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Microwave-Assisted Organic Synthesis and Transformations using Benign Reaction Media

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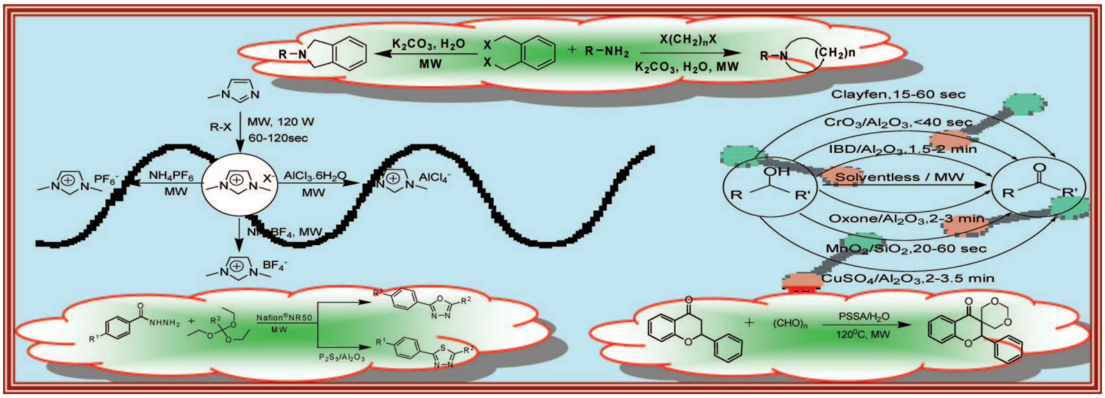
CONSPECTUS



A nonclassical heating technique using microwaves, termed "Bunsen burner of the 21st century", is rapidly becoming popular and is dramatically reducing reaction times. The significant outcomes of microwave (MW)-assisted green chemistry endeavors, which have resulted in the development of synthetic protocols for drugs and fine chemicals synthesis that are relatively more sustainable, are summarized. The use of emerging microwave-assisted chemistry techniques in conjunction with greener reaction media is dramatically reducing chemical waste and reaction times in several organic syntheses and chemical transformations. A brief historic account of our own experiences in developing MW-assisted organic transformations, which involve various benign alternatives, such as solid-supported reagents, and greener reaction media, namely, aqueous, ionic liquid, and solvent-free, for the synthesis of various heterocycles, coupling reactions, oxidation–reduction reactions, and some name reactions are described.

Synthesis of Heterocycles. The synthetic chemistry community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of heterocyclic systems required by society in a short span of time, and one of the best options to accelerate these synthetic processes is to use MW technology. The efficient use of the MW heating approach for the synthesis of various heterocyclic compounds in aqueous and solvent-free medium is discussed.

Organic Named Reactions. The application of MW chemistry for various named reaction such as the Prins reaction, the Suzuki reaction, the Heck reaction, the Aza-Michael reaction, Trost's γ-addition, and the Cannizzaro reaction are summarized.

Synthesis and Application of Ionic Liquids. Ionic liquids (ILs), being polar and ionic, in character couple with MW irradiation very efficiently and are, therefore, ideal MW-absorbing candidates for expediting chemical reactions. MW-assisted solvent-free synthesis and application of ILs are discussed.

Oxidation–Reduction Reactions. MW protocols using mineral oxides such as alumina, silica, and clay to immobilize reagents on such solid supports have been extensively explored under "dry" media conditions. Various solvent-free examples of oxidation reactions are discussed that involve mixing of neat substrates with clay-supported iron(III) nitrate (clayfen) or iodobenzene diacetate (IBD) as an oxidant; some interesting MW reduction protocols using borohydrides are also discussed.

Protection—Deprotection Reactions. The protection and deprotection of alcohols and amines are common events in multistep organic syntheses. Various protection and deprotection protocols under MW irradiation are discussed, including tetrahydropyranylation and (benzyloxycarbonyl) (Cbz)-protection, which are the most frequently employed methods.

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I. Introduction

A primary driver of synthetic organic chemistry is the development of efficient and environmentally benign synthetic protocols. As the pressure to produce the myriad of substances required by society in an environmentally benign fashion has continued to increase, microwave (MW)-assisted chemistry has emerged as a discipline that permeates all aspects of synthetic chemistry. The major goals of this endeavor are to maximize the efficient use of safer raw materials and to reduce waste.[1]

Green Chemistry utilizes a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products.[1] One of the key areas of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with relatively benign solvents. The development of solvent-free alternative processes is, of course, the best solution; however, many processes require the use of solvent. An ideal green solvent should be relatively nontoxic and nonhazardous; that is, it should not be flammable or corrosive. The solvent also needs to be contained; that is, it should not be released into the environment. Water is an ideal solvent since it fulfills many criteria; it is nontoxic, nonflammable, and abundantly available and inexpensive.[2] Moreover, owing to its highly polar character, novel reactivities and selectivities are anticipated for organometallic catalysis in water.[2] The use of water as a solvent with water-soluble homogeneous catalysts provides an opportunity to overcome known problems associated with difficulties in both recovering expensive catalysts for reuse and isolating products in high purity when organic solvents are employed. Furthermore, water at higher temperature behaves as a pseudo-organic solvent, when the dielectric constant decreases substantially and ionic product increases the solvating power toward organic molecules near that of ethanol or acetone.[3]

MW-assisted chemistry has blossomed into a useful technique for a variety of applications in organic synthesis and transformations.[4] Although MW-assisted reactions in organic solvents have developed rapidly, the focus is now shifted to environmentally friendlier methods, which use greener solvents and supported reagents. There are many examples of the successful application of MW-assisted chemistry to organic synthesis; these include the use of benign reaction media,[5] the use of solvent-free conditions[6,7] and the use of solid-supported, reusable catalysts.[8] In this Account, we have summarized our recent activity in the area of greener synthetic transformations, which explore the use MW irradiation under solvent-free conditions or using benign reaction media such as water, ionic liquids, poly(ethylene glycol) (PEG), and supported reagents.

II. Synthesis of Heterocycles

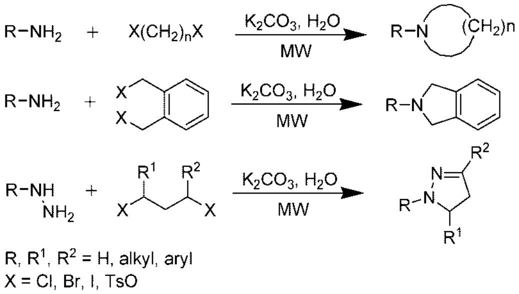
Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds.[9,10] The remarkable ability of heterocyclic nuclei to serve both as biomimetics and as reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. 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.[11] 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 a MW heating approach is potentially important in traditional medicinal chemistry and assembly of heterocyclic systems.[12]

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, and dyes.[9]

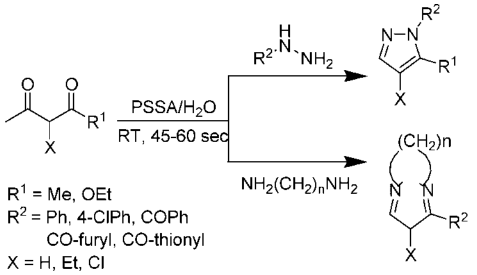
The synthesis of nitrogen-containing heterocycles, such as substituted azetidines, pyrrolidines, piperidines, azepanes, N-substituted 2,3-dihydro-1*H*-isoindoles, 4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines, has been accomplished in a basic aqueous medium using MWs; the reactions 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 pharmaceuticals.[13−15]

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 multistep reactions and functional group protection and deprotection sequences and eliminates the use of expensive phase transfer and transition metal catalysts.

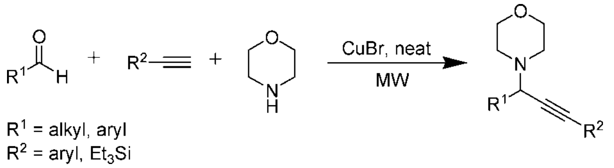
SCHEME 1. Nitrogen-Containing Heterocycles in Aqueous Media Using MW Irradiation



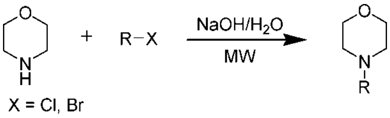
SCHEME 2. Poly(styrenesulfonic acid) (PSSA) Catalyzed Assembly of Nitrogen Heterocycles



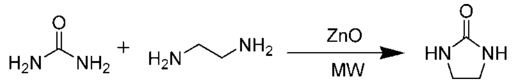
SCHEME 3. CuBr-Catalyzed Solvent-Free Route to Propargylamines



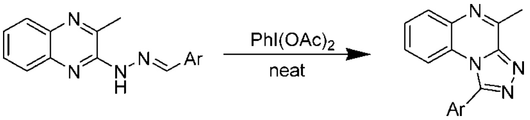
SCHEME 4. NaOH-Catalyzed N-Alkylation in Water Using MW Irradiation



SCHEME 5. ZnO-Catalyzed MW Synthesis of Imidazolidine-2-one



SCHEME 6. $PhI(OAc)_2$-Catalyzed Solvent-Free Synthesis of Triazoles



It is noteworthy that this reaction is not a homogeneous single-phase system because neither reactant is soluble in aqueous alkaline reaction medium. We believe that the selective absorption of microwaves by polar molecules and intermediates in a multiphase system could substitute as a phase transfer catalyst without using any phase transfer reagent, thereby providing the acceleration as has been observed for ultrasonic irradiation.[16]

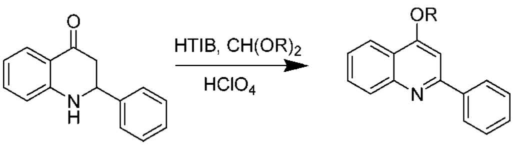
The experimental observation is consistent with the mechanistic postulation wherein the polar transition state of the reaction is favored by MW irradiation with respect to the dielectric polarization nature of MW energy transfer. In large scale experiments, the phase separation of the desired product 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, which reduces the use of volatile organic solvents.[15] 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).[17]

A direct Grignard-type addition of alkynes to *in situ* generated imines, from aldehyde and amines, catalyzed by CuBr provides a rapid and solvent-free approach access to propargylamines in excellent yields (Scheme 3).[18] This N-alkylation of nitrogen heterocycles has also been achieved in aqueous media under MW irradiation conditions (Scheme 4).[19] Shorter reaction times and higher product yields are some of the advantages that render this procedure a greener alternative to conventional chemical synthesis.

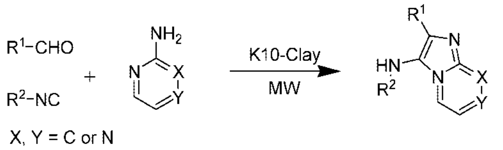
Cyclic ureas such as imidazolidine-2-one have recently attracted much attention due to their manifold applications as intermediates for biologically active molecules. A MW-assisted protocol for the direct synthesis of these cyclic ureas has been developed that proceeds expeditiously in the presence of ZnO (Scheme 5). Not only was the reaction accelerated upon exposure to MW irradiation, thus shortening the reaction time, but also the formation of byproducts was eliminated when compared with conventional heating methods.[20]

Triazoles are another important class of nitrogen heterocycles that form an integral part of therapeutically interesting compounds that display diverse biological activities. A solvent-free and expeditious synthesis of 1-aryl-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines was developed that utilizes a simple mixing of a relatively benign nonmetallic oxidant, iodobenzene diacetate ($PhI(OAc)_2$) (Scheme 6) in the absence of MW irradiation.[21a] Such mechanochemical mixing of hypervalent iodine reagents with single substrates can generate useful building blocks under solvent-free conditions.[21] On a similar line, easily accessible 2-aryl-l,2,3,4-tetrahydro-4-quinolones were readily oxidized to the corresponding 4-alkoxy-2-arylquinolines using a relatively safe hypervalent iodine reagent, [hydroxy (tosyloxy)iodo]benzene (HTIB), in high

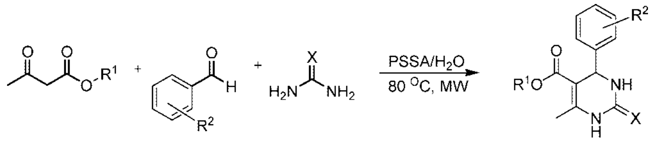
SCHEME 7. HTIB-Catalyzed Synthesis of 4-Alkoxy-2-arylquinolines



SCHEME 8. Clay-Catalyzed Solvent-Free Synthesis of Annulated Nitrogen Heterocycles



SCHEME 9. Biginelli Reaction in Aqueous Medium



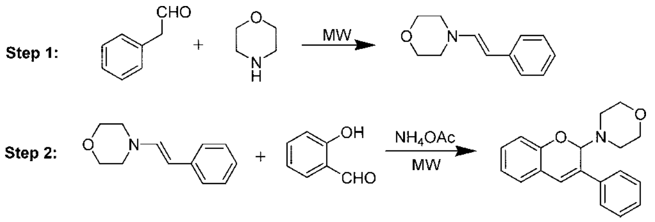
yields, thus providing a concise route to an important class of naturally occurring alkaloids (Scheme 7).[22]

The imidazo[1,2-*a*] annulated nitrogen heterocycles bearing pyridine, pyrazine, and pyrimidine moieties constitute a class of biologically active compounds that can be assembled via a rapid one-pot MW approach (Scheme 8), in the presence of recyclable montmorillonite K10 clay under solvent-free conditions.[23] This atom-economic condensation of aldehydes, amines, and isocyanides via three-component Ugi reaction was adaptable for the parallel assembly of a library of compounds. Additionally, the use of inexpensive clay and its recyclability renders this process an economical and ecofriendly procedure.[23]

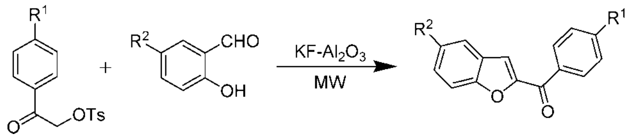
Dihydropyrimidinones are an important class of organic compounds that show prominent biological activity and were synthesized under solvent-free conditions[24] or by an environmentally benign Biginelli protocol using PSSA as a catalyst. (Scheme 9).[25] This MW protocol proceeds efficiently in water without the use of any organic solvent. Also, the use of polymer-supported, low toxicity, 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.[10]

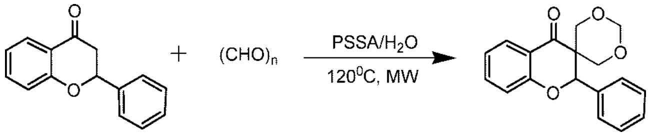
SCHEME 10. One-Pot Solvent-Free Synthesis of Isoflav-3-enes



SCHEME 11. MW-Assisted Rapid Synthesis of 2-Aroylbenzo[*b*]furans



SCHEME 12. PSSA-Catalyzed One-Pot Synthesis of 1,3-Dioxanes in Aqueous Media

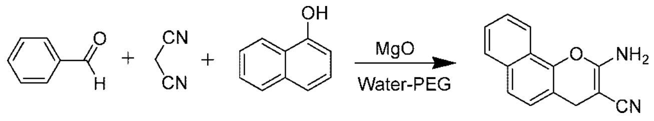


Isoflav-3-enes bearing a 2*H*-1-benzopyran nucleus form an important class of chromene intermediates that are useful in the synthesis of many natural products and medicinal agents. A solvent-free synthesis of unnatural analogues, 2-amino-substituted isoflav-3-enes, was developed that can be carried out in one pot using MWs via the in situ generation of enamines and their subsequent reactions with salicylaldehydes (Scheme 10).[26] This environmentally friendly procedure does not require azeotropic removal of water using a large excess of aromatic hydrocarbon solvents for the generation of enamines or the activation of the catalyst.

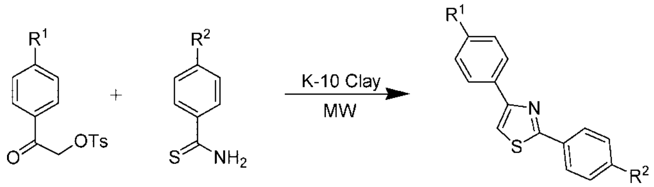
The 2-aroylbenzo[*b*]furans, initially reported from the flower heads of *Helichrysum arenarium* DC, form a group of naturally occurring compounds that possess a wide range of pharmacological activities. The expeditious solventless syntheses of 2-aroylbenzo[*b*]furans were developed from readily accessible α-tosyloxyketones and mineral oxides in processes that are accelerated by exposure to MWs (Scheme 11).[27]

Dioxane rings are common structural motifs in numerous bioactive molecules, and such 1,3-dioxanes were assembled in aqueous media via tandem bis-aldol reaction of ketones with paraformaldehyde catalyzed by PSSA under MW irradiation conditions (Scheme 12).[28] Ketones undergo efficient reaction 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

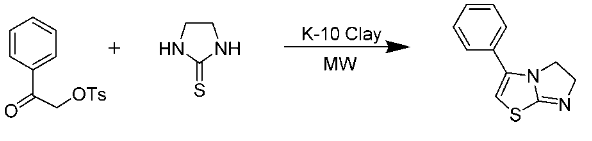
SCHEME 13. MgO-Catalyzed Synthesis of 2-Amino-2-chromenes



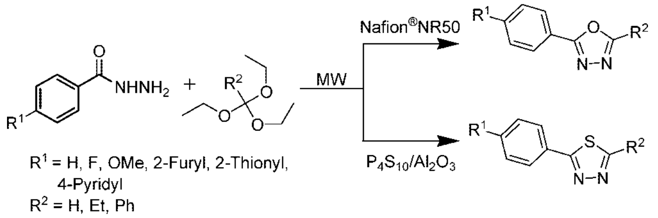
SCHEME 14. MW-Assisted Solvent-Free Synthesis of 1,3-Thiazoles



SCHEME 15. MW-Assisted Solvent-Free Synthesis of Bridgehead Thiazoles



SCHEME 16. One-Pot Solvent-Free Synthesis of 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles



design. Also, it is noteworthy to mention that these reactions were working well in an aqueous medium without using any phase-transfer catalyst (PTC). This may be due to selective absorption of microwaves by reactants, intermediates, and polar aqueous medium,[29] which accelerates the reaction even in absence of PTC.

A nanosized magnesium oxide catalyzed three-component condensation reaction of aldehyde, malononitrile, and α-naphthol proceeded rapidly in water—PEG to afford the corresponding 2-amino-2-chromenes in high yields at room temperature (Scheme 13) without microwaves. 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.[30]

Sulfur-Containing Heterocycles. Sulfur heterocycles are equally important classes of heterocycles in pharmaceuticals and organic synthesis. Generally, synthesis of these heterocyclic compounds involves utilization of lachrymatory starting materials, phenacyl halides, and hazardous reagents, requires a longer reaction time under drastic conditions, and often generates aqueous or organic solvent waste. The 1,3-thiazoles (which are not easily obtainable under classical heating conditions) were readily obtained in excellent yields from thioamides and α-tosyloxyketones catalyzed by montmorillonite K-10 clay (Scheme 14).[27]

The general protocol can be extended to a concise preparation of bridgehead 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles, which are normally difficult to obtain, require a longer heating time, and use α-haloketones or α-tosyloxyketones under strongly acidic conditions. These solventless reaction conditions for the bridgehead heterocycles merely require a mixing of α-tosyloxyketones with thioamides in the presence of montmorillonite K-10 clay. The mixture was then irradiated in MW for 3 min to afford substituted bridgehead thiazoles (Scheme 15).[27]

1,3,4-Oxadiazoles and 1,3,4-thiadiazoles have a wide range of pharmaceutical and biological activities. The extensive use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important structural class. These molecules are also utilized as pharmacophores due to their favorable metabolic profile and their ability to engage in hydrogen bonding.

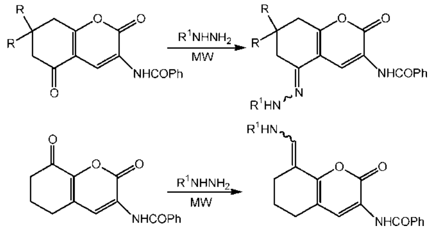
A novel one-pot solvent-free synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles via condensation of acid hydrazide and triethyl orthoalkanates under MW irradiation was recently developed (Scheme 16).[31] The use of solid-supported, relatively low toxicity, and inexpensive Nafion NR50 and P_4S_{10}/Al_2O_3 as a catalyst and the solvent-free reaction conditions are some of the ecofriendly attributes of this synthetic protocol, which may find useful application in drug discovery.

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) tautomerase activity.[32]

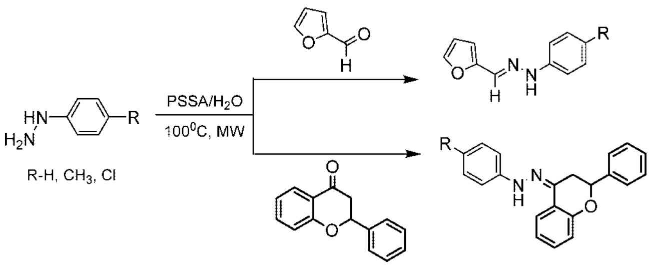
The first example of a reaction between two solids in a solvent-free and catalyst-free environment was demonstrated by Varma et al., when the reaction of neat 5- or 8-oxobenzopyran-2(1*H*)-ones with a variety of aromatic and heteroaromatic hydrazines provided rapid access to several synthetically useful heterocyclic hydrazones (Scheme 17).[33]

An aqueous protocol for the synthesis of these heterocyclic hydrazones using PSSA as a catalyst was recently developed (Scheme 18). 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.[34]

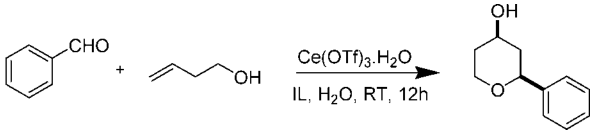
SCHEME 17. Heterocyclic Hydrazone Synthesis under Solvent-Free Conditions



SCHEME 18. Hydrazone Synthesis of Furaldehyde and Flavanone in Water



SCHEME 19. Cerium Triflate-Catalyzed Prins Reaction in Ionic Liquid



III. Organic Name Reactions

Prins Reaction. Tetrahydropyrans are prevalent subunits in an assortment of natural products including carbohydrates, polyether antibiotics, and marine toxins. The Prins cyclization, which entails the formation of a C−C bond, is a notable method for the formation of tetrahydropyran derivatives. It consists of the condensation of olefins with aldehydes under strongly acidic conditions and high reaction temperatures, which limits its potential as an effective synthetic methodology. 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 19).[35]

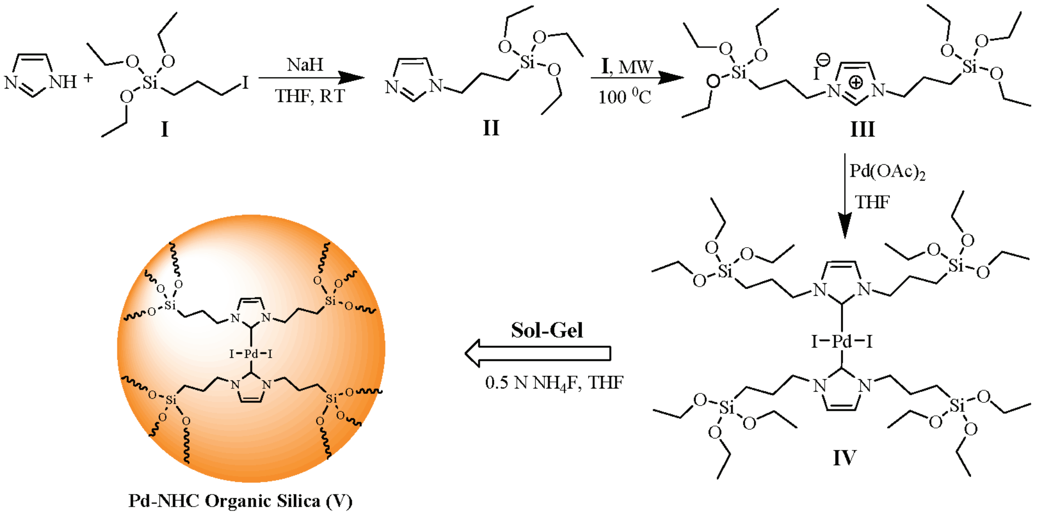
Suzuki and Heck Reactions. Palladium (Pd)-catalyzed carbon−carbon cross-coupling reactions exemplify one of the most important processes in organic chemistry. The Heck and Suzuki reactions are among the widely used reactions for the formation of carbon−carbon bonds. These reactions are generally catalyzed by soluble Pd complexes with various ligands. However, the efficient separation and subsequent recycling of homogeneous transition-metal catalysts remains a scientific challenge and an aspect of economical and ecological relevance.[36]

The first Pd−N-heterocyclic carbene (NHC) complex in the form of organic silica was prepared using a sol−gel method (Scheme 20).[37]

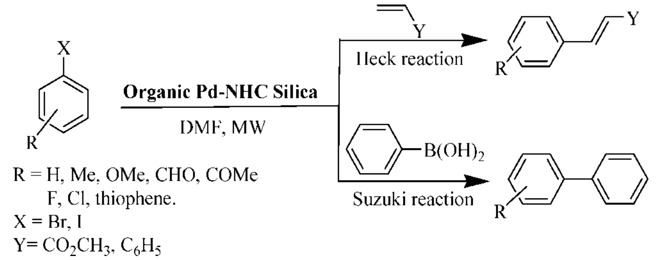
This catalyst was then used for Heck and Suzuki reactions under MW irradiation conditions (Scheme 21). These C−C coupling reactions proceeded efficiently under the influence of MW, with excellent yield, high turnover number (TON), and high turnover frequency (TOF) without any change in catalytic activity for at least five reaction cycles.[37]

PEG was also found to be an inexpensive and nontoxic reaction medium for the MW-assisted Suzuki cross-coupling of arylboronic acids with aryl halides.[5b] This environmentally friendly MW protocol offers ease of operation and enables recyclability of catalyst and synthesis of a variety of substituted biaryls employing palladium chloride as catalyst and potassium fluoride as the base.[38]

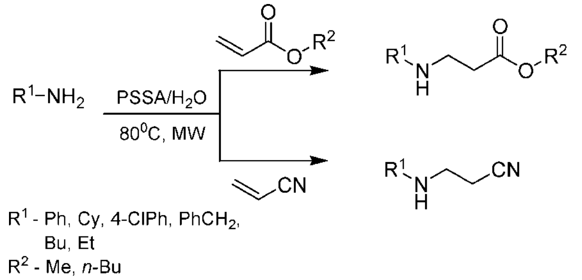
SCHEME 20. Synthesis of Pd−NHC Organic Silica Catalyst



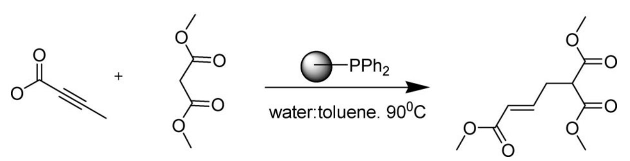
SCHEME 21. Pd–NHC Silica-Catalyzed Heck and Suzuki Reactions



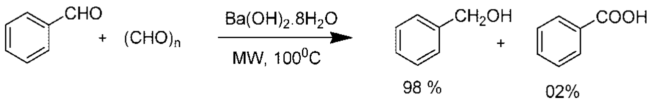
SCHEME 22. PSSA-Catalyzed Aza-Michael Reaction



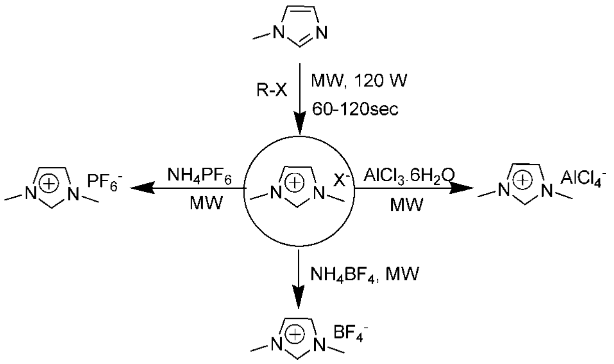
SCHEME 24. Polymer-Supported Phosphine-Catalyzed Trost's γ-Addition



SCHEME 25. Solvent-Free Cross-Cannizzaro Reaction



SCHEME 26. MW-Assisted Synthesis of Ionic Liquids



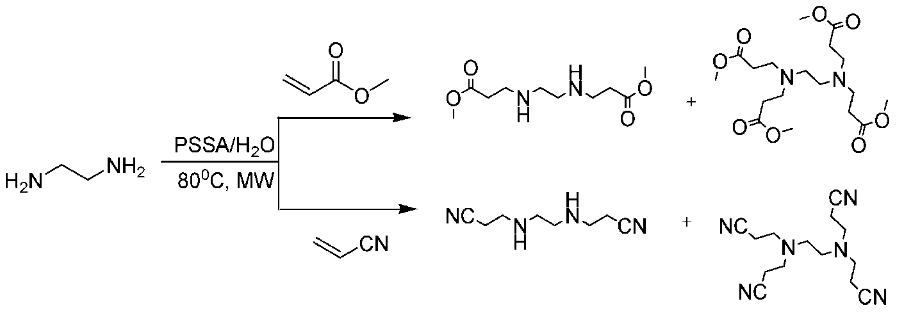
Aza-Michael Reaction. Aza-Michael addition is an important class of carbon–nitrogen bond-forming reactions and has been demonstrated to be a powerful tool in organic synthesis. We have recently developed an efficient aza-Michael addition of amines catalyzed by PSSA in aqueous medium (Scheme 22) and also studied the tandem bis-aza-Michael addition reaction of alkyl diamine with methyl acrylate and acrylonitrile (Scheme 23).[39]

This sustainable and operationally simple PSSA-catalyzed aza-Michael protocol proceeds efficiently in aqueous medium without use of organic solvent. Also, the use of polymer supported, relatively low toxicity, and inexpensive PSSA as a catalyst renders this method greener and ecofriendly.

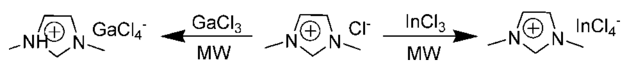
Trost's γ-Addition. Complementary to Michael reaction, Trost et al. developed the "γ-addition" of nucleophiles to 2-alkynoates catalyzed by a phosphine. In these reactions, a nucleophilic tertiary phosphine is first added to the triple bond of an electron-deficient alkyne and finally gets eliminated from the reaction product after a series of transformations; hence, the tertiary phosphine plays the role of the catalyst. Li and Varma developed a recyclable and efficient polymer-supported triphenylphosphine-catalyzed "atom-economical" Trost's addition of nucleophiles to alkynoate in aqueous media (Scheme 24).[40]

Cannizzaro Reaction. The Cannizzaro reaction, an inherently wasteful reaction, is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt and is restricted to aldehydes that lack α-hydrogens. A solvent-free and expeditious cross-Cannizzaro protocol for the preparation of alcohols was developed from aldehydes using barium hydroxide, $Ba(OH)_2 \cdot 8H_2O$ and paraformaldehyde (Scheme 25).[41] The operational simplicity, rapid reaction rates, and high yield of pure alcohol makes this is a useful and attractive procedure.

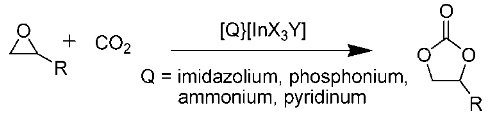
SCHEME 23. PSSA-Catalyzed Bis-aza-Michael Reaction



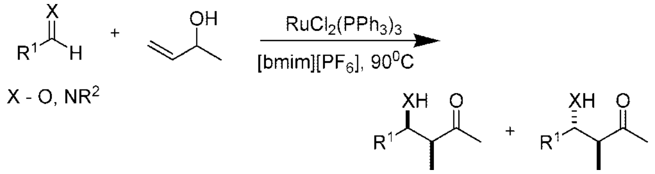
SCHEME 27. MW-Assisted Synthesis of In- and Ga-Containing Ionic Liquids



SCHEME 28. Tetrahaloindate(III)-Based IL-Catalyzed Synthesis of Cyclic Carbonates



SCHEME 29. Ruthenium-Catalyzed Aldol and Mannich-Type Reaction in Ionic Liquid



IV. MW-Assisted Synthesis of Ionic Liquids and Their Application

Ionic liquids (ILs) have received wide attention due to their potential in a variety of commercial applications such as electrochemistry, heavy metal ion extraction, phase transfer catalysis and polymerization, and as substitutes for conventional volatile organic solvents.[5c,42] ILs are polar but consist of poorly coordinating ions and provide a polar alternative for biphasic systems. Other important attributes of these ILs include negligible vapor pressure, potential for recycling, compatibility with various organic compounds and organometallic catalysts, and the ease of separation of products from reactions.

Solvent-Free Synthesis of ILs. ILs, being polar and ionic in character, couple with MW irradiation very efficiently and are, therefore, ideal MW-absorbing candidates for expediting chemical reactions. The first efficient preparation of 1,3-dialkylimidazolium halides via MW irradiation was developed by our group (Scheme 26).[43,44] The reaction time was reduced from several hours to minutes, and it avoids the use of a large excess of organic solvents as the reaction medium. These syntheses can also be carried out safely using ultrasound under solvent-free conditions.[45]

Another important metal-bearing class of ILs, [Rmim][InCl$_4$] and [bmim][GaCl$_4$], was also prepared using a solvent-free MW procedure (Scheme 27).[46] This approach was much faster, more efficient, and more ecofriendly because it does not use any organic solvent.

Synthetic Application of ILs. Within the past few years, ionic liquids have emerged as a new class of green solvents for chemical processes and transformations and have attracted considerable attention.[5c] The nonvolatile nature of ionic liquids gives them significant advantage in minimizing solvent consumption. Their polarity renders them good solvents for various organic reaction and catalysis, including the dissolutions of renewable materials such as cellulose.[47]

The reaction of CO$_2$ with a variety of epoxides has been examined in the presence of catalytic amounts of various ILs, and tetrahaloindate(III)-based ILs were found to exhibit the highest catalytic activities for the synthesis of cyclic carbonates (Scheme 28).[48]

Aldol and Mannich-type reactions, important protocols for forming carbon−carbon bonds, can also be carried out in IL without assistance from MW irradiation. Li et al. studied the cross-coupling of aldehydes and imines with allylic alcohols catalyzed by RuCl$_2$(PPh$_3$)$_3$ in IL (Scheme 29). The solvent/catalyst system could be reused for at least five times with no loss of reactivity.[49,50]

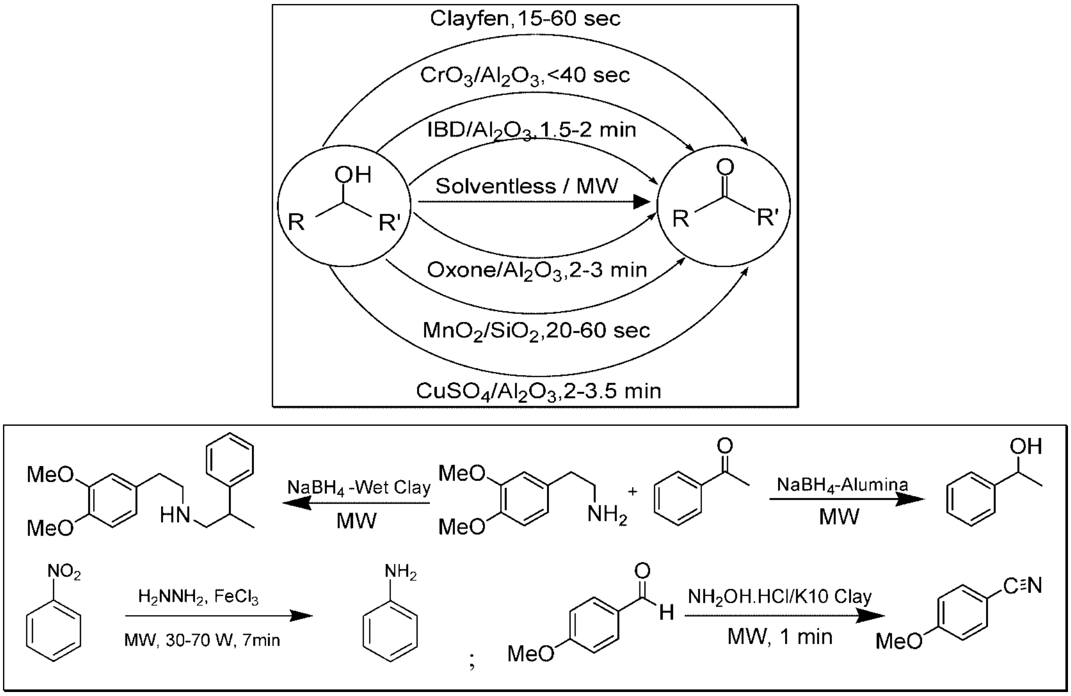
V. Oxidation–Reduction Reactions

MW protocols using immobilized reagents on solid supports have been extensively explored, an oxidation example involves simple solvent-free mixing of neat substrates with clay-supported iron(III) nitrate (clayfen) or iodobenzene diacetate (IBD) as an oxidant and a brief MW irradiation for 15−60 s.[6] The oxidation of sulfides to sulfoxides and sulfones was achieved in a similar manner using MW irradiation with desired selectivity to either sulfoxides or sulfones over sodium periodate (NaIO$_4$) on silica. An expeditious and chemoselective reduction of aldehydes and ketones that uses alumina-supported sodium borohydride (NaBH$_4$) and proceeds in the solid state was also accelerated by MW irradiation. A solvent-free reductive amination protocol for carbonyl compounds using sodium borohydride supported on moist montmorillonite K10 clay was facilitated by MW irradiation. Clay serves the dual purpose of a Lewis acid and also provides water from its inner layers that enhance the reducing ability of NaBH$_4$ (Scheme 30).[6,8,51]

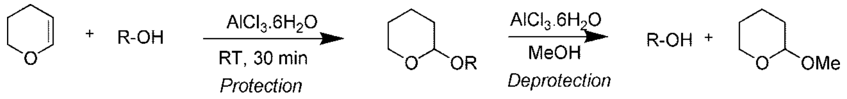
VI. Protection−Deprotection Reactions

The protection and deprotection of alcohols is a common event in multistep organic syntheses, and tetrahydropyranylation is one of the most frequently employed methods. The tetrahydropyranyl (THP) ethers are attractive because they are less expensive, easy to deprotect, and stable enough to strong basic media, oxidative conditions, reduction with hydrides, and reactions involving Grignard reagents, lithium alkyls, and

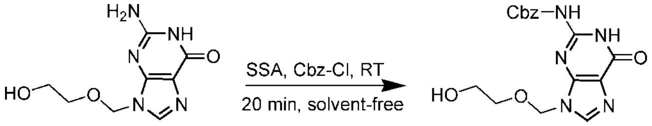
SCHEME 30. MW-Assisted Solvent-Free Oxidation and Reduction Reactions



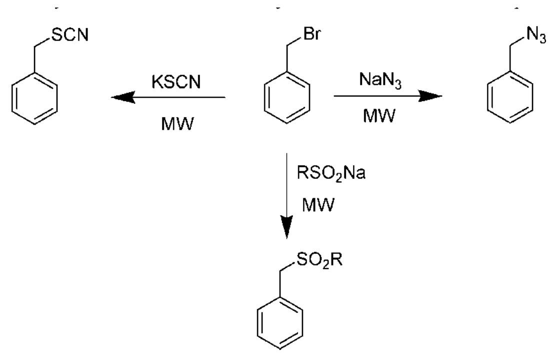
SCHEME 31. THP Protection and Deprotection of Alcohol under Solvent-Free Conditions



SCHEME 32. Cbz Protection of Amines under Solvent-Free Conditions



SCHEME 33. Synthesis of Azides, Thiocyanates, and Sulfones in Aqueous Medium



alkylating and acylating reagents. Catalytic amounts of aluminum chloride hexahydrate enabled solvent-free tetrahydropyranylation of alcohols and phenols at moderate temperatures. A simple addition of methanol regenerated the corresponding alcohols and phenols (Scheme 31), thus rendering these protection and deprotection sequences as very efficient transformations at high substrate to catalyst ratios.[52]

The (benzyloxycarbonyl) (Cbz) group is very important functionality for the protection of amines and amine derivatives, since it can be easily removed by catalytic hydrogenation without any side reactions and is stable to basic and most aqueous acidic conditions. A facile and chemoselective *N*-benzyloxycarbonylation of amines using silica-sulfuric acid that proceeds under solvent-free conditions at room temperature was achieved (Scheme 32). These reactions were applicable to a wide variety of primary (aliphatic, cyclic) and secondary amines, amino alcohols, and heterocyclic amines.[53]

VII. Nucleophilic Substitution Reactions

A practical, rapid, and efficient MW-promoted synthesis of various azides, thiocyanates, and sulfones was developed in an aqueous medium (Scheme 33). This general and expeditious MW-enhanced nucleophilic substitution approach has used easily accessible starting materials such as halides or tosylates in reaction with alkali azides, thiocyanates, or sulfinates in the absence of any phase-transfer catalyst, and a variety of reactive functional groups were tolerated.[54]

This microwave-assisted synthesis of azides, thiocyanates, and sulfones proved to be a useful alternative that avoids the use of environmentally detrimental volatile chlorinated hydrocarbons. Various functional groups such as ester, carboxylic acid, carbonyl, and hydroxyl were unaffected under the mild reaction conditions employed. This method involves simple experimental procedures and product isolation, which avoids the use of phase-transfer catalysts and will contribute to the development of a greener strategy for the preparation of various useful compounds.[54]

Conclusion

The demands for efficient and sustainable synthetic methods in the fields of healthcare and fine chemicals, combined with the pressure to produce these substances expeditiously and in an environmentally benign fashion, pose significant challenges to the synthetic chemical community. This objective can be achieved by the development of wide variety of sustainable synthetic protocols 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, ILs, and PEG. It should also be noted that the rapid development of "Green Chemistry" is due to the recognition that environmentally friendly products and processes will be economical in the long term as they circumvent the need for treating "end-of-the-pipe" pollutants and byproducts generated in conventional synthesis.

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BIOGRAPHICAL INFORMATION

Dr. Vivek Polshettiwarwas born in Mangli (India) in 1979. He received his B.Sc. (1999) and M.Sc. (2001) degrees in Chemistry from Amravati University, India. He then moved to DRDE, Gwalior, where he received his Ph.D. (2005) from Jiwaji University, Gwalior (India) under the supervision of Professor M. P. Kaushik. He investigated nanostructured functionalized silica for catalysis with Professor J. J. E. Moreau in 2006 for his postdoctoral research at ENSCM, Montpellier (France). Currently he is working as an ORISE postdoctoral fellow, researching greener synthetic methods for bioactive compounds, with Professor R. S. Varma at US EPA, Cincinnati, Ohio.

Prof. Rajender S. Varma was born in India and obtained his Ph.D. from Delhi University in 1976. After postdoctoral positions at Robert Robinson Laboratories, University of Liverpool, U.K., and University of Tennessee, he was a faculty member at Baylor College of Medicine, Senior Scientist at Houston Advanced Research Center, and Research Professor at Sam Houston State University prior to joining as senior scientist in the Sustainable Technology Division at US Environmental Protection Agency in 1999. He has over 35 years of research experience in management of multidisciplinary technical programs ranging from natural products chemistry, pulp and paper technology, and therapeutics to development of genosensor technology, specifically the applications and interface of chemical science with biology, solid-state chemistry, bioelectronics, and nanomaterials, and development of environmentally friendlier alternatives for synthetic methods using microwaves, ultrasound, and mechanochemical approaches. The primary focus is to evaluate novel and safer environmental protocols in industrial chemistry and their impact in human health and environmental sciences. He has published over 260 scientific peer-reviewed papers and has been awarded six US Patents.

FOOTNOTES

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