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REVIEW

Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis

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Multicomponent reactions have gained significant importance as a tool for the synthesis of a wide variety of useful compounds, including pharmaceuticals. In this context, the multiple component approach is especially appealing in view of the fact that products are formed in a single step, and the diversity can be readily achieved simply by varying the reacting components. The eco-friendly, solvent-free multicomponent approach opens up numerous possibilities for conducting rapid organic synthesis and functional group transformations more efficiently. Additionally, there are distinct advantages of these solvent-free protocols since they provide reduction or elimination of solvents thereby preventing pollution in organic synthesis “at source”. The chemo-, regio- or stereoselective synthesis of high-value chemical entities and parallel synthesis to generate a library of small molecules will add to the growth of multicomponent solvent-free reactions in the near future. In this review we summarized the results reported mainly within the last 10 years. It is quite clear from the growing number of emerging publications in this field that the possibility to utilize multicomponent technology allows reaction conditions to be accessed that are very valuable for organic synthesis. Therefore, diversity oriented synthesis (DOS) is rapidly becoming one of the paradigms in the process of modern drug discovery. This has spurred research in those fields of chemical investigation that lead to the rapid assembly of not only molecular diversity, but also molecular complexity. As a consequence multi-component as well as domino or related reactions are witnessing a new spring.

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1 Introduction

The chemistry of organic synthesis attracts particular attention in science fundamentally because of its immense importance to life. The extreme flexibility of bonding at carbon is well-suited to the wide variety of structures required to support living systems. Organic synthesis is one of the most important and useful disciplines of chemistry, which mainly involves the construction and cleavage of carbon–carbon (C–C) and carbon–heteroatom (C–X) bond(s). The synthetic strategies regarding how to construct and cleave the above bonds represent the central theme in organic synthesis. Due to tremendous impact of the chemical industry in our society, there is constant pressure to reduce costs and consumable resources to have less detrimental impact to the environment. Present day organic synthesis requires and even demands certain regulations and guidelines in developing any operationally simple, useful, and practical strategy, keeping the protection of the environment as a major concern. The classical ways to improve synthetic reactions are either to invent a new reagent, to invent a new catalyst or to elucidate details about the mechanism that in turn enables one to judiciously modify conditions to increase the reaction's rate and/or yield. The continual upsurge in facile and non-polluting synthetic procedures urges chemists to increase tools of their arsenal. One approach to address this challenge involves the development of eco-compatible multicomponent procedures in organic synthesis.

The literature on multicomponent reactions (MCRs) has experienced exponential growth over the last decade and the literature of MCRs under solvent-free conditions has expanded enormously, making it very difficult to keep up with the research reported in this field. Therefore, review literature has become increasingly important to researchers who are trying to keep abreast of this field. The available reviews in the literature on solvent-free synthesis and/or multicomponent reactions deal mainly with the synthesis of certain categories of organic compounds. Yet no review in the literature is available covering the wide areas of organic compounds such as acyclic, carbocyclic, and heterocyclic through a multicomponent solvent-free approach. Thus, considering the lack of such a review in the literature and in continuation of our efforts on more sustainable syntheses under solvent-free conditions, here an overview of the open literature on the development of more sustainable methodologies for the synthesis of acyclic, carbocyclic, and heterocyclic compounds under solvent-free conditions is provided. Since the main goal of this review is to enable the readers to follow new methods towards the synthesis of carbocyclic and heterocyclic compounds, we have classified the cycles according to ring simplicity and then subdivided by the number of heteroatoms present in the ring. Bearing in mind that the major interest in heterocycles is the synthesis *via* multicomponent reactions under solvent-free conditions, we have arranged the materials systematically according to the size and number of heteroatoms. The nature of the heteroatoms, and their number and positions in the molecule are used as secondary discriminators. This way, any one searching for a solvent-free synthesis of an acyclic, carbocyclic or heterocyclic scaffold will find a whole range of useful protocols. The review begins with the solvent-free reactions of acyclic compounds followed by carbocyclic and

heterocyclic systems. For clarification of ambiguity, we also have named the nucleus in the review according to the naming done by the authors in the respective journals. Thus, our aim is to provide a comprehensive and updated overview of recent developments in multicomponent approaches from 2000 to 2010 on the preparation of compounds with the emphasis on the rationale behind each synthetic procedure and the dependence of the results on a proper selection of reaction conditions.

1.1 Multicomponent reactions (MCRs)

Several methodologies such as the Merrifield synthesis, click processes, and multicomponent reactions (MCRs) are amenable to implementation as fast and efficient chemical syntheses suitable for automation. Of these, multicomponent processes have considerable economic and ecological interest as they address the fundamental principles of synthetic efficiency and reaction design. Multicomponent reactions^{1–3} have become important tools for the rapid generation of molecular complexity and diversity with predefined functionality in chemical biology and drug discovery.^{4–6} These reactions are often discovered by serendipity, but rational design strategies are now playing an increasing role because of their convergent nature, superior atom economy, and straightforward experimental procedures in the construction of target compounds by the introduction of several diversity elements in a single operation, resulting in substantial minimizations of waste, labor, time, and cost. Further, chemo- and stereoselectivities⁷ of MCRs have been widely accepted as a significant challenging task for synthetic organic chemists. MCRs, a powerful and virtually reliable target-guided synthetic approach, has extensively been used and applied for the rapid construction of molecular-level complex architectures, and interest from different branches of science is expanding exponentially.

In order to break down the complex notion of molecular diversity, we can distinguish three fundamental levels of diversity: (a) appendage diversity (combinatorial chemistry), (b) stereochemical diversity, and (c) scaffold diversity. Appendage diversity involves the introduction of different appendages to a common molecular skeleton, resulting in limited overall diversity. Stereochemical diversity involves the selective generation of as many stereoisomers of the same molecule as possible by changing the stereochemistry of the catalyst and/or chiral starting materials. Scaffold diversity is probably the most important element of diversity, which involves the generation of a collection of compounds with different molecular skeletons. This can be realized by changing the reagents added to a common substrate (reagent-based approach) or by transforming a collection of substrates with suitable pre-encoded skeletal information under similar reaction conditions (substrate-based approach). Unlike molecular diversity, which can be readily quantified on the basis of structural and physicochemical properties, molecular complexity is a less tangible property that is hard to quantify. It involves not only the number and types of atoms in the molecule, but also their connectivity. Therefore, new protocols in terms of efficiency, minimal environmental hazards, operational simplicity, and high selectivity are still demanded and would be of great relevance to both synthetic and medicinal chemists. Amongst numerous well-known multicomponent name reactions, the important ones are depicted in Fig. 1.

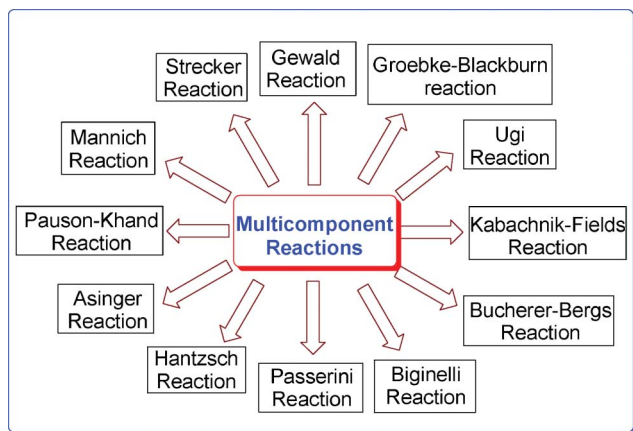


Fig. 1 Different multicomponent reactions.

1.2 Solvent-free reactions

Because of the increasing concern of the harmful effects of organic solvents on the environment and human body, organic reactions that are operated with green solvents or without conventional organic solvents have aroused the attention of organic and medicinal chemists. In the past decade, interest in solvent-free MCRs has expanded and it now encompasses wide areas of the chemical enterprise. For reasons of economy and pollution prevention, solvent-free methods⁸ are used to modernize classical procedures by making them cleaner, safer, and easier to perform. The demand for both clean and efficient chemical syntheses is becoming more urgent.⁹ Among the proposed solutions, solvent-free conditions are becoming more popular and it is often claimed that the best solvent is no solvent.¹⁰

A pressing challenge facing organic chemists, therefore, is to advance new processes that are not only efficient, selective, and

high yielding but also eco-compatible.^{11,12} Although steps toward sustainability can be made by reusing solvents, recycling is rarely accomplished with complete efficiency. An alternative strategy is to reduce the *E* factor (the *E* factor, introduced by Sheldon,¹³ is defined as the ratio of the weight of waste to the weight of product) of reactions and their impact on the environment is to conduct them under solvent-free conditions.^{14–17} The benefits of solvent-free processes are cost savings, decreased energy consumption, reduced reaction times, a large reduction in reactor size and capital investment. It has been an interesting observation that due to demerits associated with reactions carried out in conventional organic solvents, synthetic chemists are paying more attention to the development of new methodologies based on solvent-free reactions, clearly shown by the graphical representation of the growing number of solvent-free synthetic methodologies against years (Fig. 2).

2 Acyclic compounds

The synthesis of compounds occupies much of the effort of organic chemistry, and is the principal business of the chemical industry. The manufacture of drugs, pigments, and polymers entails the preparation of organic compounds on a scale of thousands to billions of kilograms per year, and there is constant research to develop new products and processes. Synthesis of new substances is carried out for many purposes beyond the goal of a commercial product. A compound of a specified structure may be needed to test a mechanistic proposal or evaluate a biochemical response such as the inhibition of an enzyme. Synthesis may provide a more dependable and less expensive source of a naturally occurring compound. Moreover, a synthetic approach permits variations in the structure that may lead to enhanced biological activity.

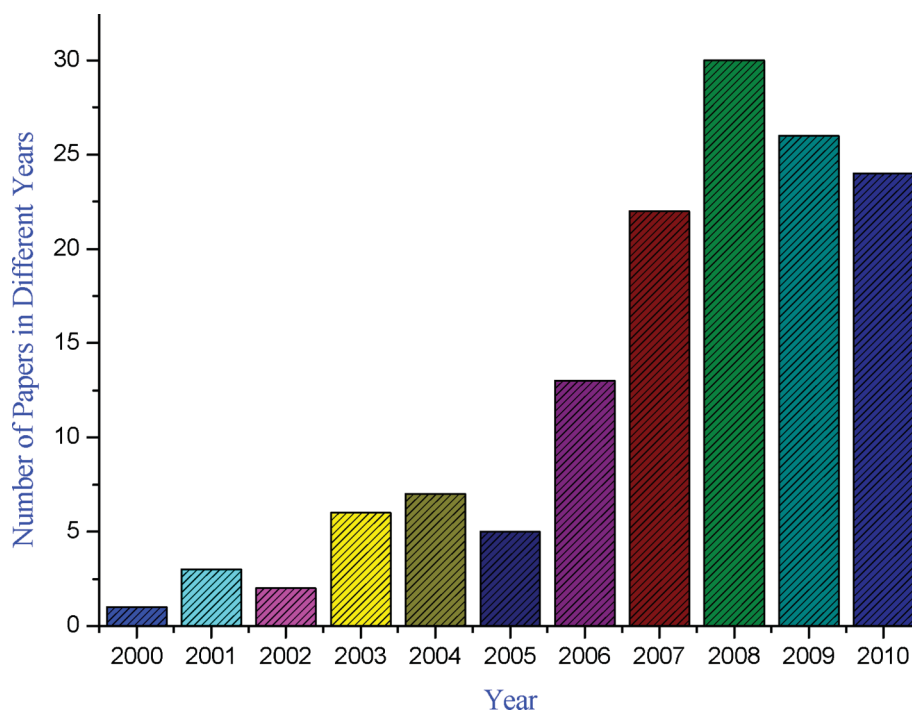


Fig. 2 Number of publications dealing with MCRs under solvent-free conditions in the period 2000–2010.

Three-component coupling of an aldehyde, alkyne, and amine (A^3 -coupling) is one of the best examples of acetylene–Mannich MCR and has received much attention in recent times. The resultant propargylamines are important building blocks for a variety of organic transformations and also valuable precursors for therapeutic drug molecules^{18,19} such as β -lactams, oxotremorine analogues, conformationally restricted peptides, isosteres, allylamines, oxazoles and other natural products. These compounds are synthesized by nucleophilic attack of lithium acetylides or Grignard reagents to imines or their derivatives²⁰ via a Mannich one-pot three-component coupling reaction of formaldehyde, secondary amines, and terminal alkynes.²¹ There has been continuing interest in developing transition-metal catalysts to accomplish the Mannich three-component reaction via C–H activation.²² Dax *et al.*²³ reported the use of copper as a transition-metal catalyst for the solid-phase Mannich condensation of amines, aldehydes, and alkynes. This polymer-supported three-component Mannich reaction requires one of the reactants immobilized on a resin. A microwave-assisted Mannich three-component coupling reaction in the presence of Cu(I) on Al_2O_3 under solvent-free conditions has also been reported,²⁴ and the enantioselective syntheses of propargylamines through a one-pot three-component coupling protocol have also been developed.²⁵

Copper(I) immobilized on organic-inorganic hybrid materials such as silica behave as a very efficient heterogeneous catalyst in the three-component Mannich coupling reaction of terminal alkynes **1**, aldehydes **2**, and amines **3** via C–H activation to afford the corresponding propargylamines **4** in high yields (82–99%) under solvent-free conditions (Scheme 1A).²⁶ The microwave-enhanced Mannich condensation of **1**, **2**, and **3** on CuI-doped alumina in the absence of solvent has been reported by Kabalka *et al.*²⁷ to produce the corresponding propargylamines **4** in good yields (Scheme 1B). The reaction has been further extended to produce 2-substituted benzo[*b*]furans in good yields (71–92%) via a Mannich condensation/cyclization sequence.

Among the cuprous salts, cuprous iodide has been found to be most effective. Recently, our group has identified $NiCl_2$ as a highly efficient and effective catalyst for a one-pot three-component (A^3) coupling of **1**, **2**, and **3** to produce propargylamines **4** in nearly quantitative yields.²⁸ Structurally divergent aldehydes (aromatic, heteroaromatic, and aliphatic) and amines were well tolerated under the reaction conditions.

β -Acetamido ketones and esters are versatile intermediates and exist in a number of biologically or pharmacologically important compounds.²⁹ Various methods for the synthesis of β -acetamido ketones and esters by multicomponent coupling have been reported, involving aldehydes, enolisable ketones, acetyl chloride, and acetonitrile.³⁰ β -Acetylaminoketones have been synthesized using $Cu(OTf)_2$, $Zn(II)$, $Bi(III)$, $Sn(II)$, $Sc(III)$ triflates, BF_3 , $CuCl_2$, $BiCl_3$, $LaCl_3$, $LiClO_4$, $InCl_3$,³¹ H_2SO_4 – SiO_2 ,³² zeolite Hb,³³ heteropolyacid,³⁴ and $K_5CoW_{12}O_{40} \cdot 3H_2O$.^{35a} Nagarapu *et al.*^{35b} have described the results of $SnCl_2 \cdot 2H_2O$ -catalyzed one-pot synthesis of β -acetamidoketones and esters **9** with aryl aldehydes **5**, enolisable ketones **6**, acetyl chloride **7**, and acetonitrile **8** under solvent-free conditions at room temperature in 76–92% yield (Scheme 2A). When methyl acetoacetate is involved in the reaction, diastereomeric mixtures can be obtained. The major diastereomer was anti in all the observed cases.

The one-pot synthesis of β' -acetamido- β -dicarbonyl compound **9** from precursor compounds **5**, **6**, **7**, and **8**, catalyzed by 20 mol% $ZrOCl_2 \cdot 8H_2O$ in solvent as well as under solvent-free conditions was described by Ghosh *et al.*³⁶ in high yields. Benzaldehyde generated the corresponding β -acetamido- β' -ketoester in 92% yield with moderate (1 : 3.7) diastereoselectivity using optimised solvent conditions. The selectivity can be well understood by incorporating a preferred chair like transition state. Under similar conditions, aromatic aldehydes containing electron-withdrawing groups in the ring gave good yields and selectivities. On the other hand, aromatic aldehydes containing



Scheme 1

Scheme	Substituents
1A	$R^1 = C_6H_5, 4-FC_6H_4, n\text{-octyl}, 4-BrC_6H_4, 4-CH_3C_6H_4, 2-FC_6H_4, n\text{-hexyl}; R^2 = H, \text{Propyl}, \text{Cyclohexyl}, C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, 4-MeOC_6H_4, 4-MeC_6H_4;$ Amine (R^3, R^4) = Piperidine, Dibenzyl-amine, Aniline, Methyl-phenyl-amine, Dibutyl-amine, 3,3,5-Trimethyl-piperidine, Morpholine.
1B	$R^1 = C_6H_5, 4-FC_6H_4, n\text{-octyl}, 4-BrC_6H_4, 4-CH_3C_6H_4, 2-FC_6H_4, n\text{-hexyl}; R^2 = H;$ Amine (R^3, R^4) = ($n\text{-C}_4\text{H}_9$) ₂ NH, ($C_6H_5CH_2$) ₂ NH, piperidine, $C_6H_5CH_2NHCH_3$, Methyl-naphthalen-1-yl-methylamine, Morpholine, 1-Phenylpiperazine, 3,3,5,5-Tetramethyl piperidine.

Scheme 1

electron-donating groups such as Cl, Me, OH, Br, and F in the ring also reacted equally well (Scheme 2B). β -Acetamido or β -amino ketones are also potential intermediates for the generation of β -amino alcohols,³⁷ the common structural units in natural nucleoside antibiotics such as nikkomycins or neopolyoxins. Zr(IV) compounds, especially ZrCl₄ have received considerable attention in various organic reactions³⁸ because of their ready availability in the earth's crust³⁹ and low toxicity.⁴⁰ However, the reported zirconium oxychloride based reactions are limited.⁴¹ It has been reported that a one-pot treatment of a mixture of **5**, **6**, **7**, and **8** at ambient temperature in the presence of ZrOCl₂·8H₂O catalyst (20 mol%) furnished the corresponding β -acetamido ketones **9** in excellent yields (Scheme 2C).⁴² α -Substituted enolizable ketones such as ethyl methyl ketone also reacted with benzaldehyde or *p*-methylbenzaldehyde producing poor to moderate diastereoselectivity, primarily forming the *anti*-isomer.

A highly efficient and eco-friendly protocol for the synthesis of β -aminoketone **13** by the coupling of aldehydes **10**, amines **11**, and ketones **12** using commercially available Fe(Cp)₂PF₆ as an efficient catalyst under solvent-free conditions has been developed (Scheme 3).⁴³

α -Amino phosphonate derivatives are increasingly useful due to their importance in pharmaceuticals and industry. Thus, the development of simple, eco-benign, and low cost protocols for the synthesis of α -amino phosphonates are highly desirable. A facile and efficient synthesis of α -amino phosphonates **17** via one-pot three-component coupling of aldehydes **14**, amines **15**, and diethyl phosphite **16** catalyzed by NBS or CBr₄ (5 mol%) under solvent-free conditions at 50 °C has been carried out (Scheme 4).⁴⁴

β -Aryl- β -mercaptoketones are valuable synthetic scaffolds for both medicinal and synthetic organic chemists. They have been utilized as precursors for the synthesis of various biologically active compounds, such as thiochromans,⁴⁵ thiopyrans,⁴⁶ benzothiazapines,⁴⁷ 4,5-dihydroisoxazoles, 4,5-dihydropyrazoles⁴⁸

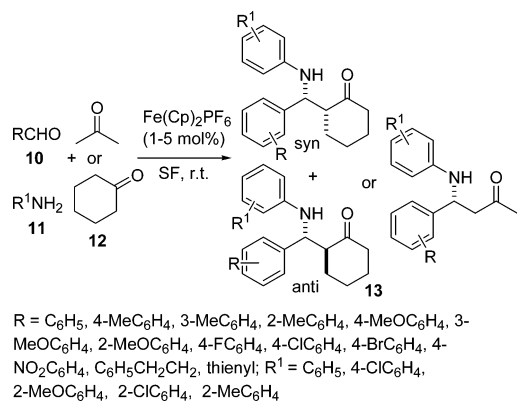
etc. Traditionally their synthesis has been performed by a sequence of two separate reaction steps, (i) synthesis of an α,β -unsaturated ketone *via* an aldol reaction, (ii) 1,4-conjugate addition of a thiol to an α,β -unsaturated ketone *via* thia-Michael addition. Michael addition of a thiol to chalcone is an efficient approach to prepare β -aryl- β -mercaptoketones. Zirconium chloride (40 mol%) efficiently catalyzes the one-pot three-component reaction of an aryl aldehyde **18**, cyclic or acyclic enolizable ketones **19**, and thiols **20** under solvent-free conditions at room temperature to afford the corresponding β -aryl- β -mercaptoketones **21** *via* an aldol-Michael addition reaction (Schemes 5).⁴⁹ Interestingly, when silica supported ZrCl₄ was used, instead of exclusive formation of the desired product **21**, the side product **22** was formed as the major one by the coupling of aldehyde and thiol (Scheme 6).

α -Aminophosphonic acids have received significant attention in synthetic organic chemistry due to their structural analogy to natural α -amino acids, displaying biological importance either in themselves or as building blocks for peptides.⁵⁰ Because of their versatile biological activities, a number of methods for the synthesis of α -aminophosphonic acids have been developed during the past two decades. Among the reported methods, three-component Mannich type reactions starting from aldehydes, amines, and phosphites catalyzed by Lewis acids such as InCl₃,⁵¹ ZrCl₄,⁵² lanthanide triflates,⁵³ TaCl₅-SiO₂,⁵⁴ SmI₂,⁵⁵ Mg(ClO₄)₂,⁵⁶ I₂ or acetyl chloride⁵⁷ are common strategies. Ranu and Hajra⁵⁸ have described a practical green approach for the synthesis of α -aminophosphonates by a three-component condensation of carbonyl compounds (aldehydes and ketones), amines, and diethyl phosphite at 75–80 °C in the absence of solvent and catalyst. Subsequently, Kumaraswamy and co-workers⁵⁹ reported the synthesis of α -aminophosphonates in good yields. Recently, a simple and efficient three-component one-pot synthesis of α -amino phosphonates has been accomplished in good yields from aldehydes, amines, and diethyl

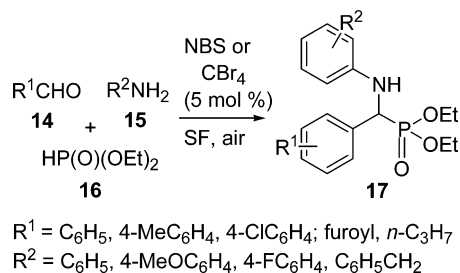


Scheme	Substituents
2A	R ¹ = H, Cl; R ² = H, Cl; R ³ = H, Cl, F, Br; R ⁴ = H; naphthyl; R ⁵ = COAr where Ar = C ₆ H ₅ , 4-ClC ₆ H ₄ , 4-MeC ₆ H ₄ ; R ⁶ = Me
2B	R ¹ = H; R ² = H; R ³ = H, NO ₂ , Cl, Me, OH, Br, F, CN, OMe; Aliphatic aldehyde = octanal; R ⁴ = COOMe; R ⁵ = COOMe, R ⁶ = Me
2C	R ¹ = H, NO ₂ , OH; R ² = H, NO ₂ , OH, OMe; R ³ = H, Cl, OMe, Me; R ⁴ = C ₆ H ₅ , 4-MeOC ₆ H ₄ , Me; R ⁵ = CH ₃ , CH ₂ CH ₃ ; R ⁶ = Ph, Me

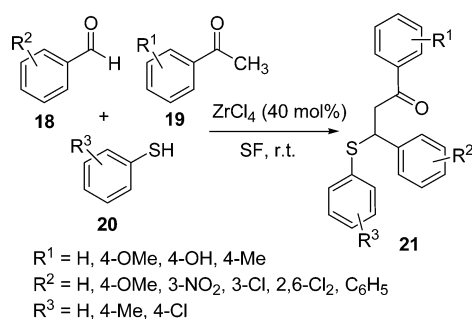
Scheme 2



Scheme 3



Scheme 4



Scheme 5



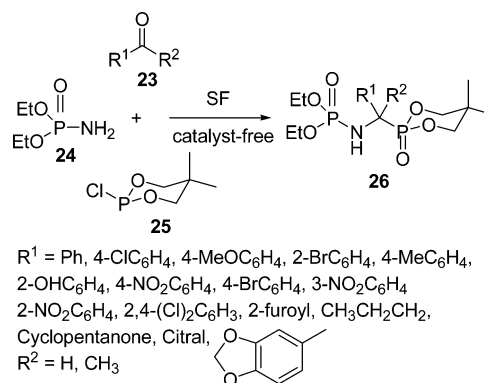
Scheme 6

phosphite using potassium hydrogen sulfate^{60a} or super magnetic nano iron oxide^{60b} as a catalyst under solvent-free conditions at ambient temperature. Zhang *et al.*⁶¹ synthesized α -aminoalkylphosphonate **26** via the one-pot condensation of aldehydes/ketones **23**, diethyl phosphoramidate **24**, and cyclic trivalent chlorophosphite **25** at 50–60 °C in the absence of solvent and catalyst (Scheme 7). Various substituted aldehydes and ketones were tested and it was found that aromatic and heteroaromatic

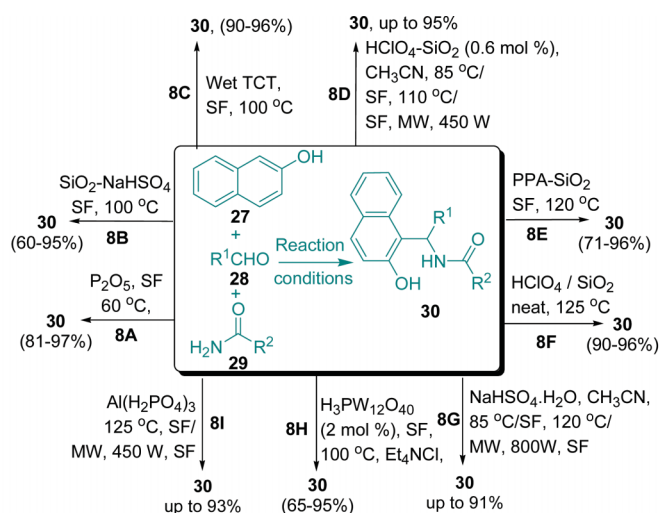
aldehydes produced better yields than ketones. However, only trace amounts of the α -aminoalkylphosphonates **26** were obtained when conjugated aliphatic aldehydes were used, and no expected products were obtained when aliphatic aldehydes and aliphatic ketones were utilized under similar reaction conditions.

Compounds with 1,3-amino oxygenated functional groups are present in a variety of biologically important natural products and in a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.⁶² 1-Amidoalkyl naphthol can be easily hydrolyzed to 1-aminoalkyl naphthol, which shows biological activities such as hypotensive and bradycardiac effects.⁶³ In addition, 1-aminoalkyl alcohol type ligands have been used for asymmetric synthesis and also as catalysts.⁶⁴ Therefore, for easy access of 1-aminoalkyl alcohols, a simple and efficient protocol is very much desirable. Nandi *et al.*⁶⁵ have reported an atom-efficient and environment-friendly approach for the synthesis of amidoalkyl naphthols **30** in excellent yields via a one-pot three-component reaction of 2-naphthol **27**, aromatic aldehydes **28**, and amides **29** promoted by P₂O₅ under solvent-free conditions at 60 °C (Scheme 8A). The reaction of 2-naphthol with aromatic aldehyde in the presence of a catalyst is known to provide a *ortho*-quinone methide (*o*-QMs) intermediate. The *ortho*-quinone methide intermediate was reacted with various amides to produce 1-amidoalkyl-2-naphthol derivatives.

Heterogeneous catalysts are generally less expensive, highly reactive, eco-friendly and are easy to handle. They reduce reaction times, impart greater selectivity and are simple to workup and the catalysts are simple to recover.⁶⁶ Silica supported sodium hydrogen sulfates have gained much importance in recent years as heterogeneous catalysts due to economic and environmental considerations.⁶⁷ The synthesis of 1-carbamatoalkyl-2-naphthol derivatives under solvent-free conditions have been described by Shaterian *et al.*⁶⁸ They have described an efficient one-pot three-component condensation of **27**, **28**, and carbamates **29** in the presence of silica supported sodium hydrogen sulfate at 100 °C to give the corresponding product **30** (Scheme 8B). The method worked well with a variety of aryl aldehydes with both electron-withdrawing and electron-donating groups such as OMe, Cl, F and NO₂. Under similar conditions, aliphatic aldehydes such as propionaldehyde or heptaldehyde and heterocyclic 2-pyridinecarbaldehyde did not give any desired



Scheme 7



Scheme 8

Scheme	Substituents
8A	$\text{R}^1 = 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4, 2\text{-OMeC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, \text{C}_6\text{H}_5, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-NMe}_2\text{C}_6\text{H}_4$; $\text{R}^2 = \text{CH}_3, \text{C}_6\text{H}_5, \text{CH}_2\text{Cl}$
8B	$\text{R}^1 = \text{C}_6\text{H}_5, 2\text{-ClC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 2,5\text{-(OMe)}_2\text{C}_6\text{H}_3, 3\text{-OMeC}_6\text{H}_4$; $\text{R}^2 = \text{OMe}, \text{OCH}_2\text{Ph}$
8C	$\text{R}^1 = \text{C}_6\text{H}_5, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-CNC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-MeOC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4$; $\text{R}^2 = \text{CH}_3, \text{Ph}, \text{NH}_2$
8D	$\text{R}^1 = \text{C}_6\text{H}_5, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_5, 4\text{-ClC}_6\text{H}_5, 2\text{-ClC}_6\text{H}_5, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 3\text{-FC}_6\text{H}_3, 4\text{-BrC}_6\text{H}_5, 4\text{-OMeC}_6\text{H}_5, 3,4\text{-(OMe)}_2\text{C}_6\text{H}_5, 4\text{-MeC}_6\text{H}_5, 2\text{-MeC}_6\text{H}_5$; $\text{R}^2 = \text{CH}_3, \text{C}_6\text{H}_5, \text{NH}_2, \text{NHMe}$
8E	$\text{R}^1 = \text{C}_6\text{H}_5, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 4\text{-NMe}_2\text{C}_6\text{H}_4, 3\text{-FC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 2,5\text{-(OMe)}_2\text{C}_6\text{H}_3, 2\text{-ClC}_6\text{H}_4, 3\text{-OMeC}_6\text{H}_4, 2\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 3,4\text{-(OMe)}_2\text{C}_6\text{H}_3$; $\text{R}^2 = \text{Me or MeCN}$
8F	$\text{R}^1 = \text{C}_6\text{H}_5, 4\text{-ClC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 4\text{-CNC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-MeOC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4$; $\text{R}^2 = \text{CH}_3, \text{C}_6\text{H}_5, \text{NH}_2$
8G	$\text{R}^1 = \text{C}_6\text{H}_5, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-FC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 2,5\text{-(MeO)}_2\text{C}_6\text{H}_3, 2\text{-ClC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 2,5\text{-(MeO)}_2\text{C}_6\text{H}_3$; $\text{R}^2 = \text{CH}_3 \text{ or MeCN}$
8H	$\text{R}^1 = \text{C}_6\text{H}_5, 4\text{-MeC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-MeC}_6\text{H}_4, 1\text{-Naphthyl}$; $\text{R}^2 = \text{CH}_3, \text{NH}_2$
8I	$\text{R}^1 = 3,4,5\text{-(OMe)}_3\text{C}_6\text{H}_2, \text{C}_6\text{H}_5, 3,4\text{-(OMe)}_2\text{C}_6\text{H}_3, 4\text{-Cl}, 4\text{-N(Me)}_2\text{C}_6\text{H}_3, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 2\text{-ClC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 2,5\text{-(OMe)}_2\text{C}_6\text{H}_3, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-FC}_6\text{H}_4$; $\text{R}^2 = \text{CH}_3, \text{Ph}$

Scheme 8

product. A direct procedure has been developed for the preparation of amidoalkyl naphthols **30** in excellent yields by the one-pot condensation of **27**, **28** and **29**, in the presence of 10 mol% wet-TCT as a catalyst under solvent-free media (Scheme 8C).⁶⁹ Shaterian and coworkers⁷⁰ have found that silica gel-supported polyphosphoric acid (PPA-SiO₂) can also act as an efficient catalyst for the multicomponent condensation of **27**, **28**, and **29** to afford the corresponding **30** in good to excellent yields (Scheme 8E). HClO₄-SiO₂⁷¹ has been utilized as a heterogeneous catalyst for the preparation of amidoalkyl naphthols by a one-pot condensation of aryl aldehydes, 2-naphthol, and urea or amides under solvent-free conditions (Scheme 8D).

Silica supported perchloric acid acts as a recyclable solid acid catalyst, which have been extensively used in organic reactions such as the protection of hydroxyl groups;⁷² the acetylation of phenols, thiols, alcohols, amines,⁷³ and β -keto enol ethers;⁷⁴ the Knoevenagel condensation, Michael addition and *cyclo*-dehydration;⁷⁵ the synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes;⁷⁶

the Friedländer synthesis of quinolines;⁷⁷ the synthesis of acylals from aldehydes;⁷⁸ the synthesis of enamines and enamino esters;⁷⁹ the synthesis of quinoxalines and dihydropyrazines, and chemoselective carbon sulfur bond formation.⁸⁰

Mahdavinia *et al.*⁸¹ have also used HClO₄-SiO₂ as a heterogeneous catalyst (1 mol%) for the preparation of amidoalkyl naphthols by a one-pot condensation of aryl aldehydes, 2-naphthol, and urea or amides in excellent yields under solvent-free conditions (Scheme 8F). The synthesis of amidoalkyl naphthols **30** using only sodium hydrogen sulfate (instead of supported by silica) as the heterogeneous catalyst has also been described (Scheme 8G).⁸² Another procedure has been developed for the preparation of amidoalkyl naphthols **30**, the condensation of aryl aldehydes **27**, β -naphthol **28** and urea or acetamide **29** in the presence of 12-tungstophosphoric acid as a heterogeneous catalyst under solvent-free conditions. A library of amidoalkyl naphthols were prepared by performing all the reactions for 80 min at 100 °C to give a 65–95% yield. Isobutyryl aldehyde did not take part in the reaction and therefore no

other aliphatic aldehydes were examined in the protocol (Scheme 8H).⁸³

A solvent-free synthesis of amidoalkyl naphthols **30** in the presence of $\text{Al}(\text{H}_2\text{PO}_4)_3$ as a heterogeneous catalyst has also been described. The reaction was carried out under thermal conditions as well as under microwave irradiation. The main feature of the catalyst is its high stability and catalytic activity. It also can be recovered and recycled at least five times after washing with acetone and drying at 100 °C. The reaction time in the case of microwave irradiation was shortened notably compared to solvent-free thermal conditions. The yield of the product was also higher (55–93%) for microwave irradiation compared to thermal conditions (50–73%) (Scheme 8I).⁸⁴ The one-pot, three-component condensation of the substrates **27**, **28**, and **29** also took place smoothly in the presence of cation-exchange resins (e.g. Indion-130, Indion-140, and Amberlyst-15) to afford the corresponding 1-amidoalkyl-2-naphthols **30** in good yields. Up to 90% yields of the products are obtained in 6–30 min at 110 °C under solvent-free conditions.⁸⁵

A novel one-pot three-component Mannich condensation between an electron-rich aromatic compound such as 5-methyl-2-hydroxyphenyl sulfide **31**, 2-aminopyrimidine **32**, and aromatic aldehydes **33** for the preparation of a series of new unsymmetrical multidentate aminophenol ligands **34** has been described in high yields (75–90%) under solvent-free conditions at 125 °C (Scheme 9).⁸⁶

The one-pot, three-component synthesis of 4-substituted 1-acylthiosemicarbazides **37** has been described by the condensation of 2-naphthol **28**, aldehydes **35**, and 1-acylthiosemicarbazides **36** catalysed by *p*-toluenesulfonic acid (*p*-TSA) in DCM at room temperature and under solvent-free conditions at 125 °C. Various aromatic aldehydes bearing electron-withdrawing and electron-releasing groups, aliphatic aldehydes, and heterocyclic aldehydes were well tolerated under the reaction conditions. Under solvent-free conditions, the reaction times were found to be much shorter than when using DCM, with almost parallel yields (Scheme 10).⁸⁷

Koszelewski *et al.*⁸⁸ have studied the effects of the substrate structure and concentration on the yield of the Passerini reaction. They have developed a new and convenient solvent-free methodology for the preparation of α -acyloxyamides **41** by the coupling of **38**, **39**, and **40**. The reaction was performed in solvent as well as under solvent-free conditions, but the yield of the product was greatly enhanced (86%) under solvent-free

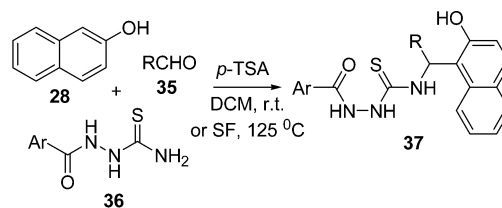
conditions compared to when using solvent (22%). When aromatic isocyanide was used, an increment of the yield (almost 50%) was observed under solvent-free conditions compared to the classical procedure. On the other hand, the products derived from aliphatic aldehydes were obtained in good yields (88–90%) when the reaction was performed in DCM. Reactions with *p*-anisaldehyde, *p*-methoxybenzoic acid, and isocyanoacetic acid ethyl ester did not give any desired product (Scheme 11).

Some novel substituted hydrazones **45** have been reported by El Kaïm and coworkers,⁸⁹ by the coupling of hydrazones **42**, aldehydes **43**, and secondary amines **44** under solvent-free conditions (Scheme 12). The reaction remains confined to coupling of hydrazones possessing electron-withdrawing groups on the hydrazone ($\text{R}^1 = \text{CO}_2\text{Et}$, CN). Simple hydrazones ($\text{R}^1 = \text{alkyl}$, aryl) did not react at all in ethanol, toluene or chlorobenzene, even after prolonged heating in the presence of several equivalents of amine and aldehyde.

Schiff bases owe their applications in metal ion complexation because they act as inhibitors of human β -thrombin and microbicides.⁹⁰ Some new bis-Schiff bases **48** have been synthesized by the coupling of 5,5'-methylenebis(2-aminothiazole) **46** and aromatic aldehydes **47** under solvent and catalyst-free conditions (Scheme 13).⁹¹

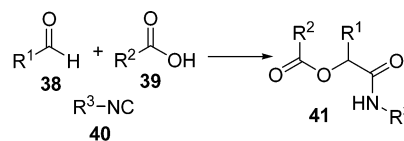
Srihari *et al.*⁹² have developed a solvent-free synthetic method catalyzed by PMA-SiO₂ (5 mol%) for the synthesis of 3-substituted indole derivatives **52** by the one-pot three-component coupling of aldehyde **49**, *N*-methylaniline **50**, and indoles **51** at room temperature. The reaction proceeded smoothly at a much faster rate under solvent-free conditions than when using solvent. The yields of the products were found to be good (85–95%) depending upon substituents (Scheme 14). Reactions involving cinnamaldehyde, butyraldehyde and *n*-octanal did not work under this protocol.

Bhuyan *et al.*⁹³ have synthesized some 3-alkylated indoles *via* the Michael addition of indoles to carbonyl compounds in



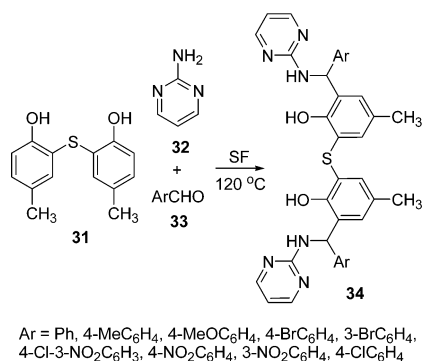
Ar = C₆H₅, 4-NO₂C₆H₄
R = C₆H₅, 4-MeC₆H₄, 4-NO₂C₆H₄, 4-ClC₆H₄,
3-MeOC₆H₄, 2-ClC₆H₄, furfuroyl, 2-pyridyl,
ethyl, propyl, 3-NO₂C₆H₄, 4-MeOC₆H₄

Scheme 10



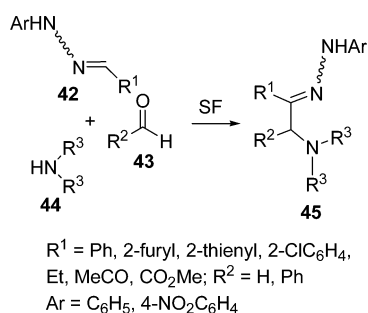
$\text{R}^1 = \text{C}_6\text{H}_5$, PhCH_2 , C_2H_5 , $(\text{CH}_3)_2\text{CHCH}_2$, C_7H_{15} ,
4-OMeC₆H₄, 4-NO₂C₆H₄, 4-FC₆H₄; $\text{R}^2 = \text{CH}_3$,
 CH_2Br , C_6H_5 , CH_3 , 4-OMeC₆H₄, 4-NO₂C₆H₄;
 $\text{R}^3 = \text{CH}_2\text{CO}_2\text{Et}$, $\text{C}_6\text{H}_5\text{CH}_2$

Scheme 11

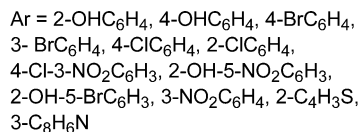
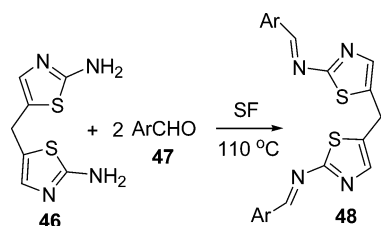


Ar = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 3-BrC₆H₄,
4-Cl-3-NO₂C₆H₃, 4-NO₂C₆H₄, 3-NO₂C₆H₄, 4-ClC₆H₄

Scheme 9



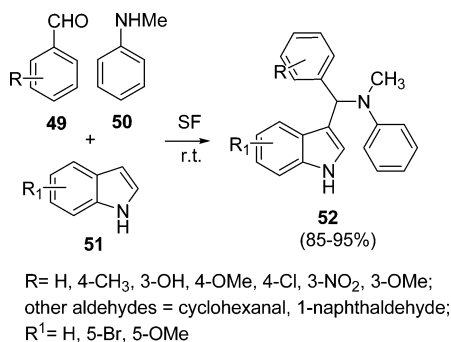
Scheme 12



Scheme 13

the absence of catalyst. The one-pot three-component coupling of 2-substituted indoles **53**, aldehydes **54**, and *N,N*-dimethylbarbituric acid **55** under solvent-free conditions at 80–150 °C for 15–25 min resulted two products **56** and **57** in good yields (Scheme 15).

Firozabadi and co-workers⁹⁴ have synthesized indole derivatives bis(indolyl)methanes **60** via the electrophilic substitution of indoles with carbonyl compounds under solvent-free conditions in high yields. In this three-component condensation, the two molecules of indole **58** and one molecule of aldehyde/ketone **59** reacted to produce the desired bis(indolyl)methane in the presence of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ /Silica gel as a new efficient and highly water-soluble catalyst. Time required for the completion of the reaction and the yields of the products depend on Z, R^1 and R^2 (Scheme 16).



Scheme 14

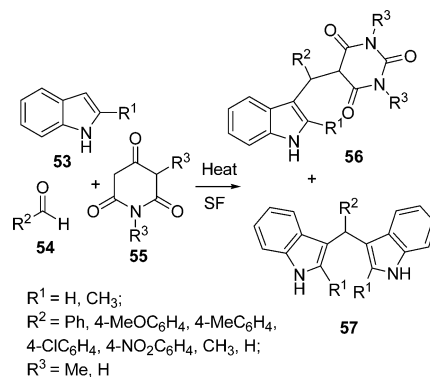
Among the various indole derivatives, 3-substituted indoles, i.e. 3-[(*N*-heteroaryl)-(aryl)methyl]indoles **64**, have recently been synthesized by the one-pot three-component domino coupling of indole **61**, aromatic aldehydes **62**, and heteroaryl amines **63** under solvent-free conditions at 80 °C in moderate to high yields (Scheme 17).⁹⁵ *N*-Substituted thioamides **68** have been synthesized from acyl halides **65** and amines **66** in the presence of recently developed thionating system $\text{H}_2\text{O/PSCl}_3$ **67** (Scheme 18).⁹⁶

O-Alkyl-2-methoxyethyl alkylphosphonates act as markers of nerve agents. A rapid and efficient surface mediated synthesis of *O*-alkyl-2-methoxyethyl alkylphosphonates from alkylphosphonic acids **69** and alcohols using DCC-Celite as a solid support under solvent-free condition is described (Scheme 19).⁹⁷

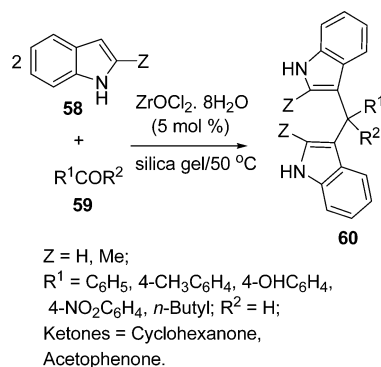
The synthesis of *S*-allyl-*N*-aryl dithiocarbamates **73** through a one-pot coupling of amines **70**, carbonyl sulfide **71**, and alkyl halide or α,β -unsaturated compounds **72** using SnCl_2 as a catalyst under solvent-free conditions is described (Scheme 20). Various substituted anilines, CS_2 , and allyl/crotyl bromide were treated under said conditions to yield the corresponding *S*-allyl-*N*-aryl dithiocarbamates.⁹⁸

3 Carbocyclic six-membered compounds

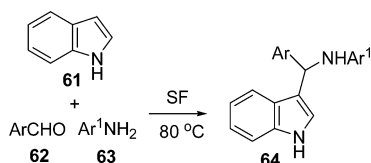
Biphenyls represent a key structural motif in a large number of compounds used as pharmaceuticals, agrochemicals, dyes, chiral ligands for metal catalysts, liquid crystals, organic semiconductors, and materials for molecular recognition devices.^{99a} Furthermore, the biaryl subunit is present in an extensive range



Scheme 15

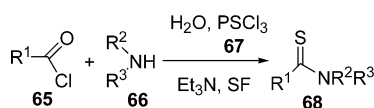


Scheme 16



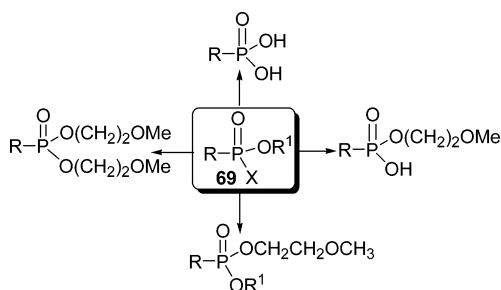
Ar = Ph, 4-ClC₆H₄, 4-BrC₆H₄, 4-FC₆H₄,
 4-NO₂C₆H₄, 2-ClC₆H₄, 2-Cl-6-FC₆H₃;
 Ar¹ = 2-pyrimidinyl, 2-pyridinyl
 4,6-dimethyl-2-pyrimidinyl

Scheme 17



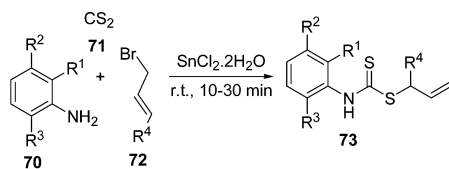
R¹ = C₆H₅, CH₃, 4-ClC₆H₄, Cl-CH₂,
 3-CH₃C₆H₄, 2-NO₂C₆H₄, C₆H₅CH₂;
 R² = C₂H₅, *o*-C₆H₁₁, *n*-C₃H₇, C₆H₅CH₂,
iso-C₃H₇, C₆H₅CH₂CH₂, -(C₂H₄)_n, C₆H₅,
 Br(CH₂)₂, *iso*-C₄H₉; R³ = H, C₂H₅

Scheme 18



Scheme 19

of natural products.^{99b} The uncatalyzed synthesis of the biphenyl system has been scarcely investigated^{100b} and solvent-free conditions have never been used. Considering the importance of this class of compounds, the development of a green approach for their synthesis has been attempted. Fringuelli *et al.*^{100a} have described the synthesis of biphenyl-2-carbonitrile derivatives **76** by an uncatalyzed and solvent-free multicomponent process, starting from an aryl aldehyde and constructing the second aryl ring by (i) the Knoevenagel reaction, (ii) Diels–Alder cycloaddition, and (iii) the final aromatization process (Scheme 21). The synthesis has been carried out by the reaction of aryl aldehydes **74**, active methylenes *e.g.* nitroacetonitrile, and 1,3-butadienes



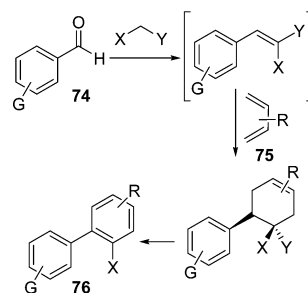
R¹ = H, CH₃, C₂H₅, Cl;
 R² = H, CH₃; R³ = H, CH₃, C₂H₅; R⁴ = H, CH₃

Scheme 20

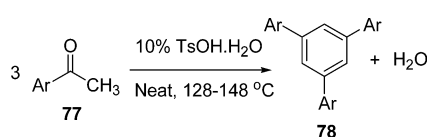
75. The aromatization of adduct was performed at 60 °C, generally in the presence of 2.0 molar equiv. of DBU under O₂ atmosphere (0.5 bar) and solvent-free conditions.

Yanan Zhao and co-workers^{100b} have developed a simple and green method for the synthesis of 1,3,5-triarylbenzenes **78** from three molecules of aryl ketone **77** catalyzed by *P*-TSA under solvent-free conditions. Acetophenones reacted smoothly to afford 1,3,5-arylbenzenes in good yields, irrespective of electron-donating or electron-withdrawing groups. When the *para*-substituents were chloro, bromo and iodo, increased yields were obtained due to their decreased electronegativity. Strong electron-donating groups such as NH₂ and OCH₃ provided lower yields than other groups such as alkyls or halogens. The reactions of *para*- or *meta*-substituted chloroacetophenones afforded slightly higher yields than sterically hindered *ortho*-substituted acetophenone, suggesting that the steric effect provides a significant contribution. Furthermore, water is the only byproduct of this reaction, which makes the present protocol environmentally benign (Scheme 22).

An improved procedure for the three-component coupling reaction of aldehydes, amides, and dienophiles (AAD-reaction) has been developed by Strubing *et al.*¹⁰¹ Using microwave technology, an *endo*-selective synthesis of *N*-acyl cyclohexenylamines **82** by the coupling of aldehydes **79** and amides **80** followed by a Diels–Alder reaction with electron-deficient dienophiles **81** (Scheme 23) was performed. The reaction has been performed both in solvents and under solvent-free conditions and it has been observed that it is comparatively high yielding under solvent-free conditions. A versatile and efficient route to 3-amino-1-aryl-9*H*-fluorene-2,4-dicarbonitrile **86** the *via* one-pot coupling of 1-indanone **83**, aromatic aldehydes **84**, and malononitrile **85** under solvent-free conditions with NaOH as the catalyst is described in Scheme 24. The reaction has been

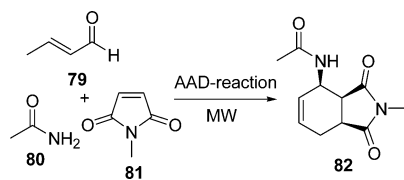


Scheme 21



Ar = C₆H₅, 4-CH₃C₆H₄, 4-NH₂C₆H₄, 4-OCH₃C₆H₄,
 4-NO₂C₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄,
 4-IC₆H₄, 2-CH₃C₆H₄, 3-CH₃C₆H₄, 3-ClC₆H₄, 2-ClC₆H₄

Scheme 22



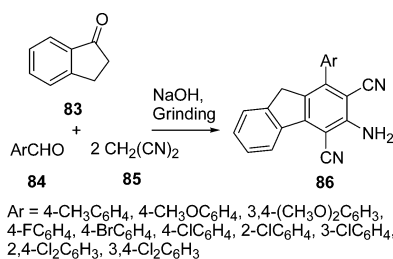
Scheme 23

performed at room temperature, which provided a 75–87% yield of the desired product within a very short time.¹⁰²

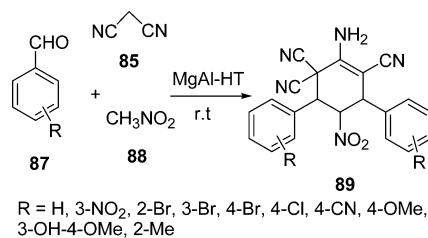
A one-pot synthesis of 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles **89** by the condensation of malononitrile **85**, aromatic aldehyde **87**, and nitromethane **88** has been carried out in the presence of Mg–Al hydrotalcite *i.e.* HTs (different Mg/Al ratios) and solid bases (Scheme 25). The reaction was performed in different solvents, such as DMF, H₂O, and MeOH but the best results were obtained under solvent-free conditions. The catalyst can be easily separated and is also recyclable.¹⁰³

4 Heterocyclic compounds

Heterocycles^{104,105} form the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially, but to the functioning of any developed human society as well. Their participation in a wide range of areas can not be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Other important practical applications of heterocycles can also be cited, for instance, additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Most of the significant advances against disease have been made by designing and testing new structures, which are often heteroaromatic derivatives. In addition, a number of pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products of immense significance to human and animal health. Therefore, researchers are in continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers following natural models. These compounds play a major part in biochemical processes and are the side groups of the most typical and essential constituents of living cells. Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel compounds. A huge number



Scheme 24



Scheme 25

of combinations of carbon, hydrogen, and heteroatoms can be designed, providing compounds with the most diverse physical, chemical, and biological properties. In fact, in the CMC database, more than 67% of the compounds listed contain heterocyclic rings, and nonaromatic heterocycles are twice as abundant as heteroaromatics. It is therefore easy to understand why both the development of new methods and the strategic deployment of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among the new synthetic transformations, cyclocondensation reactions are among the most attractive methodologies for synthesizing heterocyclic compounds, and the need for improved cyclocondensation reactions is very much desirable.

4.1 Multicomponent reactions for the synthesis of heterocycles

Multicomponent reactions in general are cyclic or acyclic condensation reactions. The cyclocondensation reaction can be defined as a kind of annulation reaction involving the formation of a ring from one or several acyclic precursors. In multicomponent reactions, coupling occurs between three, four or more components, incorporating almost all the components to give the desired product with the elimination of some small molecule(s). The condensation reactions leading to heterocycles were carried out with a range of different components and reactions types and the functional groups can react as either the electrophiles *e.g.* E¹, E², and E³ or nucleophiles *e.g.* Nu¹, Nu², and Nu³. The electrophiles are primarily functional groups containing carbon atoms bonded with other heteroatoms such as, O, N, S, halogen atoms *etc.* forming carbonyl, imine, nitrile, thiocarbonyl, unsaturated ketones, ethylcyanoacetate, mono or dihalosubstituted carbons, acetal and orthoester carbons; and the nucleophiles are either carbon atoms joined adjacent to groups such as aldehydes, ketones, enols, or enamines, or heteroatoms such as nitrogen, oxygen, and sulfur. We therefore have given the different mode of condensations schematically in Fig. 3.¹⁰⁶

4.2 Building blocks for the formation of heterocycles

The reactions mentioned in this review leading to the formation of heterocycles are mainly based on certain building blocks (Table 1). The building blocks incorporate the characteristics of electrophiles and nucleophiles, and are consequently coupled in different ways (as shown in Fig. 3) to form the corresponding heterocycles.

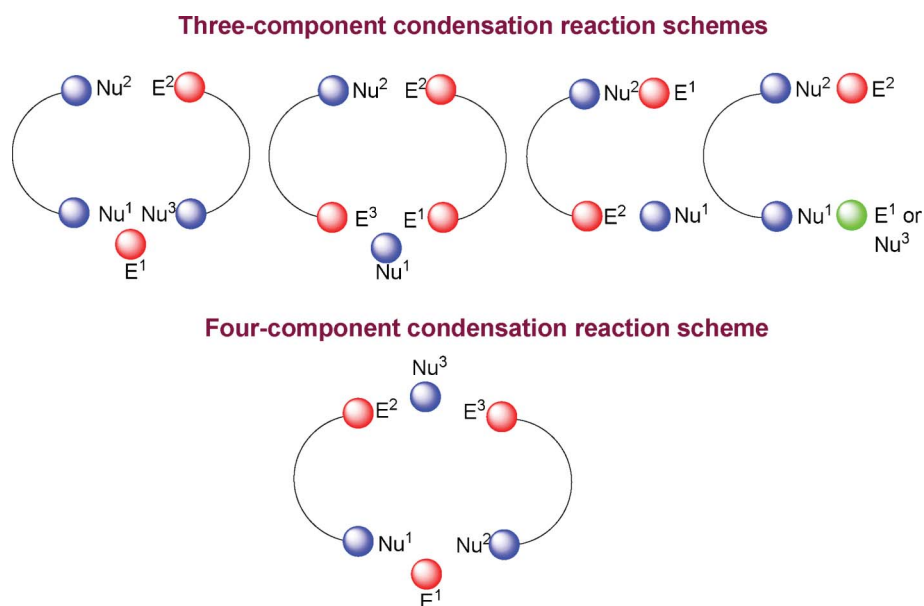


Fig. 3 Different condensation schemes of multicomponent reactions.

Building blocks for three-component reactions

No. of components	Building blocks	Products
[3 + 2 + 1]	[CCN + CC + C]	acridines
[3 + 2 + 1]	[CCO + CC + C]	chromenes/chromones
[3 + 2 + 1]	[CCS + CC + C]	thiochromenes/thiochromones
[4 + 2 + 1]	[NCCN + CC + C]	diazepines
[3 + 1 + 1]	[NCN + C + C]	imidazoles
[3 + 2 + 1]	[CCN + CC + C]	isoquinolines
[2 + 2 + 1]	[CC + CC + N]	pyrroles
[2 + 2 + 1]	[NN + CC + C]	phthalazines
[3 + 2 + 1]	[CCO + CC + C]	pyrans/chromenes/xanthenes
[3 + 2 + 1]	[CCC + CC + N]	pyridines
[3 + 2 + 1]	[CCN + CC + C]	pyridinones
[3 + 2 + 1]	[NCN + CC + C]	pyrimidines
[3 + 2 + 1]	[NCN + CC + C]	pyrimidinones/pyrimidinethiones
[3 + 2 + 1]	[CCN + CC + C]	quinolines
[4 + 1 + 1]	[CCCN + C + N]	quinazolines/quinazolinones
[3 + 1 + 2]	[NCS + C + CC]	thiazines
[2 + 1 + 1]	[CCN + C + S]	thiazolines
[2 + 1 + 2]	[CC + N + CS]	thiazolines
[3 + 2 + 1]	[NCS + CC + C]	thiazines
Building blocks for four-component reactions		
[2 + 1 + 2 + 1]	[CC + C + CC + N]	acridines
[1 + 1 + 1 + 1]	[CC + N + C + N]	imidazoles
[2 + 2 + 1 + 1]	[CC + CC + C + N]	pyridines
[3 + 1 + 1 + 1]	[CCC + N + C + N]	pyrimidines
[2 + 2 + 1 + 1]	[CC + CC + C + N]	pyridinones
[2 + 2 + 1 + 1]	[CC + CC + C + N]	quinolines

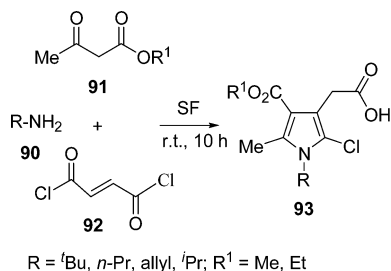
4.3 Five-membered heterocycles

4.3.1 Containing one heteroatom.

4.3.1.1 Pyrroles. Pyrrole derivatives are very important heterocycles from many points of view including medicinal, pharmaceutical, and materials science; and are common structural motifs in various biologically active molecules and pharmaceutical substances for their antioxidant, antibacterial, antitumor, anti-inflammatory, and antifungal properties. The pyrrole nucleus is the key structural motif of heme and chlorophyll, the pigments essential for life. Multicomponent reactions are one

of the most interesting concepts in modern synthetic chemistry to provide an attractive entry into pyrrole derivatives.^{107a} Recently, a solvent-free and catalyst-free synthesis of pentasubstituted pyrroles **93** has been developed in good yields (70–85%) *via* the one-pot three-component coupling of primary amines **90**, alkyl acetoacetates **91**, and fumaryl chloride **92** (Scheme 26).^{107b}

Ranu *et al.*^{108a} have synthesized substituted pyrroles **97** (Scheme 27) by coupling aldehydes/ketones/conjugated carbonyls **94**, amine **95**, and a simple or α,β -unsaturated nitroalkane **96** on the surface of a silica gel by microwave irradiation in good yields. The above method was also modified using

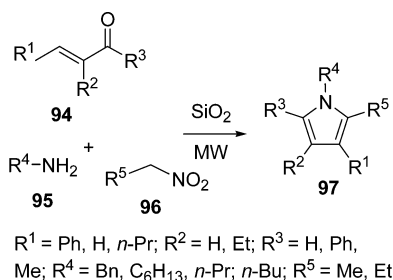


Scheme 26

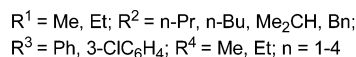
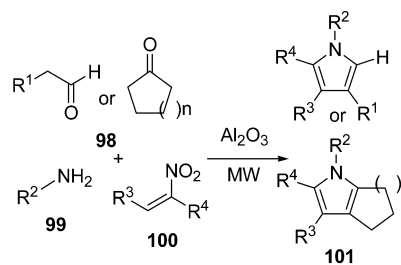
N,N-disubstituted thiobarbituric acids in place of the α,β -unsaturated aldehyde, providing pyrrolo[2,3-*d*] pyrimidines^{108b} in good yields. Furthermore, the synthesis of highly substituted and fused pyrroles **101** have also been reported by coupling acyclic/cyclic carbonyl compounds **98**, an amine **99**, and α,β -unsaturated nitro compounds **100** on an alumina surface by Ranu and co-workers (Scheme 28).^{108a,c}

Polysubstituted pyrroles **105** with complete control of pathway selectivity have been synthesized by a sequential one-pot three-component reaction of primary aliphatic amines **102**, active methylene compounds **104**, and 1,2-diaza-1,3-dienes **103** under solvent-free conditions without a catalyst (Scheme 29). Various primary aliphatic amines such as 4-methoxybenzylamine, *n*-propylamine, *n*-butylamine, allylamine, 1-amino-2-propanol, 1-amino-2-acetaldehyde diethyl acetal, and cyclohexylamine were used and effectively converted into the corresponding substituted pyrroles, which are otherwise not easy to synthesize. Pyrroles substituted with electron-withdrawing functional groups such as carboxylic acid derivatives (both symmetrical and unsymmetrical dicarboxylate scaffold, ester, amide, and/or thioester), sulfone, and phosphonate moiety at the C-3 and C-4 positions of the heterocyclic ring can be directly obtained, indicating the fitness of the scheme to all kinds of components.¹⁰⁹

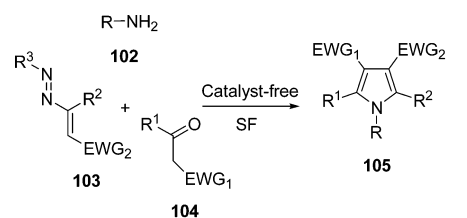
4.3.1.2 Indoles. The substituted indole nucleus is a structural component of a vast number of biologically active natural and unnatural compounds. The indole nucleus is without doubt a privileged structure in medicinal chemistry and also very abundant in nature. Substituted indoles possess several biological activities such as antioxidant, antibacterial, and insecticidal properties. They also act as colon cancer cell and tumor growth inhibitors and are employed as valuable antibiotics. The synthesis and functionalization of indoles has been the object of research for over 100 years, and a variety of well-established



Scheme 27



Scheme 28

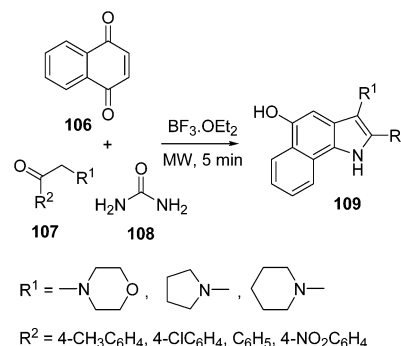


Scheme 29

classical methods are now available. To name a few of them: the Fisher indole synthesis, the Gassman synthesis of indoles from *N*-haloanilines, the Madelung cyclization of *N*-acyl-*o*-toluidines, the Bischler indole synthesis, the Batcho–Leimgruber synthesis of indoles from *o*-nitrotoluenes and dimethylformamide acetals, and the reductive cyclization of *o*-nitrobenzyl ketones.

Recently, a three-component solvent-free synthesis of a 5-hydroxy-benzo[*g*]indole scaffold **109** through a Lewis acid-catalyzed one-pot reaction of naphthaquinone **106**, ketones **107**, and urea **108** under microwave irradiation has been devised by Borthakur and co-workers¹¹⁰ (Scheme 30). The key step in the synthesis is a Michael addition followed by *in situ* aza cyclization. Urea has been used as an environmentally benign source of ammonia. This synthetic route tolerates a significant substrate variation to deliver a broad range of substituted products in 50–88% yields.

4.3.1.3 Furans. Furans are among the most important five-membered heterocycles in organic and pharmaceutical chemistry. They are not only significant as key motifs in many natural



Scheme 30

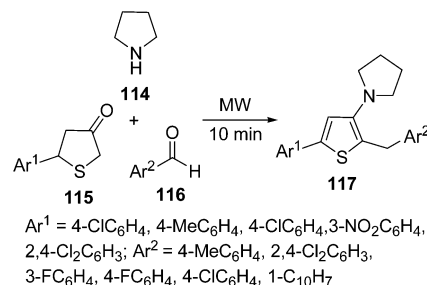
products, but also as versatile building blocks for the construction of highly complex target structures in numerous total syntheses. As an alternative to classical furan syntheses, when the mixture of *o*-ethynylphenol **110**, secondary amines **111**, and *para*-formaldehyde **112** were subjected to microwave irradiation of 30% power for 5 min under solvent-free conditions in the presence of cuprous iodide doped alumina, it underwent Mannich condensation followed by cyclization to give 2-(dialkylaminomethyl)-benzo[*b*]furans **113** in low to moderate yields (38–70%) (Scheme 31).¹¹¹ Interestingly, when *o*-ethynylphenol (2 equiv) was subjected to react with *para*-formaldehyde (excess) and piperazine (1 equiv), bis-Mannich condensation-cyclization product was formed in 40% yield.

4.3.1.4 Thiophenes. Thiophene derivatives have emerged as a class of important heterocycles because of their presence in a broad spectrum of natural and synthetic organic molecules with diverse biological properties and utility in organic synthesis as versatile intermediates. Over the years, thiophene-based materials have emerged as an important class of electrically conducting organic materials. A facile and efficient one-pot synthesis of highly substituted thiophenes **117** has been developed by Karthikeyan *et al.*¹¹² via the condensation of pyrrolidine or piperidine **114**, 5-aryldihydro-3(2*H*)-thiophenone **115**, and an aromatic aldehyde **116** under MW irradiation (Scheme 32). Moderate to good yields of thienylpyrrolidines (45–60%) were obtained by a one-pot tandem process. In the case of reactions with piperidine, the yields are lower (30–35%).

4.3.1.5 Lactams. 2-Azetidinones, commonly known as β -lactams, are the key structural motifs in the most widely used class of antibiotics, *i.e.*, β -lactam antibiotics, such as penicillins, cephalosporins, carbapenems, *etc.* The development of novel synthetic methodologies for the preparation of functionalized β -lactams and the screening of their biological activity has occupied a pivotal position in medicinal chemistry for almost a century now. Deprez *et al.*¹¹³ have synthesized five- and six-membered lactams **121** via a 4-center three-component Ugi reaction by combining amines **118**, isocyanides **119**, and ketoacids **120** under solvent-free microwave irradiation conditions (Scheme 33).



Scheme 31

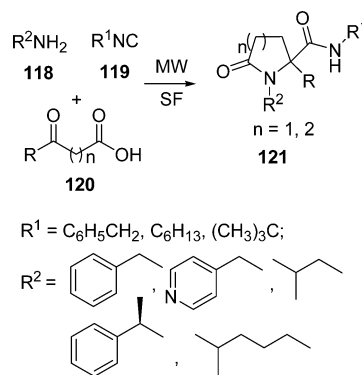


Scheme 32

4.3.2 Containing two heteroatoms.

4.3.2.1 Pyrazoles. Pyrazoles are rarely available in natural products, but they represent an important motif of man-made biologically active compounds. Many synthetic pyrazoles show *anti*-hyperglycemic, *anti*-inflammatory, anticancer, antipyretic, antibacterial, analgesic, sedative, and hypnotic activity. Some of these compounds have emerged as potent and selective γ -aminobutyric acid (GABA)-gated chloride channel antagonists, novel ligands for oestrogen receptors, and agrochemicals of economic importance. The 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles constitute the core structures of commercial drugs. Among the reported syntheses of pyrazoles, widely applicable methods are the dipolar [3 + 2] cycloadditions between CN₂ and C₂ moiety or the classical cyclocondensation of a monosubstituted hydrazine with a 1,3-dicarbonyl compound or surrogates thereof.

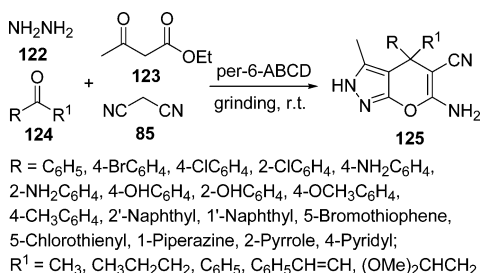
Among the various reported methods of pyranopyrazoles,^{114–117} a three-component condensation¹¹⁸ of *N*-methylpiperidone, pyrazolin-5-one, and malononitrile in absolute ethanol, and a two-component reaction¹¹⁹ between pyran derivatives and hydrazine hydrate are superior. Preparation of 1,4-dihydropyrano[2,3-*c*]pyrazoles include synthesis in aqueous media,¹²⁰ the use of piperidine as a base in water,¹²¹ *N*-methylmorpholine in ethanol,¹²² microwave irradiation¹²³ and solvent-free conditions.^{124–126} A green protocol has been developed with per-6-ABCD, which acts simultaneously as a supramolecular host as well as an efficient solid base catalyst for the solvent-free syntheses of various dihydropyrano[2,3-*c*]pyrazole derivatives **125** involving a four-component reaction of **122**, **123**, **124**, and **85** (Scheme 34). This atom-economical protocol also applies for ketones and resulted in near quantitative yields. The



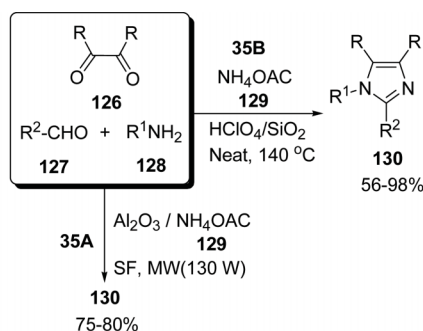
Scheme 33

catalyst can be reused at least six times without any change in its catalytic activity.¹²⁷

4.3.2.2 Imidazoles. Substituted imidazoles represent a common scaffold in numerous bioactive compounds and have a number of pharmacological properties. Imidazoles are also widely used as precursors of N-heterocyclic carbenes, organocatalysts, and ionic liquids. Due to the wide importance of this class of compounds their synthesis and functionalization reactions have been intensively studied in the field of organic synthesis. Despite many synthetic processes,¹²⁸ Khmel'nitsky *et al.*¹²⁹ have produced a solvent-free microwave assisted synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles **130** by the condensation of 1,2-dicarbonyl compounds **126**, aldehyde **127**, and amine **128** using acidic alumina impregnated with ammonium acetate **129** as the solid support in up to 80% yields (Scheme 35A). Kantevari *et al.*¹³⁰ have developed a one-pot four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles **130** by the cyclocondensation of the components using perchloric acid adsorbed on silica. The reaction was performed in different solvents using different catalysts but the highest yielding conditions was a solvent-free environment with HClO₄/SiO₂ (Scheme 35B). Depending upon different substituents, moderate to high yields (56–98%) of the products were obtained.



Scheme 34



Scheme 35

Scheme	Substituents
35A	R = Ph, 2-thienyl, 4-ClC ₆ H ₄ , 4-EtC ₆ H ₄ ; R ¹ = Ph, 4-tolyl; R ² = H, C ₆ H ₄ CH ₂ CH ₂ , 3-ClC ₆ H ₄ CH ₂ CH ₂
35B	R = Ph, Me; R ¹ = PhCH ₂ , PhCH ₂ CH ₂ , <i>iso</i> -Butyl, 4-MeC ₆ H ₄ , 3-MeC ₆ H ₄ , cyclohexyl; R ² = C ₆ H ₅ , 4-MeC ₆ H ₄ , 3-OMeC ₆ H ₄ , 3,4,5-(OMe) ₃ C ₆ H ₂ , 3-ClC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-OMeC ₆ H ₄ , 4-BrC ₆ H ₄ , 2-ClC ₆ H ₄ , 4-N(Me) ₂ C ₆ H ₄ , 4-OHC ₆ H ₄ , 2-NO ₂ C ₆ H ₄ , 4-OH-3-OMeC ₆ H ₃ , <i>iso</i> -Propyl, 2-Furyl, 3-NO ₂ C ₆ H ₄ , 4-NO ₂ C ₆ H ₄

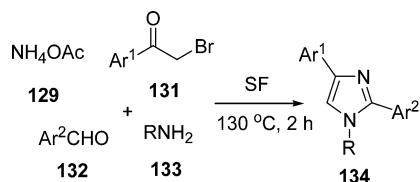
Scheme 35

Adib and co-workers¹³¹ synthesized 1,2,4-trisubstituted-1*H*-imidazoles **134** via a one-pot four-component reaction of ammonium acetate **129**, 2-bromoacetophenone **131**, aldehyde **132**, and primary amines **133** under solvent-free conditions (Scheme 36). Different aryl aldehydes, bromoacetophenones and alkyl amines have been used and were stable in this protocol. Depending upon the substituents, 80–95% yields of the product was obtained in 2 h.

Silica-supported titanium tetrachloride has been prepared and employed as a novel catalyst for the rapid and efficient synthesis of 2,4,5-trisubstituted imidazoles **137** in excellent yields by a three-component one-pot condensation of aryl aldehydes **135**, 1,2-diketones **136**, and ammonium acetate **129** under solvent-free conditions using conventional heating or microwave irradiation (Scheme 37).¹³²

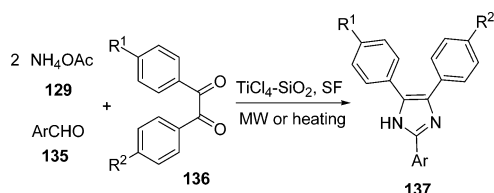
4.3.2.3 Thiazoles. Thiazoles and their derivatives are found to be associated with various biological activities. In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus, the thiazole nucleus has been much studied in the fields of organic and medicinal chemistry. Among the many synthetic procedures of thiazole or thiazole derivatives, Dawane *et al.*¹³³ have developed a method for the synthesis of thiazole derivatives **141** through the coupling of substituted *o*-hydroxy benzaldehydes **138**, substituted- α -haloketones **139**, and thiourea **140** under solvent-free conditions in 85–95% yields (Scheme 38). Anderluh and co-workers¹³⁴ have described a one-pot three-component reaction among **142**, **143**, and **144** leading to the formation of 2-amino-5-alkylidene-thiazol-4-ones **145** involving conventional heating under solvent-free conditions or microwave irradiation in low to moderate yields (Scheme 39).

An efficient procedure for the synthesis of thiazole derivatives **148** by a three-component one-pot reaction of thiourea **140**, α -haloketone **146**, and substituted pyrazolones **147** under environmentally solvent-free conditions in good yields has been developed (Scheme 40).¹³⁵



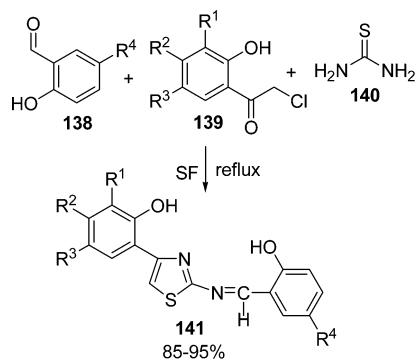
$\text{Ar}^1 = \text{C}_6\text{H}_5, 4\text{-BrC}_6\text{H}_4, \text{Ar}^2 = \text{C}_6\text{H}_5, 3\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-OMeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4; \text{R} = \text{C}_6\text{H}_5, \text{C}_6\text{H}_5\text{CH}_2, n\text{-Pr}$

Scheme 36



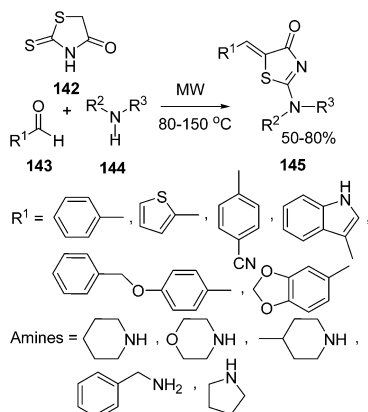
$\text{R}^1, \text{R}^2 = \text{H, F}; \text{Ar} = \text{Ph, 4-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 3\text{-MeOC}_6\text{H}_4, 3\text{-BrC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-N(Me)}_2\text{C}_6\text{H}_4, 3,4\text{-(MeO)}_2\text{C}_6\text{H}_3, 3,5\text{-(MeO)}_2\text{C}_6\text{H}_3, 3\text{-OH-4-MeOC}_6\text{H}_3$

Scheme 37



$\text{R}^1 = \text{H, Br}; \text{R}^2 = \text{H, Me}; \text{R}^3 = \text{Cl, Me}; \text{R}^4 = \text{H, Cl}$

Scheme 38

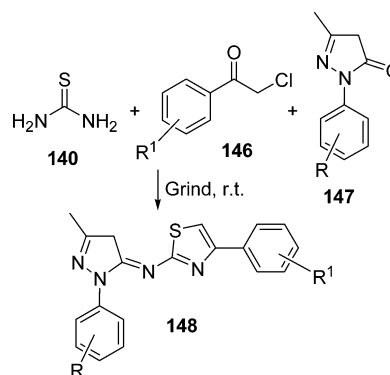


Scheme 39

4.3.2.4 Thiazolines. Thiazoline and its derivatives are important scaffolds for drug candidates due to their anticonvulsant, sedative, antidepressant, anti-inflammatory, antihypertensive, antihistaminic, and antiarthritic activities. Min Xia and co-workers¹³⁶ have synthesized 2-acylimino-3-aryl-thiazolines **152** via a three-component one-pot reaction of amines **149**, isothiocyanate **150**, and α -halocarbonyl compounds **151**. The reaction is accelerated by microwave irradiation under solvent-free conditions, resulting in the desired compounds in 83–98% yields (Scheme 41).

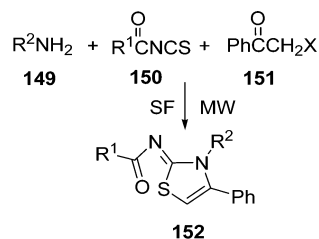
2-Thiazolines **156** have been synthesized by reaction of carboxylic acids **153** and 1,2-aminoalcohol **154** in the presence of Lawesson's Reagent **155** by microwave irradiation under solvent-free conditions.¹³⁷ The reaction was carried out using molar ratio of the reactants in 1.0 : 1.5 : 0.75 at 150 °C for 4–8 min. If the substituents in amino alcohol, $\text{R}^2, \text{R}^3 = \text{H}$ or $\text{R}^2 = \text{Me}$ and $\text{R}^3 = \text{H}$, the yield of the product increased significantly, while with substituents $\text{R}^2 = \text{H}, \text{R}^3 = \text{Ph}$ resulted in poor yields. The overall yield is 21–86% depending upon substituents (Scheme 42). The reaction is also compatible with heteroaromatic acids, e.g. pyridyl, furyl and thienyl derivatives. Aliphatic acids, such as heptanoic and decanoic acids led to the corresponding 2-thiazolines in good yields.

4.3.2.5 Thiazolidinones. Thiazolidin-4-ones are applied pharmaceutically as antimicrobial agents. Kasmi-Mir *et al.*¹³⁸ have developed an efficient one-pot three-component solvent-free



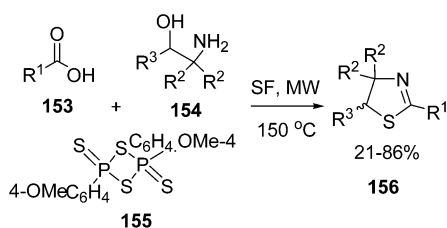
$\text{R} = \text{H, Cl, NO}_2, \text{CH}_3; \text{R}^1 = \text{Cl, F, Br, CH}_3, \text{H, NO}_2$

Scheme 40



$\text{R}^1 = \text{Ph, 4-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4$
 $\text{R}^2 = \text{Ph, 2-MeC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$

Scheme 41



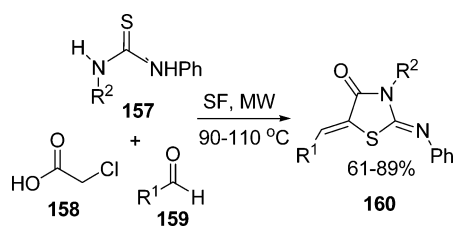
R^1 = hexyl, nonyl, $\text{H}_2\text{OC}(\text{CH}_2)_7$, Bn, Ph, 3- MeC_6H_4 , 4- MeOC_6H_4 , 2,3-(MeO) $_2\text{C}_6\text{H}_3$, 4- ClC_6H_4 , 4- BrC_6H_4 , naphth-2-yl, pyrid-3-yl, thien-2-yl, fur-2-yl
 R^2 = H, Me; R^3 = H, Ph

Scheme 42

synthesis of thiazolidine-4-one by the coupling of substituted thiourea **157**, chloroacetic acid **158**, and aldehyde **159** (1.0 : 1.2 : 1.0 molar ratio) under microwave irradiation at 90–110 °C for 10–20 min. The desired product 5-arylidene-2-iminothiazolidin-4-ones **160** have been obtained in 61–89% yields (Scheme 43). Yavari and co-workers¹³⁹ have synthesized thiazolidine-4-ones **164** in 70–83% yields through one-pot three-component reaction under solvent-free conditions at room temperature. Various 4-phenylthiosemicarbazides **161**, DMAD **162**, and aldehydes or ketones **163** were tolerated well under solvent-free conditions (Scheme 44).

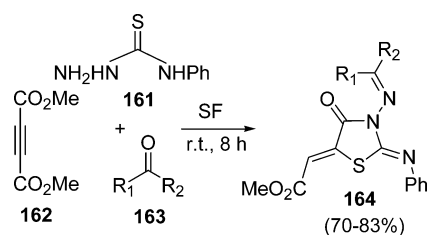
4.3.2.6 Phthalazines. Phthalazine (also called benzoorthodiazine or benzopyridazine) is a heterocyclic organic compound isomeric with quinoxaline, cinnoline, and quinazoline. Like others members of the isomeric diazine series, phthalazines have found wide applications as therapeutic agents, as ligands in transition metal catalysis, as chemiluminescent materials, and for optical applications. Heterocycles with a phthalazine moiety exhibit various pharmacological and biological activities,¹⁴⁰ such as anticonvulsant,¹⁴¹ cardiotoxic,¹⁴² and vasorelaxant¹⁴³ properties. In view of its wide range of applications in synthetic and medicinal chemistry, various methods are reported in the literature for the synthesis of phthalazine derivatives.¹⁴⁴ Sayyafi *et al.*¹⁴⁵ have derived 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives **168** from the condensation of phthalhydrazide **165**, dimedone **166**, and aromatic aldehydes **167** under solvent-free conditions in excellent yields (80–93%) within 10–20 min (Scheme 45A).

Similarly, 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives **168** have been synthesized through the three-component condensation reaction of **165**, **166**, and **167** under solvent-free conditions in the presence of reusable silica supported polypho-



R^1 = Ph, 4- MeOC_6H_4 , 4- $\text{Me}_2\text{NC}_6\text{H}_4$, benzo[3,4]dioxan-2-yl; R^2 = Ph, 4-Me-2-pyridyl

Scheme 43



R^1 = Me, Et, Ph, 4- MeC_6H_4 , 4- MeOC_6H_4 , 4- $\text{NO}_2\text{C}_6\text{H}_4$, 3- $\text{NO}_2\text{C}_6\text{H}_4$, 3- BrC_6H_4 ; R^2 = H, Me

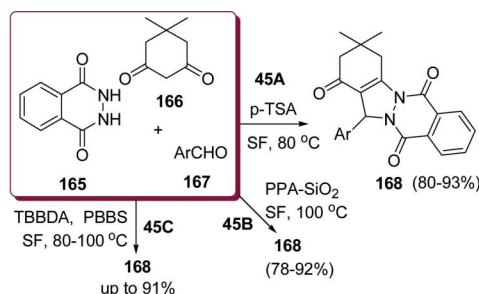
Scheme 44

spheric acid (PPA-SiO₂) as the heterogeneous acid catalyst. It was found that a catalyst loading of 0.05 mmol at 100 °C provided the desired products in 78–93% yields, depending upon the substituents on the starting materials. The catalyst was reused five times without any significant loss in its catalytic activity (Scheme 45B).¹⁴⁶ The *N,N,N',N'*-Tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly *N*-bromo-*N*-ethylbenzene-1,3-disulfonamide (PBBS) catalyzed one-pot synthesis of aliphatic and aromatic 2*H*-indazolo [2,1-*b*]phthalazinetriones **168** from various aliphatic and aromatic aldehydes **167**, **165**, and **166** at 80–100 °C under solvent-free conditions has been developed by Ghorbani-Vaghei *et al.* (Scheme 45C).^{147a} Very recently, a rapid and efficient one-pot three-component protocol for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones has been developed by our group^{147b} *via* domino coupling of phthalhydrazide, 1,3-diketones, and aldehydes under solvent-free conditions at 80 °C as well as under solvent-free ultrasound irradiation at room temperature promoted by (*S*)-camphorsulfonic acid.

4.3.3 Containing four heteroatoms.

4.3.3.1 Tetrazoles. Among tetrazoles, 1-substituted tetrazoles have been used in a variety of synthetic and medicinal chemistry applications as well as in materials science, including propellants and explosives. They are also regarded as the biological equivalent to the carboxylic acid group. Kundu and co-workers¹⁴⁸ have developed a synthetic route towards the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles **172** in excellent yields *via* a three-component condensation of amine **169**, trimethyl orthoformate **170**, and sodium azide **171** in the presence of a catalytic amount of indium triflate (5 mol%) under solvent-free conditions. The reaction proceeds smoothly to generate the corresponding 1-substituted tetrazoles in 70–92% yields upon heating at 100 °C. The reaction tolerated a wide range of anilines (containing electron-withdrawing as well as electron-donating groups) and heterocyclic amines such as 2-amino pyridine and furfurylamine furnishing the corresponding products (Scheme 46).

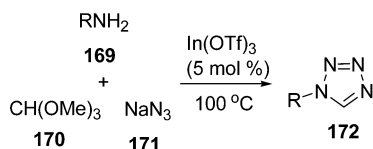
Recently click chemistry has been much focused where condensation of alkynes with azides occurs to yield the triazoles. Similarly, methods for addition of cyanides with azides to yield tetrazoles have been explored by Srihari *et al.*¹⁴⁹ The desired tetrazoles **176** have been synthesized by the coupling of Baylis Hillman acetate **173**, TMS azide **174**, and aryl nitrile **175** under solvent-free conditions in the presence of TBAF as catalyst. Some of these tetrazoles were found to be potential TNF- α inhibitors. They have found that E-isomer was the only product



Scheme 45

Scheme	Substituents
45A	Ar = C ₆ H ₅ , 4-ClC ₆ H ₄ , 4-BrC ₆ H ₄ , 4-FC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 2-ClC ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 4-CH ₃ C ₆ H ₄
45B	Ar = C ₆ H ₅ , 4-BrC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-FC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 4-MeC ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 2-ClC ₆ H ₄ , 2-MeC ₆ H ₄ , 3-ClC ₆ H ₄ , 3,4,5-(MeO) ₃ C ₆ H ₂ , 2,4-Cl ₂ C ₆ H ₃ , 4-OH-3-MeOC ₆ H ₃
45C	Ar = Ph, 4-ClC ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 4-MeC ₆ H ₄ , 2,4-Cl ₂ C ₆ H ₃ , 3,4,5-(OMe) ₃ C ₆ H ₂ , 4-NO ₂ C ₆ H ₄ , 1-naphthyl, 2-naphthyl, 2,3-Cl ₂ C ₆ H ₃ , 4-MeSC ₆ H ₄ , 3-OHC ₆ H ₄ , CH ₃ CH ₂ , CH ₃ CH ₂ CH ₂ , CH ₃ (CH ₂) ₄ , C ₆ H ₅ CH ₂ CH ₂ , MeSCH ₂ CH ₂ , CH ₃ (CH ₂) ₅ , (CH ₃) ₂ CHCH ₂

Scheme 45



R = C₆H₅, 4-MeC₆H₄, 2,3-Me₂C₆H₃, 2-MeOC₆H₄, 2-ClC₆H₄, 4-FC₆H₄, 2-Cl-3-FC₆H₃, 4-CO₂EtC₆H₄, 3-NO₂C₆H₄, 4-Vinylaniline, 2-C₅H₄N, Furfurylamine, (S)-1-Phenylethylamine, C₆H₅CH₂, *n*-Bu, Cyclohexyl, *t*-Bu

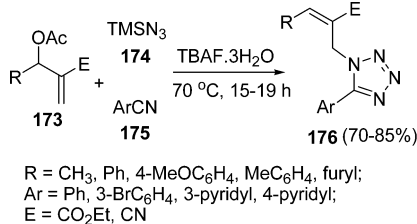
Scheme 46

formed with Baylis Hillman acetates containing ester moiety but nitrile containing Baylis Hillman acetates gave the mixture of diastereomers with *Z*-isomer as the major product. (Scheme 47).

4.4 Fused heterocycles

4.4.1 Derived from compounds containing one heteroatom.

Condensed pyridines are known for various biological activities, for example, pyrazolo[3,4-*b*]pyridines are useful for treatment of a wide variety of stress-related illnesses, such as depression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, haemorrhaged stress, drug and alcohol withdrawal symptoms, drug addiction and infertility. The pyridine nucleus is also present in many products such as drugs, vitamins, food, flavorings,



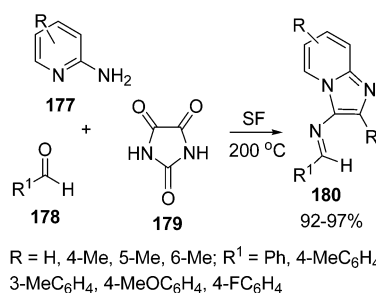
Scheme 47

plants dyes, adhesives, and herbicides. Mehdi Adib *et al.*¹⁵⁰ reported a procedure for the synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines **180** via a one-pot multicomponent reaction of 2-aminopyridines **177**, benzaldehydes **178**, and imidazoline-2,4,5-trione **179** under solvent-free conditions (Scheme 48).

Indolizines constitute the main structural part of many naturally occurring biologically important alkaloids such as (–)-dendroprimine,¹⁵¹ indalozin 167B,¹⁵² (–)-slafamine,¹⁵³ conceine¹⁵⁴ *etc.* General procedures for the synthesis of indolizine are sequential *N*-quaternisation and intramolecular cyclocondensation or cycloaddition reaction by *N*-acyl/alkyl pyridinium salts. Bora *et al.*¹⁵⁵ have developed a microwave-mediated three-component reaction of acyl bromide **181**, pyridine **182**, and acetylene **183** in the presence of basic alumina under solvent-free conditions to give indolizines **184** in excellent yields (Scheme 49).

Liu *et al.*¹⁵⁶ have synthesized substituted aminoindolizines **188** by a gold catalyzed three-component coupling/cycloisomerisation reaction of heteroaryl aldehydes **185**, amines **186**, and alkynes **187** under solvent-free conditions. The speciality of the reaction is that the coupling of enantiomerically enriched amino-acid derivatives form the corresponding *N*-indolizines, incorporating amino-acids and maintaining its enantiomeric purity (Scheme 50).

A microwave procedure was efficiently applied to the synthesis of a series of novel naphthindolizinedione derivatives **189** whose



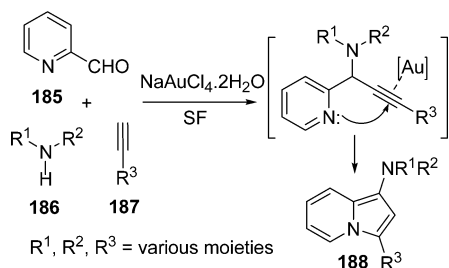
Scheme 48



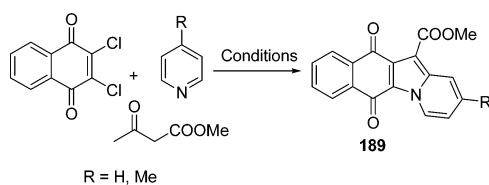
Scheme 49

structures somewhat resemble those of known antitumor agents able to interact with DNA by intercalation. An antitumor amide was obtained in a few minutes with high yields through a solventless one-pot cyclization followed by treatment with the suitable amine. This method was also used to access tetracyclic aza-compounds. The one-pot three-component cyclization was found to be more atom-efficient than the *N*-ylide sequence. To investigate the effect of structural modifications on the naphthindolizinedione skeleton, some indolizinoquinoline-5,12-dione precursors have also been prepared by the cyclization of compound 2,3-dichloro-2,3-dihydro-[1,4]naphthoquinone with ethyl acetoacetate (EAA) and pyridine or picoline (Scheme 51).¹⁵⁷

4.4.2 Derived from compounds containing two heteroatoms. A three-component synthesis of highly substituted bicyclic pyridines containing ring-junction nitrogen **193** has been described. The cyclocondensation of HKAs **190**, triethoxymethane **191**, and active methylene compounds **192** was done by refluxing under solvent-free and catalyst-free conditions to afford bicyclic pyridines in excellent yields (78–94%) within 30–59 min depending upon the nature of the substituents (Scheme 52).¹⁵⁸



Scheme 50



Scheme 51

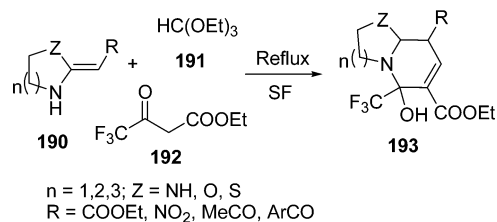
4.4.3 Derived from compounds containing more than two heteroatoms. A three-component synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines, 3-amino-2-arylimidazo[1,2-*a*]pyrazines, and 3-amino-2-arylimidazo[1,2-*a*]pyrimidines is described by Adib and co-workers.¹⁵⁹ Imine derivatives **196** of the title compounds were prepared in excellent yields by heating a mixture of 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine **194**, a benzaldehyde **195**, and imidazole-2,4,5-trione **179** under solvent-free conditions (Scheme 53).

The synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives **199** in good yields (79–90%) has been reported *via* a three-component condensation of urazole **197**, dimedone **166** and aromatic aldehydes **198** under solvent-free conditions at 80 °C in the presence of *p*-TSA as catalyst. Aliphatic aldehydes reacted poorly under similar conditions (Scheme 54).¹⁶⁰

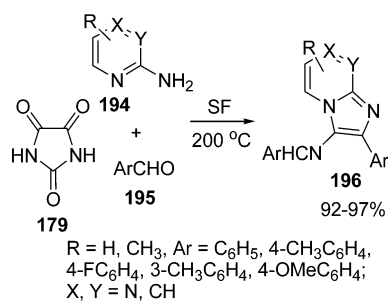
After the pivotal discovery by Sharpless *et al.*,¹⁶¹ that Cu(I) catalyzes the formation of triazoles in a 1,4-substituted fashion, the chemistry of triazoles¹⁶² was brought from oblivion to renaissance. Triazole chemistry was revisited and has seen exponential growth over the years and an enormous gain in popularity in diverse areas of chemistry such as organic, material, and medicinal chemistry. The 1,2,3-Triazole moiety is present in many compounds exhibiting different biological properties such as antibacterial¹⁶³ (cefmatilen), *anti*-HIV,¹⁶⁴ antiallergic,¹⁶⁵ and inhibitory¹⁶⁶ (tazobactam) activities. Triazolobenzodiazepines¹⁶⁷ have shown a high affinity toward benzodiazepine receptors. They are also emerging as powerful pharmacophores in their own right.

Furthermore, the importance of triazolopyrimidines is well recognized in the field of medicinal chemistry because these heterocycles have a structure similar to that of purine and adenine, differing in their fused ring systems having the pyrimidine nitrogen atom at the bridgehead position.¹⁶⁸ Triazolo pyrimidines are useful building blocks in the synthesis of herbicidal drugs, such as Metosulam, Flumetsulam, Azafenidin, Diclosulam, Penoxsulam, Floransulam, and Cloransulam *etc.* Richardson *et al.*¹⁶⁹ described the triazolopyrimidines as novel CDK2 inhibitors. In addition, these triazolopyrimidines are also useful potential anticancer,¹⁷⁰ *anti*-bronchoconstrictor,¹⁷¹ antiviral,¹⁷² diuretic,¹⁷³ antibacterial,¹⁷⁴ and antifungal¹⁷⁵ agents.

Various synthetic protocols were reported for the synthesis of triazoles and their ring fused derivatives.¹⁷⁶ Privileged scaffolds are uniquely suited to the preparation of molecular libraries for leading development in medicinal chemistry.^{177,178} Such frameworks are attractive for drug discovery because of the high hit rates and the pharmacological profiles of their derivatives relative to those of other ring systems. By varying substituents on these privileged scaffolds, one can often identify potent and selective binders for multiple biological targets from a single library. Dandia *et al.*¹⁷⁹ have investigated regioselectivity in



Scheme 52



Scheme 53

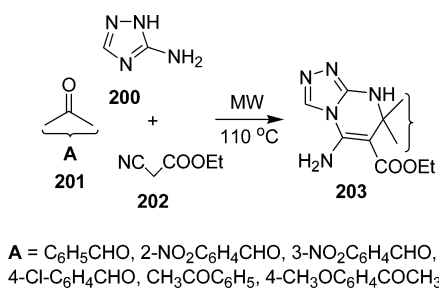


Scheme 54

multicomponent reactions of aminotriazole **200**, carbonyl compounds **201**, and α -cyanoesters **202** in the synthesis of triazolopyrimidines **203** under solvent-free conditions in excellent yields using a microwave or ultrasonic wave (Scheme 55).

4.5 Spiro-compounds

The synthesis of indenofused 5- and 6-membered heterocycles such as indenopyrrole, indenopyrazole, indenothiophene, indenopyridine and indenopyrimidine has attracted considerable attention in recent years as these classes of compounds constitute structural frameworks of several naturally occurring compounds displaying a wide range of biological activity. The indenopyridine skeleton is present in the 4-azafluorenone group of alkaloids. It is represented by its simplest member, onychnine. Indenopyrazoles and indenopyridazines are known as cyclin-dependent kinase and selective MAO-B inhibitors. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids. A number of methods have been reported for the synthesis of spirooxindole-fused heterocycles. Recently, Bazgir *et al.*¹⁸⁰ have reported a one-pot simple synthesis of spiro[diindenopyridine-indoline]triones **208**, and



Scheme 55

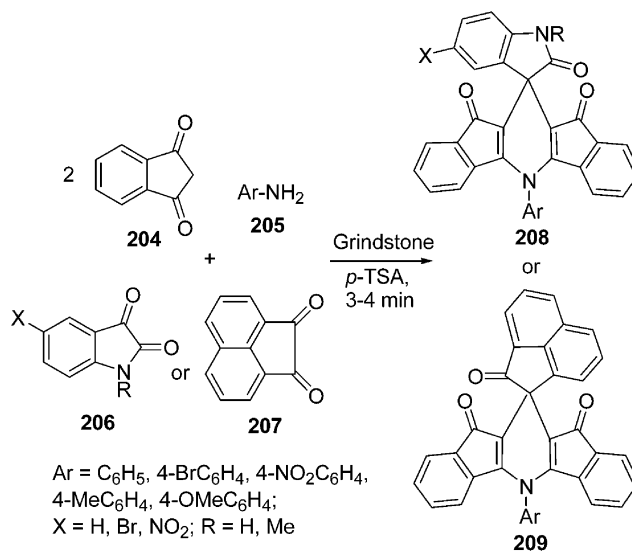
spiro[acenaphthylene-diindenopyridine]triones **209** through a pseudo four-component reaction among 1,3-indandione **204**, aromatic amines **205**, and isatins **206** or acenaphthylene-1,2-dione **207** (Scheme 56).

Raghunathan and co-workers¹⁸¹ have reported a comparative study of the synthesis of novel dispiro pyrrolo/pyrrolizidino ring systems **210**, **211** obtained by the cycloaddition of azomethine ylides. They are generated by a decarboxylation from sarcosine/proline and isatin with the dipolarophile 9-arylidene-fluorene using four different methodologies. Among them, the solvent-free microwave-assisted approach gave products with the highest yields in the shortest time. In addition to that, their solvent-free approach allowed the use of 4-*N,N*-dimethylaminobenzaldehyde, which failed to produce the desired cycloadducts under conventional processes (Scheme 57).

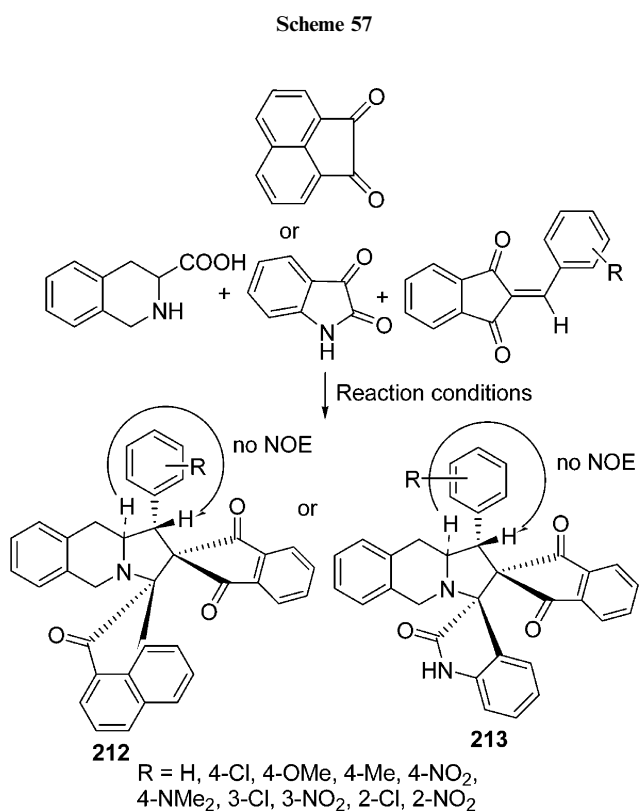
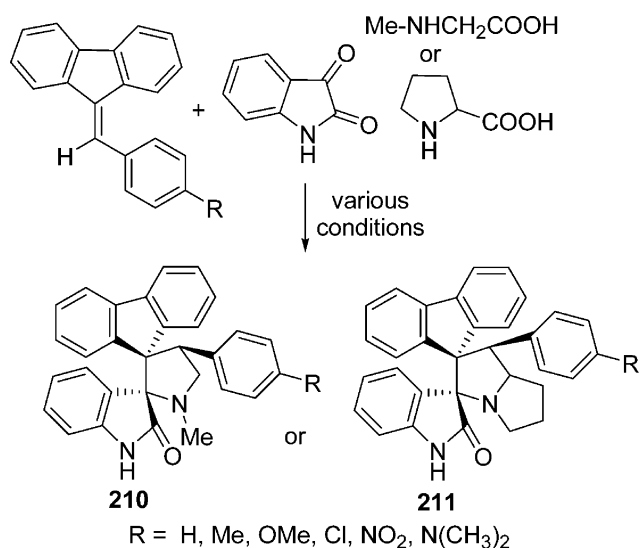
Spiropyrrolidines/pyrrolizidines have been synthesized utilizing the alkene unit of Baylis–Hillman adducts of ninhydrin with sarcosine/proline and various activated ketones through 1,3-dipolar cycloaddition through microwave-assisted protocol in good yields.¹⁸² Raghunathan *et al.*¹⁸³ have used TiO_2 -silica as an efficient solid-supported catalyst for the synthesis of a series of dispiroheterocyclic systems **212** and **213** through cycloaddition of an azomethine ylide generated by decarboxylation from tetrahydroisoquinoline-3-carboxylic acid and acenaphthenequinone/isatin with various unusual dipolarophiles *e.g.* 2-arylidene-1,3-indanediones and (*E*)-2-oxoindolino-3-ylidene acetophenones in a one-pot three-component tandem reaction (Scheme 58).

Spiro-fused heterocycles **217** have been synthesized by Shaabani *et al.*¹⁸⁴ in good yields by the pseudo four-component reaction of an aryl aldehyde **214**, urea **215**, and a cyclic β -diester or a β -diamide **216** such as Meldrum's acid or barbituric acid derivatives using microwave irradiation under solvent-free conditions. The best yields of the products were obtained in the presence of acetic acid or NaHSO_4 (Scheme 59).

Very recently, spirocompounds have been synthesized by Mobinkhaledi *et al.*¹⁸⁵ utilizing a mixture of isatin **206**, malononitrile **85** or ethylcyanoacetate **218**, and **219** or dimedone



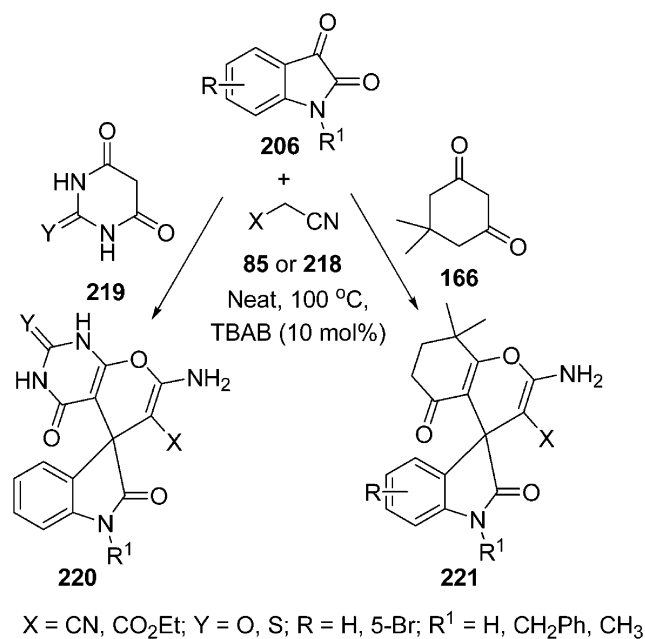
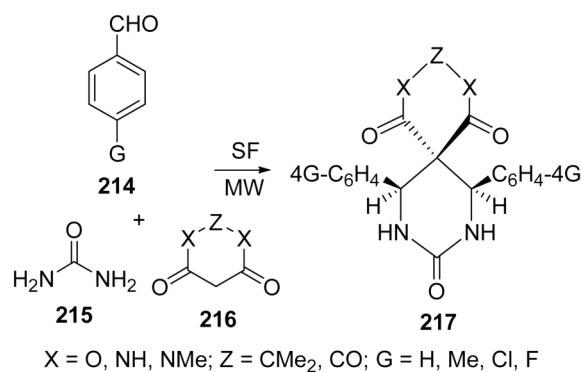
Scheme 56



166 in solvent-free media in the presence of a catalytic amount of TBAB to afford 2-amino-5-oxo-7,7-dimethyl spiro[4*H*]-5,6,7,8-tetrahydrochromene-4,3'-(3'*H*)-indol]-(1'*H*)-2'-one-carbonitrile **220** or **221** in excellent yields. The reaction with malononitrile or ethyl cyanoacetate also proceeded smoothly (Scheme 60).

4.6 Six-membered heterocycles

4.6.1 Containing one heteroatom. Heterocycles, such as pyridines, pyridones, pyrans, chromenes, quinolines, isoquinolines, acridines, and xanthenes have become increasingly



important because they have proven to be extremely useful intermediates for the preparation of new biological materials. These heterocycles are present in numerous pharmacologically and agrochemically important compounds.

4.6.1.1 Pyridines. Pyridines are the building blocks of various compounds with important medicinal properties such as anti-tumor, antimicrobial,¹⁸⁶ myasthenia gravis,¹⁸⁷ multiple sclerosis,¹⁸⁸ spinal cord injuries,¹⁸⁹ and botulism.¹⁹⁰ For that reason a number of synthetic methodologies for the synthesis of 2-aminopyridines have been reported, including the condensation of α,β -unsaturated ketones with malononitrile in the presence of ammonium acetate,¹⁹¹ nucleophilic substitution of 2-halopyridines with primary or secondary amines,¹⁹² aminolysis of 2-alkoxy pyridines, and [4 + 2]- or [3 + 3]-type ring formation reactions.¹⁹³

A three-component cyclocondensation of enamines **222**, 1,3-dicarbonyls **223**, and ammonium acetate **129** in the presence of tangstocobaltate salt as the heterogeneous catalyst has been reported by Kantevari *et al.*¹⁹⁴ under solvent-free conditions.

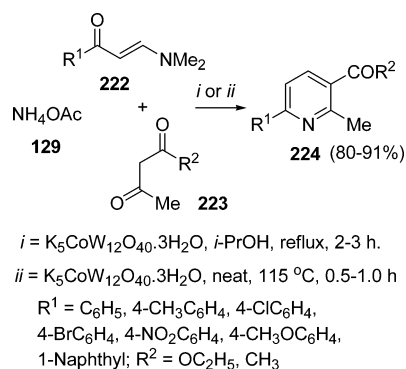
The protocol furnished the regioselective formation of 2,3,6-trisubstituted pyridines **224** in good yields (Scheme 61). The reaction was also carried out in solvent but the solvent-free conditions were found to be superior in terms of yield and time.

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are analogs of NADH coenzymes and an important class of drugs. These compounds exhibit various medicinal functions such as neuro-protectant, platelet *anti*-aggregatory, and cerebral antischemic activity in the treatment of Alzheimer's disease and chemosensitizing activity in tumor therapy. A series of 1,4-dihydropyridines **227** was obtained *via* sequential Hantzsch condensation catalyzed by morpholine in a one-pot reaction¹⁹⁵ of **225**, **226**, **166**, and **129** (Scheme 62). This reaction was also performed in solvent as well as under solvent-free conditions, but the best result was obtained in solvent-free conditions. Both electron-rich and electron-deficient aldehydes as well as heterocyclic aldehyde (furfural) worked well under this protocol.

Ishar and co-workers¹⁹⁶ have synthesized some *N*-aryl-5,6-unsubstituted-1,4-dihydropyridines *via* a regioselective [4 + 2] cycloaddition of 1-aryl-4-phenyl-1-azadienes with allenic Esters. Sridharan and co-workers¹⁹⁷ have synthesized 5,6-unsubstituted dihydropyridines using inert/anhydrous conditions in good yields (61-74%). Similar multicomponent reactions for the synthesis of substituted piperidines, dihydropyridones and tetrahydropyrans were also reported.¹⁹⁸ Atul Kumar and Maurya¹⁹⁹ have reported the use of organocatalysts for the multicomponent reaction of acetoacetate ester **228**, cinnamaldehyde **229**, and anilines **230** to yield *N*-aryl-5-unsubstituted or 5,6-unsubstituted 1,4-dihydropyridines **231** (Scheme 63). Basic amino acids like L-lysine and L-histidine give poor yields. Acidic amino acids were found to be superior but the best results were obtained with neutral amino acids like L-proline (90%) and L-pipecolic acid (85%).

Recently, Samai *et al.*²⁰⁰ reported a very simple and highly efficient one-pot method for the synthesis of unsymmetrical dihydro-1*H*-indeno[1,2-*b*]pyridine derivatives *via* a one-pot multicomponent strategy under solvent-free and catalyst-free conditions (Scheme 64). 4-Aryl-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridines **234** have been synthesized *via* four-component cyclocondensation of 1,3-indanedione **204**, aldehyde **232**, β -ketoester **233** and ammonium acetate **129** in 1 : 1 : 1 : 1.5 ratios at room temperature on grinding.

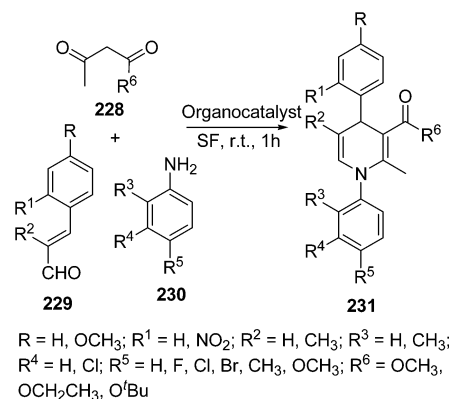
The synthesis of 1,4-dihydropyridines **236** under solvent-free conditions have been reported by Wang *et al.*²⁰¹ The reaction



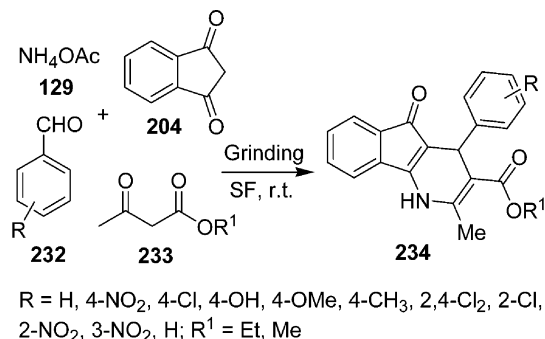
Scheme 61



Scheme 62



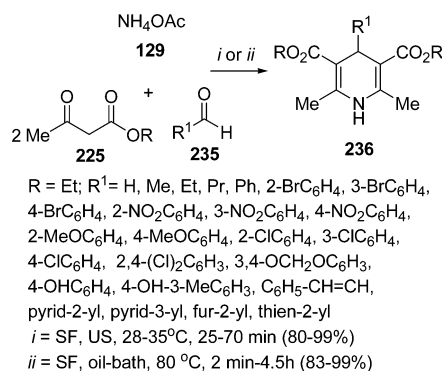
Scheme 63



Scheme 64

was performed under both with heating as well as with ultrasound irradiation. In case of ultrasound irradiation the mixture of ammonium acetate **129**, ethyl acetoacetate **225**, and aldehyde **235** in a molar ratio of 1.1 : 2.5 : 1.2 respectively, was irradiated in a water bath of ultrasonic cleaner with a nominal power of 250 W at 28–35 °C for a period of 25–70 min to give the desired products in 80–99% yields (Scheme 65). In all respects, the ultrasonic irradiation method was found to be superior to conventional heating. The reactivity of aldehydes with electron-withdrawing groups was found to be better than those with electron-donating groups.

Zolfigol and Safaiee^{202a} have reported the synthesis of 1,4-dihydropyridines under solvent-free conditions using conventional thermal heating. The mixture of aldehyde, ethyl acetoacetate, and ammonium acetate in 1 : 2 : 1.5 molar ratios respectively, were heated at 80 °C to give the desired products in



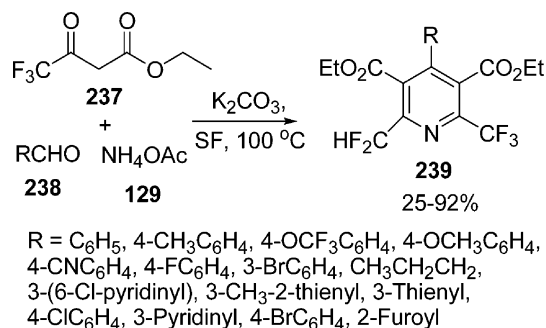
Scheme 65

83–99% yields. Recently, the synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylates **239** via one-pot three-component reaction of ethyl trifluoroacetoacetate **237**, aldehydes **238**, and ammonium acetate **129** in the presence of K_2CO_3 under solvent-free conditions through sequential Hantzsch reaction/dehydration/dehydrofluorination has been described^{202b} (Scheme 66).

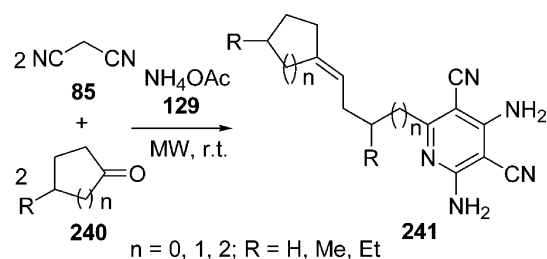
Very recently, the synthesis of highly functionalized pyridine derivatives **241** has been reported by the domino coupling of readily available malononitrile **85** and cyclic ketones **240** in the presence of ammonium acetate **129** in one-pot under microwave irradiation and solvent-free conditions in high yields. The proposed mechanism involves a novel sequence consisting of deprotonation/imine formation/anionic carbonyl addition. The reaction was also performed in different solvents like HOAc, DMF, ethyl alcohol and water but the solvent-free method was found to be most efficient (Scheme 67).²⁰³

Recently, one-pot three-component reaction for the synthesis of 1,4-dihydropyridines **245** has been developed by grinding of aldehydes **242**, amines **243**, DEAD (diethyl acetylenedicarboxylate) **244**, and malononitrile **85**/ethyl cyanoacetate **218** under catalyst-free and solvent-free domino protocol.²⁰⁴ First coupling occurs between aldehyde and active methylene compound followed by aza-Michael reaction with DEAD and aniline, which undergoes rearrangement to generate the desired product (Scheme 68).

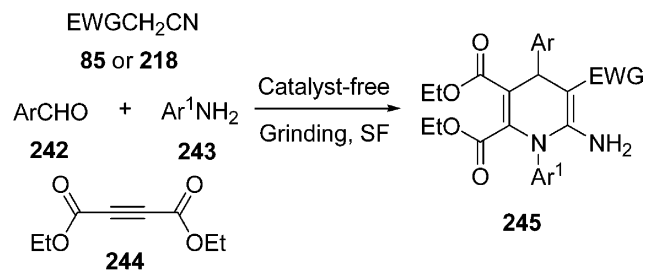
Recently, Wells–Dawson heteropolyacids ($\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62} \cdot 24\text{H}_2\text{O}$) are being used as a catalyst in various organic syntheses. Sanchez *et al.*²⁰⁵ have used it as recyclable catalyst in the synthesis of functionalized dihydropyridines **248** involving the Hantzsch reaction via the one-pot reaction of an aldehyde **246**, a β -dicarbonyl



Scheme 66



Scheme 67

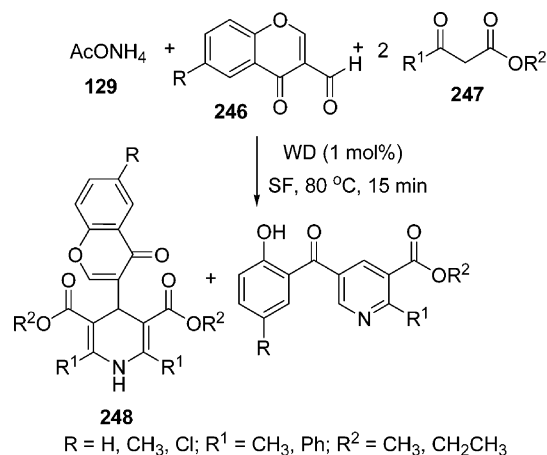


$\text{EWG} = \text{CN, COOEt}; \text{Ar} = \text{C}_6\text{H}_5, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 3,4,5\text{-(CH}_3\text{O)}_3\text{C}_6\text{H}_2, 3,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3, 2,4\text{-Cl}_2\text{C}_6\text{H}_4, 4\text{-(C}_6\text{H}_5\text{CH}_2\text{O)C}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, \text{Isatin, Cyclohexanone}; \text{Ar}^1 = \text{C}_6\text{H}_5, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-CH}_3\text{C}_6\text{H}_4, 3,4,5\text{-(CH}_3\text{O)}_3\text{C}_6\text{H}_2, 2,4\text{-(CH}_3\text{)}_2\text{C}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4,$

Scheme 68

compound **247** and an ammonia source *i.e.* ammonium acetate **129** (taken in a molar ratio of the reactants 3-formylchromone, methyl acetoacetate and ammonium acetate was 1 : 2 : 1, respectively), which provided the desired products in 60–99% yields. The pyridine functionalized at the 2-, 3-, and 5-positions was formed by opening the γ -pyrone ring after nucleophilic attack and subsequent cyclodehydration. Here, due to selectivity reasons, two products are formed in different ratios depending upon the substituents and the ratios of the starting materials (Scheme 69).

Another method for the synthesis of 6-amino-5-cyano-1,4-dihydropyridine derivatives has been developed by the one-pot reaction of ethyl acetoacetate, [(2-aryl)methylene]malononitriles,

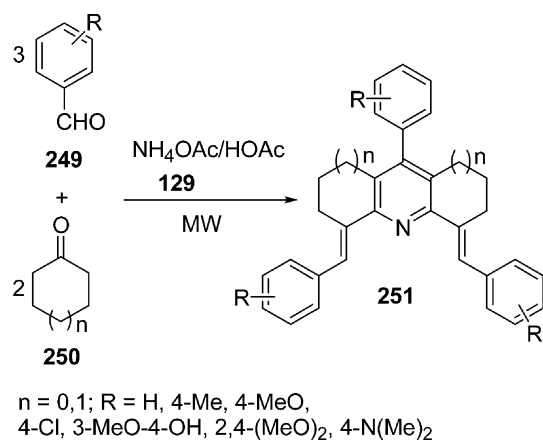


Scheme 69

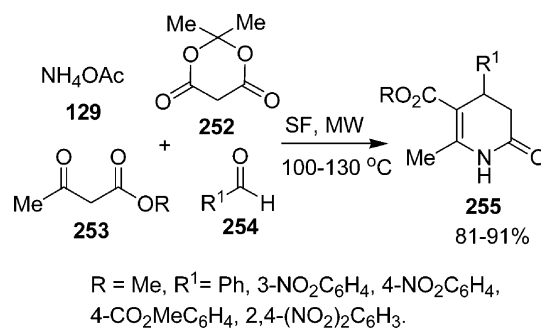
and ammonium acetate at room temperature with grinding.²⁰⁶ Under microwave irradiation, the one-pot multicomponent condensation reaction of three molar aromatic aldehydes **249** with two molar cyclic ketones with free α,α' -methylene ethylene positions such as cyclopentanone or cyclohexanone **250** in the presence of ammonium acetate **129** and acetic acid afforded dicyclocalenopyridines **251** in good yields. In similar reaction conditions, 1-tetralone, which has only one α -methylene position, results in 10-aryl-2,3:5,6-dibenzoacridines (Scheme 70).²⁰⁷

4.6.1.2 Pyridinones. Pyridinones constitute an important family of heterocyclic compounds for their potential pharmaceutical applications such as antibacterial and antifungal agents. Recently, the synthesis of 3,4-dihydropyridinones **255** by the one-pot multicomponent reaction of Meldrum's acid **252**, methyl acetoacetate **253**, and different aldehydes **254** in the presence of ammonium acetate **129** using microwave irradiation under solvent-free conditions (Scheme 71) has been reported.^{208a} Equimolar amounts of the starting compounds were irradiated under microwave at 100–130 °C for 10–15 min providing 3,4-dihydropyridinones in 81–91% yields. Carrying out the above reaction under conventional thermal heating under the same experimental conditions gave lower yields. A one-pot synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles **259** has been reported in good yields *via* the cyclocondensation of aromatic ketones **256**, aromatic aldehydes **257**, and 2-cyanoacetamide **258** under solvent-free conditions (Scheme 72).^{208b}

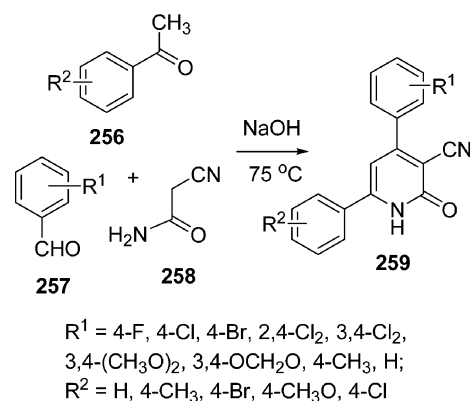
4.6.1.3 Coumarins. The coumarins (2*H*-chromen-2-ones, 2*H*-1-benzopyran-2-ones), an elite class of lactones, are important oxygen heterocycles that widely present as a structural motif in numerous natural products.²⁰⁹ Among the scaffolds of natural products, coumarins exhibit a broad range of biological²¹⁰ and therapeutic²¹¹ activities together with various applications in technological²¹² fields. Several synthetic analogs of coumarins such as novobiocin, chlorobiocin, coumermycin, simocyclinone, demiflin, and flavaxate have been developed into useful drugs.²¹³ Xanthotoxol (8-hydroxylpsoralen) is a natural psoralen with a good capability to treat Alzheimer's disease^{214a} and 4-(4-phenoxybutoxy)-7*H*-furo[3,2-*g*]chromene-7-thione is a blocker^{214b} of the lymphocyte potassium channel Kv1.3. Dibromo-7-hydroxy-4-methylchromen-2-one^{215a} is the most promising



Scheme 70



Scheme 71

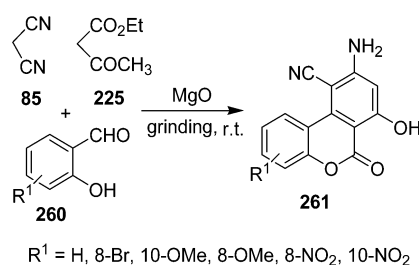


Scheme 72

inhibitor of Casein Kinase 2 (CK2). Other coumarin derivatives such as calanolide A, phenprocoumon, and warfarin have been reported as potent *anti*-HIV agents.^{215b}

Recently, a convenient and one-pot synthesis of 3-aryl/heteroaryl-2*H*-chromene-2-thiones and benzo[*f*]2*H*-chromene-2-thiones has been developed by our group *via* the condensation of β -oxodithioesters and salicylaldehydes/ α -hydroxynaphthaldehydes in the presence of indium trichloride²¹⁶ under solvent-free conditions in high yields. Valizadeh *et al.*²¹⁷, using a solventless system, have reported the synthesis of 5-amino-6-cyano-3-hydroxybenzo[*c*]coumarin derivatives **261** *via* the one-pot three-component reaction of salicylaldehydes **260**, malononitrile **85**, and ethyl acetoacetate **225** over MgO at room temperature in good yields (Scheme 73).

4.6.1.4 Pyrans. Pyrans and their derivatives are of special interest due to their biological activities. 4*H*-Benzo[*b*]pyrans are an important class of compounds, which have received considerable

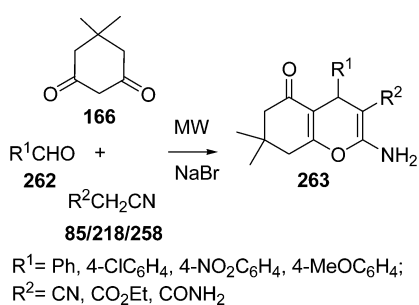


Scheme 73

attention in recent years due to their wide range of biological activities.²¹⁸ Compounds with this ring system have diverse pharmacological activities such as *anti*-coagulant, anticancer, spasmolytic, diuretic, *anti*-ancapylactia, *etc.*²¹⁹ 4*H*-Pyrans also constitute the structural unit of a series of natural products.²²⁰ A number of 2-amino-4*H*-pyrans are useful as photoactive materials.²²¹ In the conventional reported synthesis of 4*H*-benzo[*b*]pyrans, the use of organic solvents like DMF/acetic acid make the work-up procedure complicated and lead to poor yields of the products.²²² Kaupp *et al.*²²³ reported a novel method for the synthesis of benzo[*b*]pyrans utilising the reactants in a solid or molten state. This reaction has its own merit but some limitations; the two-step reaction was performed at a very high temperature and required a longer period of time and limited scope. Devi and Bhuyan²²⁴ have reported a very simple and highly efficient method for the synthesis of 4*H*-benzo[*b*]pyrans **263** via the three-component cyclocondensation reaction of **166**, **262**, and **85/218/258** under microwave irradiation using simple and inexpensive sodium bromide as the catalyst under solvent-free conditions (Scheme 74).

Recently, Khalilzadeh and co-workers²²⁵ have developed the most useful and dependable procedure for the synthesis of S-alkyl dithiocarbamates and 2*H*-pyran-3,4-dicarboxylate **266** by using **264**, **265**, and **162/244** in one-pot under solvent-free conditions in the absence of a catalyst (Scheme 75). Radi *et al.*²²⁶ have produced a rapid protocol for the synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles **270** by multicomponent microwave-assisted organocatalytic DKHDA from **267**, **268**, and **269** under both solvent and solvent-free conditions. The above procedure has been utilized for the fast generation of substituted 2,3-dihydropyran[2,3-*c*]pyrazoles with potential *anti*-tuberculosis activity (Scheme 76).

The microwave-assisted three-component coupling of barbituric acids **271**, benzaldehyde **272**, and alkyl nitriles **273** has been carried out in the absence or presence of triethylamine under both solvent and solventless conditions to afford pyrano[2,3-*d*]pyrimidines **274** in good yields (Scheme 77).²²⁷ A series of novel 4-aryl-thiopyrano[3,4-*b*]pyran-5-one derivatives **277** or **278** were synthesized through the one-pot three-component reaction of an aromatic aldehyde **276**, Meldrum's acid **252** or **85/218**, and **275** under solvent-free conditions at 80 °C. The reaction has also been carried out in different solvents like CH₃CN, CHCl₃, EtOH, HOAc, and H₂O, but the solvent-free method was found to be superior in terms of yields and time (Scheme 78).²²⁸

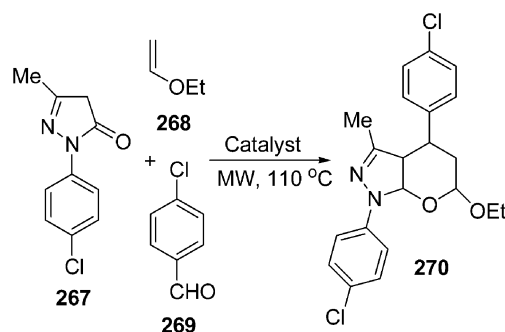


Scheme 74

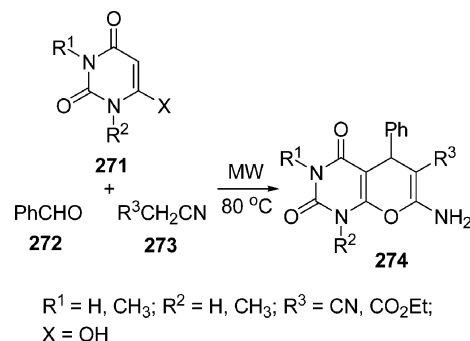


$$\begin{array}{l}
 \text{R} = \text{CO}_2\text{Et, Ph, 4-MeC}_6\text{H}_4, \text{4-NO}_2\text{C}_6\text{H}_4; \\
 \text{R}^1 = (\text{CH}_2)_4, (\text{CH}_2)_5, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2, \text{Et}; \\
 \text{R}^2 = \text{Me, Et, }^t\text{Bu}; \text{R}^3 = ^t\text{Bu, cyclohexyl,} \\
 \text{1,1,3,3-tetramethylbutyl, CH}_2\text{CO}_2\text{Et}
 \end{array}$$

Scheme 75

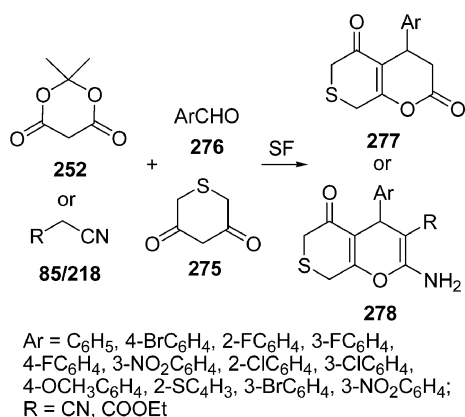


Scheme 76



Scheme 77

4.6.1.5 Chromenes. Chromenes represent an important class of compound as they are the main components of many naturally occurring products, and have been of interest in recent years due to their useful biological and pharmacological aspects, such as anticoagulant, spasmolytic, diuretic, insecticidal, anticancer, and antianaphylactic activity. 2-aminochromenes are widely employed as pigments, cosmetics, potential agrochemicals and also as components of many natural products.^{229–231} Thus, the development of an efficient methodology for the synthesis of 2-aminochromenes became highly essential. The most straightforward synthesis of this heterocyclic system involves a three-component coupling of aromatic aldehyde, malononitrile, and activated phenol in the presence of piperidine.²³² A variety of catalysts such as basic alumina, cetyl trimethyl ammonium chloride, NaOH, InCl₃, and I₂/K₂CO₃ have been tested for this multi-component reaction. Nanosized magnesium oxide has also been

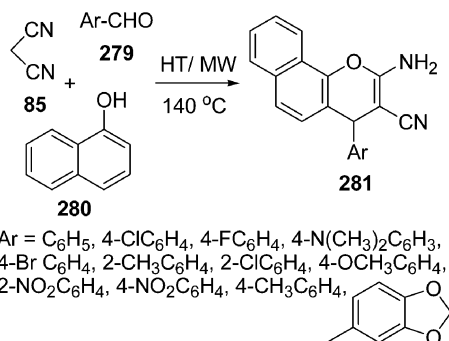


Scheme 78

shown as an effective catalyst for this reaction.²³³ A simple, clean, and environmentally benign three-component process for the synthesis of 2-amino-4H-chromenes using *N,N*-dimethylaminoethylbenzyl dimethyl ammonium chloride, [PhCH₂Me₂N⁺CH₂CH₂NMe₂]Cl⁻, as an efficient catalyst under solvent-free conditions has been described.^{234a} Recently, Surpur and co-workers^{234b} have reported the three-component condensation of aromatic aldehydes **279**, malononitrile **85**, and 1-naphthol **280** to form **281** by single-mode microwave irradiation under solvent-free conditions catalyzed by Mg/Al HT (Scheme 79).

Elinson and co-workers^{234c} directly heated the mixture of salicylaldehyde **282**, malononitrile **85** or methyl cyanoacetate **283**, and nitroalkanes **284** at 60 °C in the presence of catalytic amounts of KF or NaOAc, resulting to the formation of 2-amino-4-(1-nitroalkyl)-4H-chromene-3-carbonitriles or methyl 2-amino-4-(1-nitroalkyl)-4H-chromene-3-carboxylates **285** in 80–90% yields (Scheme 80). The three-component coupling (3CC) of Kojic acid **286**, aldehyde **287**, and dimedone **166** has been achieved in the presence of 10 mol% of InCl₃ under solvent-free conditions to afford the corresponding dihydropyrano[3,2-*b*]chromenedione derivatives **288** in good yields (Scheme 81).²³⁵

Recently, Khurana and co-workers²³⁶ have developed a novel protocol for the synthesis of biscoumarin **291** and dihydropyrano[*c*]chromene derivatives **292** by the coupling of a series of aromatic, heteroaromatic and aliphatic aldehydes **289** with 4-hydroxycoumarin **290** and **85** catalyzed by tetrabutylammonium bromide (TBAB, 10 mol%) under solvent-free neat conditions. All aldehydes reacted almost equally well to afford biscoumarins in excellent yields (Scheme 82).



Scheme 79



Scheme 80



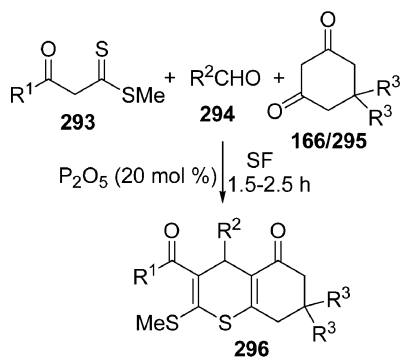
Scheme 81

4.6.1.6 Thiochromones. Thiochromone derivatives are known to exhibit versatile pharmacological activity. A regioselective synthesis of 4-aryl-3-aryl-2-methylsulfanyl-4,6,7,8-tetrahydrothiochromen-5-ones **296** has been developed by Singh *et al.*²³⁷ via the annulation of β-oxodithioesters **293** with aldehydes **294** and cyclic 1,3-diketones **166/295** under solvent-free conditions promoted by P₂O₅ in good yields (72–90%). No co-catalyst or activator is needed in this protocol. Aliphatic aldehydes and heterocyclic aldehydes failed to produce the desired product, thus limiting the scope of the reaction to some extent (Scheme 83).



Scheme 82

4.6.1.7 *Quinolines*. Quinolines and their derivatives are a very important class of compounds because of their wide occurrence in natural products²³⁸ and biologically active compounds.²³⁹ The classical method is the three-component coupling of an aldehyde, ethyl acetoacetate, and ammonia in acetic acid or refluxing alcohol.^{240,241} Kumar *et al.*²⁴² have developed an efficient synthesis of polyhydroquinolines **299** via the four-component reaction of aldehydes **297**, dimedone **166**, active methylene compounds **298**, and ammonium acetate **129** simply by grinding under solvent-free conditions at room temperature (Scheme 84A). Sapkal and co-workers²⁴³ have prepared polyhydroquinoline derivatives **299** in one-pot *via* Hantzsch condensation of **297**, **166**, **298**, and **129** using



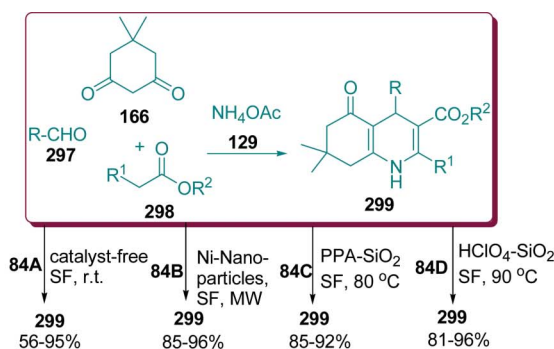
R¹ = C₆H₅, 4-MeOC₆H₄, 3-pyridyl, 2-thienyl, 2-furyl; R² = C₆H₅, 4-FC₆H₄, 4-NO₂C₆H₄, 2,4-Cl₂C₆H₃, 3-NO₂C₆H₄, 4-BrC₆H₄, 4-ClC₆H₄, 2-OMeC₆H₄, 2-ClC₆H₄, 4-Cl-3-FC₆H₃, 4-MeC₆H₄, 4-CF₃C₆H₄, 3-OHC₆H₄; R³ = H, CH₃

Scheme 83

nanosized Nickel (Ni) as a heterogeneous catalyst. The method does not involve any hazardous organic solvent or catalyst. The smaller size of Ni (80 ± 0.5 nm) with a higher surface to volume ratio has given convenient features for the reaction response (Scheme 84B). Silica gel-supported polyphosphoric acid (PPA–SiO₂) was found to be an efficient catalyst for the one-pot four-component Hantzsch condensation reaction of aryl aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate to afford the corresponding polyhydroquinoline derivatives in high yields (Scheme 84C). The main advantages of the present approach are short reaction times, clean reaction profiles and simple experimental and workup procedures. The catalyst was recovered by simple filtration in excellent yields and used in the reaction three times as fresh catalyst without any significant loss of its activity.²⁴⁴ An efficient Hantzsch condensation of polyhydroquinoline derivatives **299** was reported *via* the four-component coupling reaction of **297**, **166**, **298**, and **129** in the presence of HClO₄–SiO₂ under solvent-free conditions²⁴⁵ (Scheme 84D).

A three-component cyclocondensation of enaminones **300**, cyclic 1,3-dicarbonyl **166**, and ammonium acetate **129** in the presence of tungstocobaltate salt as a heterogeneous catalyst has been reported by Kantevari *et al.*¹⁹⁴ under solvent-free conditions. The protocol furnished the regioselective formation of 2,7,7-trisubstituted tetrahydroquinolin-5-ones **301** in good yields (Scheme 85). The reaction was also done in solvent but the solvent-free conditions were found to be superior. Wang *et al.*²⁴⁶ have reported an uncatalyzed and solvent-free multicomponent procedure for the synthesis of 1,4-arylquinoline derivatives **304** from **302**, **85**, and **303** (Scheme 86).

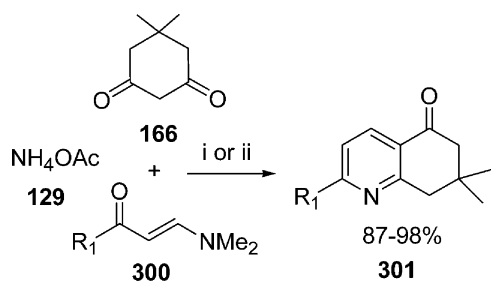
Quiroga *et al.*²⁴⁷ have developed a methodology for the synthesis of 6,8-dihydro-5*H*-benzo[*f*]pyrazolo[3,4-*b*]quinolines **308** by the three-component reaction of 2-tetralone **305** or dimedone **166**, 5-aminopyrazoles **306**, and different benzaldehydes **307** under



Scheme 84

Scheme	Substituents
84A	R = C ₆ H ₅ , 4-MeC ₆ H ₄ , 4-MeOC ₆ H ₄ , 2-ClC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 4-OHC ₆ H ₄ , 3-MeO-4-OHC ₆ H ₃ , 3-BrC ₆ H ₄ , 2-thienyl, 3-thienyl, 3,4,5-(MeO) ₃ C ₆ H ₂ , 4-N(Me) ₂ C ₆ H ₄ , CH ₃ CH ₂ CH ₂ ; R ¹ = CN or MeCO; R ² = Me, Ethyl
84B	R = 2-ClC ₆ H ₄ , 4-OH-3-CH ₃ OC ₆ H ₃ , 3-NO ₂ C ₆ H ₄ , 3-OHC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-OHC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , C ₆ H ₅ , 4-CH ₃ C ₆ H ₄ , 4-OCH ₃ C ₆ H ₄ , C ₆ H ₅ CH=CH, 4-BrC ₆ H ₄ , 2-Furyl, 2-Thienyl, 4-N(CH ₃) ₂ C ₆ H ₄ ; R ¹ = MeCO; R ² = Ethyl
84C	R = C ₆ H ₅ , 4-BrC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-OHC ₆ H ₄ , 4-OCH ₃ C ₆ H ₄ , 4-CH ₃ C ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 3-OHC ₆ H ₄ , 4-FC ₆ H ₄ ; R ¹ = CH ₃ CO; R ² = OEt.
84D	R = C ₆ H ₅ , 4-CH ₃ C ₆ H ₄ , 4-CH ₃ OC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 2,4-Cl ₂ C ₆ H ₃ , 2-ClC ₆ H ₄ , 4-FC ₆ H ₄ , 3,4,5-(OCH ₃) ₃ C ₆ H ₂ , C ₆ H ₅ CH=CH, 2-NO ₂ C ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 3,4,5-(OCH ₃) ₃ C ₆ H ₂ , 4-N(CH ₃) ₂ C ₆ H ₄ , 2-furyl, 2-thienyl, 3-thienyl, 3-pyridyl, 4-OHC ₆ H ₄ , 4-OH-3-CH ₃ OC ₆ H ₃ , 4-BrC ₆ H ₄ , C ₂ H ₅ , <i>n</i> -C ₃ H ₇ ; R ¹ = CH ₃ CO; R ² = OEt, OMe.

Scheme 84



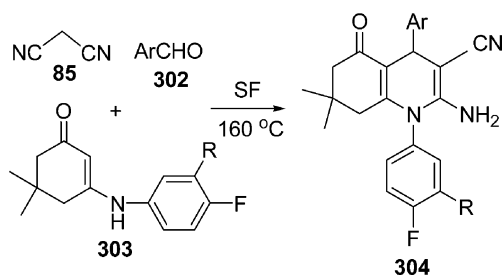
i = $K_5CoW_{12}O_{40.3}H_2O$, *i*-PrOH, reflux, 2-3 h.
 ii = $K_5CoW_{12}O_{40.3}H_2O$, neat, 115 °C, 0.5-1.0 h
 $R^1 = C_6H_5$, 4- $CH_3C_6H_4$, 4- ClC_6H_4 ,
 4- BrC_6H_4 , 4- $NO_2C_6H_4$, 4- $CH_3OC_6H_4$,
 1-Naphthyl; $R^2 = OC_2H_5$, CH_3

Scheme 85

solvent-free conditions. The isomeric 6,10-dihydro-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinolines **309** were also obtained by the reaction of amines with benzylidene derivative of β -tetralone under similar conditions (Scheme 87). It has also been observed that sometimes **305** does not react and coupling between **306** and **307** forms **310** (Scheme 88).

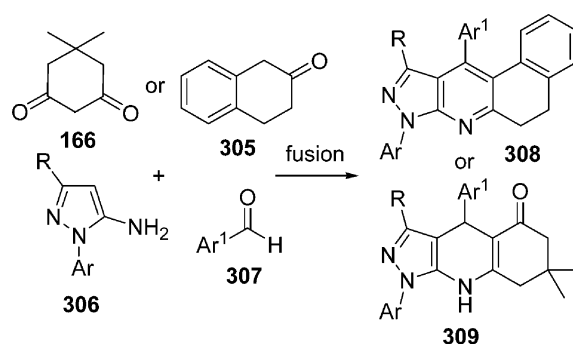
A series of thieno[3,2-*b*]quinoline derivatives **314** were designed and synthesized efficiently *via* the one-pot three-component reaction of **311**, **312**, and **313** under solvent-free and catalyst-free conditions at 90 °C in 46–86% yields. Aromatic aldehydes with electron-withdrawing groups or electron-donating groups, heterocyclic and aliphatic aldehydes are tolerated well under this protocol. Different solvents such as AcOH, $CHCl_3$, EtOH, DMF, and H_2O were also used but solvent-free conditions provided the best results (Scheme 89).²⁴⁸

4.6.1.8 Isoquinolines. The isoquinoline backbone is present in numerous natural products and has different kinds of bioactivities.^{249,250} Thus, the isoquinoline family is of vital importance to both synthetic and medicinal chemists.²⁵¹ Recently, Rong *et al.*²⁵² reported an efficient MCR involving aromatic aldehyde **315**, malononitrile **85**, and 1-methylpiperidin-4-one **316** to prepare 6-amino-8-aryl-2-methyl-1,2,3,4-tetrahydroisoquinoline-5,



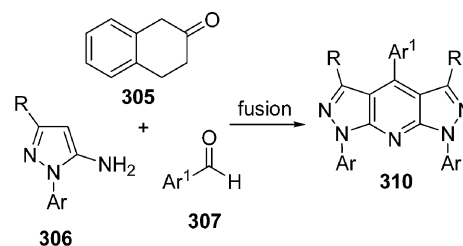
Ar = 2- ClC_6H_4 , 4- $CH_3OC_6H_4$, 4- $CH_3C_6H_4$, C_6H_5 ,
 2- $CH_3OC_6H_4$, 3- $NO_2C_6H_4$, 2,3-(CH_3O) $_2C_6H_4$,
 3- ClC_6H_4 , 2,3-(CH_3O) $_2C_6H_4$, 3- ClC_6H_4 ,
 3- $NO_2C_6H_4$, 2- $CH_3OC_6H_4$, 4- $CH_3OC_6H_4$,
 2- ClC_6H_4 , 4- $CH_3C_6H_4$; R = Cl, H.

Scheme 86

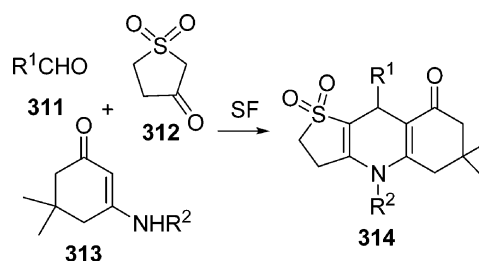


R = CH_3 , $C(CH_3)_3$; Ar = C_6H_5 , 4- ClC_6H_4 ; Ar¹ = 4- FC_6H_4 ,
 C_6H_5 , 4- ClC_6H_4 , 4- BrC_6H_4 , 4- $CF_3C_6H_4$, 4- $CH_3C_6H_4$,
 4- $CH_3OC_6H_4$, 4-Pyridyl, 3-Pyridyl

Scheme 87



Scheme 88



$R^1 = 3-FC_6H_4$, 4- FC_6H_4 , 3,4- $Cl_2C_6H_3$, 4- BrC_6H_4 ,
 4- $NO_2C_6H_4$, 3- ClC_6H_4 , 4- ClC_6H_4 , 3- BrC_6H_4 ,
 3- $NO_2C_6H_4$, 3- $CH_3OC_6H_4$, 2- FC_6H_4 , *n*- C_3H_7 ,
 3,4-(OCH_2O) C_6H_3 , Thiophene-2-yl; $R^2 = Ph$,
 4- $CH_3C_6H_4$, 4- BrC_6H_4 , 4- ClC_6H_4 , $C_6H_5CH_2$

Scheme 89

7-dicarbonitrile **317** under solvent-free conditions at 70 °C in the presence of 0.1 g of NaOH as catalyst (Scheme 90).

4.6.1.9 Acridines. The acridine moiety is an important structural unit present in many biologically important molecules such as amsacrine (cytotoxic, antiviral agent), botiacrine (antiparkinsonian drug), clomacran (tranquilizer), monometacrine (antidepressant), and in natural products such as plakinidine A and B and dercitin. Also, acridine derivatives have been employed or examined as antitumor agents, acetylcholinesterase inhibitors, anticancer agents, and DNA binding agents. Wang and Shen²⁵³

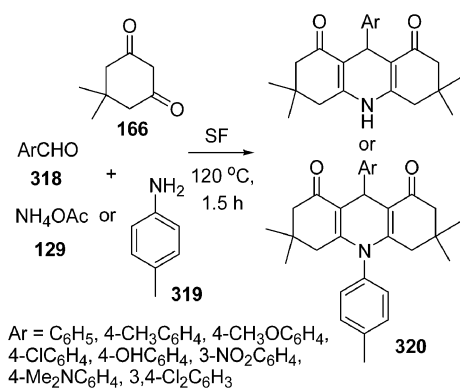


Scheme 90

have synthesized 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones or 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones **320** from **166**, **318**, and **129** or **319** respectively, under solvent-free conditions in high yields (90%). A rapid and efficient synthesis has been achieved using ammonium acetate **129** and *p*-toluidine **319** as the nitrogen source (Scheme 91).

4.6.1.10 Xanthenes. Xanthenes and benzoxanthenes are important biologically active heterocyclic compounds. They possess antiviral,²⁵⁴ anti-inflammatory,²⁵⁵ and antibacterial²⁵⁶ activities. These are used as antagonists for paralyzing action of zoxazolamine²⁵⁷ and in photodynamic therapy.²⁵⁸ In addition to that, these compounds can be used as dyes,²⁵⁹ in laser technologies²⁶⁰ and as pH sensitive fluorescent materials for the visualization of biomolecules.²⁶¹ Nandi and co-workers²⁶² have used Indium(III) chloride as a catalyst in the one-pot synthesis of 12-aryl/alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthenes-11-one derivatives **323**. This has been achieved by the three-component cyclocondensation of aldehydes **321**, β -naphthol **28**, and the cyclic 1,3-dicarbonyl compound **322** under solvent-free conditions in high yields. P₂O₅ too has been found to be an effective catalyst towards this transformation (Scheme 92A). Wang *et al.*²⁶³ has also developed an efficient protocol for the synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives **323** by the three-component coupling of **321**, **28**, and **322** in the presence of 12-tungstophosphoric acid (H₃PW₁₂O₄₀) under solvent-free conditions (Scheme 92B). The above methodologies both offer several advantages such as high yields, simple procedure, low cost, short reaction times, and mild conditions.

The preparation of 12-aryl- or 12-alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives using ammonium chloride



Scheme 91

(10 mol%) as a catalyst has been described under solvent-free conditions at 120 °C by the one-pot three-component reaction of **321**, **28**, and **322** in good yields (Scheme 92C).²⁶⁴ Wang and co-workers²⁶⁵ have described an alternative method for the synthesis of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one derivatives **323** by the coupling of **321**, **28**, and **322** catalyzed by iodine in one-pot under solvent-free conditions (Scheme 92D). A facile and efficient procedure has been developed by the one-pot coupling of **321**, **28**, and **322** for the synthesis of 8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one or 8,9-dihydrobenzo[*f*]cyclopenta[*b*]chromen-10(11*H*)-one derivatives **323** catalyzed by *p*-toluenesulfonic acid under solvent-free and sonication conditions (Scheme 92E).²⁶⁶ Recently, one more convenient multi-component solvent-free protocol to synthesize this moiety has also been developed by Oskooie *et al.*²⁶⁷

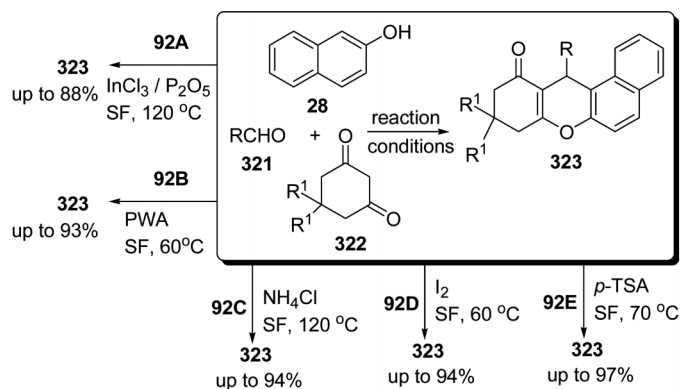
Shaterian and co-workers²⁶⁸ have used ferric hydrogensulfate as a catalyst for the one-pot preparation of aryl-14*H*-dibenzo[*a,j*]xanthene derivatives **325** by the cyclocondensation of β -naphthol **28** and aromatic aldehydes **324** under solvent-free thermal conditions in 85–91% yields (Scheme 93A). Recently, a facile, efficient and environmentally friendly protocol for the synthesis of 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes **325** has been developed by Singh and co-workers²⁶⁹ through the one-pot condensation of **28** with **324** in the presence of P₂O₅ or InCl₃ as catalysts under solvent-free conditions in high yield (Scheme 93 B).

Shen and co-workers²⁵³ have reported the synthesis of 9-aryl-3,3,6,6-tetramethyl-tetrahydroxanthene-1,8-diones **327** in nearly quantitative yields by the coupling of various aromatic aldehydes **326** and 5,5-dimethyl-1,3-cyclohexanedione **166** catalyzed by methanesulfonic acid under solvent-free conditions (Scheme 94).

4.6.2 Containing two heteroatoms.

4.6.2.1 Pyrimidines. Pyrimidines are of chemical and pharmacological interest and compounds containing the pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial, and anticonvulsant activities.^{270–272} Pyrimidines have been synthesized using different procedures^{273–282} including the reaction of amidines with various functionalities, dimerization-oxidative fragmentation of β -aryl-vinylimines, condensation of phenacyldimethyl sulfonium salts, aldehydes, and ammonia, reaction of alkynes and nitriles in the presence of TfOH, rearrangement of 2,4,5-trisubstituted imidazolines, one-pot three-component reaction of aryl halides, terminal propargyl alcohols, and amidinium salts based upon a coupling/isomerization/cyclocondensation sequence, arylation of halogenated pyrimidines *via* Suzuki coupling reaction, the reaction of *R,R*-dibromo oxime ethers with Grignard reagents, microwave-assisted reaction of amidines and alkynones, and the sequential assembly of aryl groups onto a pyrimidine core (2-methylthiopyrimidine). Zhuang and co-workers²⁸³ have reported a novel one-pot three-component synthesis of multifunctionalized 2-amine-4,6-diarylpyrimidine scaffolds **331** through the condensation of aromatic aldehydes **328**, aromatic ketones **329**, and guanidine carbonate **330** under solvent-free conditions in 88–96% yields (Scheme 95).

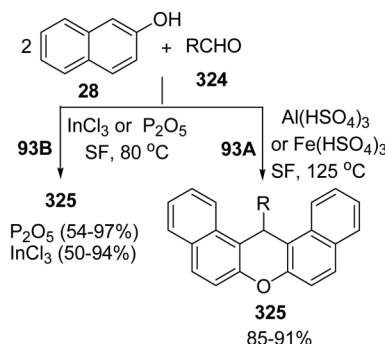
Prajapati *et al.*²⁸⁴ have synthesized pyrimido[4,5-*d*]pyrimidine derivatives **334** of biological significance involving electron rich [(dimethylamino)methylene]amino uracil **332**, which undergoes a [4 + 2] cycloaddition reaction with various glyoxylate imine **333**,



Scheme 92

Scheme	Substituents
92A	R = C ₆ H ₅ , 4-NO ₂ C ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 2-NO ₂ C ₆ H ₄ , 4-OMeC ₆ H ₄ , 2-OMeC ₆ H ₄ , 4-ClC ₆ H ₄ , 2-ClC ₆ H ₄ , 2,4-Cl ₂ C ₆ H ₃ , 4-OHC ₆ H ₄ , 3-OHC ₆ H ₄ , 5-Br-2-OHC ₆ H ₃ , 5-NO ₂ -2-OHC ₆ H ₃ , 2-OH-3-OMeC ₆ H ₃ , 2-OH-3-OEtC ₆ H ₃ , 4-MeC ₆ H ₄ , -CH=CHC ₆ H ₅ , -CH(CH ₃) ₂ , 4-BrC ₆ H ₄ , 4-FC ₆ H ₄ ; R ¹ = Me
92B	R = C ₆ H ₅ , 4-OMeC ₆ H ₄ , 4-OHC ₆ H ₄ , 4-FC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-BrC ₆ H ₄ , 3,4-Cl ₂ C ₆ H ₃ , 4-NO ₂ C ₆ H ₄ , 2-ClC ₆ H ₄ , 3-ClC ₆ H ₄ , other aldehydes = cyclohexanecarbaldehyde, butyraldehyde, 2-methylpropionaldehyde; R ¹ = H, Me
92C	R = 4-MeC ₆ H ₄ , C ₆ H ₅ , 3-MeOC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , Propanal, 3-ClC ₆ H ₄ , 4-FC ₆ H ₄ , 3-BrC ₆ H ₄ , 2-ClC ₆ H ₄ , 2-OHC ₆ H ₄ , C ₆ H ₅ C=C-; R ¹ = CH ₃
92D	R = Ph, 4-MeC ₆ H ₄ , 4-MeOC ₆ H ₄ , 4-OHC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-BrC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 3-NO ₂ C ₆ H ₄ ; R ¹ = Me, H
92E	R = C ₆ H ₅ , 3-FC ₆ H ₄ , 3-ClC ₆ H ₄ , 3-OHC ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 3-OCH ₃ C ₆ H ₄ , 3-OMe-4-OHC ₆ H ₃ , 3-Me-4-MeC ₆ H ₃ , 4-OMeC ₆ H ₄ , 4-ClC ₆ H ₄ , CH ₃ CH ₂ , 2-thiophene, 4-ClC ₆ H ₄ ; R ¹ = CH ₃

Scheme 92



Scheme 93

Scheme	Substituents
93A	R = C ₆ H ₅ , 2,4-Cl ₂ C ₆ H ₃ , 4-ClC ₆ H ₄ , 3-ClC ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 4-CH ₃ C ₆ H ₄ , 4-OHC ₆ H ₄ , 2-OCH ₃ -3-OHC ₆ H ₃ , 2,5-(OMe) ₂ C ₆ H ₃
93B	R = 4-NO ₂ C ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 2-NO ₂ C ₆ H ₄ , 2-ClC ₆ H ₄ , 4-ClC ₆ H ₄ , 4-OMeC ₆ H ₄ , C ₆ H ₅ , 4-MeC ₆ H ₄ , 3-OHC ₆ H ₄ , 3-OEt-2-OHC ₆ H ₃ , 4-BrC ₆ H ₄ , 4-FC ₆ H ₄ , 2-OH-3-OMeC ₆ H ₃ , 2,4-Cl ₂ C ₆ H ₃ , 2-OMeC ₆ H ₄ , 4-OHC ₆ H ₄ , 2-OHC ₆ H ₄ , Me ₂ CH, C ₆ H ₅ CH=CH, CH ₃ CH ₂ , Me ₂ CHCH ₂

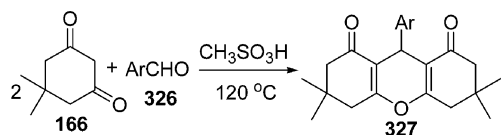
Scheme 93

(generated *in situ*) followed by oxidative aromatisation under solvent-free conditions as well as microwave irradiation (Scheme 96).

An efficient and convenient method for the preparation of 2,4-diamino-6-arylpyrimidine-5-carbonitrile derivatives **336** has been reported by the one-pot reaction of aromatic aldehydes **335**, malononitrile **85**, and guanidine carbonate **330** in the presence of

sodium hydroxide under solvent-free conditions in good yields (Scheme 97).²⁸⁵

4.6.2.2 Pyrimidinones and pyrimidinethiones. 3,4-Dihydropyrimidine-2-ones/thiones are useful targets in chemical synthesis as they have been associated with a diverse range of therapeutic and medicinal properties. The dihydropyrimidinone scaffold is also



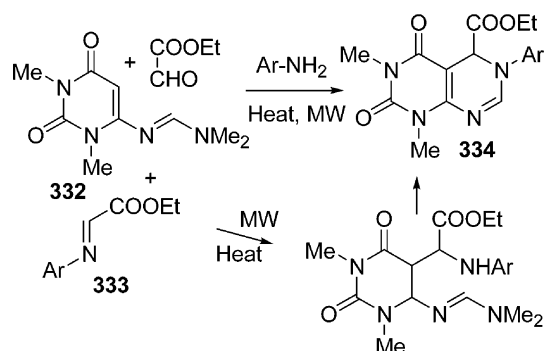
Ar = C₆H₅, 4-CH₃C₆H₄, 4-CH₃OC₆H₄, 4-ClC₆H₄,
4-BrC₆H₄, 3-NO₂C₆H₄, 4-Me₂NC₆H₄, 3,4-Cl₂C₆H₃

Scheme 94



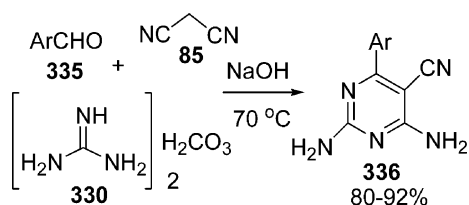
Ar¹ = 4-CH₃C₆H₄, 4-FC₆H₄, 4-ClC₆H₄, C₆H₅,
2-ClC₆H₄, 4-BrC₆H₄, 2,4-Cl₂C₆H₃, 4-CH₃OC₆H₄,
Ar² = C₆H₅, 4-ClC₆H₄, 4-CH₃OC₆H₄

Scheme 95



Ar = Ph, 4-ClC₆H₄, 4-MeC₆H₄,
4-MeOC₆H₄, 4-NO₂C₆H₄, 4-BrC₆H₄

Scheme 96



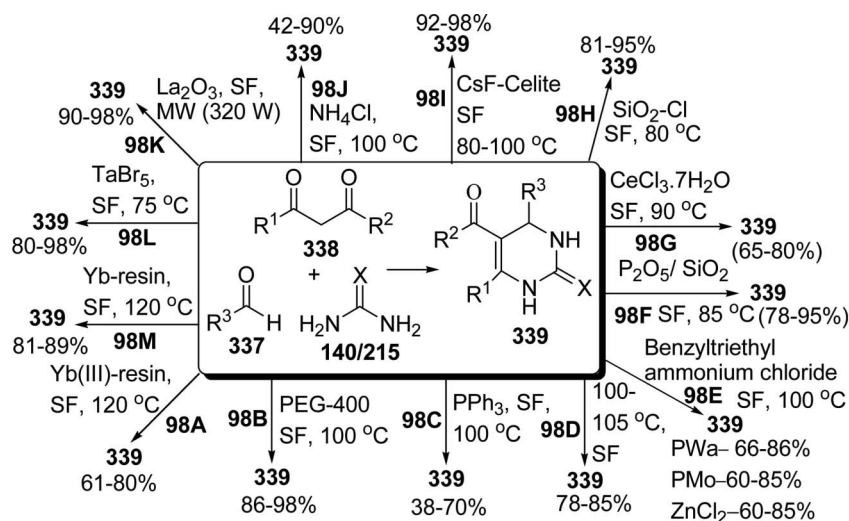
Ar = C₆H₅, 4-CH₃C₆H₄, 4-CH₃OC₆H₄,
3,4-(CH₃)₂C₆H₃, 4-BrC₆H₄, 3-ClC₆H₄,
4-ClC₆H₄, 3,4-Cl₂C₆H₃, 4-FC₆H₄

Scheme 97

The simple and direct method for the synthesis of DHPMs known as the Biginelli reaction involves the one-pot condensation of an aldehyde, a β -ketoester, and urea under strong acidic conditions, which was first reported by Biginelli in 1893.²⁸⁷ However, the yields of products were low (20–50%). Since then, many new techniques such as microwave-assisted synthesis, ionic liquids, ultrasound irradiation, solvent-free conditions, and many new catalysts such as BF₃,^{288a} FeCl₃,^{288b} InCl₃,^{288c} BiCl₃,^{288d} LaCl₃,^{288e} LiClO₄,^{288f} Mn(OAc), CAN²⁸⁹ *etc.*, were used to improve this transformation. Dondoni and Massi²⁹⁰ have developed an efficient synthesis of an array of 3,4-dihydropyrimidin-2-(1*H*)-ones **339** using a solid-supported ytterbium(III) reagent from aldehydes **337**, 1,3-dicarbonyl compounds **338**, and urea **140/215** (Biginelli reaction) under solvent-free conditions (Scheme 98A). Jain and co-workers²⁹¹ have reported a PEG-assisted solvent and catalyst-free synthesis of 3,4-dihydropyrimidinones **339** by the coupling of the same components under neutral reaction conditions (Scheme 98B). An efficient synthesis of dihydropyrimidinones **339** from the **337**, **338**, and **140/215** under solvent-free conditions using fluoroboric acid as the catalyst has been described by Chen *et al.*²⁹²

The use of Lewis base TPP as a new catalyst for the one-pot Biginelli coupling of **337**, **338**, and **140/215** under neutral and solvent-free conditions to afford the corresponding dihydropyrimidinones **339** in moderate to good yields has been reported by Debache *et al.* (Scheme 98C).²⁹³ A simple, efficient, green, and cost-effective procedure for the synthesis of dihydropyrimidinones **339** has been developed by Ranu *et al.*²⁹⁴ via the coupling of **337**, **338**, and **140/215** under solvent and catalyst-free conditions (Scheme 98D). Bose and co-workers²⁹⁵ have developed a simple, efficient, and cost-effective method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **339** via the one-pot three-component cyclocondensation of **337**, **338**, and **140/215** using benzyltriethylammonium chloride as the catalyst under solvent-free conditions (Scheme 98E). A synthetic procedure for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones **339** from **337**, **338**, and **140/215** in the presence of a catalytic amount of silica-supported P₂O₅ (P₂O₅/SiO₂) at 85 °C has been given by Hasaninejad *et al.*²⁹⁶ in high yields (Scheme 98F). A solvent-free coupling of **337**, **338**, and **140/215** in the presence of CeCl₃·7H₂O (30 mol%) afforded the corresponding dihydropyrimidinones **339** in 65–80% yields (Scheme 98G).²⁹⁷ Karade *et al.*²⁹⁸ described an improved procedure for the efficient and facile synthesis of 4-aryl substituted 3,4-dihydropyrimidinones **339** from **337**, **338**, and **140/215** under mild reaction conditions in excellent yields using inexpensive silica chloride under solvent-free conditions (Scheme 98H). Recently, a synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **339** via the coupling of **337**, **338**, and **140/215** catalyzed by CsF–Celite (10 mol%) has been developed by Chancharunee *et al.*²⁹⁹ (Scheme 98I). Shaabani and co-workers³⁰⁰ performed the Biginelli condensation in one-pot utilizing **337**, **338**, and **140/215** under solvent-free conditions to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones **339** in high yields (Scheme 98J). A synthesis of 3,4-dihydropyrimidinone **339** derivatives has been reported using lanthanum oxide as a catalyst, from aldehydes **337**, **338**, and **140/215** without solvent under the irradiation of microwave (98 K).³⁰¹ Furthermore, A Biginelli reaction for the syntheses of

found in various marine alkaloids, which have been shown to possess antiviral, antitumor, antibacterial, and *anti*-inflammatory activities. Pyrimidinones are of considerable interest both in the industry and in academia because of their promising biological activities as calcium channel blockers, antihypertensive agents, and anticancer drugs.²⁸⁶



Scheme 98

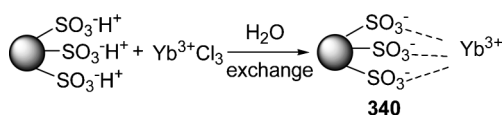
Scheme	Substituents
98A	$\text{R}^1 = \text{CH}_3$; $\text{R}^2 = \text{OEt, OMe, OP}^i, \text{OBn, Me}$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-FC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 3\text{-MeOC}_6\text{H}_4, 2\text{-BrC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-CF}_3\text{C}_6\text{H}_4$; $\text{X} = \text{O, S}$
98B	$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{OMe, OEt, Me}$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, \text{C}_6\text{H}_5, 4\text{-ClC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 2\text{-Pyridyl, 2-Furyl, } n\text{-CH}_3\text{CH}_2\text{CH}_2, (\text{CH}_3)_2\text{CH, } n\text{-CH}_3(\text{CH}_2)_2\text{CH}_2, \text{C}_6\text{H}_5\text{CH}=\text{CH}$; $\text{X} = \text{O, S}$
98C	$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{OEt, CH}_3$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-MeOC}_6\text{H}_4, 2\text{-MeOC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 3\text{-MeC}_6\text{H}_4, 4\text{-HOC}_6\text{H}_4, \text{C}_6\text{H}_5\text{CH}=\text{CH, 2-Thienyl}$; $\text{X} = \text{O, S}$
98D	$\text{R}^1 = \text{Me, Et}$; $\text{R}^2 = \text{OMe, OEt, Me, Ph}$; $\text{R}^3 = \text{Ph, 4-NO}_2\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4, 3\text{-OMeC}_6\text{H}_4, 4\text{-OH-3-OMeC}_6\text{H}_3, \text{PhCH}=\text{CH, } n\text{-Pr, } i\text{-Pr, } n\text{-C}_6\text{H}_{13}$; $\text{X} = \text{O, S}$
98E	$\text{R}^1 = \text{CH}_3, \text{C}_2\text{H}_5$; $\text{R}^2 = \text{OCH}_3, \text{OC}_2\text{H}_5, \text{C}(\text{CH}_3)_2$; $\text{R}^3 = \text{Ph, 4-OCH}_3\text{C}_6\text{H}_4, 4\text{-(NCH}_3)_2\text{C}_6\text{H}_4, 3\text{-OHC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 2,4\text{-(OCH}_3)_2\text{C}_6\text{H}_3, 3,4\text{-(OCH}_3)_2\text{C}_6\text{H}_3, \text{C}_6\text{H}_5\text{-CH}=\text{CH, CH}_3\text{CH}_2\text{CH}_2, (\text{CH}_3)_2\text{CH, 3,4,5-(OCH}_3)_3\text{C}_6\text{H}_2, 2\text{-NO}_2\text{C}_6\text{H}_4$; $\text{X} = \text{O, S}$
98F	$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Me, Et}$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-MeC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-OHC}_6\text{H}_4, 2\text{-OMeC}_6\text{H}_4, 2,3,4\text{-(OMe)}_3\text{C}_6\text{H}_2$; $\text{X} = \text{O, S}$
98G	$\text{R}^1 = \text{CH}_3, \text{C}_2\text{H}_5$; $\text{R}^2 = \text{OCH}_3, \text{OC}_2\text{H}_5, \text{C}(\text{CH}_3)_2$; $\text{R}^3 = \text{Ph, 4-OCH}_3\text{C}_6\text{H}_4, 4\text{-NMe}_2\text{C}_6\text{H}_4, 2,4\text{-(OCH}_3)_2\text{C}_6\text{H}_3, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, \text{CH}_3, 3,4\text{-(OCH}_3)_2\text{C}_6\text{H}_3, \text{C}_6\text{H}_5\text{-CH}=\text{CH, CH}_3, \text{CH}_3\text{CH}_2\text{CH}_2, \text{CH}_3, (\text{CH}_3)_2\text{CH, 3,4,5-(OCH}_3)_3\text{C}_6\text{H}_2, 2\text{-NO}_2\text{C}_6\text{H}_4$; $\text{X} = \text{O, S}$
98H	$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{OEt, OMe}$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-NMe}_2\text{C}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 3\text{-BrC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-FC}_6\text{H}_4$; $\text{X} = \text{O, S}$
98I	$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{OEt}$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-(CH}_3)_2\text{NC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 3\text{-HOC}_6\text{H}_4$; $\text{X} = \text{O, S}$
98J	$\text{R}^1 = \text{Me, 2-Thienyl, Ph; Alkyl, Aryl}$; $\text{R}^2 = \text{OMe, OEt, OBn, Me, CF}_3$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-OMeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, \text{CH}_3, \text{C}_3\text{H}_7, \text{C}_4\text{H}_9$; $\text{X} = \text{O, S}$
98K	$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{OEt}$; $\text{R}^3 = \text{C}_6\text{H}_5, 2\text{-ClC}_6\text{H}_4, 2\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 3,4,5\text{-(CH}_3\text{O)}_3\text{C}_6\text{H}_2$; $\text{X} = \text{O, S}$
98L	$\text{R}^1 = \text{Me, CF}_3$; $\text{R}^2 = \text{OEt, OCH}_2\text{C}_6\text{H}_5$; $\text{R}^3 = \text{C}_6\text{H}_5, 4\text{-BrC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-FC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-HOC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, \text{trans-C}_6\text{H}_4\text{CH}=\text{CH, 4-}^i\text{ButC}_6\text{H}_4$; $\text{X} = \text{O, S}$
98M	$\text{R}^1 = \text{CH}_3$; $\text{R}^2 = \text{OC}_2\text{H}_5, \text{CH}_3, \text{C}_6\text{H}_5$; $\text{R}^3 = \text{C}_6\text{H}_5, 3\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-CH}_3\text{OC}_6\text{H}_4, 3\text{-CH}_3\text{OC}_6\text{H}_4, 3,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3, 4\text{-ClC}_6\text{H}_4, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-CH}_3\text{OC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4$; $\text{X} = \text{O, S}$

Scheme 98

3,4-dihydropyrimidin-2(1H)-ones (DHPMs) and their thione analogs **339**, catalyzed by TaBr_5 as a novel Lewis acid (5–10 mol%) under solvent-free conditions has been reported (98L).³⁰² The solid catalyst combines the Lewis acid properties of the lanthanide and the advantage of solid phase. Due to the versatility of this new type of solid-phase Lewis acid, A ytterbium(III) reagent supported on ion exchange resin **340** is applied in a number of important organic transformations under

solvent-free conditions. Yu *et al.*³⁰³ have developed a novel method to support the lanthanide(III) on ion exchange resin (Scheme 99).

The one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-thiones **339** was described by Jiang and Chen³⁰⁴ by the cyclocondensation of **337**, **338**, and **140/215** utilizing recyclable ytterbium(III) reagent in good yields. They have prepared the Yb(III) catalyst supported on Amberlyst 15 resin which is a Yb-resin containing



Scheme 99

0.75 mmol g⁻¹ Yb(III), which was determined through EDTA titration. A series of solvents such as toluene, THF, DCM, MeCN, and H₂O were tested. In all cases the reaction afforded the product in good yields. The yield of the desired compound was found to be best under solvent-free conditions (Scheme 98M).

Another simple and efficient synthesis of 3,4-dihydropyrimidines/thiones **339** via cyclocondensation of **337**, **338**, and **140/215** in the presence of silica-supported ceric sulfate [Ce(SO₄)₂-SiO₂] as a heterogeneous catalyst at 110 °C under solvent-free conditions has been described.³⁰⁵ The heterogeneous catalyst Ce(SO₄)₂-SiO₂ can be easily isolated by filtration from the reaction mixture, which was recovered and reused without further activation. Only 5% reduction in the catalytic activity was found during the consecutive use of recovered catalyst. A novel version of the Biginelli reaction using an acylal **341** as masked carbonyl functionality together with ethyl acetoacetate **225** and urea or thiourea **140/215** to give dihydropyrimidinones **342** has been reported by Khabazzadeh *et al.*³⁰⁶ The reaction is catalyzed by PWA, PMo or zinc chloride and has been performed in one-pot under solvent-free conditions (Scheme 100). In the optimized conditions, 10 mol%, 20 mol%, and 80 mol% of PWA, PMo, and ZnCl₂ were used, respectively to get the best yields. The reaction was highly affected by the electronic factors and steric hindrance.

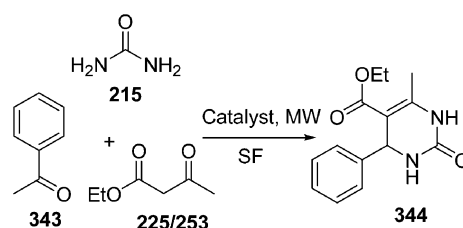
Singh *et al.*³⁰⁷ have described a novel multicomponent one-pot protocol for the synthesis of dihydropyrimidinones **344** by the coupling of ketone **343**, urea **140**, and β-ketoester **225/253** using Zr-PILC as a mild recyclable solid acid catalyst under solvent-free conditions via both thermal and microwave heating (Scheme 101). A novel method for the synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1H)-ones **347** has been developed from **215**, **345**, and **346** by microwave-assisted Biginelli reactions in a short and concise manner employing ZnI₂ as a catalyst under solvent-free conditions (Scheme 102).³⁰⁸

A zeolite-catalyzed, simple, one-pot, solvent-free and environmentally benign process for the synthesis of dihydropyrimidones **349** from **225**, **348**, and **140/215** has been described by



X = O, S; R = Ph, 4-ClC₆H₄, 2-ClC₆H₄, 3-O₂NC₆H₄, 4-O₂NC₆H₄, 1-Naphthyl, 4-CH₃C₆H₄, 2-CH₃C₆H₄, 4-CH₃OC₆H₄, 2, 4-(Cl)₂C₆H₃; Catalysts = PWA, PMo, ZnCl₂

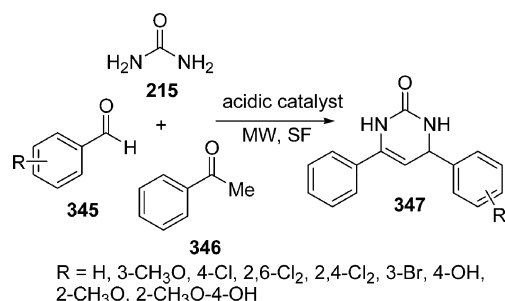
Scheme 100



Scheme 101

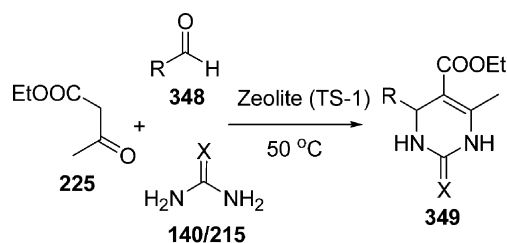
Kulkarni *et al.*³⁰⁹ This reaction is scalable to the multigram scale and the catalyst is recyclable (Scheme 103). Trivalent lanthanides are usually considered hard acids, which can effectively activate the carbonyl and related compounds,³¹⁰ for example, Ln(OTf)₃ can catalyze a variety of important organic reactions under mild conditions.^{311,312}

Singh and co-workers³¹³ have developed a one-pot three-component cyclocondensation reaction between aromatic aldehydes **350**, cyclic-1,3-diketones **166/295** or **204** and 1,3-dimethylbarbituric acid **54** for the preparation of 9-oxa-1,3-diazanthracene-2,4,5-triones **351** and 6,10-dihydro-5-oxa-6,8-diaza-benzo[*b*]fluorene-7,9,11-triones **352**, which are of potential synthetic and pharmacological interest, in the presence of 10 mol% of InCl₃ or 20 mol% of P₂O₅ under solvent-free conditions at 100 °C (Scheme 104). This protocol tolerates a variety of aromatic aldehydes containing both electron-withdrawing and electron-donating substituents at *ortho*-, *meta*- or *para*-positions. However, when some aliphatic aldehydes such as propionaldehyde, isobutyraldehyde, cinnamaldehyde, and cyclohexanecarboxaldehyde were used in this protocol under the above optimized conditions, it led to a mixture of products in



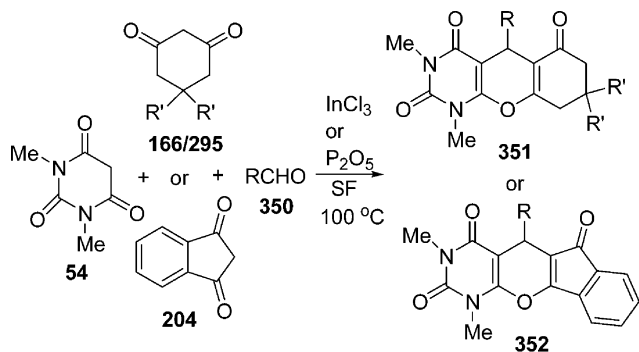
R = H, 3-CH₃O, 4-Cl, 2,6-Cl₂, 2,4-Cl₂, 3-Br, 4-OH, 2-CH₃O, 2-CH₃O-4-OH

Scheme 102



X = O, S; R = Ph, CH₃, CH₃CH₂, CH₃CH₂CH₂, 4-OHC₆H₄, 3-OHC₆H₄, 2-NO₂C₆H₄, 4-ClC₆H₄, Ph-CH=CH, 3,4-(OMe)₂C₆H₃, 2-furyl, 5-methyl-2-furyl

Scheme 103



R = 4-FC₆H₄, 4-NO₂C₆H₄, 3-NO₂C₆H₄, 2-NO₂C₆H₄, 4-MeOC₆H₄, 2-MeOC₆H₄, 4-ClC₆H₄, 3-ClC₆H₄, 4-MeC₆H₄, 3-OHC₆H₄, 4-BrC₆H₄, 2-OH-3-MeOC₆H₃, C₆H₅, 2,4-Cl₂C₆H₃, 2-ClC₆H₄; 1,3-diketone = Dimedone, Cyclohexane-1,3-dione, Indane-1,3-dione

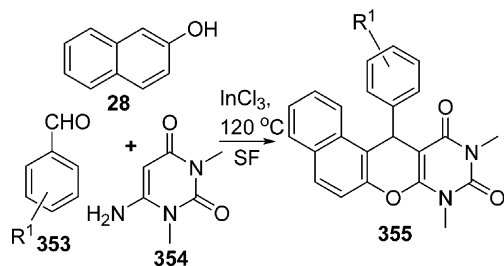
Scheme 104

low yields. This may be attributed to an aldol condensation as a side reaction.

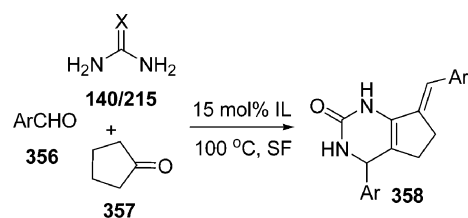
Nandi and co-workers³¹⁴ have developed a highly efficient InCl₃ catalyzed three-component one-pot protocol for the synthesis of 8,12-dihydro-8,10-dimethyl-12-aryl-9*H*-naphtho[1',2':5,6]pyrano-[2,3-*d*]pyrimidine-9,11-(10*H*)-dione **355** via the condensation of aldehydes **353**, 2-naphthol **28**, and 6-amino-1,3-dimethyluracil **354** under solvent-free conditions in good yields (Scheme 105). A synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones by condensation of ethylacetoacetate, aldehydes, and urea or thiourea in the presence of methylimidazolium hydrogensulfate has also been reported. Aromatic and aliphatic aldehydes reacted easily to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones and thiones under solvent-free conditions.³¹⁵

Pyrimidinone derivatives **358** have also been synthesized from the reaction of aromatic aldehydes **356**, cyclopentanone **357**, and urea or thiourea **140/215** in the presence of *N*-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulfate([TEBSA][HSO₄]) as the Brønsted acidic ionic liquid as well as an effective catalyst under thermal and solvent-free conditions (Scheme 106).³¹⁶

The one-pot synthesis of substituted pyrimidine derivatives from acetylenedicarboxylate, amine, and orthoformate has been developed recently by Reddy and Nagarajan.³¹⁷ The solvent and catalyst-free synthesis of pyrano[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **361** has been described by the ball-milling of aldehyde **359**, cyanoacetonitrile **85**, and **360** by Naimi-Jamal and Mashkouri (Scheme 107).³¹⁸



Scheme 105

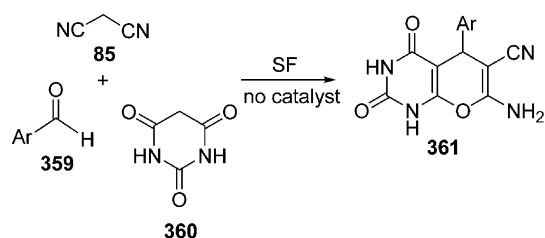


IL = (CH₃CH₂)₃N⁺CH₂(CH₂)₂CH₂SO₃H HSO₄⁻
 X = O, S; Ar = C₆H₅, 2-ClC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 3-O₂NC₆H₄, 4-O₂NC₆H₄, 4-NCC₆H₄, 4-CH₃OCOC₆H₄, 4-FC₆H₄, 2-MeOC₆H₄, 3-MeOC₆H₄, 4-MeOC₆H₄, 4-MeC₆H₄, 1-Naphthyl, 2-Naphthyl,

Scheme 106

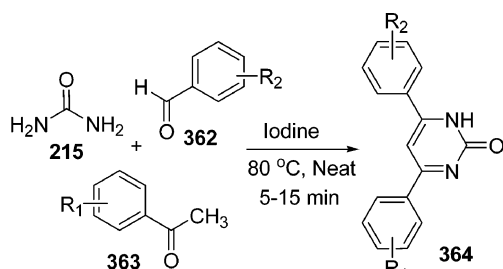
A solvent-free one-pot three-component coupling between aldehyde **362**, ketone **363**, and urea **215** in the presence of iodine as a catalyst to give 4,6-diarylpyrimidin-2(1*H*)-ones (DAPMs) **364** in excellent yields (90–96%) has been described very recently by Reddy *et al.*³¹⁹ (Scheme 108). The synthesis of polyfunctional tetrahydropyrimidines **367** via a one-pot three-component reaction involving diethylacetylene dicarboxylate **244**, amine **365**, and aldehyde **366** in the presence of Lewis acid catalyst has been developed by Jiang and Zhang³²⁰ in good yields (Scheme 109).

A three-component one-pot synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones and 9-phenyl-8-oxa-10,12-diazatricyclo[7.3.1.0]trideca-2(7),3,5-trien-11-one **370** has been reported by the condensation of acetophenone derivatives **368**, aldehydes **369**,



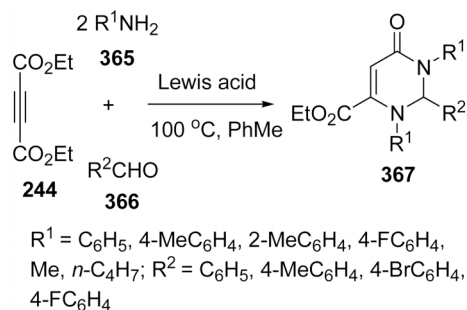
Ar = C₆H₅, 2-ClC₆H₄, 4-ClC₆H₄, 2-NO₂C₆H₄, 3-NO₂C₆H₄, 4-NO₂C₆H₄, 4-BrC₆H₄, 4-CH₃OC₆H₄

Scheme 107

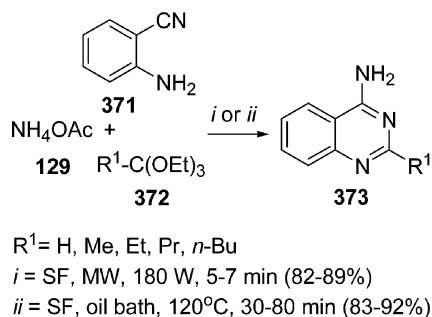


R¹ = H, 4-NO₂, 4-OCH₃, 4-Cl; R² = H, 4-OCH₃, 4-Cl, 4-OH, 2,4-(OCH₃)₂, N,N-(CH₃)₂,

Scheme 108



Scheme 109



Scheme 111

and urea **215** in the presence of trimethylsilyl chloride in 1.5 : 1 : 1 : 1 molar ratios, respectively utilizing $H_6P_2W_{18}O_{62} \cdot 18H_2O$ as a catalyst under solvent-free conditions at $70\text{ }^\circ\text{C}$ (Scheme 110).³²¹

4.6.2.3 Quinazolines. Quinazoline compounds are known for their anticonvulsant,³²² antihypertensive,³²³ anti-inflammatory,³²⁴ and phosphodiesterase inhibitor properties.³²⁵ These properties created interest for the synthesis of the quinazolinic structure, which has led to a number of different synthetic pathways (e.g., Niementowski's synthesis,³²⁶ Bischler's synthesis,³²⁷ and Riedel's synthesis³²⁸). Quinazoline derivatives have also been synthesized from anthranilic acid³²⁹ and benzonitrile.³³⁰

Thus, considering the importance of this class of compounds, Rad-Moghadam and Samavi³³¹ developed microwave-assisted as well as conventional thermal heating methods for the preparation of quinazolines **373** by the coupling of 2-aminobenzonitrile **371**, orthoester **372**, and ammonium acetate **129** in a molar ratio of 1 : 2 : 1, respectively under solvent-free conditions (Scheme 111). The excess of orthoester was necessary to diminish the side reactions. In the microwave-assisted synthesis, the products were obtained in 82–89% yields and the time needed for the formation of the products was 5–7 min and in the conventional thermal heating method it was observed that the yields were almost parallel (83–92%), although it required higher reaction time (30–80 min). The reaction has also been performed in refluxing ethanol for 180–240 min to furnish the products in 71–81% yields.

4.6.2.4 Quinazolinones and quinazolinthiones. Quinazolinones have various biological activities, including anticancer,³³² anti-diuretic,³³³ and anticonvulsant³³⁴ properties. The common

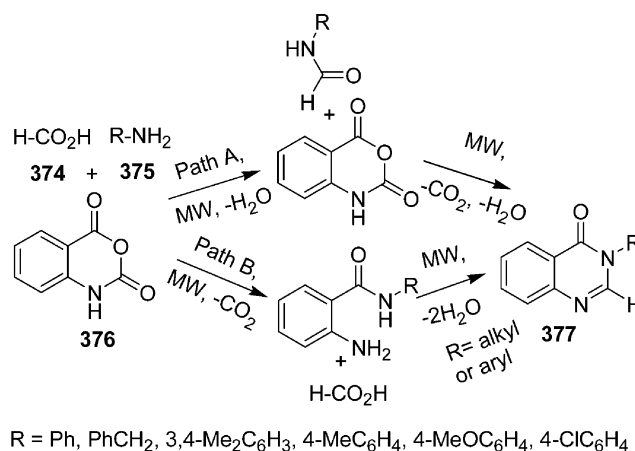


Scheme 110

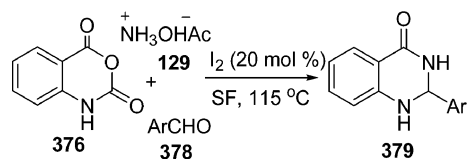
synthetic methods for aryl-substituted quinazolinone derivatives contain cyclization of *o*-acylaminobenzamides,³³⁵ amidation of 2-aminobenzonitrile followed by oxidative ring closure,³³⁶ solid phase synthesis of 2-arylamino-substituted quinazolines,³³⁷ reduction of the azide functionality,³³⁸ preparation from isatoic anhydrides and Schiff bases,³³⁹ and Pd-catalyzed heterocyclization of nitroarenes.³⁴⁰ The synthesis of 3-substituted quinazolin-4(3*H*)-ones **377** via convergent coupling of formic acid **374**, a primary amine **375**, and isatoic anhydride **376** under solvent-free microwave irradiation conditions has been described by Rad-Moghadam and co-workers³⁴¹ (Scheme 112).

A simple one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives under solvent-free conditions using a catalytic amount of iodine has been reported by Rostamizadeh *et al.*³⁴² in excellent yields. This methodology provides easy, quantitative access to various 2,3-dihydroquinazolin-4(1*H*)-one derivatives **379**, using **376**, **378**, and ammonium acetate **129** in the presence of commercially available iodine as a catalyst (Scheme 113).

Kidwai *et al.*³⁴³ reported a microwave-assisted protocol for the preparation of quinazolin-5-ones **381** via classical Biginelli reaction using equimolar amounts of aldehyde **380**, dimedone **166**, and urea or thiourea **140/215** (Scheme 114). The mixture was irradiated in a domestic microwave oven to afford the products in 85–92% yields. When this reaction was performed in refluxing ethanol, the use of the catalyst Nafion-H (100 mol%) was required and the reaction took 10 h to complete, leading to the desired compound in a 72% yield, showing greater efficiency

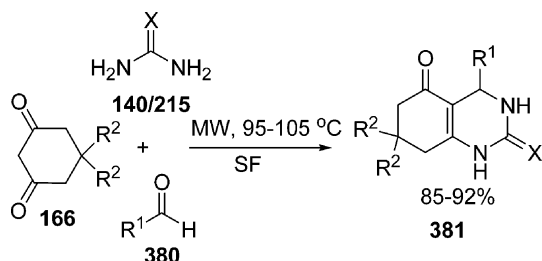


Scheme 112



Ar = 3-NO₂C₆H₄, 4-NO₂C₆H₄, 4-CNC₆H₄,
4-PhCH₂OC₆H₄, 4-BrC₆H₄, 2-ClC₆H₄,
2,3-Cl₂C₆H₃, 4-FC₆H₄, 4-ClC₆H₄, 4-MeC₆H₄,
2-MeOC₆H₄, 4-MeOC₆H₄, C₆H₅, 3-BrC₆H₄

Scheme 113



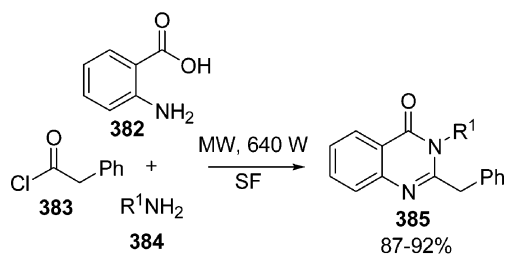
X = O, S; R¹ = Ph, 4-ClC₆H₄, benzo[3,4]dioxan-2-yl,
2-Cl-quinol-3-yl; R² = Me;

Scheme 114

in the solvent-free method. Dandia and co-workers³⁴⁴ synthesized a series of disubstituted quinazolin-4-ones **385** from a multicomponent cyclocondensation reaction between anthranilic acid **382**, phenyl acetyl chloride **383**, and substituted anilines **384** utilizing equimolar amounts under solvent-free and domestic microwave oven conditions (Scheme 115). Products were obtained in 87–92% yields within a short reaction time (4–5 min).

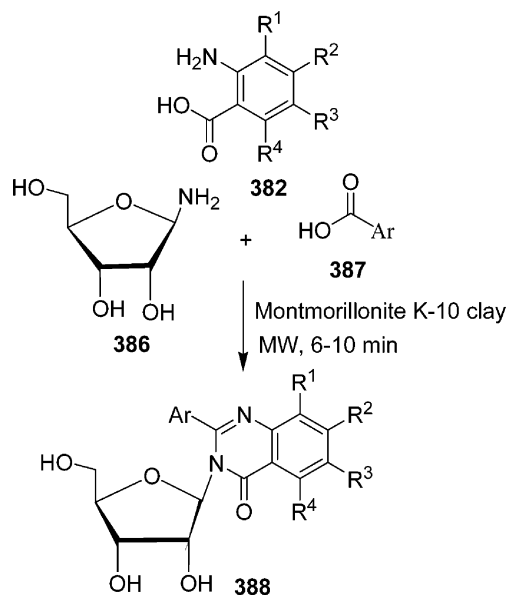
Siddiqui and co-workers³⁴⁵ have reported the synthesis of 2-aryl-3-(β-D-ribofuranosyl)-3H-quinazolin-4-one **388** in good yields as a novel N-nucleoside by the one-pot three-component coupling of substituted/unsubstituted anthranilic acid **382**, ribosylamine **386**, and substituted/unsubstituted benzoic acid **387** in the presence of montmorillonite K-10 clay under solvent-free microwave irradiation conditions (Scheme 116).

As an extension of the study on the solid-supported reagent, Jiang *et al.*³⁰⁴ reported a one-pot synthesis of the derivatives of quinazolin-4(3H)-ones **391** from anthranilic acid **382**, trialkyl orthoformate **389**, and anilines **390** in the presence of a Yb-resin catalyst under solvent-free conditions (Scheme 117). Anilines



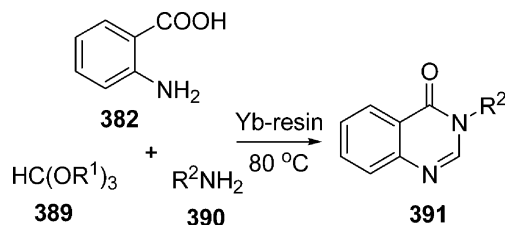
R¹ = 2-FC₆H₄, 2-CF₃C₆H₄, 3-FC₆H₄,
3-CF₃C₆H₄, 3-CF₃-4-ClC₆H₃

Scheme 115



Ar = C₆H₅, 4-ClC₆H₄; R¹ = H, OCH₃;
R² = H, Cl; R³ = H, Br; R⁴ = H, NO₂.

Scheme 116



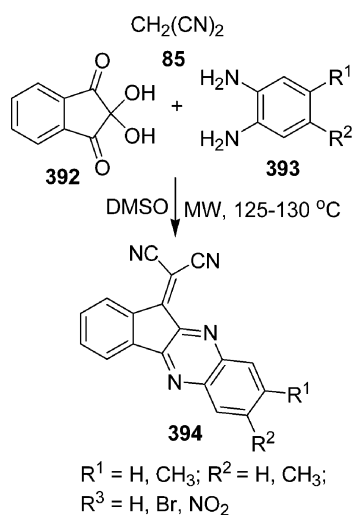
R¹ = CH₃, C₂H₅; R² = C₆H₅, 2-CH₃C₆H₄,
3-CH₃C₆H₄, 4-CH₃C₆H₄, 3,4-(CH₃)₂C₆H₃,
3-OCH₃C₆H₄, 4-OCH₃C₆H₄, 2-ClC₆H₄,
3-ClC₆H₄, 4-ClC₆H₄, 4-FC₆H₄, 2-NO₂C₆H₄

Scheme 117

with strong electron-withdrawing substitutes such as F and NO₂ gave generally lower yields.

4.6.2.5 Quinoxalines. A microwave assisted one-pot three-component procedure was developed by Azizian *et al.*³⁴⁶ for the synthesis of some dicyanomethylene derivatives of indenoquinoline and tryptanthrin **394** under solvent-free conditions by the coupling of **392**, **393**, and **85** (Scheme 118).

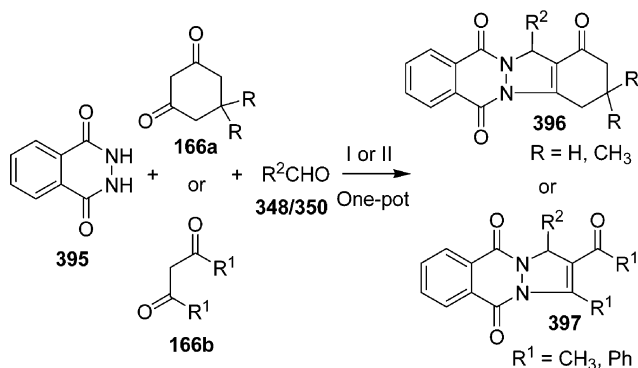
4.6.2.6 Phthalazines. The reported methods for the synthesis of phthalazine derivatives show varying degrees of success, and limitations include harsh reaction conditions, expensive catalysts/reagents, toxic organic solvents, low product yields, long reaction times, and co-occurrence of several side products. Therefore, there still remains a high demand for the development of more general, efficient, economically viable, and eco-compatible protocols to assemble such scaffolds. Very recently, we reported a facile



Scheme 118

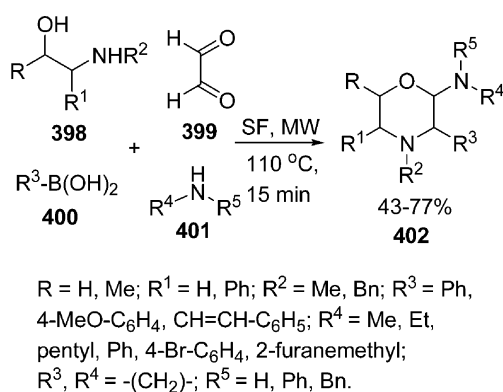
one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones **396** and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **397** via the three-component coupling of phthalhydrazide **395**, 1,3-diketones **166**, and aldehydes **348/350** under solvent-free conditions at 80 °C as well as under solvent-free ultrasound irradiation at room temperature (Scheme 119).³⁴⁷

4.6.2.7 Oxazines. Oxazines have attracted special attention as pharmaceutical drug candidates and are amply represented in patent literature.³⁴⁸ In particular, 1,4-oxazines show interesting properties including antidepressant, anticancer, and *anti*-inflammatory activities, that explain the constant interest of synthetic chemists.³⁴⁹ The oxazine core has been synthesized by the Mitsunobu reaction, which involves a diol cyclization.³⁵⁰ Regnier *et al.*³⁵¹ reported the synthesis of 2-aminomorpholines **402** under solvent-free and microwave assisted conditions by a straightforward four-component reaction between 1,2-aminoalcohols **398**, glyoxal **399**, boronic acids **400**, and aliphatic or aromatic amines **401** (Scheme 120). The reaction was carried out under microwave irradiation at 110 °C and the reactants were used in a molar ratio of 1 : 1 : 1 : 1.5, respectively to afford the desired products in 43–77% yields.



Reaction conditions: I: (S)-CSA (20 mol %), 80°C, solvent-free
 II: (S)-CSA (20 mol %), rt, solvent-free

Scheme 119

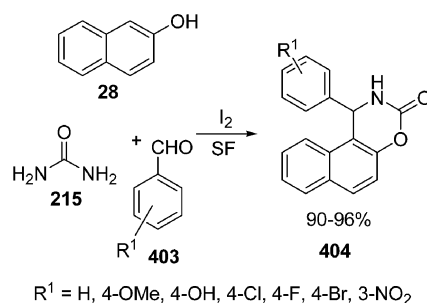


Scheme 120

A mixture of β -naphthol **28**, arylaldehydes **403**, and urea **215** in the presence of a catalytic amount of iodine as a catalyst under solvent-free conditions was heated for 5 min on a preheated hot plate to get the corresponding 1,2-dihydro-1-aryl-naphtho[1,2-*e*][1,3]oxazine-3-ones **404** in very good yields (Scheme 121).³⁵²

4.6.2.8 Thiazines. Thiazines are six-membered heterocycles containing four carbons, one nitrogen and one sulfur atom, which have been used for dyes, tranquilizers and insecticides. In the huge molecular library of heterocyclic compounds, nitrogen and sulfur are ubiquitous elements. The 1,3-thiazine nucleus is the active core of cephalosporins, which are among the most widely used lactam antibiotics. Because of their chemical and biological interest, syntheses of various 1,3-thiazines have been reported.^{353–356} 1,3-Thiazines incorporating a thiol function are not accessible through any of the known synthetic routes.

Yadav *et al.*³⁵⁷ reported the synthesis of 1,3-thiazines **408** from the reaction of equimolar amounts of 1,3-oxathiolan-5-one **405**, aromatic aldehydes **406**, and an *N*-aryl dithiocarbamic acid **407** under microwave irradiation and solvent-free conditions for the first time. Although the authors did not discuss the microwave equipment used in the reaction, they reported that the mixture was irradiated for 8–10 min, affording 1,3-thiazines in 76–90% yields with >96% diastereoselectivity. The reactions were also carried out using a thermostat controlled oil bath at the same temperature (85 °C) for 3–5 h, which led to the respective 1,3-thiazines in 40–54% yields. A diastereomeric ratio of 96 : 4 was found in cases of reactions with MW activation, while a ratio of 55 : 45 was observed for conventional thermal heating (Scheme 122).



Scheme 121



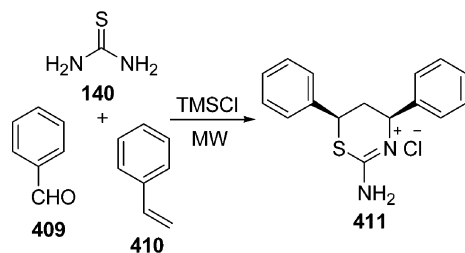
Scheme 122

Microwave irradiation was found to efficiently promote the three-component reaction of aromatic aldehyde **409**, thiourea **140**, and vinylbenzene **410** for the synthesis of 2-amino-4,6-diaryl-5,6-dihydro-4*H*-1,3-thiazines **411** in the presence of TMSCl under solvent-free conditions (Scheme 123).³⁵⁸ Both electron-withdrawing and electron-donating groups on both the aromatic aldehydes and vinylbenzene were tolerated well under the reaction conditions with no distinguishable electronic effects. When aliphatic aldehydes are used, no desired products were obtained.

4.7 Seven-membered heterocycles

4.7.1 Diazepines. Compounds derived from the 1,4-benzodiazepine ring system, which has been suggested to serve as a structural mimic of peptide β -turns and α -helices bind to a multitude of targets, including G-protein coupled receptors, ligand-gated ion channels, and enzymes. Accordingly, it is hardly surprising that 1,4-benzodiazepines are found in a large number of pharmaceutical agents. Biologically active natural products such as asperlicin and anthramycin also possess 1,4-benzodiazepine substructure.

The synthesis of benzodiazepines is of interest, as they possess large number of pharmacological properties such as anti-onvulsant, *anti*-anxiety, analgesic, hypnotic, sedative, antidepressant and *anti*-inflammatory agents. The benzodiazepines also used as valuable precursors in the synthesis of various fused heterocyclic systems such as triazolo-, oxazino-, oxadiazolo- and furano-benzodiazepines. In addition to this they also find a commercial use as dyes for acrylic fibers. An efficient and clean synthesis of benzodiazepines is described by the reaction of *o*-phenylenediamine with different types of methyl/methylene ketones in the presence of catalytic amounts of $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$



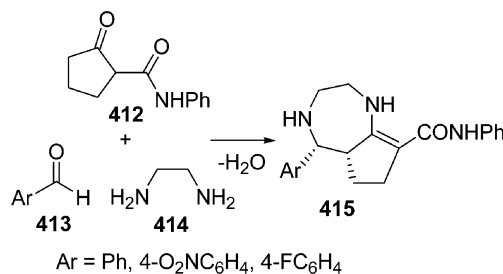
Scheme 123

under solvent-free conditions at room temperature in excellent yields.³⁵⁹

A series of 6-substituted 4-sulfonyl-1,4-diazepane-2,5-diones were designed, synthesized, and evaluated as human chymase inhibitors.³⁶⁰ Structure activity relationship (SAR) studies led to the identification of a potent inhibitor, (6*S*)-6-(5-chloro-2-methoxybenzyl)-4-[(4-chlorophenyl)sulfonyl]-1,4-diazepane-2,5-dione, with an IC_{50} of 0.027 μM . A stereoselective one-pot synthesis of polysubstituted 1,4-diazepine derivatives **415** has been achieved by Sotoca *et al.*³⁶¹ via solvent and catalyst-free multicomponent domino reaction from β -ketoamides **412**, aldehydes **413**, and diamino compounds **414** (Scheme 124).

5 Conclusions and outlook

The broad field of one-pot multicomponent procedures discussed in the sections above prove the fact that this field of research is a general method applicable to various synthesis examples in organic chemistry. The interest in synthesizing heterocycles has always been enormous. Combinatorial chemistry has gained significant importance as a tool for the synthesis of a wide variety of useful compounds including pharmaceuticals. In this context, the multiple component condensation (MCC) approach is especially appealing in view of the fact that products are formed in a single step, and the diversity can be readily achieved simply by varying the reacting components. The generation of small-molecule libraries requires the development of efficient methodologies with special emphasis on manipulative ease of the reaction. In conclusion, this eco-friendly, solvent-free multicomponent approach opens up numerous possibilities for conducting rapid organic synthesis and functional group transformations more efficiently. Additionally, there are distinct advantages of these solvent-free protocols since they provide reduction or elimination of solvents thereby preventing pollution in organic synthesis “at source”. The chemo-, regio- or stereoselective synthesis of high-value chemical entities and parallel synthesis to generate a library of small molecules will add to the growth of multicomponent under solvent-free reactions in the near future. In this review we have summarized the results reported mainly within the last 10 years. It is quite clear from the growing number of emerging publications in this field that the possibility to utilize multicomponent technology allows reaction conditions to be accessed that are very valuable for organic synthesis. Another important issue is the question of scale-up. Most of the reactions described in this review were performed in < 1 g scale, which reflects the current limitation of this technology when it comes to processing larger volumes. In



Scheme 124

order for multicomponent chemistry to be a valuable tool for the process chemist, new multicomponent scale-up technology needs to be developed, which is both economically viable and environmentally sustainable if one considers the energy balance. However, in comparison to solution-based processes, the solvent-free methods offer several advantages, making them an interesting tool for organic synthesis. In general, increased selectivities and reactivities have been found when working in one-pot multicomponent protocol. In some cases even unique selectivities have been demonstrated, which are not contrivable in solution. Thus, the route is opened for the synthesis of new products with advanced properties. As a consequence multicomponent as well as domino or related reactions are witnessing a new spring. Coupling these one-pot processes with solid-phase synthesis offers new perspectives for the preparation of both primary and thematic libraries. The progresses recently made in this field that perfectly suits the needs of modern drug discovery are the subject of the present review.

Future strategies for the development of new MCRs will most likely focus more on the one-pot combination of sequential, orthogonal reactions. For example, (multicomponent) reactions with high functional group compatibility allow their straightforward one-pot combination with other reactions, thereby leading to highly atom- and step-economical procedures. Furthermore, modular reaction sequences allow a stepwise expansion of scaffold diversity. Some MCR purists may claim such sequential one-pot reactions are not true multicomponent reactions, since the reagents can not all be added simultaneously. In our opinion, it is more practical to consider what we wish to achieve with an MCR, that is, a practical, atom-economic, one-pot procedure that delivers complex products with high variability. For this purpose, a true MCR must: 1) involve a true one-pot procedure without intermediate workup; 2) incorporate essentially all of the atoms of the reactants into the product, with the exception of small condensation by-products, and 3) involve only inputs that can be independently varied. In addition, the variability of each of the components should be sufficient to ensure high overall appendage diversity.

6 Abbreviations

AAD	aldehydes, amides, and dienophiles
Bn	benzyl
Bmim	1-butyl-3-methyl-1 <i>H</i> -imidazolium
CAN	cerric(IV)ammonium nitrate
CDK2	cyclin-dependent kinase 2
CMC	comprehensive medicinal chemistry
Cy	cyclohexyl
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DHP	dihydropyridine
DKHDA	domino Knoevenagel/hetero Diels–Alder reaction
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
HKA	heterocyclic ketene aminal

HIV	Human Immuno deficiency Virus
HT	hydrotalcite
MAO-B	monoamine oxidase-B
MCR	multicomponent reaction
MW	micro wave
NBS	<i>N</i> -bromosuccinimide
<i>o</i> -QM	<i>ortho</i> -quinone methides
PEG	polyethylene glycol
per-6-ABCD	per-6-amino- β -cyclodextrin
PMA-SiO ₂	phosphomolybdic acid-silica
PMo	12-molybdophosphoric acid
PPA	poly(phosphoric acid)
PTC	potassium thiocarbonate
PTSA	<i>para</i> -toluenesulfonic acid
PWA	12-tungstophosphoric acid
SEM	scanning electron microscope
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TPP	triphenylphosphine
TS	transition state
US	ultrasound
wet-TCT	wet-cyanuric chloride
Zeolite(TS-1)	Zeolite Titanium silicalite-1
Zr-PILC	ZrO ₂ -pillared clay

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