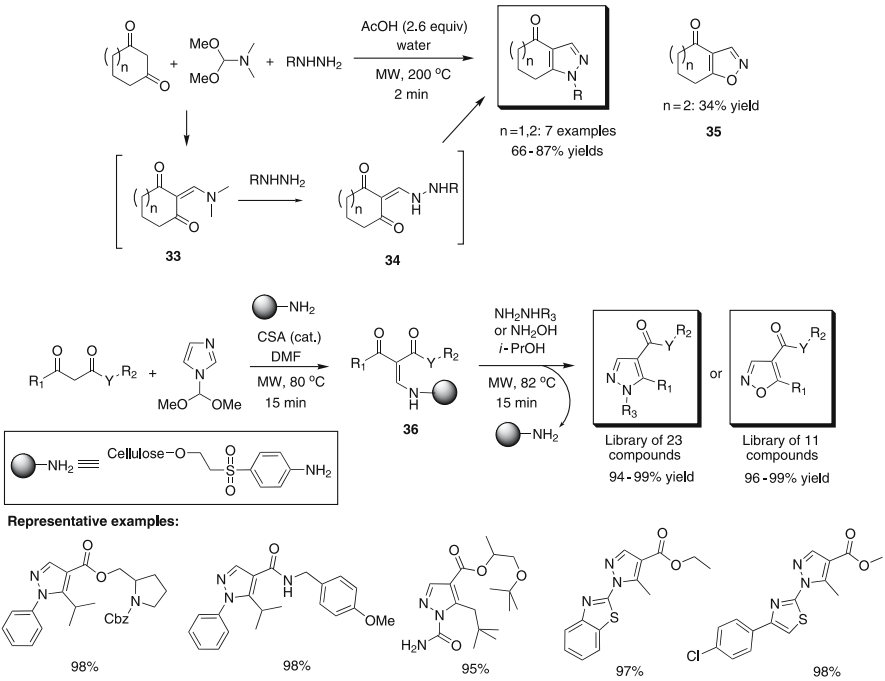
Scheme 20 Synthesis of benzimidazoles using soluble PEG matrix

isolation of products as PEG-bound products were precipitated selectively from a suitable combination of solvents. Similarly, after microwave-assisted cleavage of the substituted benzimidazoles from the polymer support, MeO – PEG – OH was removed from the homogeneous solution by precipitation and filtration. Notably, all polymer-supported intermediates and the polymer support itself remained stable under microwave exposure. Unlike the solid-phase synthesis, soluble polymer-supported reactions could be easily monitored by conventional analytical methods. In later works, Sun and co-workers demonstrated that the microwave-assisted conversion of diamine **31** to benzimidazoles **32** (via the intermediate *N*,*N*′-disubstituted thiourea) could be facilitated by $HgCl_2$ [57] and $BiCl_3$ [58] catalysis. A soluble PEG-matrix was also employed in a microwave-assisted combinatorial synthesis of libraries of hydantoins [59, 60] and thiohydantoins [61]. A parallel synthesis of 1,5-disubstituted hydantoins and thiohydantoins was reported [62] under solvent free conditions in the presence of polyphosphoric ester. A collection of 3,5,5-trisubstituted hydantoins was also prepared in a microwave-assisted condensation of substituted benzils with ureas, followed by N^3-alkylation [63].

2.5
Pyrazoles, Isoxazoles, Indazoles

A small library of pyrazoles was synthesized in a MCR of cyclic 1,3-diketones, DMF–DMA and hydrazines [64]. Although the reaction presumably proceeds via cyclodehydration of the intermediate hydrazonoketone **34**, the use of wa-

ter as a solvent nevertheless was found to be beneficial. Microwave heating of the reaction at 200 °C for 2 min in water was equal in terms of yields to the reflux reaction in an oil-bath for 4 hours. Moreover, the desired pyrazoles were easily isolated by simple filtration from the aqueous reaction mixture, thus simplifying the workup and rendering the procedure especially useful for the production of compound libraries (Scheme 21). The use of hydroxylamine instead of hydrazine brought about the formation of isoxazole **35**. The cyclocondensation of monosubstituted hydrazines with *N*,*N*-dialkyl enaminones (such as **33**) or *N*,*N*-dialkyl enamino-β-keto esters (derived from ketones or β-keto-esters, respectively, and DMF–DMA) has been widely employed both in the solution phase [65, 66] and in the polymer-supported synthesis [67] of substituted pyrazoles. Thus, the attachment of enamino-β-keto esters to cellulose beads [68] was accomplished through the enamine moiety, which is a leaving group in the subsequent reaction with phenylhydrazine or hydroxylamine. As a result, concomitant release of the desired pyrazoles or imidazoles from the polymer-supported intermediate **36** into solution occurred upon the cyclization reaction. The catch and release approach delivered a library of trisubstituted pyrazoles with minimal purification and without the need for cleavage of the final product from the resin. The use of microwave dielectric heating both in the cellulose-bound enaminone formation step and

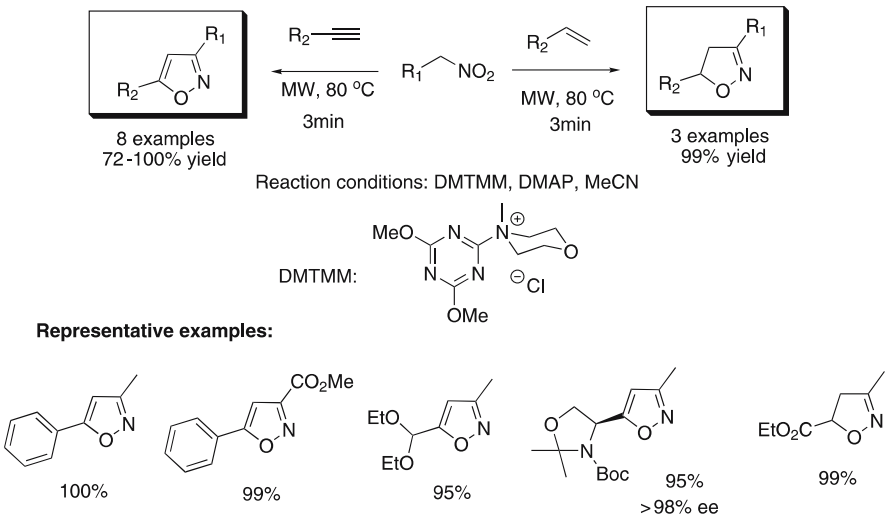


Scheme 21 Microwave-promoted multicomponent synthesis of pyrazoles and isoxazoles

in the subsequent cyclization step dramatically reduced the overall reaction time from 49–53 hours to 30 minutes. The cellulose-supported aniline could be recycled up to 10 times without any reduction in yields and purity. Similarly, the use of hydroxylamine instead of hydrazine delivered a 11-membered library of isoxazoles (Scheme 21).

1,3-Dipolar cycloaddition of nitrile oxides to olefins and acetylenes is among the most widely exploited synthetic routes towards isoxazoles and isoxazolines. It is well-known that microwave irradiation in cycloaddition reactions considerably reduces reaction times. Indeed, the use of dielectric heating (microwave-heated reactions were performed in a flask with a reflux condenser mounted outside the apparatus) allowed for a remarkable reduction of the cycloaddition reaction time from 6–12 hours to merely 3 minutes [69]. Simple aqueous workup provided the target isoxazoles and isoxazolines. The requisite nitrile oxides for the cycloaddition reaction were generated in situ from the corresponding nitroalkanes, 4-(4,6-dimethoxy [1, 3, 5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) and 4-dimethylaminopyridine (DMAP) (Scheme 22).

A remarkable improvement of the cycloaddition process was observed also in the synthesis of isoxazolidine **37** under microwave irradiation conditions [70] (Scheme 23). Thus, microwave dielectric heating of nitrone and allyl alcohol for merely 1 hour was equivalent in terms of yields to the oil-bath heating for as long as 15 days. The addition of $Zn(OTf)_2$ not only improved the diastereoselectivity of the process, but also resulted in a substantial reduction of the reaction time. Still, microwave irradiation at 120 °C delivered the diastereomerically pure isoxazolidine **37**-*cis* in just 15 minutes,

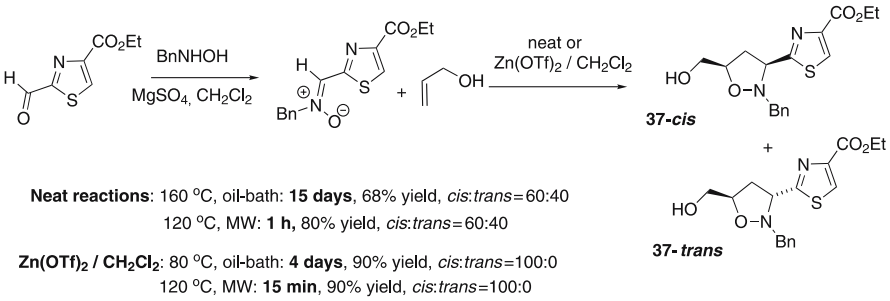


Scheme 22 Rapid 1,3-dipolar cycloaddition of nitrile oxides to olefins and acetylenes

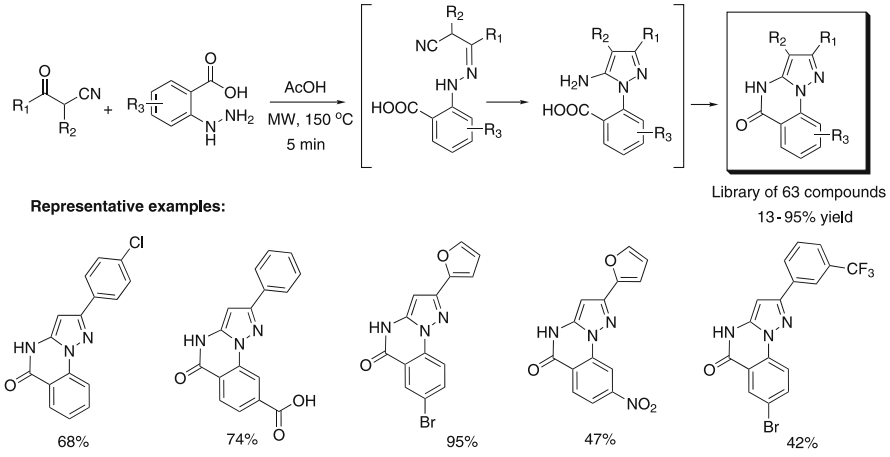
while the corresponding oil-bath reaction at 80 °C was remarkably slower (4 days) (Scheme 23).

A 63-membered library of pyrazoloquinazolinones was prepared from nine hydrazinobenzoic acids and seven cyanoketones [71] in a microwave-assisted tandem α-aminopyrazole formation—an amide bond-forming ring closure reaction. In many cases, the products precipitated out of the reaction mixture and simple washing with diethyl ether furnished the products with purities greater than 95%. Alternatively, heterocycles were isolated in a high-throughput fashion via preparative HPLC (Scheme 24).

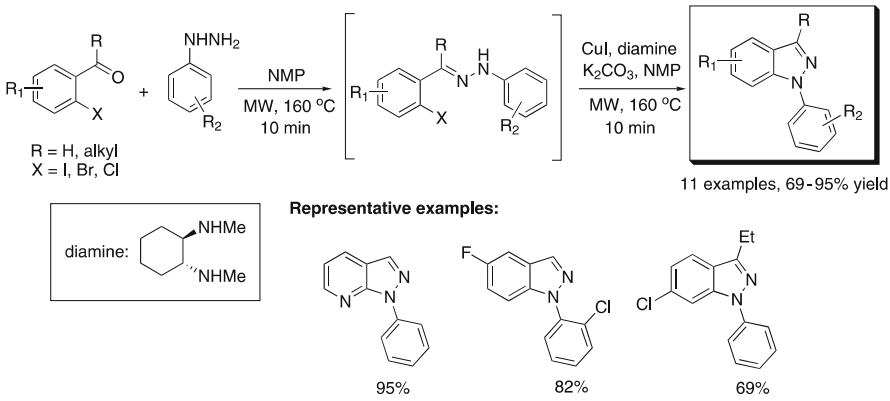
A microwave-assisted one-pot two-step approach towards 1-arylindazoles relied on a copper-catalyzed intramolecular *N*-arylation–cyclization of in situ formed arylhydrazones [72]. Traditionally, the CuI-diamine-complex catalyzed *N*-arylation reactions occurred at elevated temperatures (up to 110 °C) and required prolonged time (up to 24 h) to go to completion [73]. The com-



Scheme 23 Microwave-accelerated preparation of isoxazolidines



Scheme 24 One-pot synthesis of a library of pyrazoloquinazolinones under microwave irradiation



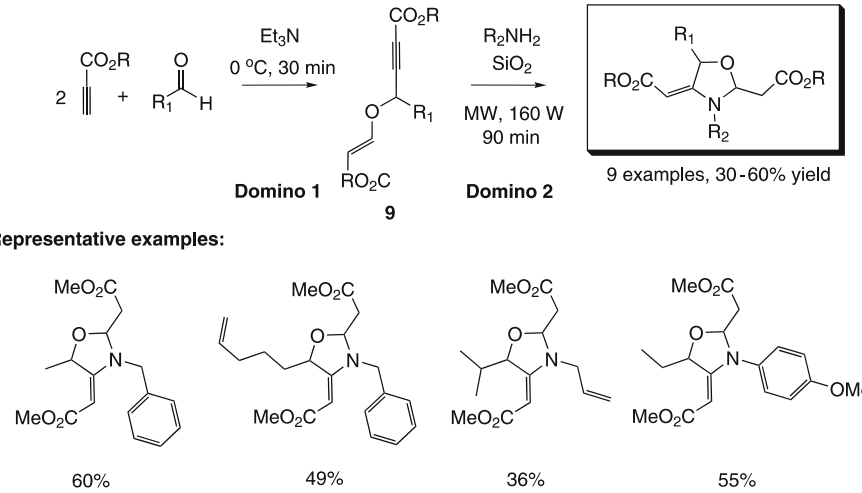
Scheme 25 Cu-catalyzed cyclization of transient arylhydrazones

bination of microwave dielectric heating at 160 °C with the use of a polar high boiling solvent—NMP (*bp* = 202 °C) reduced the *N*-arylation reaction time substantially to merely 10 minutes. It is noteworthy that not only aryl iodides and bromides, but also aryl chlorides were reactive in the intramolecular *N*-arylation reaction (Scheme 25).

2.6 Oxazoles, Benzoxazoles

Polysubstituted 1,3-oxazolidines were prepared in a one-pot diversity oriented four-component reaction (4-MCR), comprising two linked domino processes. Thus, domino synthesis of enol ethers **9** was followed by a sequential amine addition–cyclization sequence [74]. While strong microwave irradiation (900 W) of silica-gel absorbed conjugated alkynoates **9** and amines afforded tetrasubstituted pyrroles (via the skeletal rearrangement of 1,3-oxazolidines, see Sect. 2.1 and Scheme 5) [24], the use of milder microwave conditions (160 W power, 90 min) furnished 1,3-oxazolidines. Under these mild conditions the 1,3-oxazolidines did not rearrange to pyrroles and with respect to diastereoselectivity, the 1,3-oxazolidines were obtained as mixtures of syn/anti isomers. Overall, the formation of one C – C bond, one C – O bond, two C – N bonds and a ring in this MCR required less than 3 hours and utilized simple and commercially available reagents (Scheme 26).

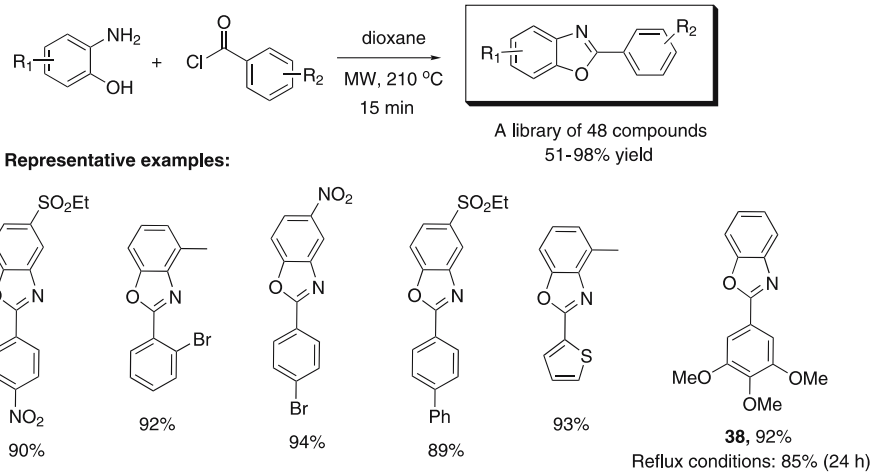
A microwave-assisted one-pot approach towards 2,4,5-trisubstituted oxazoles employed a hypervalent iodine (III) catalyst to bring about the reaction of ketones, 1,3-diketones and β-keto-carboxylic acid derivatives with amides [75]. Microwave dielectric heating was also successfully utilized in a solid-supported, solvent-free synthesis of 2-phenyl-oxazol-5-ones (azlactones) [76] as well as in a solution phase synthesis of isomeric 2-phenyl-oxazol-4-ones (oxalactims) [77].



Scheme 26 Domino synthesis of polysubstituted 1,3-oxazolidines

Benzoxazoles are routinely prepared in a two-step sequence comprising base-catalyzed bis-acylation of *ortho*-aminophenols followed by a Lewis-acid-assisted cyclization–dehydration reaction. Microwave flash heating of readily available acid chlorides and *ortho*-aminophenols in sealed reaction vessels delivered benzoxazoles in a one-pot process without aid of any additive such as base or Lewis acids [78]. Presumably, microwave heating (210 °C, 15 min) of *ortho*-aminophenols and acid chlorides produced monoacylated aminophenols and gaseous HCl as a byproduct. Because the reactions were performed in sealed tubes, gaseous HCl remained in the reaction media and catalyzed the concomitant cyclization–dehydration towards benzoxazoles. For comparison, conventional dioxane reflux at ambient pressure required 24 hours to give an 85% yield of benzoxazole **38**. Although toluene and dioxane were equally efficient as solvents, the latter rendered the isolation of the desired heterocycles more convenient. Thus, the reaction mixture was simply diluted with water and the precipitated benzoxazoles were collected by filtration. To demonstrate the suitability of the developed methodology (comprising rapid synthesis and simple workup) in medicinal and combinatorial chemistry, a representative 48-membered focused library of benzoxazoles was prepared (Scheme 27).

In a closely related publication, carboxylic acids were employed instead of acid chlorides in a microwave-assisted direct synthesis of 2-substituted benzoxazoles [79]. The reactions with 2-aminophenol were performed in a household microwave oven and worked well with aromatic, heteroaromatic, α,β-unsaturated and arylalkyl carboxylic acids (35–82% yields). Phthalic acid formed only mono-benzoxazoles, while the use of succinic acid led to a mixture of mono- and bis-benzoxazoles. Phthalic and succinic anhydrides could



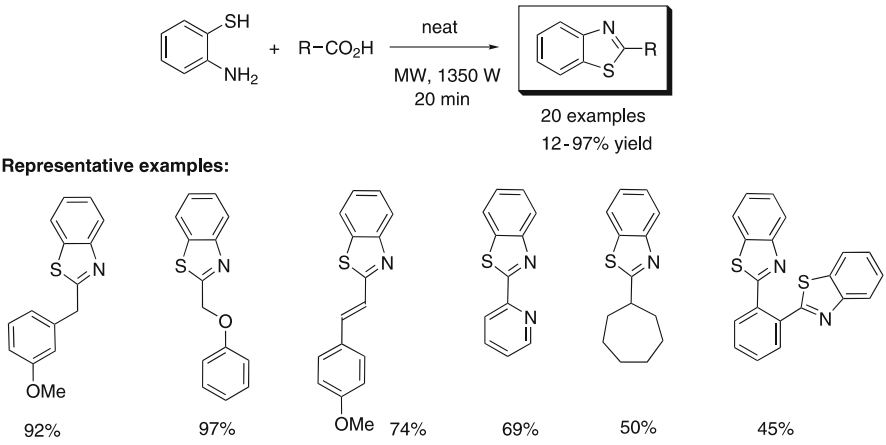
Scheme 27 Microwave-assisted preparation of a library of benzoxazoles

be conveniently used in place of the acids. A related microwave-assisted cyclocondensation of 5-amino-4-hydroxy-3(2*H*)-pyridazinones with various carboxylic acids in the presence of polyphosphoric acid furnished oxazolopyridazinones [80].

2.7 Benzothiazoles

Benzothiazoles were obtained by a direct cyclocondensation of 2-aminothiophenol with a variety of carboxylic acids in the absence of any catalyst or dehydrating agent. The heterocycles were readily formed within 20 minutes in a household microwave oven [81]. Although direct comparison with the conventional thermal conditions was not made, reported literature precedents employed oil-bath heating of aminothiophenol with carboxylic acid at 220 °C for 4 hours in the presence of polyphosphoric acid [82] or $P_2O_5 - MeSO_3H$ (70 °C, 10 h) [83]. Consequently, the microwave methodology rendered clear advantages both in terms of reaction speed and milder conditions. A variety of carboxylic acids (aromatic, heteroaromatic, α,β-unsaturated, arylalkyl and cycloalkylcarboxylic acids) could be used and the reaction conditions were compatible with different functional groups such as chlorine, methoxy, phenoxy and thiophenoxy moieties. Bis-benzothiazoles could be obtained in the reaction with succinic and phthalic acids (Scheme 28).

Reduction of the reaction time was achieved by the use of microwave dielectric heating in synthesis of 2-cyanobenzothiazoles from anilines and 4,5-dichloro-1,2,3-dithiazolium chloride [84, 85]. $Mn(OAc)_3$ promoted the radical-mediated cyclization of aryl- and benzoyl-thioformanilides. The re-

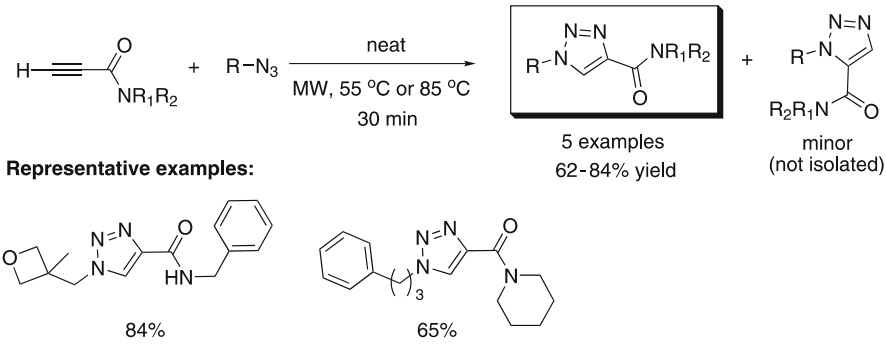


Scheme 28 Cyclocondensation of 2-aminothiophenol with neat carboxylic acids

action required microwave heating in acetic acid at 110 °C for 6 minutes (household oven) to furnish a number of 2-substituted benzothiazoles [86]. The reactions in an oil-bath needed 6–10 hours to obtain comparable yields.

2.8 Triazoles

1,2,3-Triazoles are generally prepared by the 1,3-dipolar cycloaddition of an alkyne with an azide at elevated temperatures. Thus, reaction of organic azides with acetylenic amides was significant only after 12 h refluxing in toluene. As a contrast, microwave dielectric heating at 55–85 °C under solvent-free conditions furnished the corresponding disubstituted 1,2,3-triazoles within 30 minutes [87]. Heterocycles were formed as a mixture of two regioisomers and the major regioisomer was separated from



Scheme 29 1,3-dipolar cycloaddition of alkynes with an azide

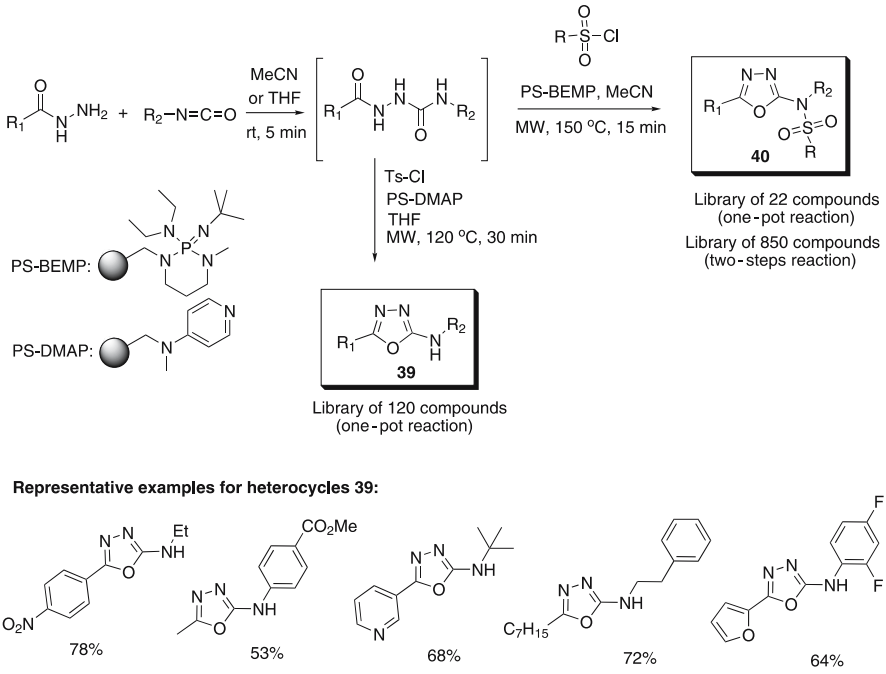
the mixture by fractional recrystallization (Scheme 29). 1,2,4-Triazoles have also been synthesized in a condensation reaction of acid hydrazide, *S*-methyl isothioamide hydroiodide and NH_4OAc on the surface of silica gel under microwave irradiation [88].

2.9 Oxadiazoles, Thiadiazoles

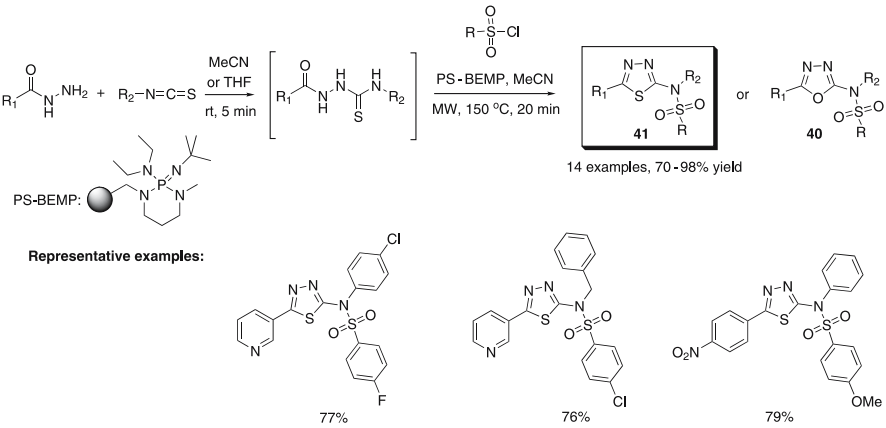
Ley and co-workers developed a methodology for the preparation of 5-substituted-2-amino-1,3,4-oxadiazoles, their 2-aminosulfonylated analogues as well as the corresponding thiadiazole analogues [89]. Several features rendered the developed procedure especially useful for high-throughput automated synthesis of large compound libraries. First, the approach was diversity-oriented as it was based on a one-pot, three-component coupling of acylhydrazines, isocyanates (or isothiocyanates) and sulfonyl chlorides. Second, the methodology was designed to be divergent, allowing for selective formation of either 2-amino-1,3,4-oxadiazoles **39** or their 2-aminosulfonylated analogues **40** simply by choice of the appropriate base. Third, the attachment of a base to a polymer support rendered workup of the reaction mixture simple and convenient. Specifically, the polymer was removed by simple filtration and the product was isolated after passing through a silica cartridge. Finally, the use of microwave flash heating in combination with polymer-supported reagents resulted in rapid and clean transformations. Moreover, the use of a dedicated microwave synthesizer with an integrated liquid handling robot produced individual compounds for large compound libraries in an automated manner. Altogether, a 120-membered library of 5-substituted-2-amino-1,3,4-oxadiazoles and an impressive 850-membered library of distinct and isolated 2-aminosulfonylated analogues were prepared (Scheme 30).

Comprehensive screening of polymer-supported bases revealed that many bases could catalyze cyclodehydration to afford heterocycles **39**, but only especially strong bases such as PS-BEMP [for an earlier report on microwave-assisted cyclodehydration of 1,2-diacylhydrazines using polymer-supported phosphazene base (PS-BEMP) and TsCl see: [90]] catalyzed both cyclodehydration and subsequent sulfonamidation towards structures **40**. PS-DMAP was the most efficient base to promote the cyclodehydration en route to 2-amino-1,3,4-oxadiazoles **39**. To separate the desired heterocycles **39** from unreacted ureas, a difference in solubility and basicity between the starting materials and products **39** was exploited, using catch and release purification with a silica-bonded sulfonic acid sorbent. Workup and purification was facile also in the case of sulfonamides **40**, requiring only filtration through a short plug of silica and solvent evaporation.

A substrate-dependent transformation to either thiadiazoles **41** or oxadiazoles **40** occurred upon cyclodehydration of thiosemicarbazides and the selectivity of the reaction was found to be highly dependent on the electronic



Scheme 30 Preparation of oxadiazole libraries using polymer-supported reagents

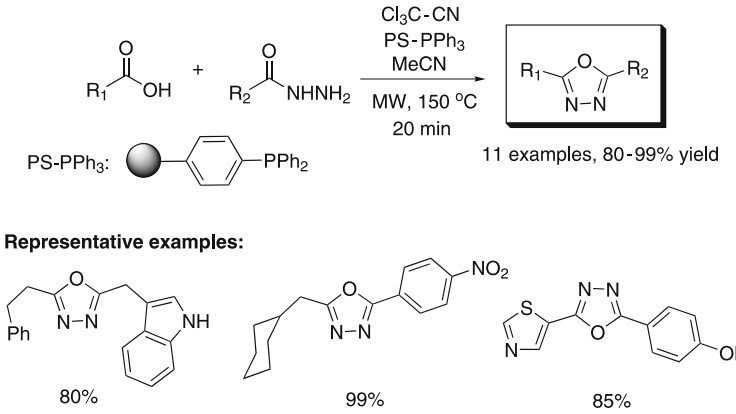


Scheme 31 Microwave-promoted cyclodehydration of thiosemicarbazides

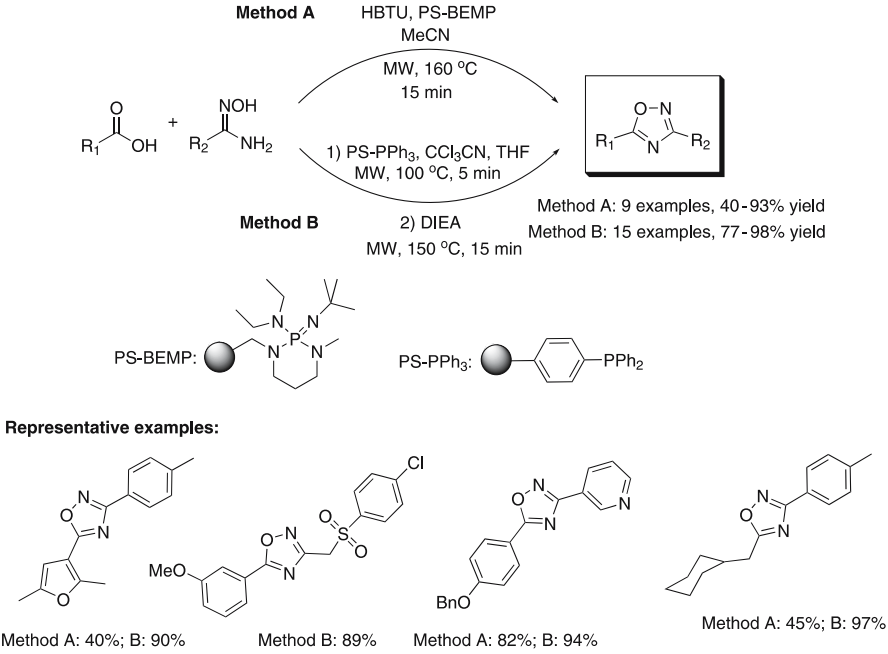
characteristics of the R_1 and R_2 substituents [89]. Thus, electron-withdrawing R_1 substituents directed the formation of thiadiazoles **41**, while electron-donating R_1 groups or simple alkyl substituents in urea afforded oxadiazoles **40** in the cyclocondensation step (Scheme 31). Alternatively, thiadia-

zoles were prepared in a microwave-assisted thionation–cyclization sequence from 1,2-diacylhydrazines and Lawesson's reagent under solvent-free conditions [91].

A one-step synthesis of 1,3,4-oxadiazoles from readily available carboxylic acids and acid hydrazides was mediated by the polymer-supported reagent



Scheme 32 One-step synthesis of 1,3,4-oxadiazoles under microwave irradiation



Scheme 33 Rapid generation of libraries of 1,2,4-oxadiazoles using solid-phase reagents

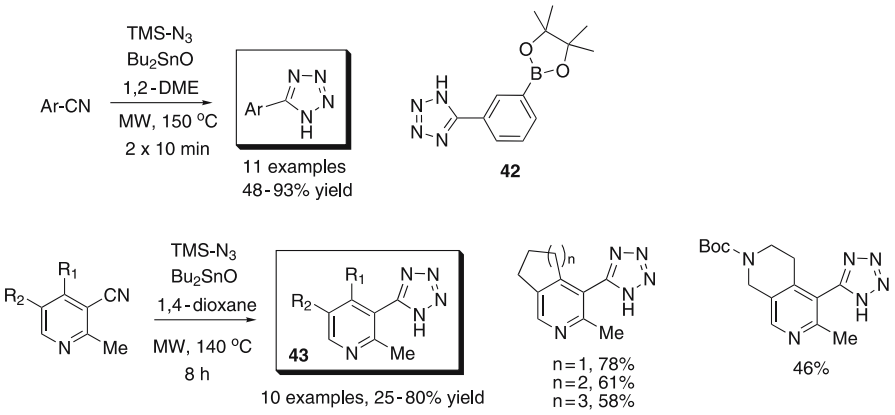
PS – PPh_3. A combination of PS – PPh_3 and CCl_3CN not only facilitated the formation of intermediate 1,2-diacylhydrazides by in situ conversion of carboxylic acids to acid chlorides, but also assisted subsequent cyclization to 1,3,4-oxadiazoles. The workup comprised simple filtration of the resin and evaporation of solvents, followed by flash chromatography. The cyclocondensation occurred within 20 min when heated in acetonitrile by microwaves in a sealed vial at 150 °C (68 °C above the boiling point) [92] (Scheme 32).

Two complementary methodologies were designed for rapid generation of libraries of 3,5-disubstituted 1,2,4-oxadiazoles from widely available carboxylic acids and amidoximes [93]. Both methods employed solid-phase reagents to simplify the purification process. Carboxylic acids were directly condensed with amidoximes in the presence of HBTU and an excess of PS-BEMP in acetonitrile (150 °C, 15 min). Alternatively, carboxylic acids were in situ converted to acid chlorides (with PS – PPh_3/CCl_3CN in THF) and subsequently reacted with amidoximes to furnish disubstituted oxadiazoles in good to excellent yields (Scheme 33).

2.10 Tetrazoles

The tetrazole functional group is of particular interest in medicinal chemistry since it is widely used as a bioisoster of the carboxyl group. Tetrazoles are usually prepared by the reaction of nitrile with various azide sources. Aryltetrazole boronate esters were prepared by the microwave-assisted reaction of the corresponding nitriles with TMS – N_3 in the presence of Bu_2SnO in 1,2-dimethoxyethane (DME) [94]. Characteristically, reflux for 22 hours in DME (~ 86 °C) in an oil bath was equal in terms of conversion to microwave irradiation for merely 20 min at 150 °C (99% yield of tetrazole **42**). Apparently, rapid heating by microwaves in conjunction with the use of a closed reaction vessel allowed the reaction to be performed well above the boiling point of the solvent, thus accelerating the cycloaddition. Indeed, a similar level of conversion (90% of tetrazole **42**) was observed in an oil bath utilizing the same conditions as the microwave-assisted reaction (150 °C, sealed tube, 20 min). These comparisons demonstrate that microwave heating in closed reaction vessels is a more effective and convenient method than conventional thermal techniques. The microwave-assisted cycloaddition could be readily scaled-up and run at higher concentrations in a sealed 80 mL microwave vessel (Scheme 34).

The sterically highly hindered di-*ortho*-substituted tetrazoles **43** were synthesized under similar conditions (TMS – N_3/Bu_2SnO in 1,4-dioxane, 140 °C) from the corresponding nitriles. Full conversion to the desired tetrazoles was not achieved even after prolonged reaction times (8 hours, 25–80% yield) and 15–63% of the starting nicotinonitriles were recovered [95] (Scheme 34).



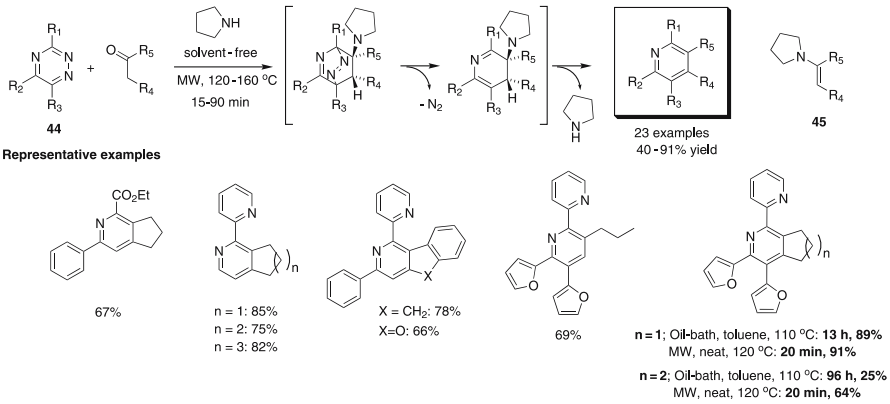
Scheme 34 Microwave-accelerated synthesis of tetrazoles

Tricyclic fused tetrazoles were prepared in a microwave-assisted tandem cycloaddition between TMS – N_3 and aromatic nitriles, followed by ring closure via an intramolecular *N*-allylation [96].

3
Six-membered Heterocycles

3.1
Pyridines, Dihydropyridines, Piperidines

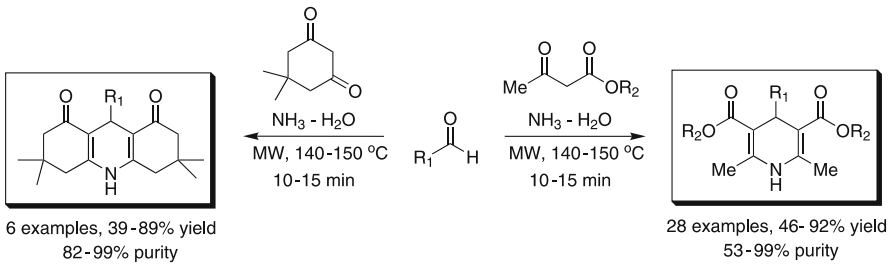
Steroidal, alicyclic or aromatic annulated pyridines were prepared via a microwave-assisted, base-catalyzed Henry reaction of β-formyl enamides and nitromethane on an alumina support [97]. Highly substituted tri- and tetrasubstituted pyridines were synthesized in a Bohlmann–Rahtz reaction from ethyl β-aminocrotonate and various alkynones. The reaction involved a Michael addition–cyclodehydration sequence and was effected in a single synthetic step under microwave heating conditions [98]. An alternative approach towards polysubstituted pyridines was based on a reaction sequence involving an inverse electron-demand Diels–Alder reaction between various enamines **45** and 1,2,4-triazines **44** (Sect. 3.6), followed by loss of nitrogen and subsequent elimination–aromatization. Enamines **45** were formed in situ from various ketones and piperidine under one-pot microwave dielectric heating conditions [99]. Furthermore, a remarkable acceleration of the reaction speed (from hours and days to minutes) was observed in a microwave-assisted cycloaddition. Unsymmetrically substituted enamines **45** afforded mixtures of regioisomers (Scheme 35).



Scheme 35 Inverse electron-demand Diels–Alder reaction of enamines and 1,2,4-triazines

The Hantzsch synthesis of dihydropyridines represents a classical example of MCR, generating an array of diversely substituted heterocycles in a one-pot reaction procedure. Given that the reaction requires elevated temperatures and extended reaction times to proceed, acceleration of the process by microwave irradiation could be envisioned. Indeed, dielectric heating of aldehyde (aliphatic or aromatic) and 5 equivalents of β-ketoester in aqueous 25% NH_4OH (used both as reagent and solvent) at 140–150 °C for merely 10–15 min furnished 4-aryl-1,4-dihydropyridines in 51–92% yield after purification on a silica gel column [100]. The Hantzsch synthesis under reflux conditions (~ 100 °C) featured a remarkably longer time (12 hours) and lower yields (15–72%). To demonstrate the suitability of the procedure for the needs of combinatorial chemistry, a 24-membered library of 1,4-dihydropyridines (DHP) was prepared (Scheme 36).

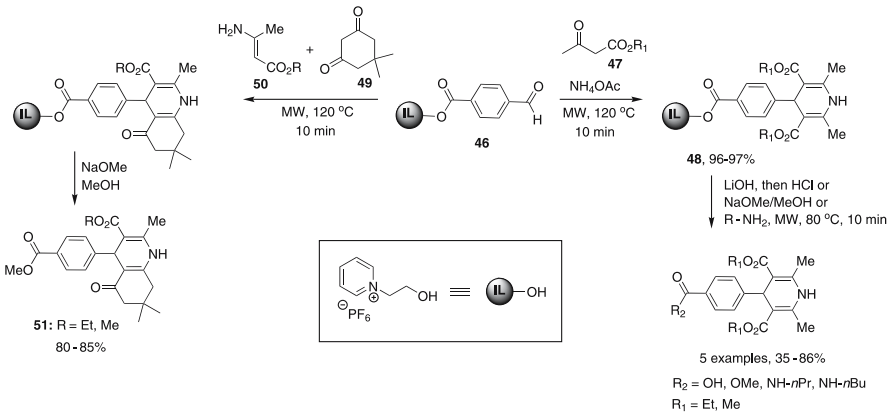
Notwithstanding the reduced reaction times and improved yields, the need to use column chromatography to purify the target 1,4-DHP encumbers the application of the procedure for the fast preparation of screening libraries. To address the purification issue, various phase-separation techniques could be employed, such as solid-phase organic synthesis (SPOS).



Scheme 36 Microwave-promoted Hantzsch synthesis

However, the SPOS is usually associated with relatively long reaction times (due to the heterogeneous reaction conditions) as well as difficulties in monitoring the progress of the reaction. On the contrary, the use of soluble polymeric matrices allows the reaction to proceed under standard liquid phase conditions, while still keeping the advantages of purification using phase-separation techniques. For example, ionic liquids (IL), being immiscible both with a wide range of organic solvents and with water, can form a non-aqueous two-phase system. Consequently, the product isolation requires only extraction and washings. Moreover, after the first reactant is anchored to an IL phase, the excess reagents and by-products in subsequent reactions can be removed easily by solvent washing. Finally, the use of task-specific IL as a soluble polymeric matrix under the dielectric heating conditions intuitively seems to be especially beneficial, because ILs interact very efficiently with microwaves through the ionic conduction mechanism. Thus, condensation of IL-supported aldehyde **46**, β-ketoester **47** and NH_4OAc furnished IL-supported 1,4-dihydropyridines **48** (96–97% yield) after microwave heating at 120 °C for 10 min [101]. Product cleavage from the IL-support afforded carboxylic acids, esters or amides, depending on the cleavage conditions. Unsymmetrically substituted 1,4-DHP **51** were obtained in a similar way from IL-supported aldehyde **46**, dimedone **49** and aminocrotonate **50**, followed by transesterification (Scheme 37).

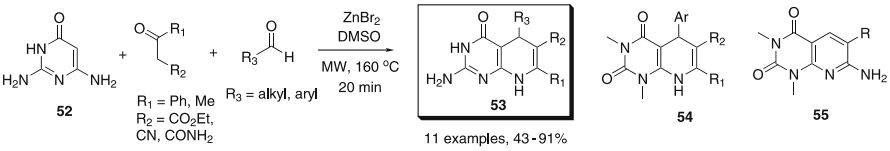
The use of 2,6-diaminopyrimidin-4-one **52** in a related solution phase cyclocondensation reaction with various aldehydes and 1,3-dicarbonyl compounds furnished a number of pyrido[2,3-d]pyrimidines **53** [102]. The $ZnBr_2$-catalyzed reactions proceeded much faster under microwave heating conditions than in an oil-bath, requiring only 20 min dielectric heating at 160 °C (vs. 3 days at 110 °C with oil-bath heating) to go to comple-



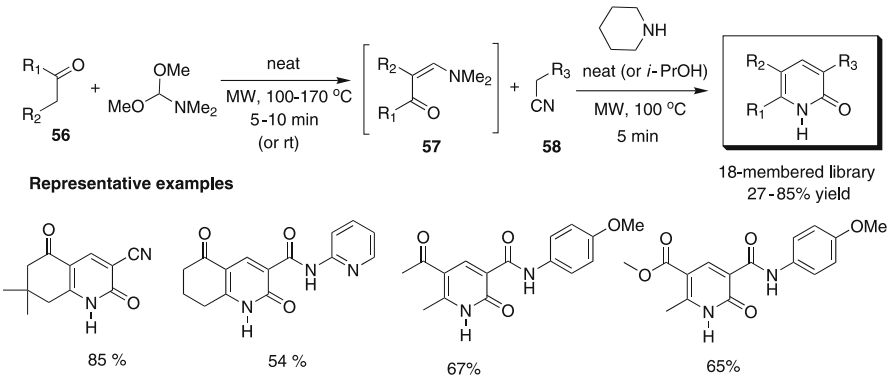
Scheme 37 Synthesis of dihydropyridines using task-specific ionic liquids as a soluble polymeric matrix

tion. The target heterocycles **53** were conveniently isolated by precipitation from the reaction mixture (Scheme 38). A number of related reports dealt with microwave-assisted preparation of fused pyrido[2,3-*d*]pyrimidines **54** and **55**, both under solvent-free conditions [103, 104] and on solid support [105]. *N*-hydroxylacridines were synthesized in another example of a microwave-assisted Hantzsch-type cyclocondensation of aryl aldoximes and dimedone [106].

An 18-membered library of highly substituted 2-pyridones has been prepared in a solution-phase one-pot, two-step MCR [107]. In the first step, preparation of enamines **57** from CH-active carbonyl compounds **56** and DMF–DMA was in all but two cases expedited by dielectric heating (100–170 °C, 5–10 min, solvent-free conditions). Subsequent cyclocondensation of enamines **57** with methylene-active nitrile **58** in the presence of a catalytic amount of piperidine occurred readily within 5 min upon microwave heating at 100 °C. It is noteworthy that the workup generally involved simple filtration of the target 2-pyridones, which precipitated from the reaction mixture upon cooling (Scheme 39). A series of *N*-aryl piperidines were obtained in a microwave-accelerated double *N*-alkylation of various anilines [12, 13] (see also synthesis of pyrrolidines, Sect. 2.1). Tetrahydropyridines were also prepared in a microwave-assisted intramolecular aza-Wittig reaction of chloro alkanes in the presence of NaN_3 and $(EtO)_3P$. The cyclization proceeded via in situ formation of alkyl azides [108].



Scheme 38 Microwave-promoted preparation of fused pyrimidines



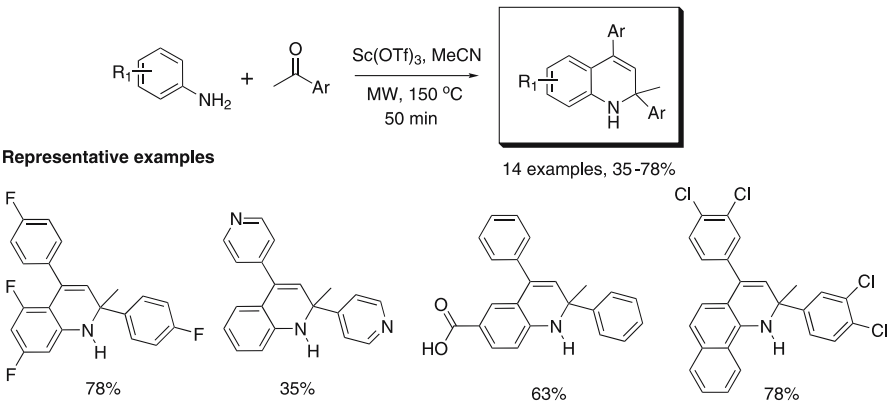
Scheme 39 Fast microwave-assisted synthesis of 2-pyridone libraries

3.2 Quinolines

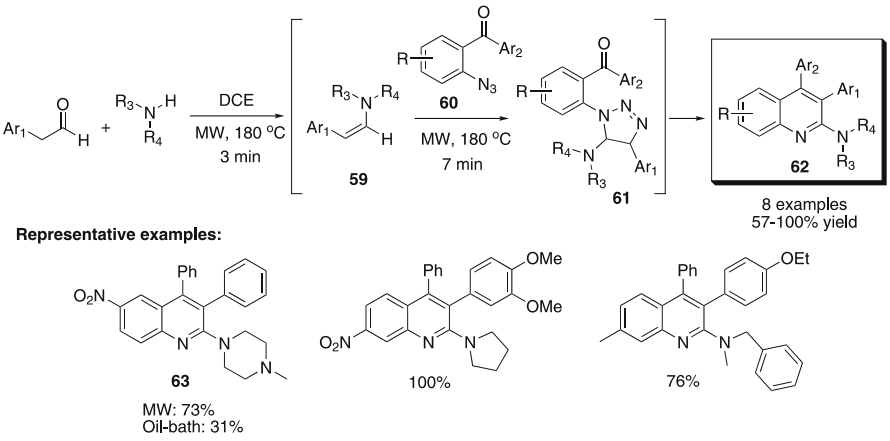
The use of $Sc(OTf)_3$ as the catalyst facilitated the Skraup synthesis of 1,2-dihydroquinolines from anilines and a variety of dialkyl ketones at mild conditions (room temperature). Nevertheless, an elevated temperature was necessary if acetophenone was employed in the cyclocondensation with anilines [109]. Microwave dielectric heating at 150 °C for 50 min was sufficient to bring about the formation of the desired 1,2-dihydroisoquinolines (Scheme 40).

2-Aminoquinolines **62** have been prepared in a two-step, one-pot, three-component reaction of 2-azidobenzophenones, secondary amines and arylacetaldehydes [110]. The microwave-assisted reaction proceeded via the initial formation of enamines **59**. Subsequent addition of 2-azidobenzophenones **60** afforded the triazoline intermediates **61**, which underwent thermal rearrangement and cyclocondensation to furnish 2-aminoquinolines **62** (Scheme 41). Direct comparison with conventional thermal conditions demonstrated the superiority of microwave dielectric heating in terms of yields (73% vs. 31% of heterocycle **63** after 10 min at 180 °C). Furthermore, the formation of by-products due to decomposition of azide **60** was diminished in the microwave-assisted synthesis. Purification of the products was achieved using solid-phase extraction techniques.

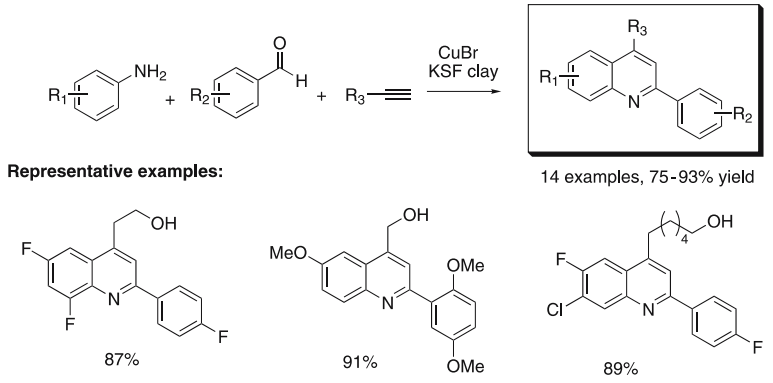
Microwave irradiation considerably improved the reaction speed and yields of 2,4-disubstituted quinolines in a MCR of aldehydes, anilines and alkynes [111]. The cyclocondensation was catalyzed by montmorillonite clay doped with copper(I) bromide and was completed within 3–5 minutes (pulsed irradiation technique—1 min with 20 s off interval), when performed in a household microwave oven. Oil-bath heating at 80 °C for 3–6 hours was necessary to achieve comparable yields of quinolines (71–90%) (Scheme 42).



Scheme 40 Microwave-promoted Skraup synthesis of 1,2-dihydroquinolines

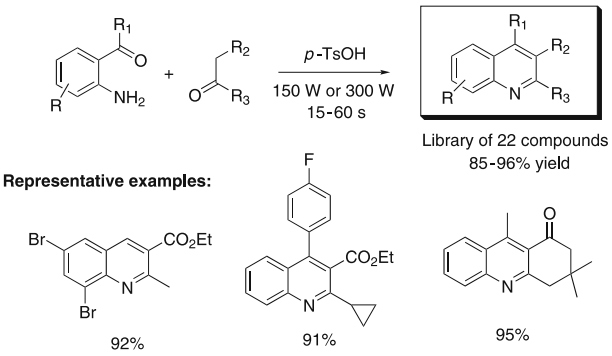


Scheme 41 Rapid synthesis of aminoquinolines under microwave irradiation



Scheme 42 Solvent-free one-pot synthesis of 2,4-disubstituted quinolines

The Friedländer annulation is one of the most straightforward approaches towards poly-substituted quinolines. Thus, a 22-membered library of quinolines was synthesized in a TsOH-catalyzed cyclocondensation–dehydration of 2-aminoaryl ketones and 2-aminoarylaldehydes with ketones in a household microwave oven (with power control) under solvent-free conditions [112]. It was observed that the Friedländer reaction occurred readily also in an oil-bath (at 100 °C). To compare the conventional and dielectric heating conditions precisely, a purpose-built monomode microwave system with temperature control was employed instead of the household oven. The experiments at 100 °C under otherwise identical conditions demonstrated that the dielectric heating protocol was only slightly faster. Products were isolated by a simple precipitation–neutralization sequence (in the case of solid products) or neutralization–extraction for oily or low melting point products (Scheme 43).



Scheme 43 Preparation of poly-substituted qinolines in the Friedländer annulation

Pyrido-fused tetrahydroquinolines were assembled in a $Sc(OTf)_3$ catalyzed aza-Diels–Alder MCR of 1,4-dihydropyridines, anilines and aldehydes. Although the cyclocondensation occurred within 12 hours at room temperature, the possibility to reduce the reaction time to just 5 min was demonstrated by microwave dielectric heating at 80 °C [113].

3.3 Pyrimidines

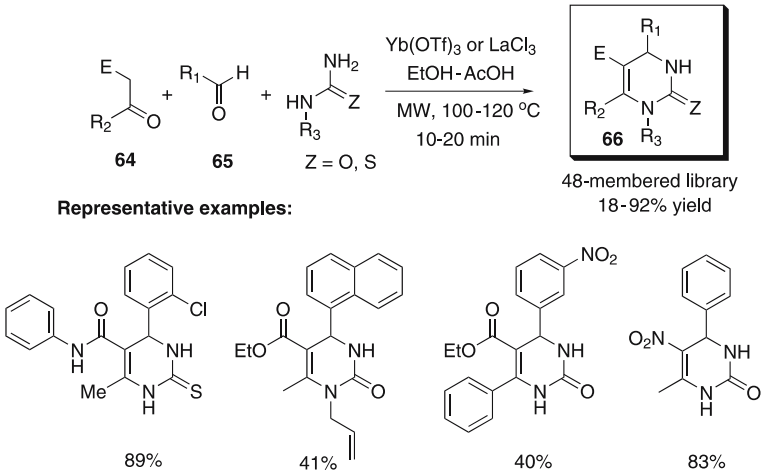
Dihydropyrimidinones are routinely synthesized in the Biginelli three component cyclocondensation reaction between CH-acidic carbonyl compounds, aldehydes and ureas (or thioureas) under strongly acidic conditions. Several improved protocols employed Lewis acids instead of traditional mineral acids with microwave heating. Thus, recent reports utilized montmorillonite KSF clay under solventless conditions [microwave heating in a household oven for 5–17 min (1200 W) vs. 6 h oil-bath at 110 °C] [114], NBS in *N*,*N*-dimethylacetamide (3–6 min, 600 W) [115] and catalytic amounts (10 mol %) of iodine adsorbed on neutral alumina (1 min, 90 °C) [116]. Alternatively, lanthanide catalysts ($Yb(OTf)_3$ or $LaCl_3$) were used by Kappe and Stadler in an automated sequential microwave-assisted synthesis of a 48-membered dihydropyrimidine library via the Biginelli reaction [117]. $Yb(OTf)_3$ catalyzed the cyclocondensation with ureas, while $LaCl_3$ was the superior catalyst in the case of thioureas. Microwave flash heating at 120 °C in pressurized vials, well above the boiling point of the solvents ($bp_{(EtOH)} = 78$ °C and $bp_{(AcOH)} = 117–118$ °C) brought down the reaction time from 4–12 hours (under reflux conditions) to 10–20 min. This rendered the sequential generation of a 48-membered library feasible within 12 hours. The library was generated in a fully automated and unattended mode using stock solutions of starting materials (CH-acidic compounds **64** and aldehydes **65**) and the liquid handling tools of the microwave synthesizer. Consequently, the solvents

(EtOH – AcOH 1 : 3) were chosen to ensure the complete dissolution of the starting components. Workup and isolation of the products became a critical issue in the context of the high speed of the methodology. The proper choice of the above-mentioned solvents made the workup simple and efficient as the formed products many times precipitated directly from the reaction mixture after completion of the reaction (Scheme 44).

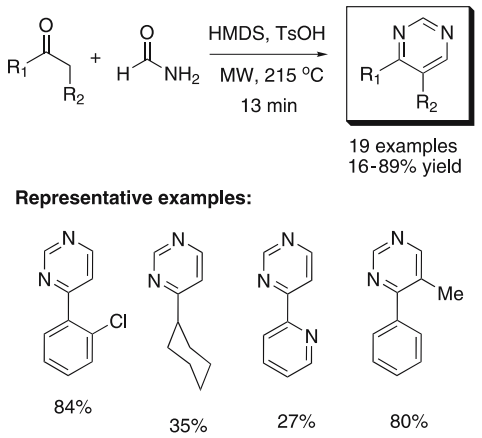
An alternative solution to the workup issue relied on the attachment of CH-acidic compounds **64** to a soluble polymer support (PEG-4000). The approach improved the yields of the dihydropyrimidinones **66** by the use of a 2-fold excess of other components—urea and aldehyde in the microwave-assisted solvent-free cyclocondensation [118]. Another single-step approach towards 4,5-disubstituted pyrimidines was based on cyclocondensation of a variety of aromatic, heterocyclic and aliphatic ketones, formamide and HMDS as the ammonium source [119]. The high temperature (215 °C) required to effect the formation of pyrimidines was secured by microwave dielectric heating in sealed vessels (Scheme 45).

A small library of di- and trisubstituted pyrimidines was prepared by condensation of amidines and guanidines with a range of alkynones. The reaction could be performed under conventional conditions (reflux in acetonitrile, ca. 82 °C), albeit 2 hours was required for the reaction to go to completion. Microwave dielectric heating in sealed vessels at 120 °C (ca. 38 °C above the boiling point of acetonitrile) diminished the reaction time to 40 min [120, 121] (Scheme 46).

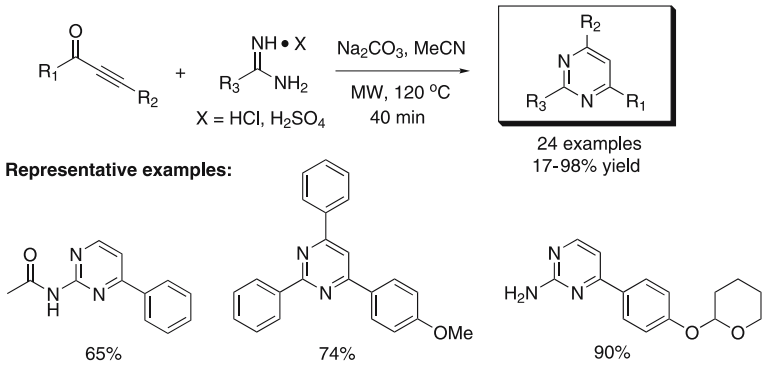
Pyrido[2,3-*d*]pyrimidines **70** were synthesized in a one-pot three-component cyclocondensation of α,β-unsaturated esters **67**, CH-active nitriles **68** and amidines **69** [122]. While reflux in THF or MeOH for 24 hours was required



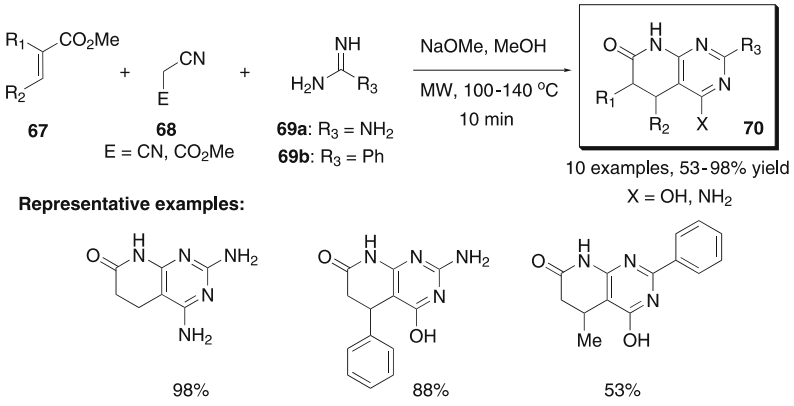
Scheme 44 Microwave-promoted automated synthesis of dihydropyrimidine library



Scheme 45 A single-step synthesis of pyrimidines



Scheme 46 Rapid condensation of amidines and guanidines with alkynones



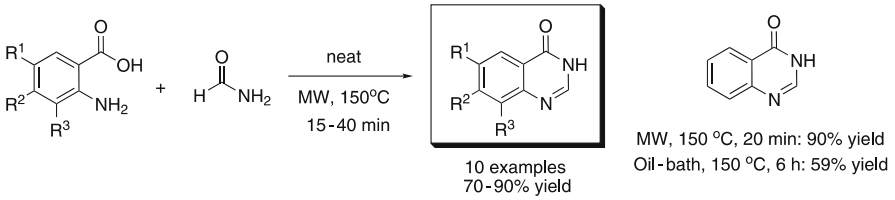
Scheme 47 Three-component synthesis of pyrido[2,3-*d*]pyrimidines

to complete the cyclocondensation in an oil-bath, full conversion was effected after merely 10 min by microwave heating in sealed vessels at 100–140 °C. Notably, pyrido[2,3-*d*]pyrimidines **70** were conveniently isolated from the reaction mixture by simple filtration when guanidine **69a** ($R_3 = NH_2$) was used in the cyclocondensation. The amidine **69b** ($R_3 = Ph$) derived target heterocycles **70** required purification by flash chromatography (Scheme 47).

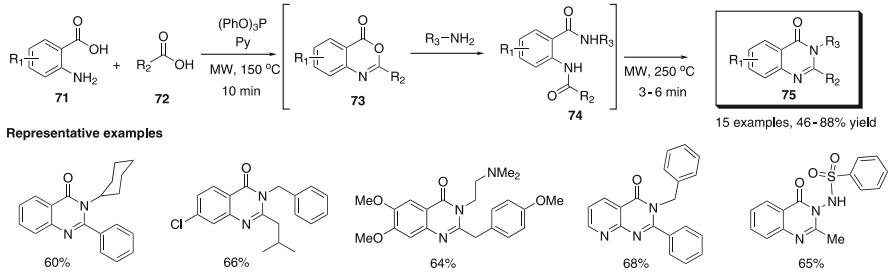
3.4 Quinazolines

The most common synthetic method towards quinazolin-4-ones is the Niementowski reaction, a cyclocondensation of anthranilic acid with formamide which requires high temperatures (130–150 °C) and long reaction times (6 hours). It is noteworthy that a remarkable reduction of the reaction time (20 min) was achieved under microwave heating conditions (150 °C) [123]. Moreover, microwave-accelerated reactions were cleaner and afforded higher yields than those under conventional thermal conditions (Scheme 48).

Liu and co-workers have developed an efficient three-component, one-pot, two-step synthesis of 3*H*-quinazolin-4-ones from readily available carboxylic acids and amines [124] (Scheme 49). The versatility of the methodology is remarkable. Simple variation of the starting materials allows not only for the decoration of the quinazolin-4-one core with diverse substituents, but also



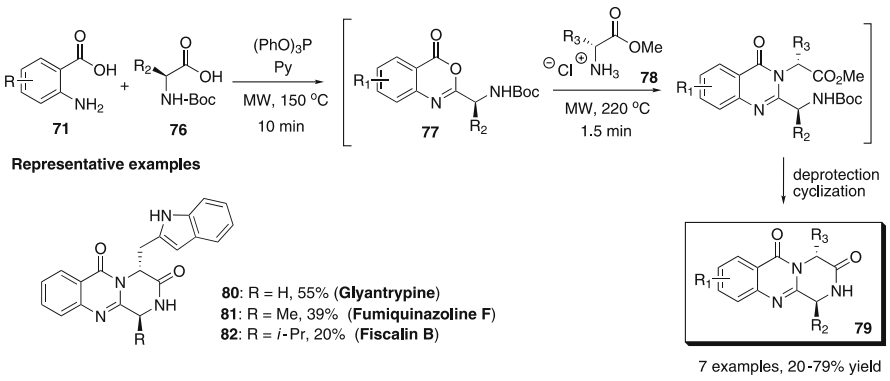
Scheme 48 Microwave-assisted Niementowski reaction



Scheme 49 Preparation of 3*H*-quinazolin-4-ones under microwave irradiation

for the construction of a variety of highly complex quinazolinone-derived heterocyclic systems such as pyrazino[2,1-*b*]quinazolines [125], pyrrolo[2,1-*b*]quinazolines [126] and quinazolinobenzodiazepines [127]. Thus, a variety of pharmacologically relevant complex heterocyclic systems and biologically active natural products could be synthesized rapidly and in an automated manner. Along with acceleration of the reaction speed, the use of microwave dielectric heating induced transformations that were difficult to effect in an oil-bath. The microwave-promoted cyclocondensation of anthranilic acid **71** with a carboxylic acid **72** in the presence of $(PhO)_3P$, followed by dehydration, afforded intermediate benzoxazinones **73**. Subsequent reactions with amines under conventional thermal conditions (reflux in pyridine) were sluggish, resulting in moderate yields of the desired heterocycle **75** (< 50%), which was accompanied by the intermediate diamide **74** and multiple side products (Scheme 49). On the contrary, dielectric heating at 150 °C effected clean conversion to the desired quinazolinone **75**, thus providing access to hitherto unavailable substitution patterns. Acid chlorides could be employed instead of carboxylic acids **72** and sulfonyl hydrazide performed as well as aliphatic and aromatic amines (Scheme 49).

The methodology was successfully extended to a one-pot total synthesis of complex heterocyclic systems such as pyrazino[2,1-*b*]quinazolines **79**, encountered in nature as alkaloids **80–82** (Scheme 50) [125]. To assemble the pyrazino[2,1-*b*]quinazoline core, *N*-Boc protected amino acid **76** was employed instead of carboxylic acid **72** (Scheme 49) in the synthesis of the corresponding intermediate benzoxazinones **77**. The subsequent reaction with an amine moiety of another amino acid ester **78** was accompanied by concomitant cleavage of the *N*-Boc protecting group and diketopiperazine-like cyclization (for the one-pot deprotection–cyclization reaction of *N*-Boc dipeptide esters to afford 2,5-piperazinedione under microwave dielectric heating, see: [128]) to afford the target heterocycle **79**. Hence, the total

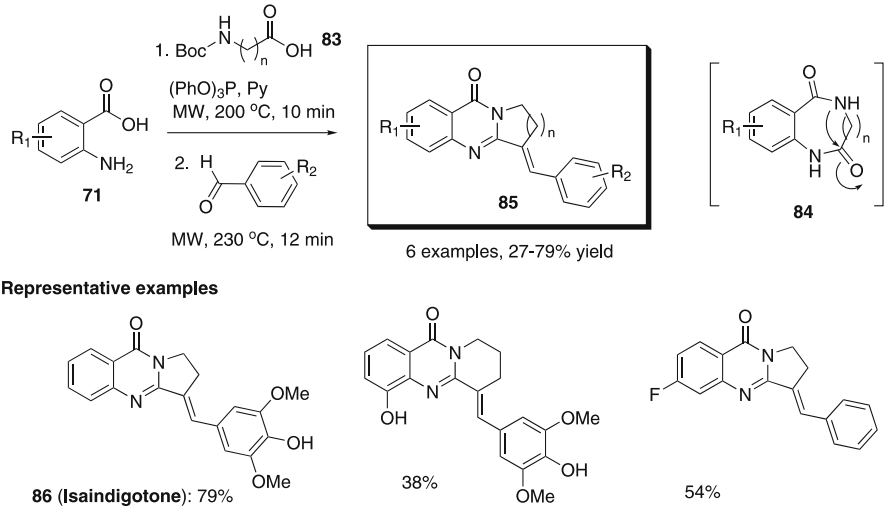


Scheme 50 One-pot total synthesis of pyrazino[2,1-*b*]quinazolines

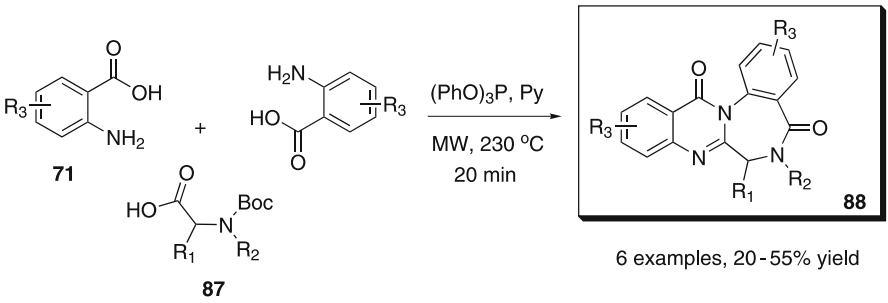
synthesis of alkaloids **80–82** was effected in a one-pot reaction comprising a three-component, four-step sequential process. Although partial epimerization of both stereogenic centers took place under the microwave heating conditions, simple recrystallization of quinazolines **80–82** increased the optical purity to > 99% ee. The wide chemistry scope of the methodology renders it suitable for preparation of natural product-templated libraries (Scheme 50).

An alternative protocol towards pyrazino[2,1-*b*]quinazolines **79** relied on cyclocondensation of diketopiperazine-derived lactim ethers with anthranilic acid. Microwave dielectric heating in a domestic oven (600 W irradiation power) furnished heterocycles **79** within 3–5 min, while the corresponding reaction in an oil-bath required 2 hours heating at 120–140 °C [129]. The use of *N*-protected *ω*-amino acids **83** in the microwave-assisted reaction with anthranilic acid **71** furnished pyrrolo[2,1-*b*]quinazolines **85** via transannular cyclization of the intermediate cyclic diamide **84** [126]. Subsequent in situ condensation with a variety of aldehydes furnished isaindigotone **86** and analogues, possessing cytotoxic activity (Scheme 51).

A microwave-assisted domino reaction of two equivalents of anthranilic acid **71** and *N*-Boc amino acid **87** to furnish quinazolinobenzodiazepinones **88** was elaborated [127] (Scheme 52). The development of the domino process was possible because the homo-coupling of anthranilic acid was presumably slower than the desired reaction between acids **71** and **87**. The use of microwave dielectric heating was beneficial as the formation of the seven-membered benzodiazepine ring required a higher temperature (230 °C) and a longer reaction time (20 min) compared to the six-membered analogues **79**



Scheme 51 Microwave-promoted preparation of pyrrolo[2,1-*b*]quinazolines



Scheme 52 Domino synthesis of fused benzodiazepinones

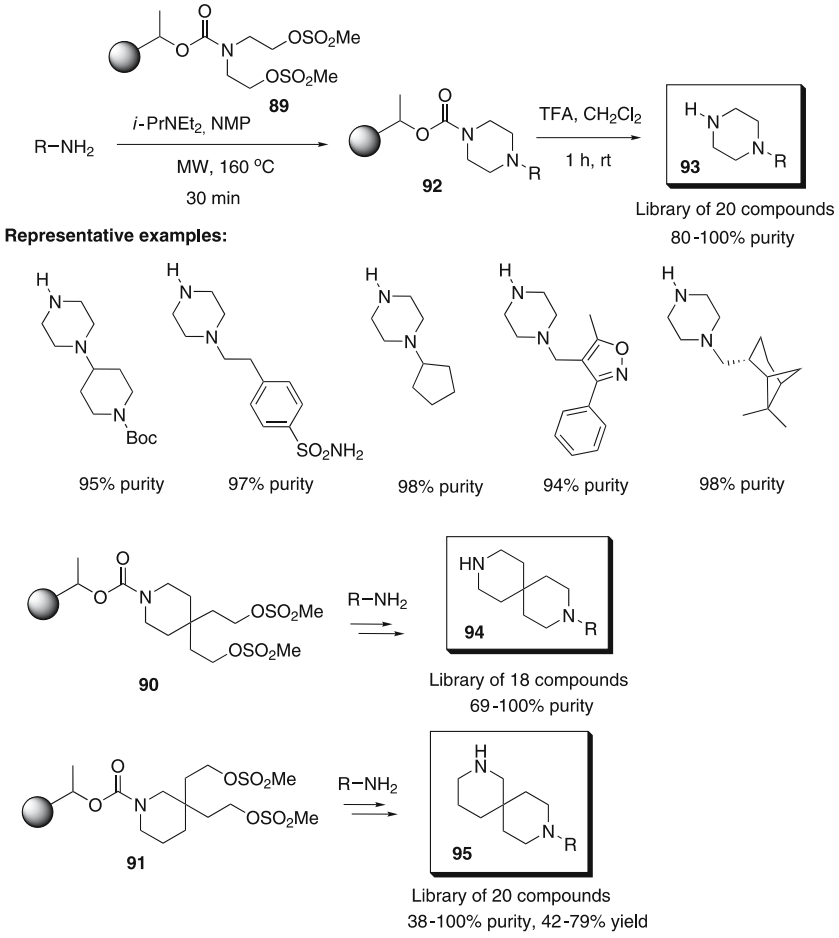
and **85** ($n = 2$). The desired heterocycles were purified by preparative HPLC (Scheme 52).

3.5
Piperazines, Pyrazines

A 20-membered library of piperazines **93** has been prepared in a parallel format utilizing microwave-assisted direct annulation of primary amines with resin-bound bis-mesylate **89**. Diazaspiro[5.5]undecane scaffolds **94** and **95** were obtained in a similar way employing the corresponding polymer-supported reagents **90** and **91** [130] (Scheme 53). The use of resin-bound bis-mesylates **89–91** allowed the utilization of a large excess of amine (10 equivalents) to bring the annulation to completion. The excess amine was subsequently removed by simple filtration and washing. Furthermore, the attachment of bis-mesylate **89** to a polymer support prevented possible contamination of the target heterocycles **93–95** with products from oligomerization side-reactions. It is worthwhile to note that solid-phase synthesis has also several drawbacks due to the heterogeneous nature of the process, such as relatively long reaction times, causing the thermal degradation of the polymer support. The use of microwave dielectric heating not only secured the high temperature (160 °C) necessary to drive the annulation to completion, but also reduced the reaction time, thus avoiding the degradation of the polymer backbone (it has been demonstrated that resins can withstand microwave irradiation even at 200 °C for short reaction times such as 20–30 min [131]). As the resin itself is a rather poor microwave absorber, sufficiently strong absorbtion of microwave energy was achieved by the use of a polar solvent—NMP. Moreover, the high boiling point (202 °C) of NMP allowed the annulation to be performed in open vessels. Subsequently, libraries of heterocycles **93–95** were prepared in a 96-well plate in a specialized microwave synthesizer designed for parallel synthesis. The workup of the annulation reaction (washing and filtration) and the cleavage from the resin was performed in an automated manner. The

whole process exemplifies the automated parallel synthesis of a small focused library (Scheme 53).

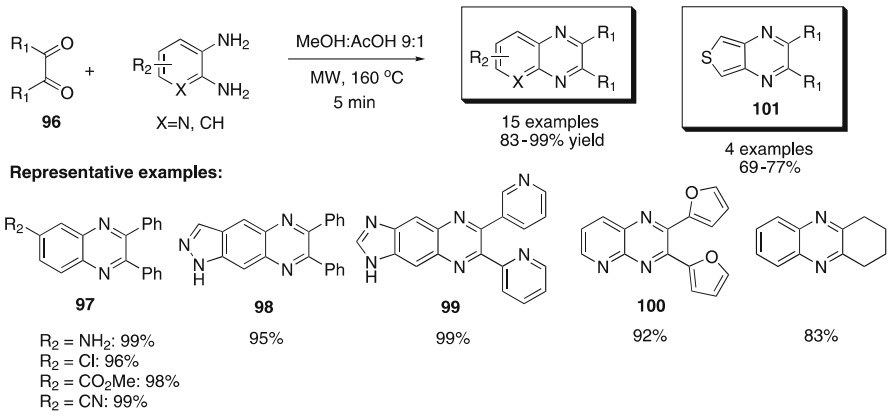
Lindsley and co-workers developed a general procedure towards the collection of diverse heterocyclic scaffolds from common 1,2-diketone intermediates **96**. Substituted quinoxalines **97**, fused pyrazolo[4,5-*g*]quinoxalines **98** and imidazolo[3,4-*g*]quinoxalines **99** as well as pyrido[2,3-*b*]pyrazines **100** and thieno[3,4-*b*]pyrazines **101** have been prepared in excellent yields [132] (Scheme 54), employing optimized reaction conditions (microwave heating of equimolar mixtures of 1,2-diketone **96** and diamine components at 160 °C for 5 min in 9 : 1 MeOH – AcOH). The use of microwave irradiation resulted in reduced reaction times (5 min vs. 2–12 hours), improved yields as well as the suppressed formation of polymeric species; a characteristic of traditional



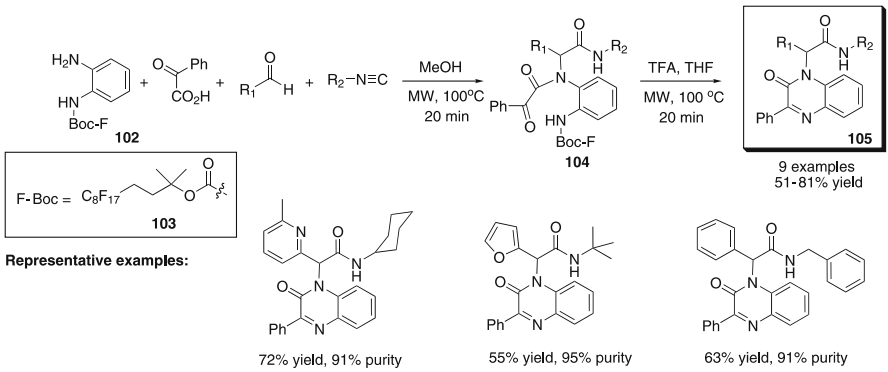
Scheme 53 Annulation of primary amines with resin-bound bismesylate reagents

thermal conditions. Thus, in contrast to heating in an oil-bath (at 50–70 °C) and even to the room temperature reactions, microwave irradiation at 160 °C for 5 min afforded thieno[3,4-*b*]pyrazine **101** (R_1 = Ph) in 72% yield with no detectable polymerization side-product (Scheme 54). The developed methodology was employed for the rapid preparation of two 200- and 50-membered focused libraries of 2,3-diaryl quinoxalines during lead generation and optimization of allosteric AKT protein kinase inhibitors [133]. Mono-substituted quinoxalines could be accessible also from α-hydroxyketones and symmetrical diamines in microwave-assisted solventless reactions provided that catalytic amounts (1 mol %) of an in situ oxidant (activated MnO_2) were employed [134].

Microwave dielectric heating accelerated Ugi four-component condensations of *N*-Boc aniline, acid, aldehyde and isonitrile, leading to quinoxalinones **105** and benzimidazoles [135]. To simplify the purification of the Ugi condensation products, fluorous phase organic synthesis was employed as an alternative to other, traditional phase separation techniques, for example, polystyrene resins. Thus, attachment of a fluorous *N*-Boc protecting group ("fluorous tag") **103** to a starting diamine **102** delivered the Ugi four-component condensation product **104**, which was soluble in fluorocarbon solvents while being immiscible with water, as well as many common organic solvents. Subsequently, the Ugi product **104** containing the F-Boc group was conveniently separated from the reaction mixture by fluorous solid-phase extraction (FSPE). Cleavage of the F-Boc protecting group was accompanied with concomitant cyclization to furnish the substituted quinoxalinones **105** (and benzimidazoles). The target heterocycles were obtained in moderate to excellent purity after FSPE (Scheme 55) [135]. Related microwave-assisted Ugi three-component MCR furnished 2,5-diketopiperazines [136]. Alternatively, 2,5-piperazines were prepared in a microwave-accelerated cyclocon-



Scheme 54 Preparation of diverse fused pyrazines



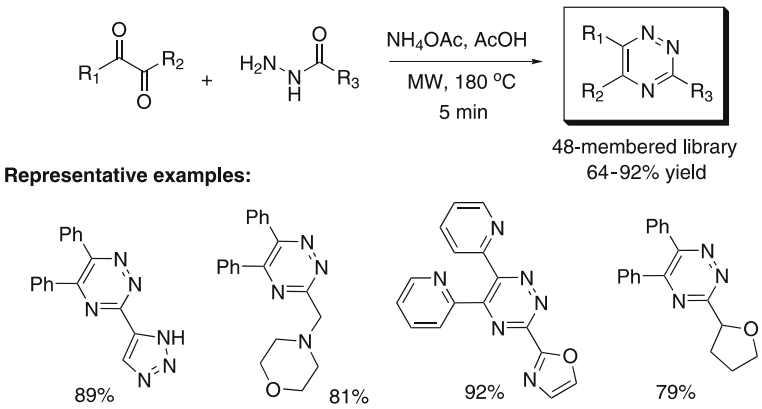
Scheme 55 Microwave-assisted fluorous phase Ugi four-component condensation

densation of Boc-protected dipeptide esters [128]. The use of microwave irradiation accelerated the synthesis of benzopiperazinones [137] as well as chiral quinoxalinones [138] on a soluble PEG polymer-support (Sect. 2.4).

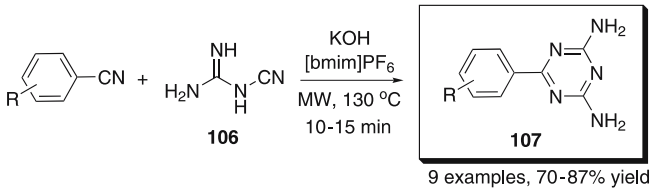
3.6 Triazines

The 1,2,4-triazine core is a synthetically important scaffold because it could be readily transformed into a range of different heterocyclic systems such as pyridines (Sect. 3.1) via intramolecular Diels–Alder reactions with acetylenes. 1,2,4-Triazines have been synthesized by the condensation of 1,2-diketones with acid hydrazides in the presence of NH_4OH in acetic acid for up to 24 h at reflux temperature. Microwave dielectric heating in closed vessels allowed the reaction to be performed at 180 °C (60 °C above the boiling point of acetic acid). As a result, the reaction time was reduced to merely 5 minutes. Subsequently, a 48-membered library of 1,2,4-triazines was generated from diverse acyl hydrazides and α-diketones [139]. Two thirds of the desired heterocycles precipitated from the reaction mixture upon cooling with > 75% purity, while the remaining part of the library was purified by preparative LCMS (Scheme 56).

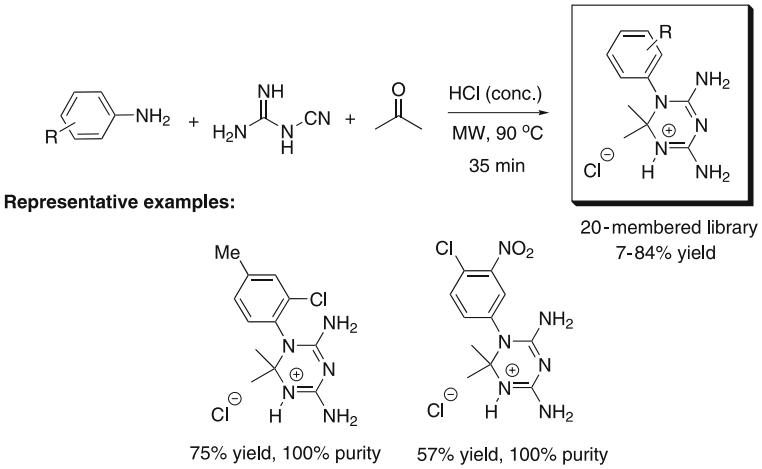
The "specific microwave effects" were presumably responsible for the observed 40-fold acceleration in microwave-assisted synthesis of 1,3,5-triazines **107** compared to conventional thermal conditions. Thus, microwave heating of benzonitrile and dicyandiamide **106** in an ionic liquid ([bmim]PF_6) in the presence of powdered KOH at 130 °C for just 12 min afforded 2,4-diaminotriazine **107** in 87% yield. Under otherwise identical conditions the reaction in a pre-heated oil-bath (130 °C temperature) took 8 hours to afford the target heterocycle **107** in 79% yield [140] (Scheme 57).



Scheme 56 Synthesis of a library of 1,2,4-triazines



Scheme 57 Microwave-accelerated synthesis of 1,3,5-triazines in ionic liquid



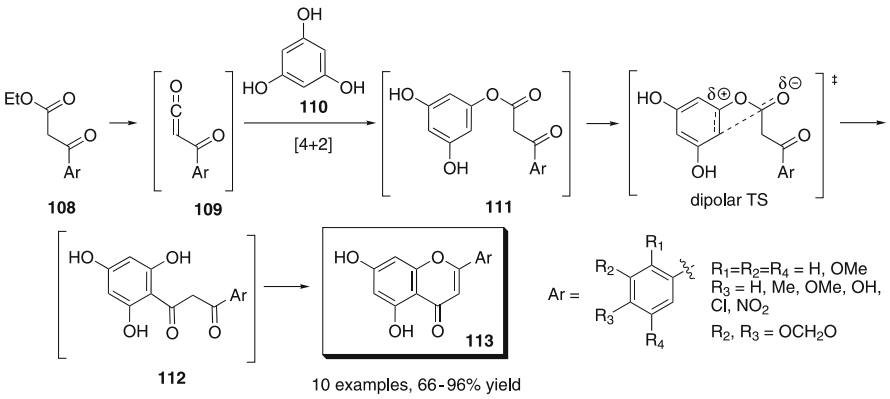
Scheme 58 Parallel synthesis of 1,3,5-triazine library

A 20-membered library of 1,3,5-triazines was prepared in a parallel format employing a one-pot, three-component condensation of anilines, dicyandiamide and acetone. The reaction time was reduced from 22 hours (reflux in

acetone at ~ 60 °C) to 35 min by using microwave dielectric heating at 90 °C in a sealed tube [141]. It is noteworthy that the workup consisted simply of cooling the reaction mixture to 4 °C and a subsequent filtration of the precipitated product (Scheme 58).

3.7 Benzopyrones (Coumarines, Chromones)

Specific microwave effects were proposed to accelerate the synthesis of chromones via cyclocondensation of phloroglucinol with β-ketoesters under solvent-free conditions [142]. The reaction presumably proceeded via formation of an intermediate β-diketone **112** in a [4 + 2] cycloaddition reaction of α-oxo ketene **109** with phloroglucinol **110**, followed by a Fries rearrangement. As the magnitude of heating by microwaves depends on the dielectric properties of the molecules, the greater the polarity of reacting species, the more efficient is the absorbance of the microwave energy. Consequently, for solvent-free reactions, where the polarity of the system is increased along the reaction coordinate (from the ground state to the transition state), enhancement of reactivity would be anticipated [143]. Microwave dielectric heating presumably facilitated both the [4 + 2] cycloaddition step and the subsequent Fries rearrangement of intermediate β-keto-ester **111**, because development of charges in the transition states during the reaction path could be envisioned (Scheme 59). Indeed, the yields under microwave irradiation were 4-fold higher than those in a conventionally heated reaction under otherwise identical conditions (reaction time 10 min, equal speed of heating from 25 °C to 125 °C). Accordingly, a series of chromones **113** was synthesized within 3–12 min by microwave heating of neat phloroglucinol and β-ketoesters at 240 °C. The workup involved a simple acid-base extraction (Scheme 59).



Scheme 59 Microwave-promoted synthesis of chromones

Alternatively, *ortho*-hydroxy β-diketones (such as **112**, Scheme 59) have been obtained in a microwave-assisted Baker–Venkataraman rearrangement of *O*-benzoylated *ortho*-hydroxyacetophenones in the presence of base (pyridine/KOH) [144]. Subsequent dehydrative cyclization of β-diketones under dielectric heating conditions was catalyzed by H_2SO_4 or $CuCl_2$ [145]. The closely related solvent-free cyclocondensation of β-ketoesters with phenoles (the Pechmann reaction) furnished coumarins in the presence of various acid catalysts such as montmorillonite K10 [147]. Graphite was employed as a chemically inert support to increase the efficiency of microwave absorbtion as it has been shown that graphite couples strongly with microwaves and efficiently transfers thermal energy to the absorbed reagents [147].

4 Conclusions

The speed and efficiency of dielectric heating renders the microwave technology particularly suitable for the rapid and automated production of heterocyclic libraries. Furthermore, the proper choice of microwave processing techniques (solvent-free, solid- or polymer-supported conditions, etc.) can simplify the workup and avoid laborious and time consuming purification of target products. Utilization of specific microwave effects (selective heating of reacting species) imparts an unusual reactivity that many times cannot be achieved by conventional heating.

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