Aqueous microwave chemistry: a clean and green synthetic tool for rapid drug discovery

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The development of "Greener Organic 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 by-products generated by conventional synthesis. The fundamentals and significant outcomes of microwave-assisted organic synthesis in aqueous medium are summarized in this *tutorial review*, which have resulted in the development of relatively sustainable and environmentally benign protocols for the synthesis of drugs and fine chemicals.

Introduction

A new kind of chemical revolution, "*green chemistry*", is brewing—150 years after the first chemical revolution transformed modern life with a host of conveniences—which protects the environment, not by cleaning it up, but by inventing new chemistry and new chemical processes that prevent pollution. In essence, it prompts the chemical and pharmaceutical manufacturer to consider how human life is impacted after these chemicals are generated and introduced into their society.[1,2] By rethinking chemical design from the ground up, chemists are developing new ways to manufacture products that fuel the economy and lifestyles, without the damages to the environment that have become all too evident in recent years.

The medicinal chemistry community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of drugs required by society in short periods of time. Because of high molecular complexity in drug discovery processes accompanied by time constraints, the primary driver of pharmaceutical green chemistry has become the development of efficient and environmentally benign synthetic protocols. This can be achieved through the proper choice of starting materials, atom economic methodologies with a minimum number of chemical steps, the appropriate use of greener solvents and reagents, and efficient strategies for product isolation and purification. Thus, green chemistry has emerged as a discipline that permeates all aspects of synthetic chemistry. A major goal of this endeavor must then be to simultaneously maximize the efficient use of safer raw materials and to reduce the waste produced in the process.[3]

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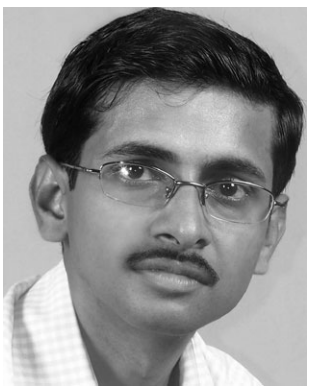
Is your synthetic protocol *green*?

This is a big question for a medicinal chemist, which invariably is perplexing. Twelve principles of green chemistry can be used to assess a particular synthetic protocol's greenness.[1] These principles address several concerns, such as use of various solvents and the amount of chemical waste produced; the use of catalyst and reagents (quantity and reusability); the number of chemical steps (energy efficiency) and atom economy; and the use of safer chemicals and reaction conditions (Fig. 1). It is very difficult for a new synthetic protocol to satisfy all 12



Vivek Polshettiwar

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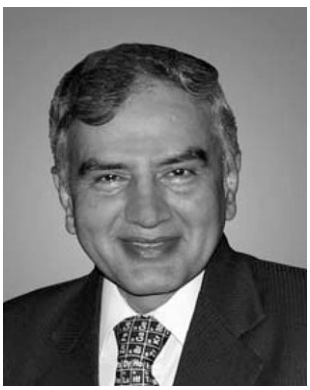

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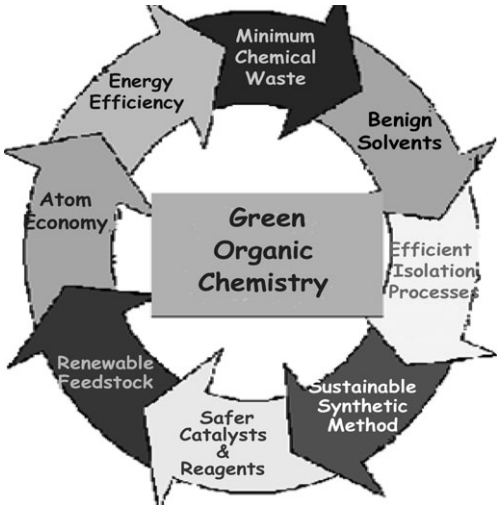


Fig. 1 Principles of green and sustainable organic chemistry.

principles, which is not expected, but the more a protocol satisfies, the greener the developed process will be.

There is a variety of approaches for the development of sustainable methods, which reflects the enormity and complexity of this field. Alternative reaction media is one of the ways to make a protocol greener. However, solvent replacement in itself may not be enough. The whole process must be well thought-out, and the solvent is only one part of this puzzle. The atom efficiency, energy uses and deployment of renewable resources must also be taken into account.

Solvents define a major part of the environmental performance of processes in chemical industry and also impact cost, safety, and health issues. Being volatile and highly inflammable, they are the main root of environmental pollution and are high on the green-chemistry agenda.[4] Use of solvents in reactions cannot be avoided as they are necessary for various processes like the mixing of reactants, constant and uniform supply of energy by transfer of heat, and in some cases, control of the regio- and chemo-selectivity of reactions. However, the use of organic solvents for isolation and purification of products (which involves the use of large amounts per mass of final products) can be prevented or minimized by developing atom-economic synthetic methods, which selectively generate the desired product without producing any by-products.

Environmental improvements, in terms of solvents, can be achieved by implementing several alternative methodologies as described below;

(1) Replacement of hazardous solvents with those that show superior ecological, health, and safety properties.

(2) Bio-solvents: solvents produced with renewable resources such as ethanol produced by fermentation of sugar-containing feeds and starchy feed materials.

(3) Substitution of organic solvents with supercritical fluids such as CO_2 that are environmentally benign, and with benign ionic liquids that have low vapor pressure, and thus, curb release into the environment.

(4) Biphasic technologies: using fluorous and regenerable ionic liquids along with aqueous systems and supercritical carbon dioxide.

Is *water* the green solvent?

The idea of "green" solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production, thus identifying green solvents is a top priority for the organic chemist. Use of no-solvent, *i.e.* solvent-free reactions is another solution, however, this may work for only a few reactions; a lack of reaction medium may lead to overheating of the reaction mixture, in view of the poorly understood heat- and mass-transfer issues.[5] Biphasic technologies, using fluorous and ionic liquids[6] along with aqueous systems[7] and supercritical carbon dioxide, have formed the main thrust of this movement. However, the cost and toxicity of ionic liquids are big concerns in using them as a solvent.[8] Thus, naturally abundant water appears to be a better option because of its non-toxic, non-corrosive and non-flammable nature. Also, water can be contained because of its relatively high vapor pressure as compared to organic solvents, which are favorable traits to render water as a sustainable alternative.

What are the *limitations* of water as a solvent?

The main difficulty with water as a solvent is that most organic substrates are insoluble in it, which makes the reaction mixture heterogeneous. This can be overcome by using phase transfer catalysts, but this will cause the process to be more expensive. Also, the isolation of products from aqueous medium is another concern. For this, evaporation of water from the reaction mixture may be an option, but this is not an energy-efficient process. However, some of these issues can be overcome by using microwave (MW) heating for reactions in aqueous medium.

How do *microwaves* promote the reaction in aqueous medium?

Water is rapidly heated to high temperatures under microwave irradiation, enabling it to act like a pseudo-organic solvent. Also, precise control of the reaction temperature can be achieved efficiently because of the very high heat capacity of water. MW-enhanced chemistry is based on the efficiency of the interaction of molecules in a reaction mixture (substrates, catalyst and solvents) with electromagnetic waves generated by a "microwave dielectric effect". This process mainly depends on the specific polarity of molecules. Since water is polar in nature, it has good potential to absorb microwaves and convert them to heat energy, thus accelerating the reactions in an aqueous medium as compared to results obtained using conventional heating.[9]

This can be explained by two key mechanisms: dipolar polarization and ionic conduction of water molecules (Fig. 2). Irradiation of a reaction mixture in an aqueous medium by MW results in the dipole orientation of water molecules and reactants in the electric field. This causes two distinguishing effects:

(i) *Specific microwave effect*: the electrostatic polar effects which produce the dipole–dipole type interaction of the dipolar water molecules and reactants with the electric field component of MW, resulting in energy stabilizations of an electrostatic nature (Fig. 2b). This concept of a specific MW

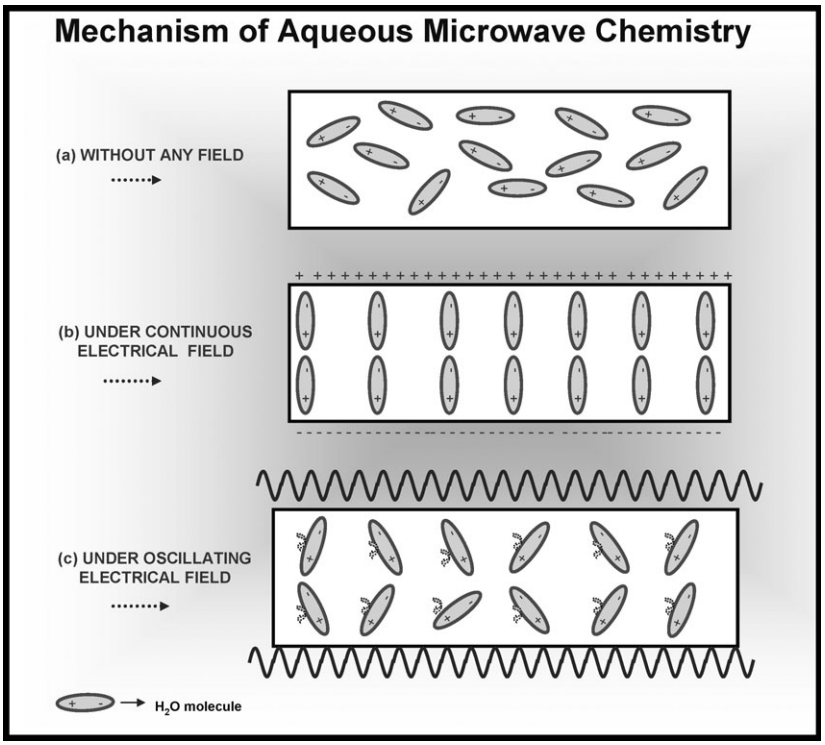


Fig. 2 Effect of microwaves on the reaction mixture in aqueous medium.

(non-thermal) effect is controversial and the subject of debate among various chemists. Recent studies by Kappe *et al*. have shown that this effect is essentially due to thermal phenomena and is thus, not non-thermal;[10] however, more in-depth study is required to obtain a definite answer.

(ii) *Thermal effect*: the dielectric heating that ensues from the tendency of dipoles (mostly water molecules in addition to reactants) to follow the inversion of alternating electric fields and induce energy dissipation in the form of heat through molecular friction and dielectric loss, which allows more regular repartition in reaction temperatures compared to conventional heating (Fig. 2c).

Antonio and Deam recently proposed a new hypothesis based on enhanced diffusion. According to them, "If the transport of an active species is a rate limiting step in a reaction (such as for diffusion limited reactions), and if microwave enhances the diffusion of that species, then overall reaction rate would change under microwave heating compared with conventional heating".[11]

It is noteworthy to mention that various organic reactions can be conducted in an aqueous medium using MW irradiation without using any phase-transfer catalyst (PTC). This is because water at higher temperature behaves as a pseudo-organic solvent, as the dielectric constant decreases substantially and an ionic product increases the solvating power towards organic molecules to be similar to that of ethanol or acetone.[12]

How does *aqueous microwave chemistry* expedite organic synthesis?

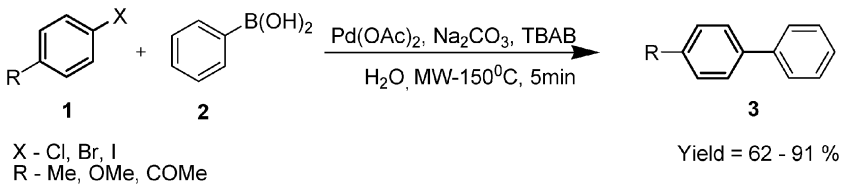
MW-assisted chemistry has blossomed into a useful technique for a variety of applications in drug discovery[13] and organic synthesis.[14] Although MW-assisted reactions in organic solvents have developed rapidly, the focus has now shifted to the more environmentally benign methods, which use greener solvents and supported renewable catalysts. There are many examples of the successful application of MW-assisted chemistry to organic synthesis; these include the use of benign reaction media, solvent-free conditions, and the use of solid-supported and reusable catalysts.[3,13–15]

To illustrate the advantages of aqueous MW chemistry in rapid and greener organic synthesis, we have reviewed some representative reactions/synthetic pathways developed in recent years in aqueous reaction medium using microwave irradiation.

Coupling reactions

Carbon–carbon cross-coupling reactions are one of the most important processes in organic chemistry. The Heck[16] and Suzuki[17] reactions are among the widely used reactions for the formation of carbon–carbon bonds. These reactions are generally catalyzed by soluble palladium (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. Heterogeneous Pd catalyst systems were found to be highly effective in overcoming some of these issues;[18] however, MW-assisted coupling (as discussed below) in aqueous medium is a recent choice of chemists.

Leadbeater and Marco[19] studied Suzuki reactions in aqueous medium using MW irradiation (Scheme 1), and prepared various biaryl derivatives (**3**) from aryl halides and phenylboronic acid. Although the above aqueous processes were generally good in terms of yield and reaction time, the yield



Scheme 1 Aqueous MW Suzuki reaction.

for aryl chloride was poor as compared to other halides. This problem was circumvented by conducting the reaction in aqueous medium using a simultaneous cooling technique in conjugation with MW heating.

The proven versatility of the Suzuki reaction has also been demonstrated in the synthesis of natural products and heterocyclic compounds. In this regard, Vanelle *et al.* advanced an aqueous protocol that involves the reaction of heterocycle-imidazo[1,2-*a*]pyridines (**4**) with a range of arylboronic acids under MW irradiation conditions (Scheme 2).[20]

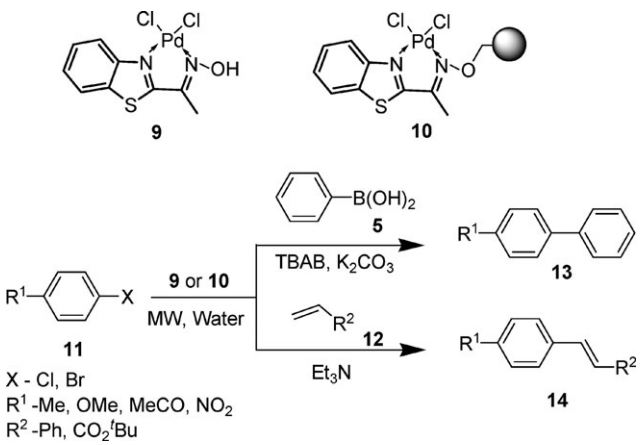
5-Aryltriazole acyclonucleosides (**8**) with various aromatic groups on the triazole ring occupy a pivotal position in the arsenal of drug candidates for combating various viruses. They were synthesized *via* the Suzuki coupling reaction in aqueous solution and promoted by MW irradiation (Scheme 3).[21] This coupling method directly afforded the product and involved no protection and deprotection steps thus providing a convenient one-step procedure for 5-aryltriazole acyclonucleosides in good yields.

Benzothiazole-based Pd(II)-complexes **9** and **10** were found to be efficient and highly active catalysts in Suzuki and Heck cross-coupling reactions of aryl chlorides and bromides with olefins and arylboronic acids under aqueous MW irradiation conditions. Deactivated aryl bromides were more efficient for both C–C cross-coupling reactions than their chloride analogs. The immobilized catalyst **10** was found to have high durability compared with the mobilized catalyst **9**. The high turnover number associated with the catalytic activity of these catalysts is highly important for mass production on industrial scale (Scheme 4).[22]

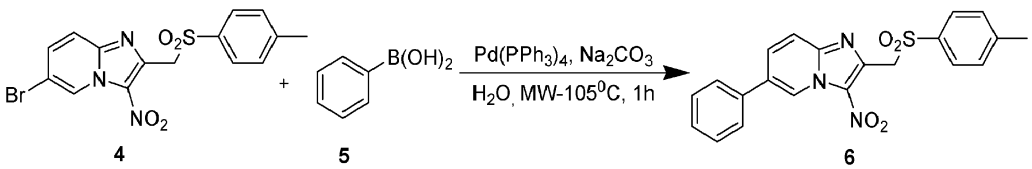
Similarly, a chitosan-supported Pd(0) catalyst, which was prepared by the adsorption of $Pd(OAc)_2$ on chitosan beads followed by simple reduction and cross-linking, was also used in Suzuki reaction in water under MW conditions. The use of chitosan beads allowed high loading of Pd because of the high metal ion sorption capacity of chitosan.[23]

Heck reactions between aryl halides and alkenes also continue to attract attention within the chemistry community because of the versatility of these reactions.[16] Arvela and Leadbeater performed the Heck coupling reaction in water using MW heating (Scheme 5), with Pd-catalyst concentrations as low as 500 ppb.[24]

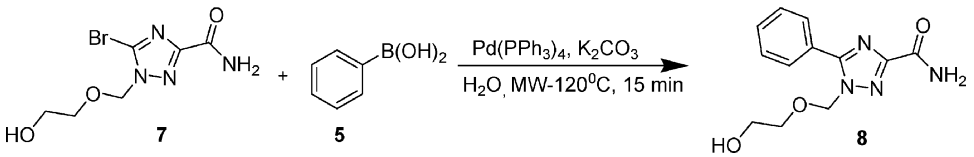
Recently, Larhed *et al.* reported highly regio-selective and fast Pd(0)-catalyzed internal R-arylation of ethylene glycol vinyl ether (**18**) with aryl halides (**15**) in aqueous medium (Scheme 6).[25] Aryl bromides and iodides were efficiently converted to corresponding acetophenones (**20**) in high yields in water using ethylene glycol vinyl ether as the olefin and potassium carbonate as the base. This Pd(0)-catalyzed method is highly advantageous as no heavy metal additives or ionic liquids are necessary. It proceeded cleanly without any noticeable by-product formation, avoided the need for inert atmosphere, and allowed easy purification of the products. Also,



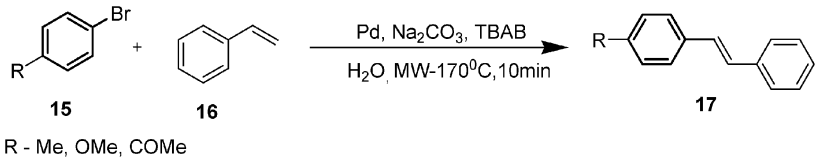
Scheme 4 Aqueous MW Suzuki reaction using benzothiazole-based Pd(II)-complexes.



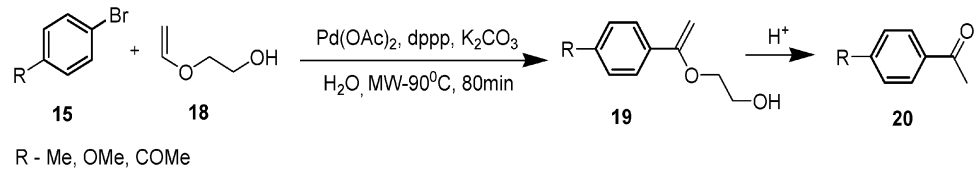
Scheme 2 Aqueous MW Suzuki reaction of heterocyclic compounds.



Scheme 3 (a) Aqueous MW Suzuki reaction of triazoles.



Scheme 5 Aqueous MW Heck reaction.



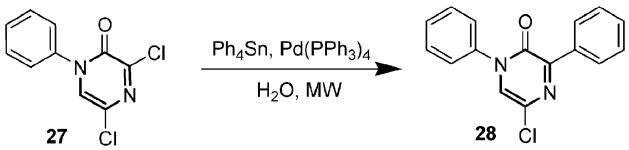
Scheme 6 Aqueous internal Heck reaction.

MW irradiation was shown to be beneficial in the activation of aryl chlorides towards the internal Heck arylation.

Sonogashira cross-coupling reaction of terminal acetylenes (**22**) with aryl or vinyl halides is yet another powerful method for the creation of carbon–carbon bonds. An aqueous Sonogashira-type coupling reaction was studied by Eycken *et al.* under MW irradiation (Scheme 7), that precludes the need for copper(I) or any transition-metal–phosphane complex, which overcame the problem of intrinsic toxicity and air sensitivity of transition-metal complexes, as well as the use of expensive phosphane ligands.[26]

Organosilanes have also emerged as premier agents for effecting the cross-coupling reaction because they are relatively benign and stable to diverse reaction conditions. These Hiyama cross-coupling reactions between vinylalkoxysilanes (**25**) and aryl halides (**24**) promoted by aqueous sodium hydroxide under fluoride-free conditions were carried out using MW irradiation in aqueous medium (Scheme 8). These reactions were catalyzed by palladium(II) acetate or a 4-hydroxyacetophenone oxime-derived palladacycle at 120 °C with low catalyst loading in the presence of TBAB in air.[27]

Stille reaction between organo-tin compounds and aryl halides was also achieved by aqueous MW chemistry by Van der Eycken *et al.*[28] Although the rate of reaction was accelerated by MW using organic solvent, the yield was less in aqueous medium (Scheme 9).



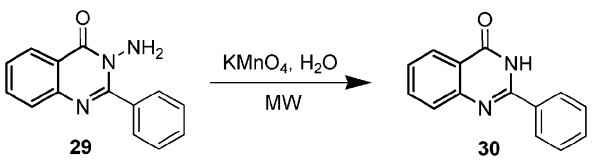
Scheme 9 Aqueous MW Stille reaction.

Oxidative deamination reaction

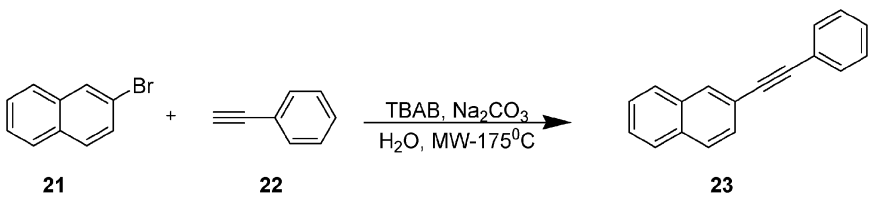
MW-Assisted deamination of aryl 3-amino-4(3*H*)-quinazolinone derivatives (**29**) using cheaper, readily available potassium permanganate as an oxidant in aqueous medium was achieved, which provided significantly higher yields than obtained under conventional heating (Scheme 10).[29]

N-Arylation of amino acids

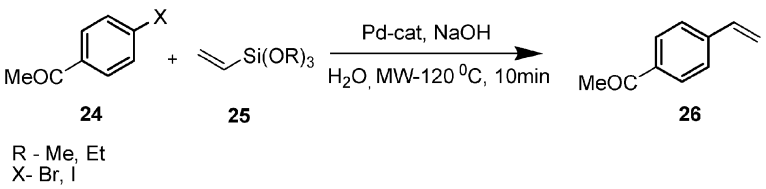
Copper-catalyzed aqueous MW protocol for *N*-arylation of amino acids was reported by Larhed *et al.*[30] These reactions



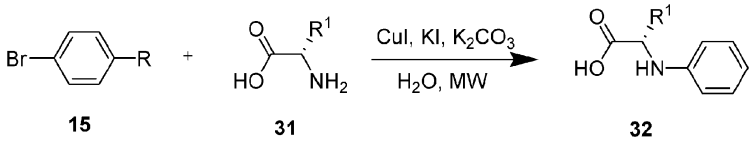
Scheme 10 Water promoted oxidative deamination reaction.



Scheme 7 Aqueous MW Sonogashira reaction.



Scheme 8 Aqueous MW Hiyama reaction.



Scheme 11 Aqueous MW protocol for *N*-arylation of amino acids.

between amino acids (**31**) and a variety of substituted aryl bromides (**15**) proceed in less than 40 min, with good yields of non-protected *N*-arylated amino acids (**32**) having minor racemization (Scheme 11).

Aminocarbonylation reaction

Aryl bromides were rapidly converted to the corresponding secondary and tertiary benzamides in aqueous medium, by using $Mo(CO)_6$ as the source of carbon monoxide using MW heating (Scheme 12).[31] It is important to note that despite the use of water as solvent, aminocarbonylation strongly dominated over hydroxycarbonylation, providing good yields of both secondary and tertiary benzamides (**35**).

Direct transformation of amines to ketones

Although the selective transformation of amines to ketones is a relatively common biological process, chemical conversions of amines to ketones are rather limited. The first example of a retro-reductive MW-assisted Pd-catalyzed amination reaction for direct conversion of amines (**36**) to ketones (**37**) in water was reported by Olah *et al.* (Scheme 13).[32] This expeditious and selective reaction proceeds smoothly without any heavy metal-based oxidant or volatile organic solvents.

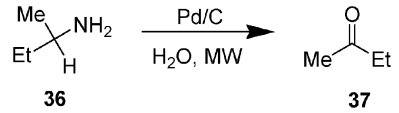
Kröhnke reaction

Kröhnke reaction for the synthesis of substituted pyridines (**40**), which are prominent building blocks in supramolecular chemistry, was also carried out in aqueous medium using MW irradiation. This one-pot condensation of aromatic ketones with arylaldehydes in the presence of ammonium acetate occurs under MW irradiation within 6–10 min (Scheme 14).[33]

Deprotection of acetals and ketals

Acetals and ketals are frequently used to protect the carbonyl function during complex synthetic pathways, and a wide variety of methods have been developed for their deprotection. Recently, Procopio and co-workers have used deionized water for this deprotection (Scheme 15) wherein simple, efficient and catalyst-free MW-assisted cleavage of ketals (**41**) and acetals (**43**) occurs essentially under neutral reaction conditions.[34]

This protocol is compatible with the presence of other functional groups in the substrates such as carbonyl, alkyne, and hydroxyl groups; moreover, the method may be suitable



Scheme 13 MW-assisted aqueous retro-reductive amination reaction.

for selectively deprotecting acetals and ketals in the presence of other protecting groups.

Nucleophilic substitution of 6-chloropurine

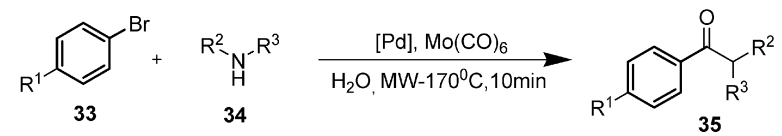
Nucleosides play important roles in various biological processes and several modified nucleoside analogues have been investigated for their antiviral and anticancer activities. Kinase inhibitors, C6-cycloamine-substituted purines and their analogues (**46**), were synthesized *via* a mild aqueous MW protocol that afforded the desired compounds in higher purity and yield, making this methodology suitable for rapid drug discovery (Scheme 16).[35]

Decarboxylation of cinnamic acid

A metal-free protocol for decarboxylation of substituted α-phenylcinnamic acid derivatives (**47**) in aqueous media was developed by Sinha *et al.*,[36] wherein a remarkable synergism between methylimidazole and aq. $NaHCO_3$ in polyethylene glycol (PEG) under MW irradiation conditions furnished the corresponding *para*/*ortho* hydroxylated (*E*)-stilbenes (**48**) (Scheme 17). This approach provides a clean alternative to the hitherto indispensable multistep methods involving toxic quinoline and a copper salt combination as the common decarboxylating agent. The critical role of water in facilitating the decarboxylation imparts an interesting facet to the synthetic utility of water mediated organic transformations.

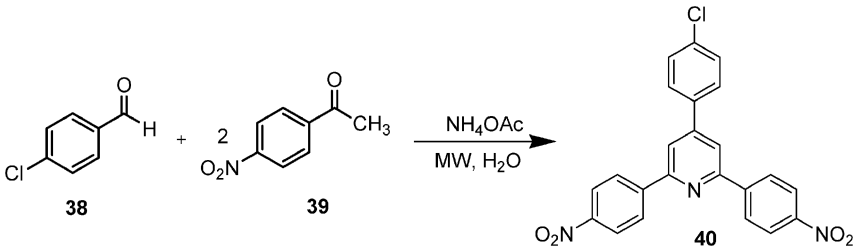
Reaction in near-critical water

Kappe *et al.* investigated MW-assisted organic synthesis in near-critical water (NCW) in the 270–300 °C temperature range. Several useful transformations, such as the hydrolysis of esters or amides, the hydration of alkynes, Diels–Alder cycloadditions, pinacol rearrangements, and the Fischer indole synthesis, were successfully performed in MW-generated NCW without the addition of an acid or base catalyst.[15] This study has demonstrated that it is technically feasible to perform MW synthesis in water on scales from 15–400 ml at

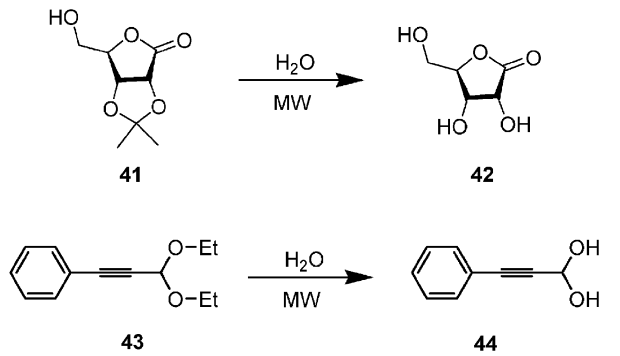


R^1 - Me, OMe, CF_3
R^2, R^3- H,Bu, t-Bu, Cy, $PhCH_2$

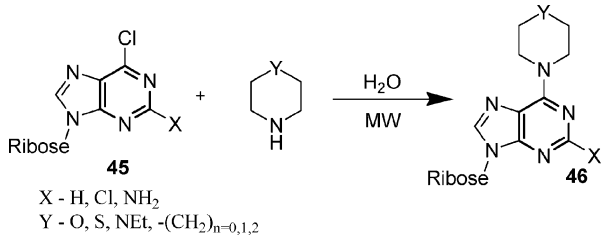
Scheme 12 Aqueous MW aminocarbonylation reaction.



Scheme 14 Kröhnke synthesis for substituted pyridines in aqueous medium.



Scheme 15 Deprotection of acetals and ketals in aqueous medium using microwaves.



Scheme 16 Aqueous protocol for C6-cyclo-*sec*-amine-substituted purine synthesis.

temperatures of up to 300 °C and 80 bars of pressure in a multimode MW reactor.

Ring-opening of epoxides in aqueous medium

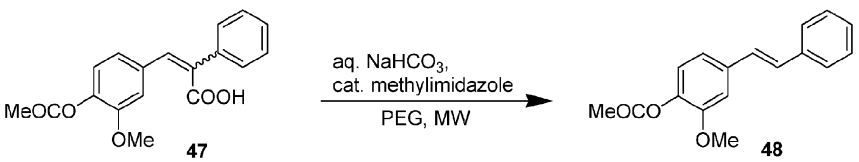
β-Hydroxy sulfides (**51**) and β-hydroxy sulfoxides (**52**, **53**) are versatile building blocks in organic synthesis and find useful application in the preparation of naturally occurring compounds such as leukotrienes. Pironti and Colonna achieved the synthesis of these molecules by ring-opening of epoxide (**49**) in aqueous medium (Scheme 18).[37] This rapid one-pot thiolysis protocol *via* ring-opening of the epoxide and the subsequent sulfoxidation were facilitated by MW irradiation with excellent yield of diastereoisomers (**52**, **53**), in the absence of any toxic metal catalyst.

Aqueous microwave chemistry for *drug discovery*

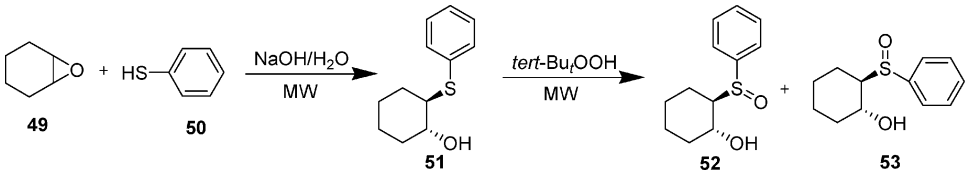
Human life depends on drug discovery research to fight against various new diseases. However, current protocols for drug discovery are not sustainable in terms of the time required for synthetic research and coping with the accompanying adverse environmental impact. In drug discovery a variety of techniques such as combinatorial synthesis, parallel synthesis, and automated library production to increase the output of pharmaceutically active chemical entities have been developed. Although most of these techniques are rapid and productive, they generate significant quantities of chemical waste, forcing us to develop new methods with reduced environmental footprint. The use of water as a non-toxic reaction medium, together with the employment of microwave heating appears to be promising and enabling greener alternatives to tackle this issue.

Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds.[38,39] 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. In both lead identification and lead optimization processes, there is an acute need for new small organic entities. 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.[40] The synthetic chemical community has been under increasing pressure to produce, in an environmentally benign fashion, the myriad of substances required by society in a short span of time. One of the alternatives is to accelerate these synthetic processes using 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), which is potentially important in traditional medicinal chemistry and the assembly of heterocyclic systems.[3,13,14]

Nitrogen heterocycles are abundant in nature and are of great significance to life because their structural subunits exist

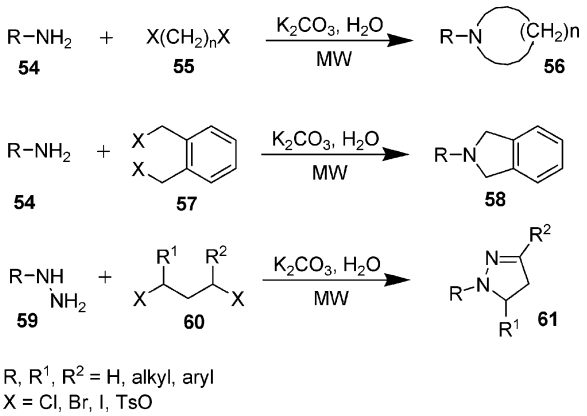


Scheme 17 Decarboxylation of cinnamic acid in aqueous medium using microwaves.



Scheme 18 Aqueous MW protocol for synthesis of β-hydroxy sulfides and β-hydroxy sulfoxides.

in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides and dyes.[38] The synthesis of nitrogen-containing heterocycles, such as substituted azetidines, pyrrolidines (**56**), piperidines, azepanes, *N*-substituted 2,3-dihydro-1*H*-isoindoles (**58**), 4,5-dihydropyrazoles (**61**), pyrazolidines, and 1,2-dihydrophthalazines, has been accomplished in a basic aqueous medium using MW. The reactions proceed *via* double *N*-alkylation of primary amines and hydrazine derivatives (Scheme 19) with readily available alkyl dihalides (or ditosylates), thus providing facile entry to important classes of building blocks in natural products and pharmaceuticals.[41–43]

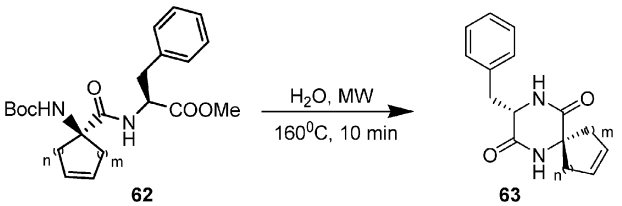


Scheme 19 Synthesis of nitrogen-containing heterocycles in aqueous media using MW irradiation.

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

It is noteworthy to mention that this reaction is not a homogeneous single phase system as neither reactant is soluble in aqueous alkaline reaction medium. 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 usage of volatile organic solvents.[43]

Spiro-amino acids incorporated into bioactive peptides are useful for both restricting the flexibility of the peptide and providing information on the topographical requirements of peptide receptors. An efficient method for the synthesis of spiro-2,5-diketopiperazines (**63**) (spiro-DKPs) was developed by cyclization of Boc-protected dipeptides (**62**) containing spiro-amino acids using MW heating in water (Scheme 20).[44]

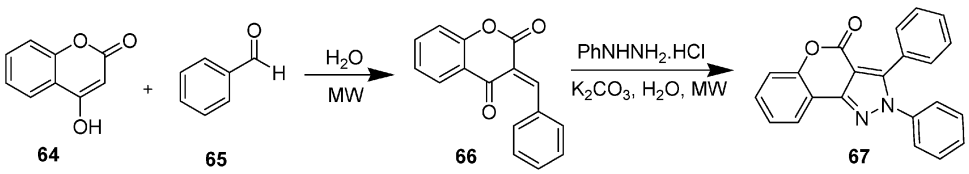


Scheme 20 Synthesis of spiro-DKPs in aqueous media using MW irradiation.

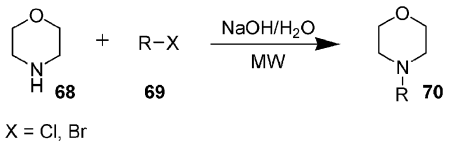
Benzopyrano[4,3-*c*]pyrazoles (**67**) were also synthesized by heterocondensation reaction between *in situ* generated 3-arylidene-2,4-chromanediones (**66**) and *N*-substituted hydrazine moieties avoiding the use of organic solvents. This high yielding protocol for pharmaceutically useful molecules was carried out in water as a solvent under MW irradiation conditions (Scheme 21).[45]

The *N*-alkylation of nitrogen heterocycles (**68**) has also been achieved in aqueous medium under MW irradiation conditions (Scheme 22).[46] Shorter reaction times and higher product yields are some of the advantages that render this procedure a greener alternative to conventional chemical synthesis.

Triazines (**75**) and tetrazoles (**76**) are another important class of nitrogen heterocycles that forms an integral part of therapeutically interesting compounds which display diverse biological activities. Various heterocycles were prepared from primary alcohols and aldehydes, which were treated with



Scheme 21 Synthesis of benzopyrano[4,3-*c*]pyrazoles in aqueous medium.



Scheme 22 NaOH-catalyzed *N*-alkylation in water using MW irradiation.

iodine in aqueous ammonia under MW irradiation to yield nitriles, which further underwent [2 + 3] cycloaddition reaction with dicyandiamide and sodium azides, to produce triazines and tetrazoles, with high optical purity (Scheme 23).[47]

Preparation of non-substituted tri- (**79**), tetra- (**80**) and pentapyrranes (**81**), important precursors for porphyrin and porphyrin analog synthesis, was achieved by MW-assisted one-step condensation of aqueous formaldehyde with pyrrole (Scheme 24). Shorter reaction times and environmentally friendly aqueous reaction medium are the advantages of this protocol.[48]

Biologically important dihydropyrimidinones (**85**), an important class of organic compounds, were synthesized by an environmentally benign aqueous MW Biginelli protocol using PSSA as a catalyst (Scheme 25).[49] The use of polymer-supported, low toxic and inexpensive PSSA as a catalyst renders this method eco-friendly, with a very simple isolation procedure that entails the filtration of the precipitated products.

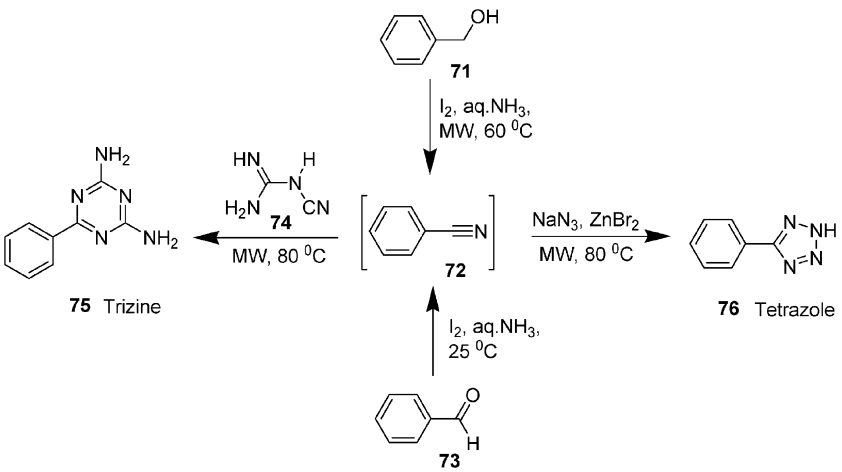
Another important class of molecules, 2-amino-4-aryl-6-ferrocenylpyridine (**88**) derivatives, were synthesized *via* the one-pot catalyst-free reaction of aromatic aldehydes, malononitrile or ethyl cyanoacetate, acetylferrocene (**87**) and ammonium acetate in aqueous medium under MW irradiation (Scheme 26).[50]

Oxygen heterocycles are important classes of building blocks in organic synthesis and several derivatives of these oxygen heterocycles have attracted much attention from medicinal chemists over the years.[39] Dioxane rings are common structural motifs in numerous bioactive molecules and can be synthesized *via* tandem bis-aldol reaction of ketones (**89**) with paraformaldehyde (**90**) in aqueous medium catalyzed by PSSA under MW irradiation conditions to produce 1,3-dioxanes (**91**) (Scheme 27).[51]

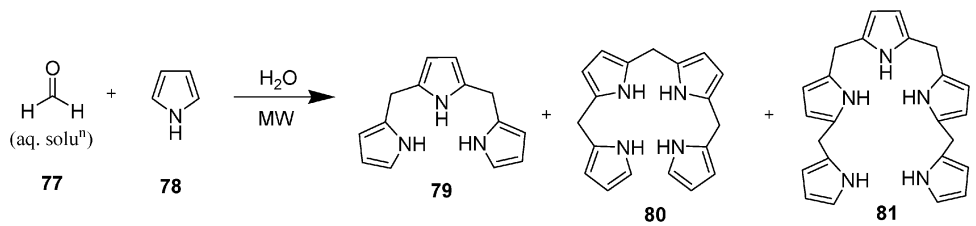
Ketones undergo efficient reaction with paraformaldehyde in water to afford the desired 1,3-dioxanes in good yield. This approach establishes a convenient and flexible method to attach functional arms to indanone and flavanone for further elaboration in synthetic design. Also, it is noteworthy to mention that these reactions work 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,[9] which accelerates the reaction even in the absence of PTC.

The reaction presumably involved the addition of protonated formaldehyde (generated by MW exposure of paraformaldehyde with PSSA/water) to ketone (enol) to form β-hydroxy ketone **92**. This was followed by the addition of another protonated formaldehyde molecule to **92** to yield diol **93**, that in turn attacks the third formaldehyde molecule to give adduct **94**, which after dehydration yields the final product 1,3-dioxane **95** (Scheme 28).[51]

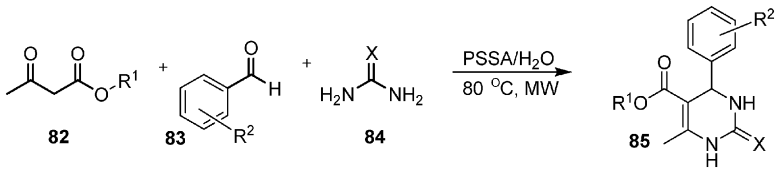
Heterocyclic hydrazones constitute an important class of compounds in organic chemistry and recently they have also found to be useful as anti-malaria drugs and as inhibitors of macrophage migration inhibitory factor (MIF) tautomerase



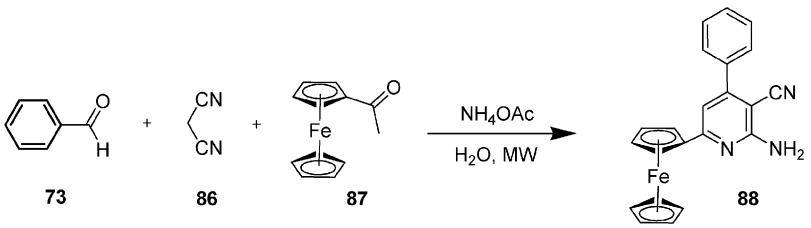
Scheme 23 Aqueous synthesis of triazines and tetrazoles using MW irradiation.



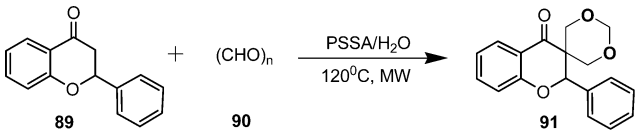
Scheme 24 Aqueous synthesis of tri-, tetra- and pentapyrranes using MW.



Scheme 25 Biginelli reaction in aqueous medium.



Scheme 26 Synthesis of 2-amino-4-aryl-6-ferrocenylpyridine derivatives.

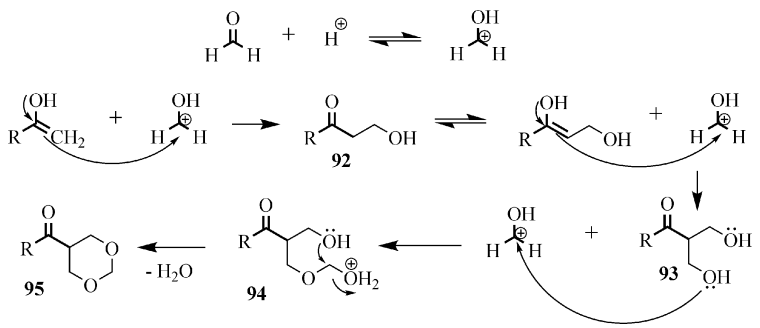


Scheme 27 PSSA-catalyzed one-pot synthesis of 1,3-dioxanes in aqueous media.

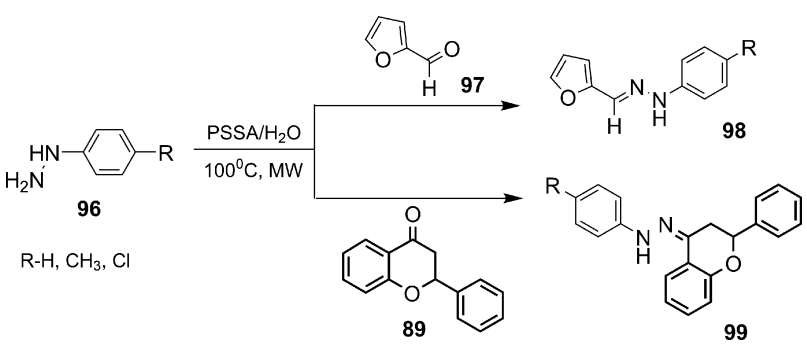
activity. An aqueous MW protocol for the synthesis of these heterocyclic hydrazones (**98** and **99**) using PSSA as a catalyst has also been developed (Scheme 29) which proceeds efficiently in the absence of any organic solvent and involves basic filtration as the product isolation step.[52]

Bicyclo[2.2.2]oct-7-enes (**100**), important bio-active molecules found in the skeleton of naturally occurring Kopsia alkaloids, can serve as multifunctional building blocks in drug discovery. Kočevar *et al*. developed an aqueous MW method for the synthesis of fused *N*-aminosuccinimide derivatives of bicyclo[2.2.2]oct-7-enes (**101**) from fused anhydrides and a variety of hydrazines (Scheme 30). The reaction occurs under neutral conditions with high selectivity, without the use of any catalyst.[53] They also extended this aqueous reaction to acetyl-containing derivatives of bicyclo[2.2.2]oct-7-enes (**102**) with range of amines (Scheme 31), which delivered succinimide derivatives (**104**) chemoselectively with the acetyl group remaining unchanged.[54]

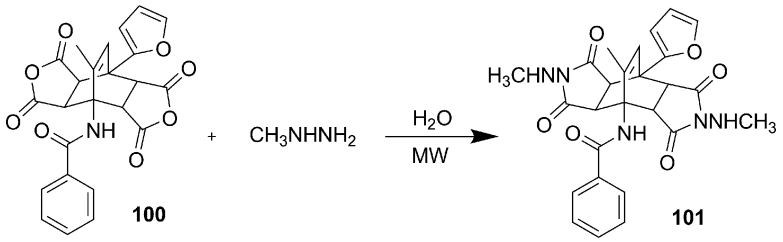
Indenoquinoline derivatives (**108**) are important heterocyclic compounds in drug discovery, which exhibit a diverse range of biological properties such as 5-HT-receptor binding,



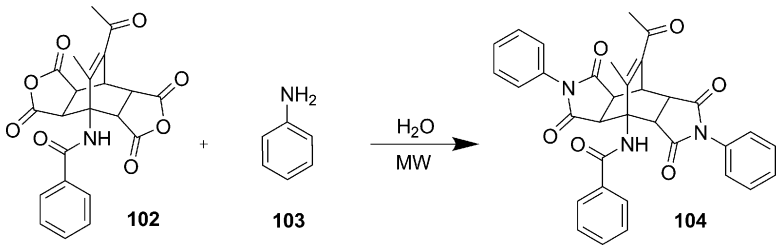
Scheme 28 Mechanism of bis-aldol reaction.



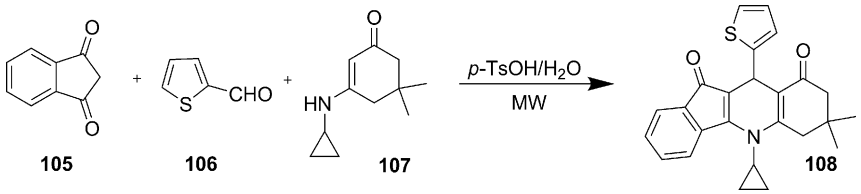
Scheme 29 Synthesis of hydrazone derivatives of furaldehyde and flavanone in water.



Scheme 30 Aqueous protocol for derivatives of bicyclo[2.2.2]oct-7-enes synthesis.



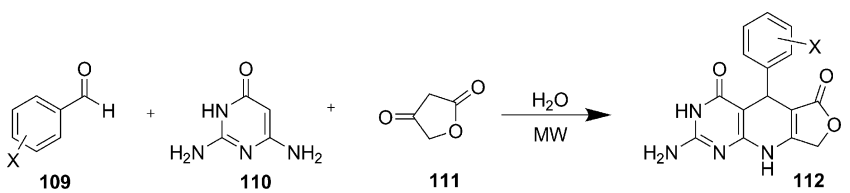
Scheme 31 Aqueous protocol for chemoselective synthesis of succinimide derivatives.



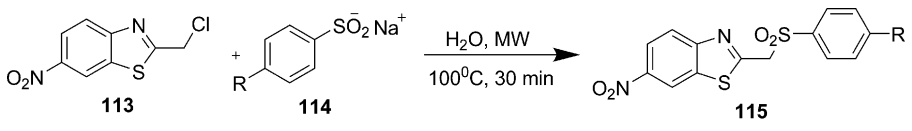
Scheme 32 Aqueous protocol for indenoquinoline derivatives.

antitumor agents, antimalarials and potential topo I/II inhibitors. Tu and co-workers developed the synthesis of these molecules *via* three-component reaction between aldehydes, 1,3-indanedione and enaminones (Scheme 32) in aqueous medium.[55] This reaction was catalyzed by *p*-toluene sulfonic acid (*p*-TsOH) under MW irradiation conditions, with high yield of product in 3–7 minutes. The synthesis of a series of related furo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine derivatives (**112**) was also accomplished by three-component reactions between an aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one, and tetronic acid/indane-1,3-dione, without using any catalyst (Scheme 33).[56]

The benzothiazole nucleus is an important building-block in various synthetic drugs and displays a broad biological spectrum of activities such as antiparasitic, antibacterial, antiviral and cytotoxic properties, *e.g.* 2-(4-aminophenyl)benzothiazoles showed excellent antitumour activities and represent a pharmacotherapeutic group different from clinically used anticancer agents. The sulfonyl derivative of benzothiazole (**115**) was prepared in water using MW heating (Scheme 34) wherein addition of 2-chloromethyl-6-nitrobenzothiazole (**113**) and the sodium salt of benzenesulfinic acid (**114**) in an aqueous solution followed by 30 min MW irradiation at 100 °C, gave the corresponding product in 70–90% yield.[57]



Scheme 33 Aqueous protocol for pyrimidine derivatives.



Scheme 34 Aqueous MW protocol for the sulfonyl-derivative of benzothiazole.

Conclusion

The demand for green 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, in part, through the development of aqueous synthetic protocols using MW heating. However, the paucity of success in implementing these aqueous protocols in large-scale operations leaves the area wide open for a considerable amount of research.

Acknowledgements

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References

1. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 2000.
2. M. Poliakoff and P. Licence, *Nature*, 2007, **450**, 810–812.
3. V. Polshettiwar and R. S. Varma, *Pure Appl. Chem.*, 2008, **80**, 777–790.
4. J. H. Clark and S. J. Tavener, *Org. Process Res. Dev.*, 2007, **11**, 149–155.
5. R. S. Varma, *Green Chem.*, 1999, **1**, 43–55.
6. N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123–150.
7. C. J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68–82.
8. Y. Zhang, B. R. Bakshi and E. SahleDemessie, *Environ. Sci. Technol.*, 2008, **42**, 1724–1730.
9. A. Loupy and R. S. Varma, *Chim. Oggi*, 2006, **24**, 36–40.
10. M. A. Herrero, J. M. Kremsner and C. O. Kappe, *J. Org. Chem.*, 2008, **73**, 36–47.
11. C. Antonio and R. T. Deam, *Phys. Chem. Chem. Phys.*, 2007, **9**, 2976–2982.
12. C. R. Strauss and R. W. Trainor, *Aust. J. Chem.*, 1995, **48**, 1665–1692.
13. V. Polshettiwar and R. S. Varma, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 723–737.
14. V. Polshettiwar and R. S. Varma, *Acc. Chem. Res.*, 2008, **41**, DOI: 10.1021/ar700238s.
15. D. Dallinger and C. O. Kappe, *Chem. Rev.*, 2007, **107**, 2563–2591.
16. R. F. Heck and J. P. Nolly, *J. Org. Chem.*, 1972, **37**, 2320–2322.
17. N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, **36**, 3437–3440.
18. V. Polshettiwar and A. Molnar, *Tetrahedron*, 2007, **63**, 6949–6976.
19. N. E. Leadbeater and M. Marco, *J. Org. Chem.*, 2003, **68**, 888–892.
20. M. D. Crozet, C. Castera-Ducros and P. Vanelle, *Tetrahedron Lett.*, 2006, **47**, 7061–7065.
21. R. Zhu, F. Qu, G. Quéléverb and L. Peng, *Tetrahedron Lett.*, 2007, **48**, 2389–2393.
22. K. M. Dawood, *Tetrahedron*, 2007, **63**, 9642–9651.
23. S.-S. Yi, D.-H. Lee, E. Sin and Y.-S. Lee, *Tetrahedron Lett.*, 2007, **48**, 6771–6775.
24. R. K. Arvela and N. E. Leadbeater, *J. Org. Chem.*, 2005, **70**, 1786–1790.
25. R. K. Arvela, S. Pasquini and M. Larhed, *J. Org. Chem.*, 2007, **72**, 6390–6396.
26. P. Appukkuttan, W. Dehaen and E. V. der Eycken, *Eur. J. Org. Chem.*, 2003, 4713–4716.
27. E. Alacida and C. Nájera, *Adv. Synth. Catal.*, 2006, **348**, 2085–2091.
28. N. Kaval, K. Bisztray, W. Dehaen, C. O. Kappe and E. Van der Eycken, *Mol. Diversity*, 2003, **7**, 125–133.
29. M. Arfan, R. Khan, S. Anjum, S. Ahmad and M. I. Choudhary, *Chin. Chem. Lett.*, 2008, **19**, 161–165.
30. S. Röttger, P. J. R. Sjöberg and M. Larhed, *J. Comb. Chem.*, 2007, **9**, 204–209.
31. X. Wu and M. Larhed, *Org. Lett.*, 2005, **7**, 3327–3329.
32. A. Miyazawa, K. Tanaka, T. Sakakura, M. Tashiro, H. Tashiro, G. K. Surya Prakash and G. A. Olah, *Chem. Commun.*, 2005, 2104–2106.
33. S. Tu, R. Jia, B. Jiang, J. Zhang, Y. Zhang, C. Yaoa and S. Jib, *Tetrahedron*, 2007, **63**, 381–388.
34. A. Procopio, M. Gaspari, M. Nardi, M. Oliverio, A. Tagarellib and G. Sindona, *Tetrahedron Lett.*, 2007, **48**, 8623–8627.
35. G.-R. Qu, L. Zhao, D.-C. Wang, J. Wu and H.-M. Guo, *Green Chem.*, 2008, **10**, 295–297.
36. V. Kumar, A. Sharma, A. Sharma and A. K. Sinha, *Tetrahedron*, 2007, **63**, 7640–7646.
37. V. Pironti and S. Colonna, *Green Chem.*, 2005, **7**, 43–45.
38. L. Garuti, M. Roberti and D. Pizzirani, *Mini-Rev. Med. Chem.*, 2007, **7**, 481–489.
39. J. B. Sperry and D. L. Wright, *Curr. Opin. Drug Discovery Dev.*, 2005, **8**, 723–740.
40. C. O. Kappe, *Curr. Opin. Chem. Biol.*, 2002, **6**, 314–320.
41. Y. Ju and R. S. Varma, *Tetrahedron Lett.*, 2005, **46**, 6011–6014.
42. Y. Ju and R. S. Varma, *Org. Lett.*, 2005, **7**, 2409–2411.
43. Y. Ju and R. S. Varma, *J. Org. Chem.*, 2006, **71**, 135–141.
44. F. Jam, M. Tullberg, K. Luthman and M. Grøtli, *Tetrahedron*, 2007, **63**, 9881–9889.
45. M. Kidwai, Priya, K. Singhal and S. Rastogi, *Heterocycles*, 2007, **71**, 569–576.
46. Y. Ju and R. S. Varma, *Green Chem.*, 2004, **6**, 219–221.
47. J.-J. Shie and J.-M. Fang, *J. Org. Chem.*, 2007, **72**, 3141–3144.
48. I. Saltsman and Z. Gross, *Tetrahedron Lett.*, 2008, **49**, 247–249.
49. V. Polshettiwar and R. S. Varma, *Tetrahedron Lett.*, 2007, **48**, 7343–7346.
50. Q. Zhuang, R. Jia, S. Tu, J. Zhang, B. Jiang, Y. Zhang and C. Yao, *J. Heterocycl. Chem.*, 2007, **44**, 895–900.
51. V. Polshettiwar and R. S. Varma, *J. Org. Chem.*, 2007, **72**, 7420–7422.
52. V. Polshettiwar and R. S. Varma, *Tetrahedron Lett.*, 2007, **48**, 5649–5652.
53. M. Martelanc, K. Kranjc, S. Polanc and M. Kočevar, *Green Chem.*, 2005, **7**, 737–741.
54. J. Hren, K. Kranjc, S. Polanc and M. Kočevar, *Synthesis*, 2008, 452–458.
55. S.-J. Tu, B. Jiang, J.-Y. Zhang, R.-H. Jia, Y. Zhang and C.-S. Yao, *Org. Biomol. Chem.*, 2006, **4**, 3980–3985.
56. S.-J. Tu, Y. Zhang, H. Jiang, B. Jiang, J.-Y. Zhang, R.-H. Jia and F. Shi, *Eur. J. Org. Chem.*, 2007, 1522–1528.
57. A. Gellis, N. Boufatah and P. Vanelle, *Green Chem.*, 2006, **8**, 483–487.