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SUSTAINABLE SYNTHESIS OF BIOACTIVE NITROGEN CONTAINING HETEROCYCLES : AN EXPERIMENTAL STUDY

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Abstract: The utilization of green chemistry techniques is dramatically reducing chemical waste and reaction times as has recently been proven in several organic syntheses and chemical transformations. To illustrate these advantages in the synthesis of bioactive heterocycles, we have studied various environmentally benign protocols that involve greener alternatives. Microwave (MW) irradiation of neat reactants catalyzed by the surfaces of recyclable mineral supports, such as alumina, silica, clay, or their "doped" versions, enables the rapid onepot assembly of heterocyclic compounds, such as flavonoids, related benzopyrans, and quinolone derivatives. The strategy to assemble oxygen and nitrogen heterocycles from in situ generated reactive intermediates via enamines or using hypervalent iodine reagents is described. Examples of multicomponent reactions that can be adapted for rapid parallel synthesis include solventless synthesis of dihydropyrimidine-2(1*H*)-ones (Biginelli reaction), imidazo[1,2-*a*]annulated pyridines, pyrazines, and pyrimidines (Ugi reaction). The relative advantages of greener pathways, which use MW irradiation and eco-friendly aqueous reaction medium, for the synthesis of various heterocycles, such as *N*-aryl azacycloalkanes, isoindoles, 1,3-dioxane, 1,3,4-oxadiazole, 1,3,4-thiadiazole, pyrazole, and diazepines, are also summarized.

Keywords: green chemistry; heterocycles; microwave irradiation; aqueous medium; solventfree reactions; supported reagents.

INTRODUCTION

Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs[1]. In both lead identification and lead optimization processes, there is an acute need for new small organic molecules. Conventional methods of organic synthesis are orders of magnitude too slow to satisfy the demand for generation of such compounds. The fields of combinatorial and automated medicinal chemistry have emerged to meet the increasing requirement of new compounds for drug discovery, where speed is of the essence. The synthetic chemical community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of substances required by society in short periods of time, and the best option to accelerate these synthetic processes is to use microwave (MW) technology. The efficiency of MW flash-heating has resulted in dramatic reductions in reaction times (reduced from days and hours to minutes and seconds). The time saved by using the MW heating approach is potentially important in traditional organic synthesis and assembly of heterocyclic systems[2].

Also, in the context of green chemistry, there are several issues which influence the choice of solvent. It should be relatively nontoxic and relatively nonhazardous (e.g., not flammable or corrosive). The solvent should also be contained, that is, it should not be released to the environment. All these traits are ideally fulfilled by water, which is nontoxic, nonflammable, abundantly available, and inexpensive. Moreover, owing to its highly polar character, one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, this provides an opportunity to overcome a serious shortcoming of homogeneous catalysts, namely, the cumbersome recovery and recycling of the catalysts.

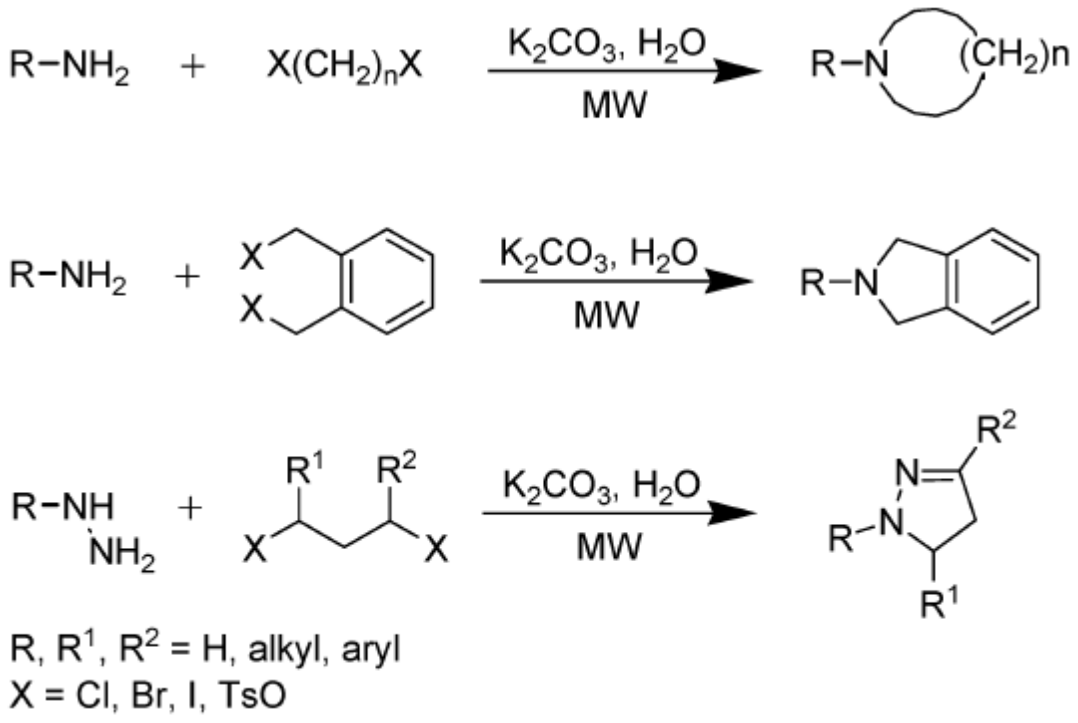
To illustrate the advantages of greener alternatives in the synthesis of bioactive heterocyclic compounds, we have developed various environmentally benign protocols. In this report, we have summarized our recent activity in the area of greener synthetic transformations

which use MW irradiation, under solvent-free conditions[3], or using aqueous medium[4] or supported reagents[5].

NITROGEN-CONTAINING HETEROCYCLES

Nitrogen heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds[6].

The synthesis of nitrogen-containing heterocycles such as substituted azetidines, pyrrolidines, piperidines, azepines, N-substituted 2,3-dihydro-1*H*-isoindoles, 4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines has been accomplished in a basic aqueous medium that occurs under the influence of MWs; the reactions proceed via double N-alkylation of primary amines and hydrazine derivatives (Scheme 1) with readily available alkyl dihalides (or ditosylates), thus providing facile entry to important classes of building blocks in natural products and pharmaceutical synthesis[7–9].



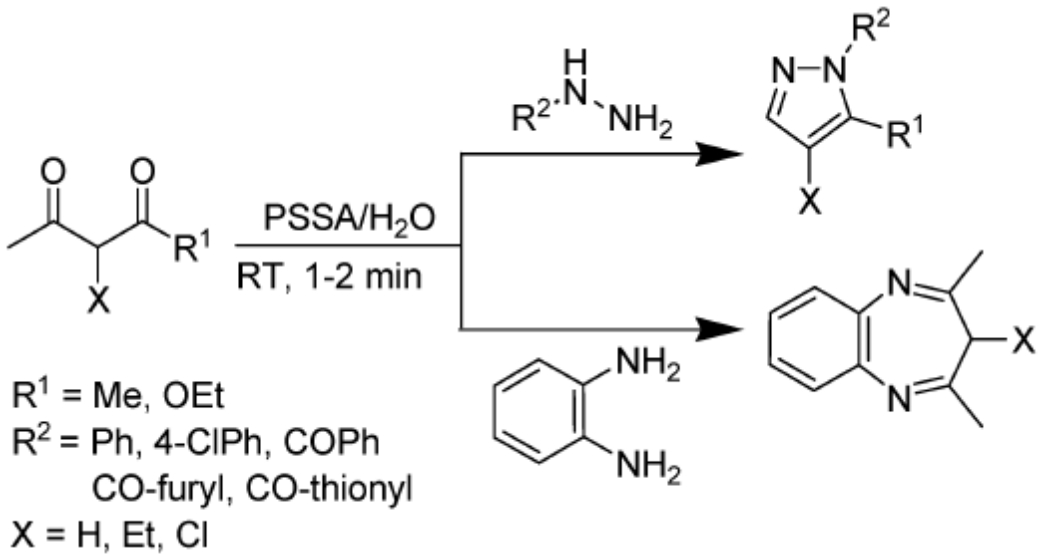
Scheme 1 Nitrogen-containing heterocycles in aqueous media using MW irradiation.

This MW-accelerated general approach shortened the reaction time significantly and utilized readily available amines and hydrazines with alkyl dihalides or ditosylates to assemble two C–N bonds in a simple S_N2-like sequential heterocyclization experimental protocol which has never been fully realized under conventional reaction conditions. The strategy circumvents multi-step reactions, functional group protection/deprotection sequences, and eliminates the use of expensive phase-transfer and transition- metal catalysts.

It is noteworthy that this reaction is not a homogeneous single-phase system as neither reactant is soluble in the aqueous alkaline reaction medium. We believe that the selective absorption of MWs by polar molecules and intermediates in a multiphase system could substitute as a phase-transfer catalyst (PTC) without using any phase-transfer reagent, thereby providing the observed acceleration as has been observed for ultrasonic irradiation[10].

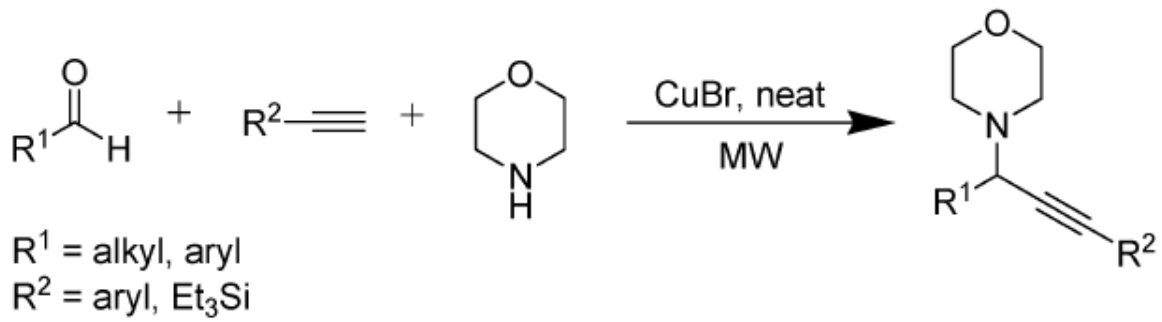
The experimental observation is consistent with the mechanistic postulation wherein the polar transition state of the reaction is favored by MW irradiation with respect to the dielectric polarization nature of MW energy transfer. In large-scale experiments, the phase separation of the desired product in either solid or liquid form from the aqueous media can facilitate product purification by simple filtration or decantation instead of tedious column chromatography, distillation, or extraction processes. This eventually reduces the usage of volatile organic solvent required for extraction or column chromatography.

A variety of nitrogen heterocycles have been synthesized by the condensation of hydrazine, hydrazide, and diamines with diketones and β-keto esters, respectively (Scheme 2)[11].



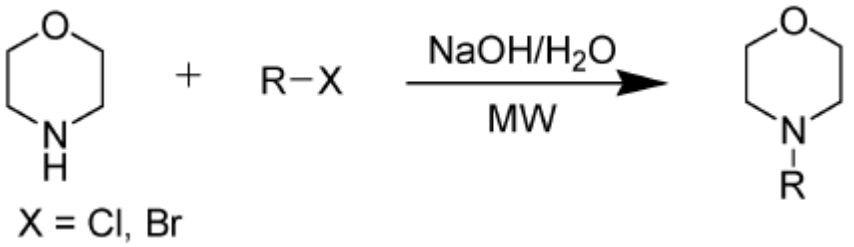
Scheme 2 Polystyrenesulfonic acid (PSSA)-catalyzed assembly of nitrogen heterocycles in water.

A direct Grignard type of addition of alkynes to in situ generated imines, from aldehyde and amines, catalyzed by CuBr provides a rapid and solvent-free approach to substituted *N*-heterocycles such as propargylamines in excellent yields (Scheme 3)[12].



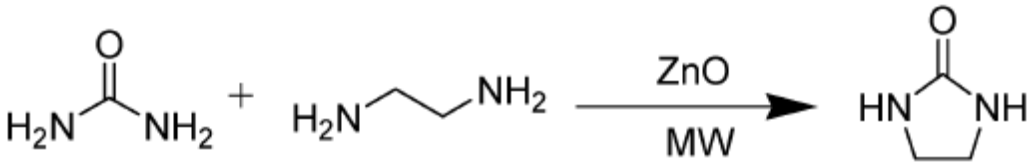
Scheme 3 CuBr-catalyzed solvent-free route to propargylamines using MW irradiation.

This N-alkylation of nitrogen heterocycles has also been achieved in aqueous media under MW irradiation conditions (Scheme 4)[13]; shorter reaction times and higher product yields are some of the advantages that render this procedure a greener alternative to conventional chemical synthesis.



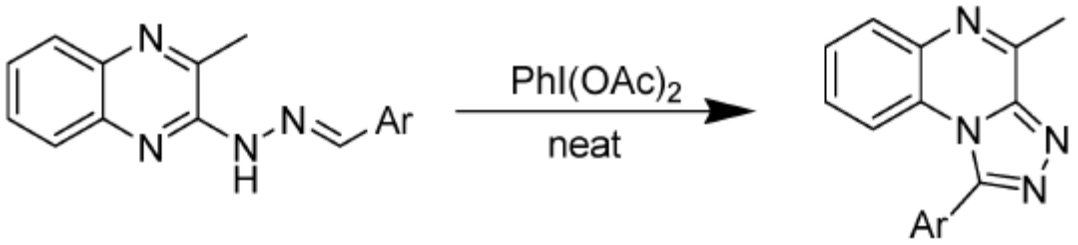
Scheme 4 NaOH-catalyzed N-alkylation in water using MW irradiation.

Cyclic ureas such as imidazolidine-2-one have recently attracted much attention due to their manifold applications as intermediates for biologically active molecules, such as the HIV protease inhibitors, DMP 323 and DMP 450, fine chemicals, pharmaceuticals, cosmetics, and pesticides[14]. A MW-assisted protocol for the direct synthesis of these cyclic ureas has been developed that proceeds expeditiously in the presence of ZnO (Scheme 5). The reaction was not only accelerated upon exposure to MW irradiation, thus shortening the reaction time, but also the formation of byproducts was eliminated when compared to the conventional heating methods[15].



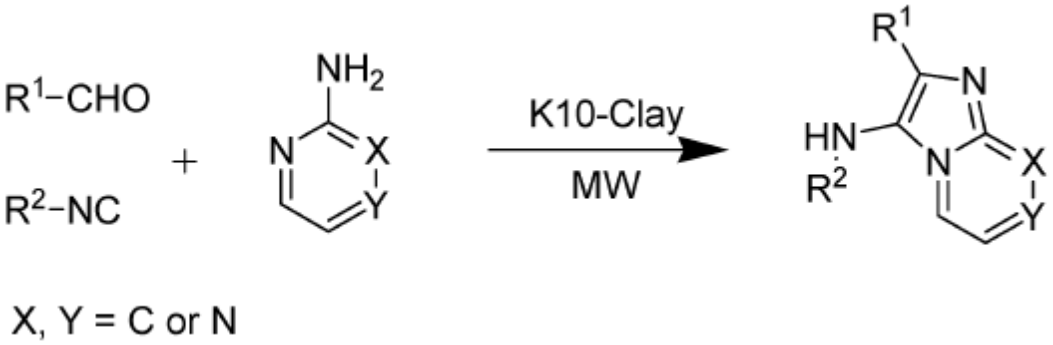
Scheme 5 ZnO-catalyzed MW synthesis of imidazolidine-2-one.

Triazoles are another important class of nitrogen heterocycles, and, specifically, the 1,2,4-triazole nucleus has been found to be an integral part of therapeutically interesting compounds that display significant antibacterial, central nervous system (CNS) stimulative, sedative, antifungal, and antitumor activities[16]. Consequently, the synthesis of this heterocyclic nucleus has gained great importance in organic synthesis. A solvent-free and expeditious synthesis of 1-aryl-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines is now possible that utilizes a simple mixing of a relatively benign nonmetallic oxidant, iodobenzene diacetate [$PhI(OAc)_2$] (Scheme 6)[17].



Scheme 6 $PhI(OAc)_2$-catalyzed solvent-free synthesis of triazoles.

The imidazo[1,2-*a*] annulated nitrogen heterocycles bearing pyridine, pyrazine, and pyrimidine moities constitute a class of biologically active compounds that are potent anti-inflammatory agents, antibacterial agents, inhibitors of gastric acids secretion, and calcium channel blockers[18]. A rapid onepot MW synthesis of imidazo[1,2-*a*] annulated pyridines, pyrazines, and pyrimidines was developed

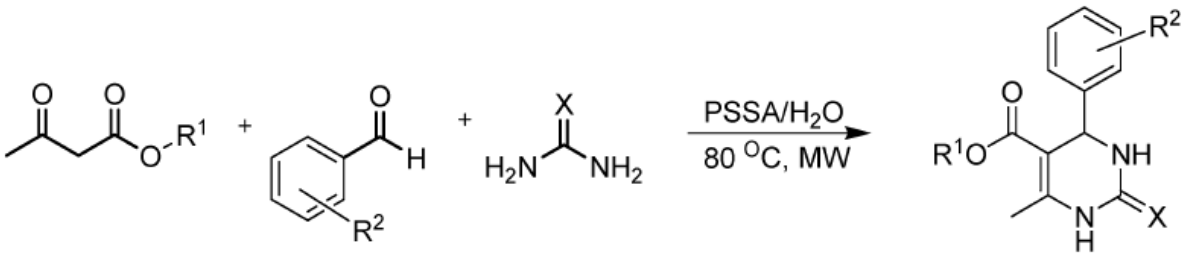


Scheme 7 Clay-catalyzed solvent-free synthesis of annulated nitrogen heterocycles.

(Scheme 7), which occurs in the presence of recyclable montmorillonite K10 clay under solvent-free conditions[19].

It has been demonstrated that the condensation of aldehydes, amines, and isocyanides provides a rapid and solventless method for the synthesis of multisubstituted imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrazines, and imidazo[1,2-a]pyrimidines using MW irradiation, a process that is adaptable for the parallel assembly of a library of compounds. Additionally, the use of inexpensive clay and its recyclability renders this an economical and eco-friendly procedure.

Dihydropyrimidinones are an important class of organic compounds which show prominent biological activity, and were synthesized by an environmentally benign aqueous Biginelli protocol using polystyrenesulfonic acid (PSSA) as a catalyst. (Scheme 8)[20], or under solvent-free conditions[21].



Scheme 8 Biginelli reaction in aqueous medium.

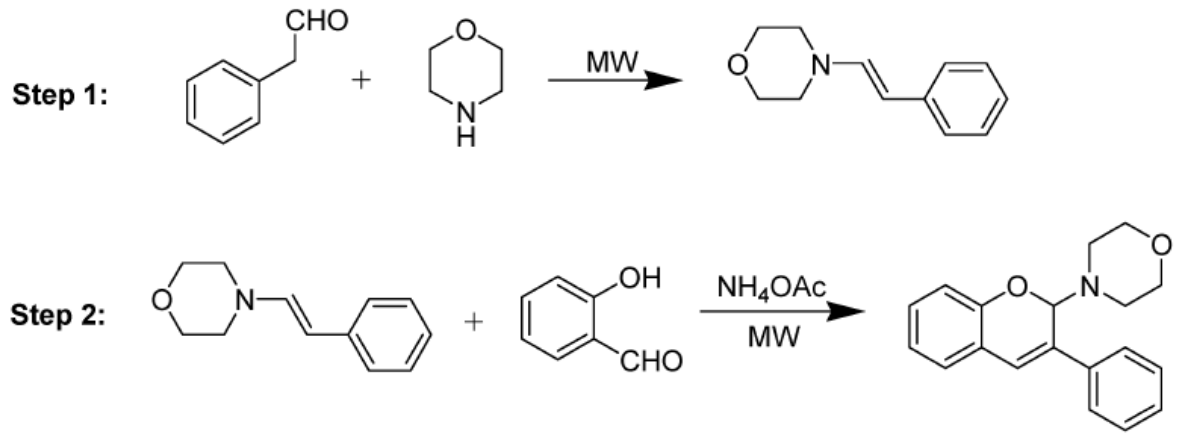
This MW protocol proceeds efficiently in water without the use of any organic solvent. Also, the use of polymer-supported, low-toxic, and inexpensive PSSA as a catalyst renders this method ecofriendly, with a very simple isolation procedure that entails the filtration of the precipitated products.

OXYGEN-CONTAINING HETEROCYCLES

Oxygen heterocycles are important classes of building blocks in organic synthesis, and several derivatives of these oxygen heterocycles have attracted much attention of medicinal chemists over the years.

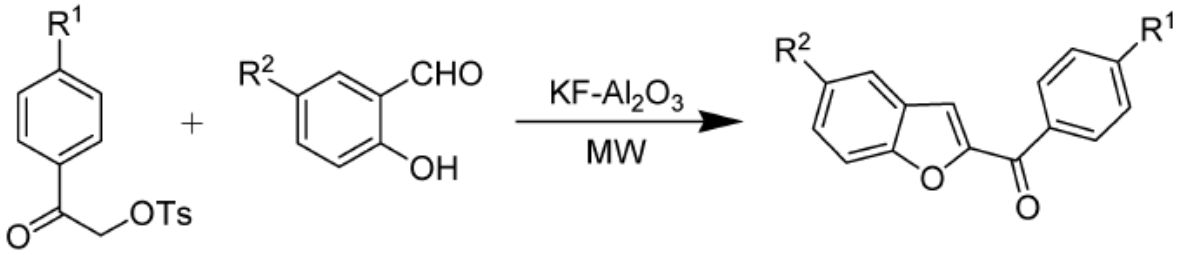
Isoflav-3-enes bearing a 2*H*-1-benzopyran nucleus form an important class of chromene intermediates that are useful in the synthesis of many natural products and medicinal agents such as potassium- channel activating drugs. Their basic structural framework is a common feature of many tannins and polyphenols found in fruits, vegetables, teas, and red wines, which have gained popularity because of their health-promoting effects. The solvent-free synthesis of unnatural analogs, 2-aminosubstituted isoflav-3-enes, has been developed, which can be carried out in one pot using microwaves via the in situ generation of enamines and their subsequent reactions with salicylaldehydes (Scheme 9). This environmentally friendly procedure does not require

azeotropic removal of water using large excess of aromatic hydrocarbon solvents for the generation of enamines or the activation of the catalyst[22].



Scheme 9 One-pot solvent-free synthesis of isoflav-3-enes.

The 2-aroylbenzo[*b*]furans, initially reported from the flower-heads of *Helichrysum arenarium* DC, form a group of naturally occurring compounds which possess a wide range of pharmacological activities. The expeditious solventless syntheses of 2-aroylbenzo[*b*]furans was developed from readily accessible α-tosyloxyketones and mineral oxides in processes that are accelerated by exposure to MWs (Scheme 10)[23].

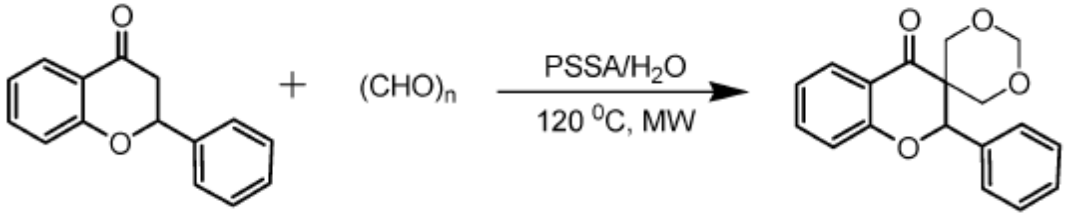


Scheme 10 MW-assisted rapid synthesis of 2-aroylbenzo[*b*]furans.

Dioxane rings are common structural motifs in numerous bioactive molecules such as (+)-dactylolide (a cytotoxic agent), derivatives of 2-substituted-1,3-dioxanes (antimuscarinic agents), and (+)-SCH 351448 (a novel activator of low-density lipoprotein receptor promoters). A variety of biologically active molecules have been identified from libraries of diverse, natural

product-like 1,3-dioxanes. Recently 1,3-dioxane derivatives have been found to be effective modulators for multi-drug resistance[24].

While dioxanes have great potential as drug candidates, the synthetic protocol of this important molecule has been largely untapped. We have developed a novel tandem bis-aldol reaction of ketones with paraformaldehyde in aqueous media catalyzed by PSSA under MW irradiation conditions to produce 1,3-dioxanes (Scheme 11)[25].



Scheme 11 PSSA-catalyzed one-pot synthesis of 1,3-dioxanes in aqueous media.

Various ketones reacted efficiently with paraformaldehyde in water to afford the desired 1,3-dioxanes in good yield. This approach establishes a convenient and flexible method to attach functional arms to indanone and flavanone for further elaboration in synthetic design. Also, it is noteworthy to mention that these reactions work well in an aqueous medium without using any PTC. This may be due to selective absorption of MWs by reactants, intermediates, and polar aqueous medium[26], which accelerates the reaction even in the absence of PTC.

This PSSA-catalyzed tandem bis-aldol reaction of ketone with paraformaldehyde in water may proceed via the following mechanism (Scheme 12).

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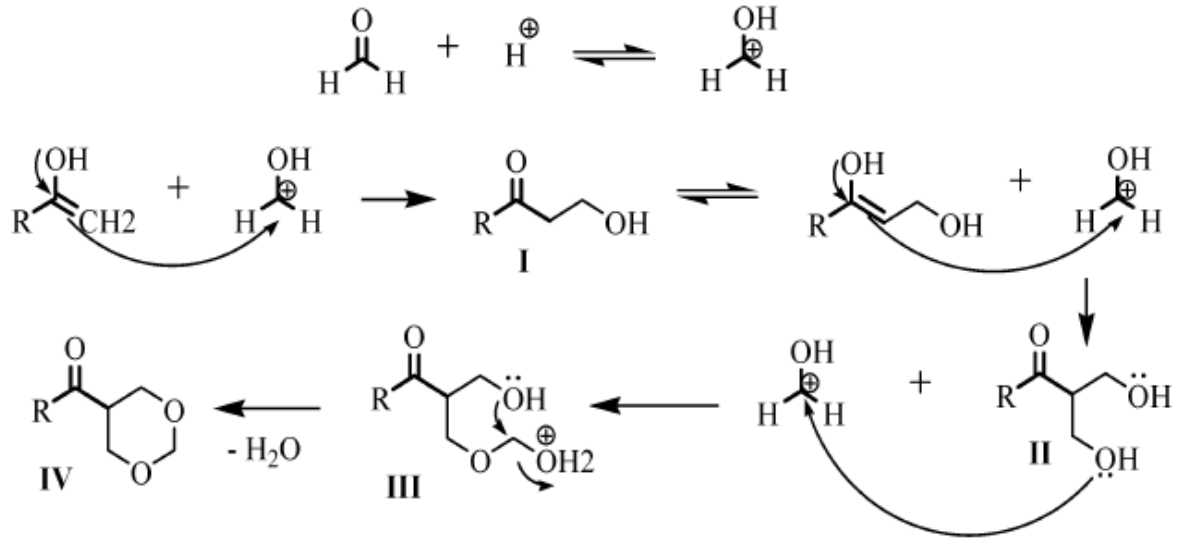
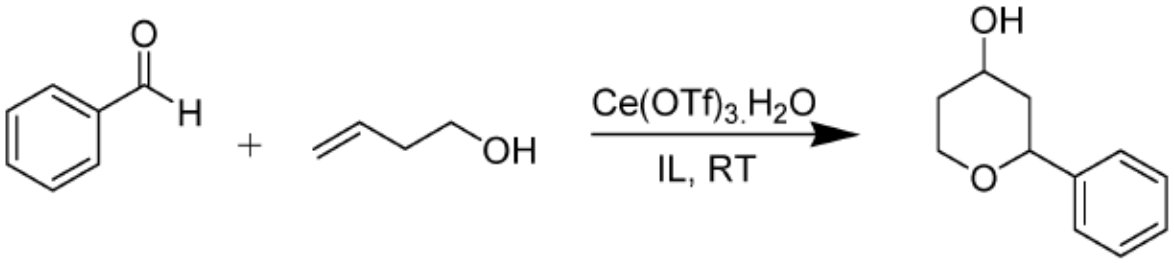


Scheme 12 Mechanism of PSSA-catalyzed bis-aldol reaction.

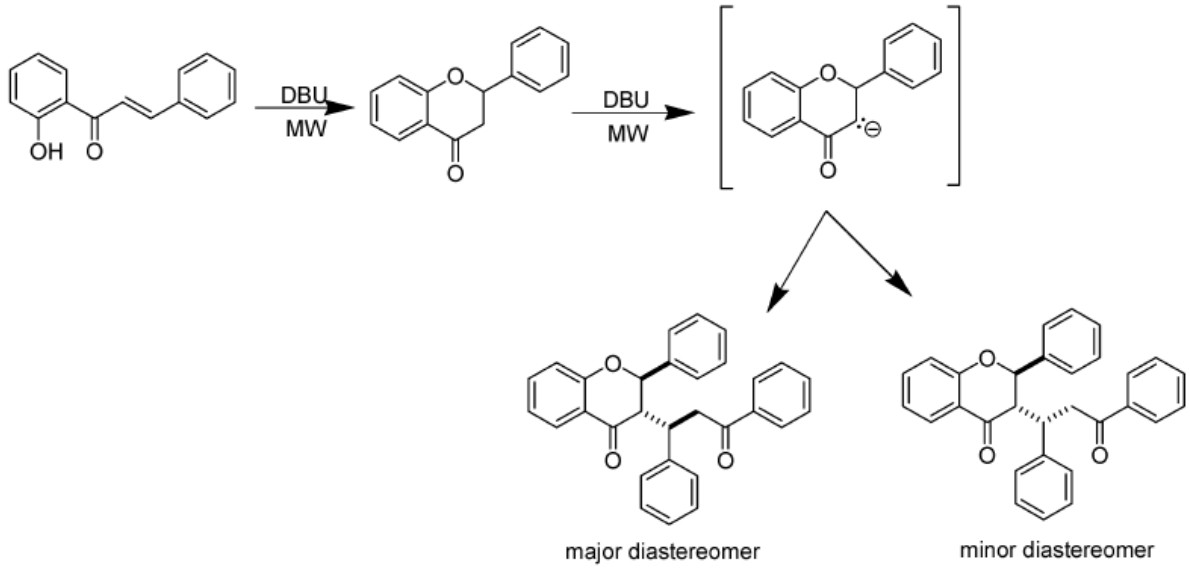
The reaction involved the addition of protonated formaldehyde (generated by MW exposure of paraformaldehyde with PSSA/water) molecule to ketone (enol) to form β-hydroxy ketone **I**. This was followed by the addition of another protonated formaldehyde molecule to **I** to yield diol **II**, that in turn attacks the third formaldehyde molecule to give adduct **III**, which after dehydration yields the final product 1,3-dioxane **IV**.

Tetrahydropyrans are prevalent subunits in an assortment of natural products including carbohydrates, polyether antibiotics, and marine toxins. Utilizing a simple homoallyl alcohol and an aldehyde in the presence of a catalytic amount of cerium triflate, the direct stereoselective formation of tetrahydropyranol derivatives in ionic liquid was achieved (Scheme 13)[27].



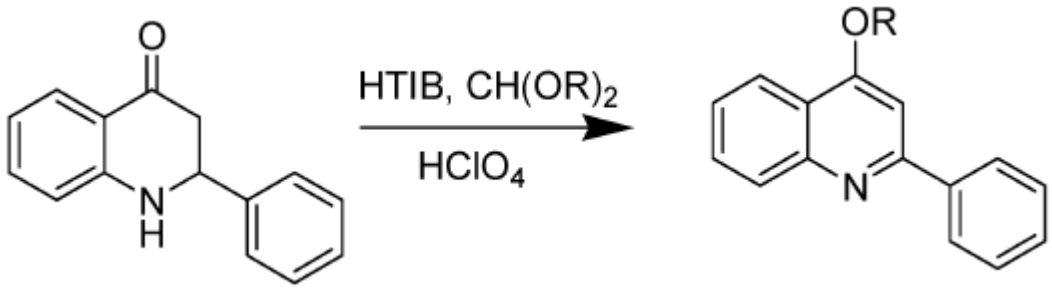
Scheme 13 $Ce(OTf)_3$-H_2O-catalyzed synthesis of tetrahydropyranol in ionic liquid.

MW-assisted reaction of 2'-hydroxychalcones in the presence of 1,5-diazabicyclo[5.4.0]undec-7- ene (DBU) resulted in the formation of hitherto unknown dimers by conjugate addition of the intermediate cyclic ketone to the starting enone (Scheme 14)[28,29].



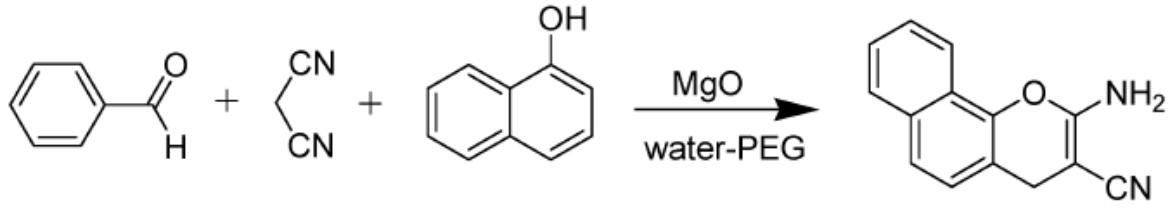
Scheme 14 MW-assisted formation of dimers of 2'-hydroxychalcones.

The leaves of *Lunasia amara* and *Galipea longiflora* (family *Rutaceae)* are a rich source of alkaloids bearing an alkoxylated 2-arylquinoline nucleus. Specifically, the 4-alkoxy-2-arylquinoline derivatives have attracted attention due to their biological activity. Easily accessible 2-aryl-l,2,3,4-tetrahydro- 4-quinolones are readily oxidized to the corresponding 4-alkoxy-2-arylquinolines using a relatively safe hypervalent iodine reagent [hydroxy (tosyloxy)iodo]benzene (HTIB), in high yields, thus providing a concise route to an important class of naturally occurring alkaloids (Scheme 15)[30].



Scheme 15 HTIB-catalyzed synthesis of 4-alkoxy-2-arylquinolines.

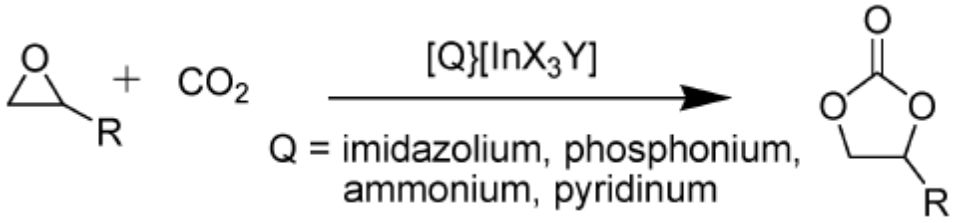
A nano-sized MgO-catalyzed three-component condensation reaction of aldehyde, malononitrile, and α-naphthol proceeded rapidly in water–polyethylene glycol (PEG) to afford the corresponding 2-amino-2-chromenes in high yields at room temperature (Scheme 16). The greener protocol was found to be fairly general, and the catalyst was reused in subsequent reactions with consistent activity[31].



Scheme 16 MgO-catalyzed synthesis of 2-amino-2-chromenes.

The nano-sized magnesium oxide has been employed for the first time as a novel and efficient catalyst for the benign synthesis of various substituted 2-amino-2-chromenes in a three-component condensation approach. The attractive features of this protocol are the simple experimentation procedure, use of benign reaction solvents, cost effectiveness, the recyclability of catalysts, and its adaptability for the synthesis of a diverse set of 2-amino-2-chromenes.

One of the most promising endeavors in the area is the coupling reaction of carbon dioxide (CO_2) with epoxides to generate the five-membered cyclic carbonates. These compounds find numerous applications, for example, as precursors for polymeric materials such as polyurethanes and polycarbonates, as aprotic polar solvents in various chemical processes, and as intermediates in the production of pharmaceutical and fine chemicals. The reaction of CO_2 with a variety of epoxides has been examined in the presence of catalytic amounts of various ionic liquids (ILs), and tetrahaloindate(III)-based ILs were found to exhibit the highest catalytic activities for the synthesis of cyclic carbonates (Scheme 17)[32].

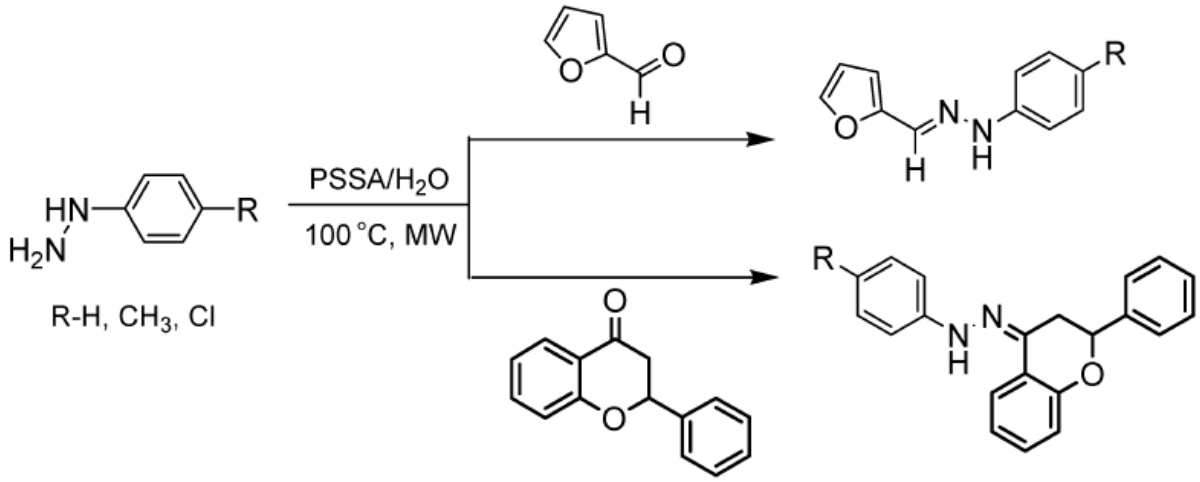


Scheme 17 Tetrahaloindate(III)-based IL-catalyzed synthesis of cyclic carbonates.

HETEROCYCLIC HYDRAZONES

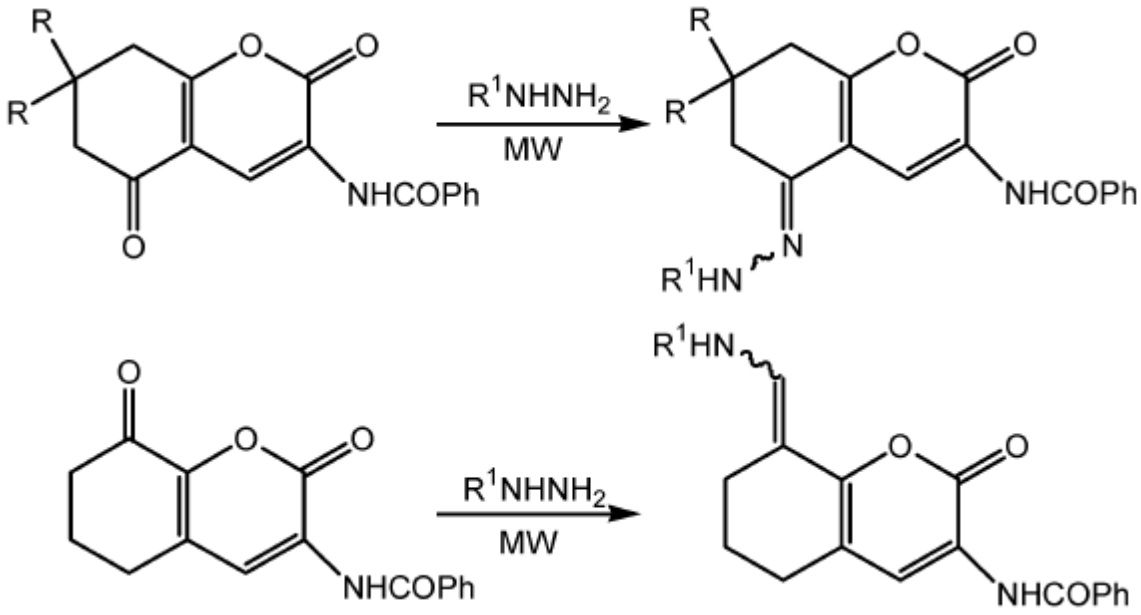
Heterocyclic hydrazones constitute an important class of compounds in organic chemistry, and recently they have also been found useful as antimalaria drugs and as inhibitors of macrophage migration inhibitory factor (MIF) and tautomerase activity[35].

An environmentally benign aqueous protocol for the synthesis of these heterocyclic hydrazones using PSSA as a catalyst has been developed (Scheme 21). The simple reaction proceeds efficiently in water in the absence of any organic solvent under MW irradiation and involves basic filtration as the product isolation step[36].



Scheme 21 Hydrazone synthesis of furaldehyde and flavanone in water.

The only example of a reaction between two solids, in a solvent- and catalyst-free environment, was demonstrated by Varma et al., when the reaction of neat 5- or 8-oxobenzopyran-2(1*H*)-ones with a variety of aromatic and heteroaromatic hydrazines provided rapid access to several synthetically useful heterocyclic hydrazones (Scheme 22)[37,38].



Scheme 22 Heterocyclic hydrazone synthesis under solvent-free conditions.

EXPERIMENTAL

Some of the earlier solvent-free reactions were performed using an unmodified household Panasonic MW oven equipped with invertor technology in open glass containers with neat reactants. More recent work has been conducted in a commercial MW (CEM Discover focused MW synthesis system) in a 10-ml crimp-sealed, thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer operating at 2450 MHz. The general procedure involves simple mixing of neat reactants with the catalyst, their adsorption on mineral or "doped" supports, and subjecting the reaction mixture to MW irradiation followed by extraction or filtration to isolate the products. Some representative MW-promoted chemical syntheses conducted in aqueous medium by our research group are summarized below:

Synthesis of azacycloalkanes *(Scheme 1)*: 1.0 mmol aniline (0.093 g), 1.1 mmol 1,4-dibromobutane (0.237 g), and 1.1 mmol potassium carbonate (0.162 g) in 2 ml distilled water were placed in a 10-ml crimp-sealed, thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in a CEM Discover focused MW synthesis system, operated at 120 ± 5 °C, power 70–100 W, and pressure 40–80 psi for 20 min. After completion of the reaction, the or ganic portion was extracted into ethyl acetate. Removal of the solvent under reduced pressure and flash column chromatography using hexane/ethyl acetate (90/10) as eluent afforded the crude product 1-phenylpyrrolidine in 89 % (90 % pure) yield.

Synthesis of 2,3-dihydro-1*H*-isoindoles *(Scheme 1)*: 1.0 mmol aniline (0.093 g), 1.1 mmol 1,2-bisbromomethyl-benzene (0.270 g), and 1.1 mmol potassium carbonate (0.162 g) in 2 ml distilled water were placed in 10-ml crimp-sealed, thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in a CEM Discover focused MW synthesis system, operated at 120 ± 5 °C, power 80–100 W, and pressure 40–80 psi for 20 min. After completion of the reaction, the solid product was separated from the aqueous phase, filtered, and washed with cold hexanes three times. This afforded the off-white solid analytically pure 2-phenyl-2,3-dihydro-1*H*-isoindole in 92 % yield.

Synthesis of 1,3-dioxane *(Scheme 11)**:*** The ketone (5 mmol) and paraformaldehyde (20 mmol) were placed in a 10-ml crimp-sealed, thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The contents were dissolved in 20 % PSSA solution in water (five times the weight of ketone) and the reaction tube was placed inside the cavity of a CEM Discover focused MW synthesis system, operated at 120 ± 5 °C (temperature monitored by a built-in infrared sensor), power 40–140 W, and pressure 40–70 psi for 30 min. After completion of the reaction, the phase separation of the desired product from the aqueous media occurred, facilitating the isolation of crude product by simple decantation, which was subjected to column chromatography to afford pure 1,3-dioxanes.

Synthesis of 2-amino-2-chromenes *(Scheme 16)**:*** A mixture of benzaldehyde (2 mmol), malononitrile (2 mmol), α-naphthol (2 mmol), and MgO (50 mg) in methanol (15 ml) was heated at refluxed for 1 h. After completion of the reaction, as indicated by thin-layer chromatography

(TLC), MgO was removed by filtration and excess methanol was distilled off. The crude product so obtained was recrystallized from methanol to afford the pure product in 96 % yield.

Synthesis of hydrazones *(Scheme 21)**:*** The carbonyl compound (1 mmol) and hydrazine (1.2 mmol) were dissolved in 20 % PSSA solution in water (three times the weight of ketone/aldehyde). This homogeneous reaction mixture was then exposed to microwaves at 100 °C in a closed system for 8 min and 5 min for ketones and aldehydes, respectively. After completion of the reaction, products were isolated with simple filtration (1–2 ml of water was added to facilitate easy filtration) and washed with methanol to afford pure hydrazones.

CONCLUSION

The demands for new bioactive heterocycles in the fields of health care, combined with the pressure to produce these substances expeditiously and in an environmentally benign fashion, pose significant challenges to the synthetic chemical community. We have successfully synthesized a wide variety of these heterocyclic compounds by using various greener techniques, such as selective MW-heating of neat reactants under solvent-free conditions, using supported reagents, or using benign solvents such as water and PEG.

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