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RECENT ADVANCES IN THE CYCLIZATION OF *N*-HETEROCYCLES: THE ROLE OF ENABLING TECHNIQUES (REVIEW)

The so-called "enabling techniques" can dramatically promote the synthesis of *N*-heterocycles. Besides facilitating very quick cyclization, these technologies bring with them process intensification, safer protocols, cost reduction, energy savings, and waste minimization. We herein describe a series of efficient *N*-heterocycle cyclizations carried out under microwave and/or ultrasound irradiation.

Keywords: *N*-heterocycles, cyclization, enabling techniques, microwaves, ultrasound.

Nowadays, the production of fine chemicals, including *N*-heterocyclic compounds, requires new, cheaper and more environmentally sustainable technologies which utilize heterogeneous catalysis and also give due importance to reactor engineering aspects and non-conventional energy sources. Chemical reactions on the lab scale are typically heated using hot plates under stirring which has proved to be a rather slow and inefficient method for promoting heat and mass transfer. In conventional processes, heat is transferred to reagents by convection, conduction and radiation phenomena through the external material surface in the presence of thermal gradients. In contrast, microwave (MW) heating leads to efficient internal heating with a homogeneous heating profile. In dielectric heating, energy transfer occurs by dipole rotation and ionic conduction *via* dipole reversal and the displacement of charged ions present in the reaction mixture. The efficiency of MW irradiation used in chemical syntheses is strictly related to the conversion of electromagnetic energy to heat. MW heating, if properly applied, dramatically enhances the rate of most chemical reactions by 10 to 1000 times. This remarkable acceleration can be achieved under either MW or simultaneous MW/ultrasound (US) irradiation and has caused an impressive reduction in catalyst loading in several types of chemical reactions. In fact, when extremely low catalyst amounts are used, reaction rate is often too low and space time yield decreases [1, 2]. The use of dielectric heating to promote chemical reactions is now well established as a reliable technique which can be applied on a range of scales, from milliliters to kilograms [3]. High-intensity US induces strong acoustic cavitation and streaming which enable efficient mixing, catalyst surface activation, and particle dispersion to occur [4]. Their ability to enhance reaction rates, yields, and selectivity may become additive when US is used in combination with MW [5], either in a sequential or simultaneous fashion as has been revealed in recent examples from the literature [6].

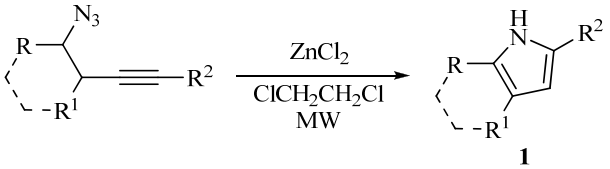
The formation of *N*-heterocycles is of particular interest in organic syntheses because these structures are often embedded in bioactive natural compounds and pharmaceutical products. Cyclization reactions require efficient catalysts and suitable physical activation. Herein, a series of recent examples of efficient MW- or US-assisted *N*-heterocycle synthesis is reported.

* Здесь и далее в номере фамилия автора, с которым следует вести переписку, отмечена звёздочкой.

CYCLIZATION UNDER MICROWAVES

Lewis acids and clays

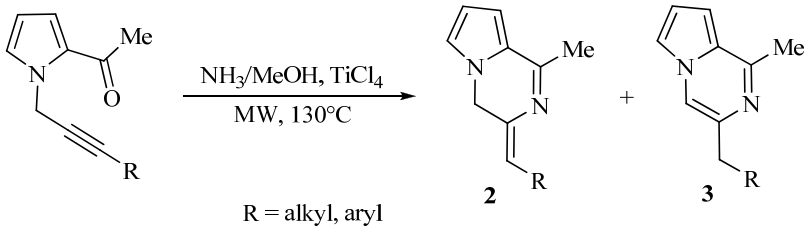
The syntheses of pyrroles and their *N*-substituted derivatives under non-conventional conditions have been widely described in the literature. Due to relatively easy access, azides are useful starting materials for cyclization and lead to the expulsion of N_2. Wyrebek *et al*. [7] have described a fast MW-assisted synthesis of substituted pyrroles from but-3-yn-1-yl azides, using $ZnCl_2$ etherate as catalyst. The ligand-free 5-*endo-dig* cyclization of 1,4-di- and 1,2,4-trisubstituted but-3-yn-1-yl (homopropargyl) azides in dichloroethane at elevated temperature provides 2,5-di- and 2,3,5-trisubstituted pyrroles **1** in good yields. Zinc is much cheaper than other metal catalysts, such as Au/Ag or Pt. It does, however, require higher reaction temperatures, indicating that it is not as able to stabilize a cyclic cationic intermediate as other metal catalysts.



1

R, R^1, R^2 = alkyl, cycloalkyl, aryl

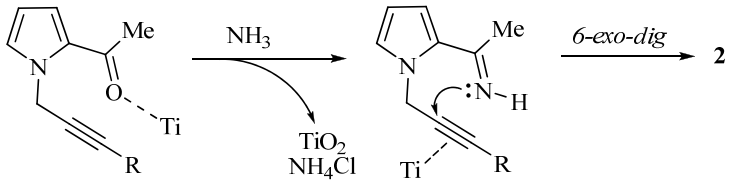
This versatile method facilitates the insertion of any kind of substituent into the heterocyclic ring (aryl, alkyl, or cycloalkyl group). Alfonsi *et al*. [8] have described the regioselective MW-assisted synthesis of pyrazino[1,2-*a*]indole. The reaction consists of the sequential imination/annulation of 2-carbonyl-*N*-propargylindoles in a slight $TiCl_4$ excess in ammonia solution in methanol. This approach has been investigated as a means to construct the pyrrolo[1,2-*a*]pyrazine nucleus from *N*-alkynylpyrroles.



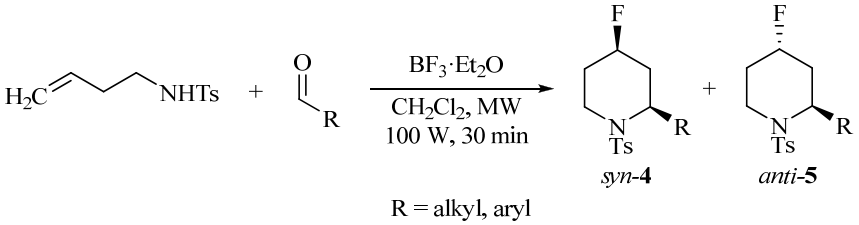
2 **3**

R = alkyl, aryl

The proposed mechanism involves the Lewis acid catalyzed formation of the imine intermediate which undergoes a stereoselective 6-*exo-dig* cyclization at the triple bond, which is either activated by $TiCl_4$ itself or by a catalytically active species generated *in situ* from $TiCl_4$ and ammonia [8]. The annulation step gives 3,4-dihydropyrrolo[1,2-*a*]pyrazines **2**, which can isomerize to the thermodynamically more stable pyrrolo[1,2-*a*]pyrazines **3** (yields 40–85%). MW irradiation strongly increased reaction rate, yield and selectivity as compared to conventional heating.

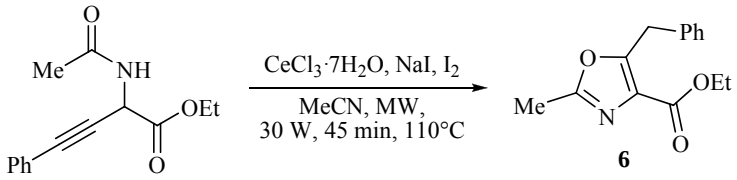


The selective incorporation of a C–F bond plays a pivotal role in pharmaceutical and material chemistry. This can be achieved using $BF_3 \cdot OEt_2$ as the Lewis acid in the Prins cyclization reaction. Launay *et al.* [9] have exploited a MW-assisted aza-Prins reaction of *N*-tosylhomoallylic amines to generate the corresponding 4-fluoropiperidines **4** and **5**.

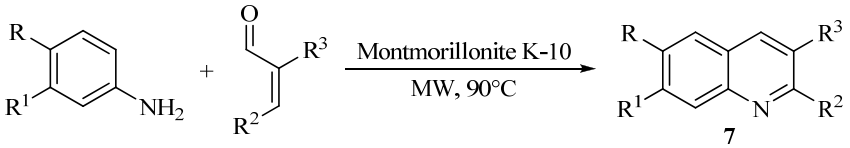


Despite poor diastereoselectivity (generally 1.2–1.9 : 1 *syn*/*anti*), conversions were good (60–85%) [9].

Functionalized polysubstituted oxazoles are an important class of five-membered N,O-heterocycles that occur widely in the structures of natural products and fine chemicals. In recent years, cerium trichloride-promoted carbon–carbon and carbon–heteroatom bond-forming methodologies have become central tools for the synthesis of biologically active molecules. In particular, the combination of $CeCl_3 \cdot 7H_2O$ and NaI can promote the cyclization of functionalized propargyl amides to oxazoles **6**, which are otherwise inaccessible by conventional routes. Bartoli *et al.* [10] have published a rapid and efficient MW-assisted synthesis of oxazoles *via* the 5-*exo*-*dig* cyclization of functionalized *N*-propargyl carboxamides. It was observed, after a range of conditions were screened, that the addition of iodine gave higher selectivity and better yields: the resulting monomeric $CeCl_3 \cdot 7H_2O$–NaI–I_2 complex is a stronger Lewis acid promoter.



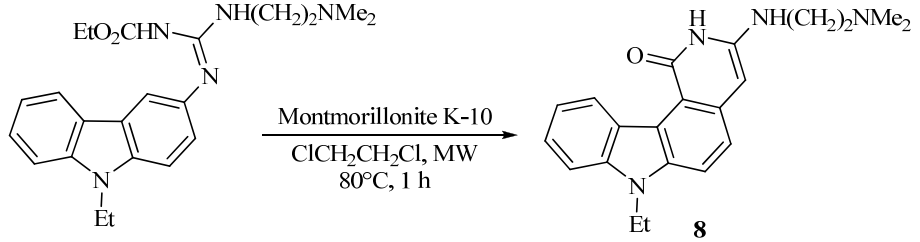
The environmental concern over traditional mineral acids and Lewis acids has prompted their replacement by solid acids as safer alternatives. Clays, zeolites, metal oxides, and acidic ion-exchange resins have become the catalysts of choice in research laboratories and industrial processes. These catalysts are stable, easy to store and handle and do not produce hazardous waste, moreover, the application of such heterogeneous catalysts at MW conditions entails a reduction in solvent use. Commercially available montmorillonite K-10, a stable, inexpensive, and strong solid acid which is active under MW, is certainly worthy of mention. De Paolis *et al.* [11] have described an environmentally benign MW-assisted solid acid-catalyzed synthesis of quinolines **7** from anilines and cinnamaldehydes. The catalyst ensures effective condensation and cyclization and promotes aromatization to the final product. The use of this green catalyst results in a one-pot process during which the solvent-free cyclization and oxidation steps readily take place in a domino process. The same reaction was very slow under conventional heating, whereas dielectric heating provided the products in good to excellent yields and selectivity in just a few minutes.



7

R, R^1 = H, alkyl, halogen; R^2 = aryl; R^3 = H, alkyl

The carbazole nucleus is very important in drug design. The pyrido[4,3-*b*]-carbazole family and pyrimido[4,5-*b*]carbazole analogs have been extensively studied. Debray *et al*. [12] have reported the synthesis of pyrimido[4,5-*c*]carbazole **8** and pyrimido[5,4-*b*]indole **9** using an original methodology.



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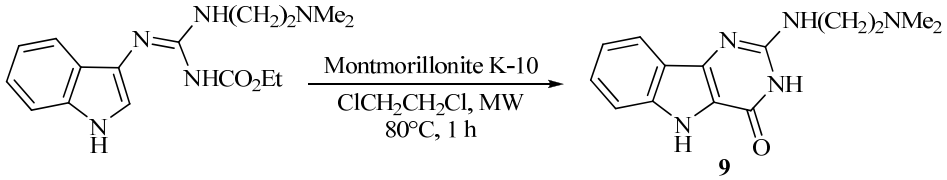
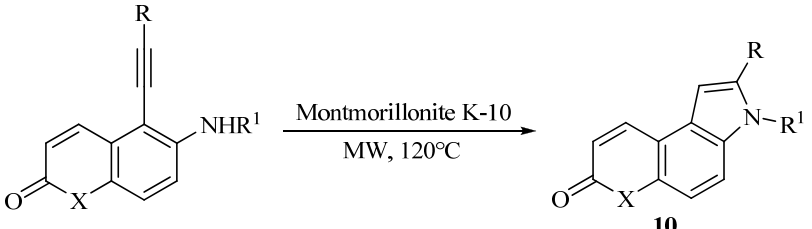


9

The key step of the synthesis is a Friedel–Crafts type cyclization of ethoxy-carbonyl-protected guanidine intermediates in which the Lewis acid catalyst (halosilanes or $AlCl_3$) is replaced by the acidic montmorillonite K-10 clay [12]. The reaction mixture was heated at 80°C in dichloroethane and required a prolonged reaction time (24 h), while MW irradiation shortened the time to 1 h and enabled the procedure to be carried out in the absence of solvent. This efficient method can also be used for the synthesis of substituted pyrano[3,2-*e*]indolone and pyrrolo[3,2-*f*]quinolones.

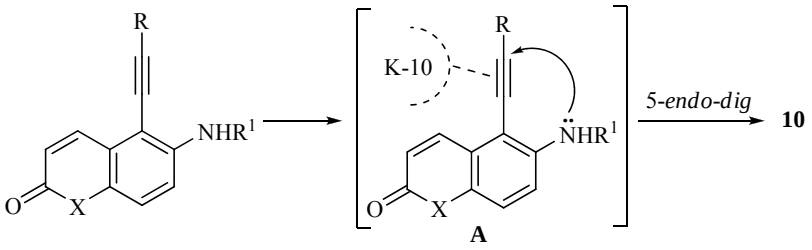
Majumdar *et al*. [13] studied the cycloisomerization of coumarin and quinolone to pyranoindolone and pyrroloquinolone **10** and compared the effects of conventional and dielectric heating on the reaction (CEM Discover). The reactions gave much higher yields under MW (96%, 120°C, in 15 min *vs* 70–84% yield under classic heating at 90–120°C for 90 min). It was found that both aromatic and aliphatic substituents are equally as effective in the terminal alkyne position.



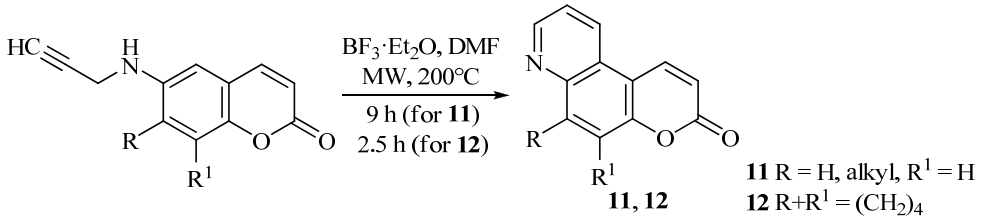
10

R = alkyl, aryl; R^1 = H, alkyl; X = O, NMe

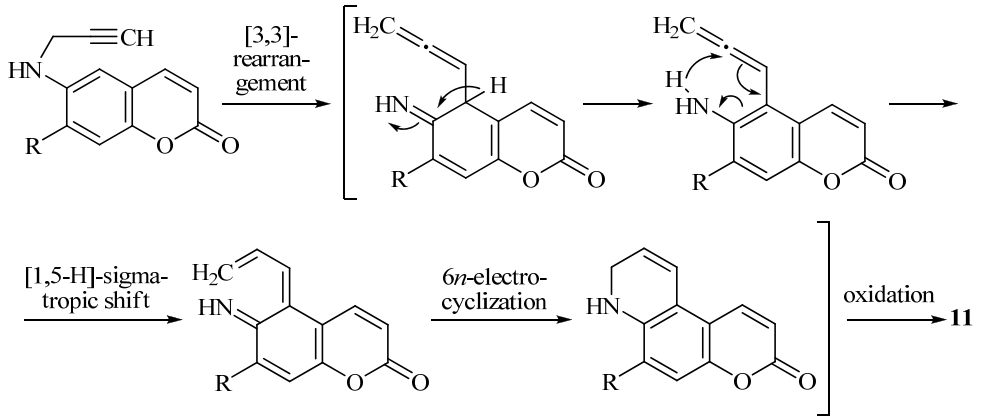
Initially, the montmorillonite K-10 may activate the triple bond of the alkyne to give an intermediate **A** [13]. The resulting electron-deficient triple bond undergoes intramolecular nucleophilic attack by the less basic nitrogen of the amine group to give products **10** *via* a 5-*endo-dig* cyclization, because the 4-*exo-dig* cyclization is disfavored.



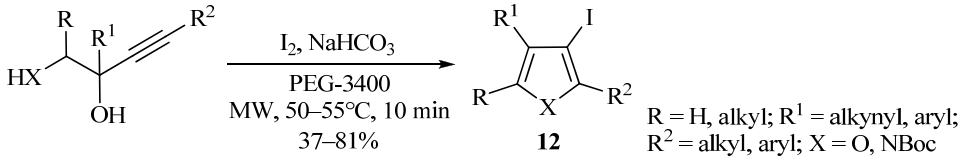
Symeonidis *et al*. [14] prepared [5,6]-fused pyranoquinolines **11** and **12** *via* an aza-Claisen rearrangement and the subsequent *in situ* cyclization of 6-propargyl-aminocoumarins under MW irradiation in the presence of boron trifluoride diethyl etherate in DMF.



The overall mechanism proposed for the cyclization that leads to fused pyrano-quinolines involves the initial [3,3]-rearrangement of propargylaminocoumarin to the allenyl intermediate which then undergoes aromatization to the *o*-aminoallenyl derivative [14]. A [1,5-H]-shift leads to vinylmethylidene imine intermediate, which cyclizes to the dihydropyridine nucleus and then undergoes oxidization to pyranoquinoline **11**.



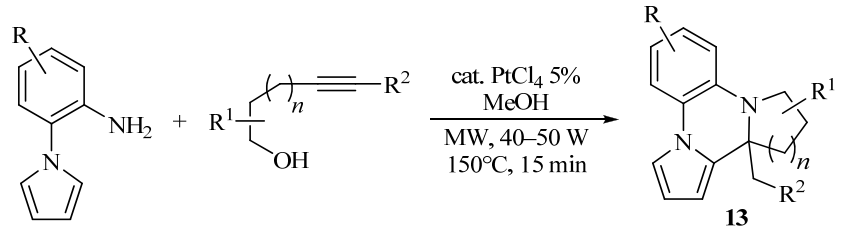
A green version of the iodocyclization of a series of alk-3-yne-1,2-diols and 1-(Boc-amino)-2-hydroxyalk-3-ynes carried out to give iodofurans or iodopyrroles **12**, respectively, has been reported by Spina *et al*. [15]. They used solid poly-ethyleneglycol PEG-3400 in the electrophilic iodo-mediated cyclization reaction of either diols or *N*-protected 1,2-amino alcohols under MW irradiation. In the course of this reaction, the C≡C triple bond on the substrate was activated by the electrophilic halogenating reagent (I^+), and then underwent a 5-*endo-dig* intramolecular cyclization triggered by the O- or N-nucleophile.



This method was extended to other substrates, such as β-amino alcohols bearing aromatic or aliphatic substituents on the triple bond. This rapid (only 10 min) and eco-friendly MW-assisted protocol has opened a straightforward synthetic route to pyrrole.

Transition metals

Carbophilic transition metal-catalyzed cascade reactions are a highly attractive synthetic path to polycyclic heterocompounds. Most of them are triggered by the attack of a nucleophile on the C≡C triple bond, which possesses enhanced electrophilicity due to its π-coordination with a transition metal. An example of $PtCl_4$-catalyzed, one-pot, tandem hydroamination – Mannich reaction – dehydratation MW-assisted cyclizations for the synthesis of pyrrolo[1,2-*a*]quinoxalines **13**, indolo[3,2-*c*]quinolines and indolo[1,2-*a*]quinoxalines has been reported by Patil *et al*. [16].

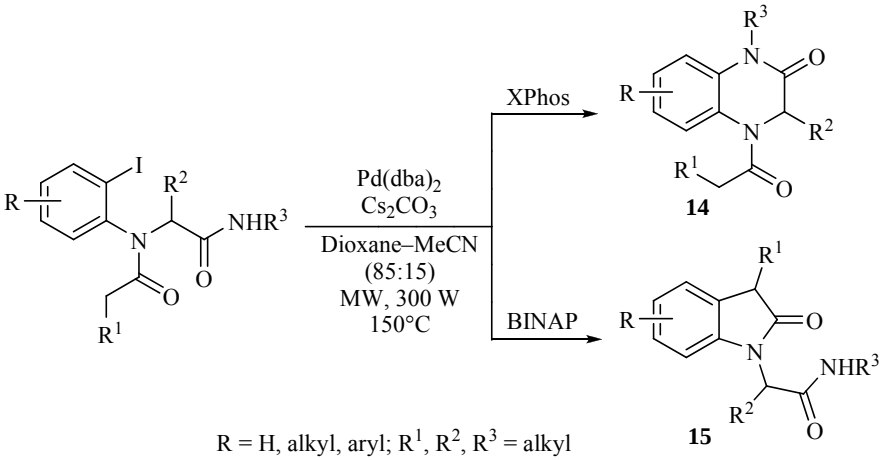


13

n = 1, 2; R = electron withdrawing or donating groups; R^1 = alkyl, aryl; R^2 = H, alkyl

Although the reaction is driven only thermally under MW, cyclization occurred in high yields, while the tetracyclic product was only obtained in a 20% yield in a preheated oil bath at 150°C during the same time.

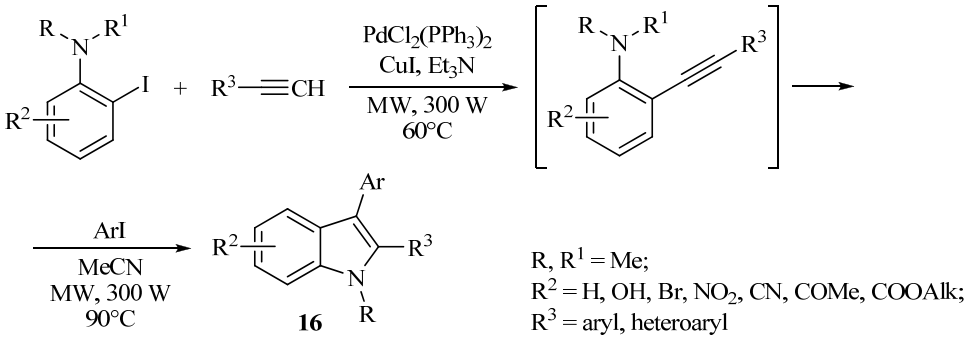
Several MW-assisted Ugi four-component reactions have been described. Erb *et al*. [17] converted linear amides, prepared in a one step four-component reaction, to 3,4-dihydroquinoxalin-2-ones **14** and to 2-(2-oxoindolin-1-yl)acetamides **15** under MW. As shown for the monodentate XPhos (monodentate biaryl monophosphine) and BINAP in the following scheme, the ligand type changed the reaction pathways.



R = H, alkyl, aryl; R^1, R^2, R^3 = alkyl

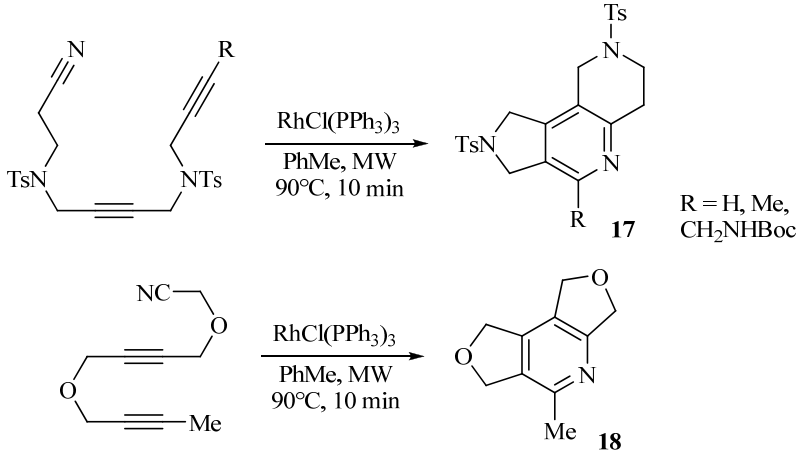
A substantial number of methods for the preparation of indoles have been developed. Of the methods developed so far, palladium-catalyzed indole syntheses have received an extraordinary amount of attention due to the relatively mild reaction conditions employed in the processes and the fact that they usually tolerate

a wide variety of functional groups thus avoiding protecting group chemistry. High regioselectivities and chemical yields are also generally achieved. Recently, Larock and coworkers [18] have reported a MW-assisted, one-pot, three-component reaction to synthesize substituted indoles **16** using the Sonogashira coupling.



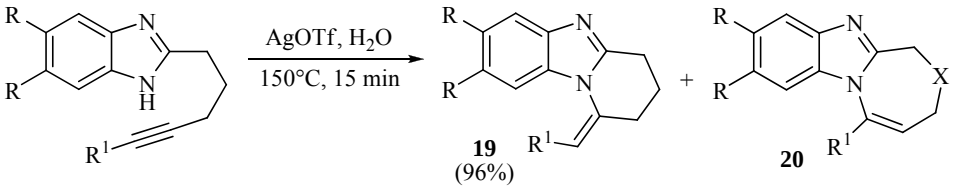
A variety of functionalities such as nitro, ester, hydroxyl, cyano and halide groups are all tolerated in this coupling/cyclization process. The desired indoles were obtained in good overall yields, making this MW-assisted procedure an ideal synthetic approach for the parallel synthesis of an indole library.

Transition-metal-catalyzed [2+2+2]-cycloadditions are very useful reactions when one wishes to prepare increasingly complex target molecules. The preparation of complex polycyclic pyridine derivatives is a major goal because these compounds have taken on an important role in various fields of research. Cycloaddition between two alkynes and a nitrile is one of the most powerful methods for creating a large number of substituted pyridines. The [2+2+2]-cycloaddition of cyanodiynes opens the way for the one-step preparation of new polycyclic fused pyridine displaying scaffolds that can be found in naturally occurring bioactive compounds. Garcia *et al*. [19] presented Rh(I)-catalyzed [2+2+2]-cycloaddition reactions of *N*-tosyl-, carbon-, and oxygen-tethered cyanodiynes which gave highly functionalized tricyclic-fused pyridines **17** and **18** using conventional and/or MW heating. The latter was found to favor cycloaddition in shorter reaction times. Furthermore, it was even successful in cases where conventional heating failed altogether.



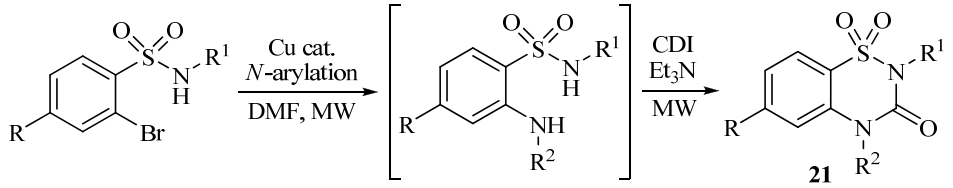
In recent years, Ag(I) salts have been applied as versatile catalysts for the synthesis of functionalized heterocycles, such as isoquinolines, (2*H*)-1,2-oxaphosphorin 2-oxides and 5-substituted proline derivatives. Zhang *et al*. reported the synthesis of fused benzimidazoles **19** and **20** *via* an Ag(I)-catalyzed chemo- and

regioselective intramolecular cyclization in aqueous media [20]. Excellent yields were obtained in the presence of AgOTf (5 mol %) in H_2O at 150°C under MW. This efficient, environmentally friendly approach was compatible with several functional groups. Product yields were markedly affected by substituent type and position.



R = H, Cl, Me; R^1 = H, Me, aryl

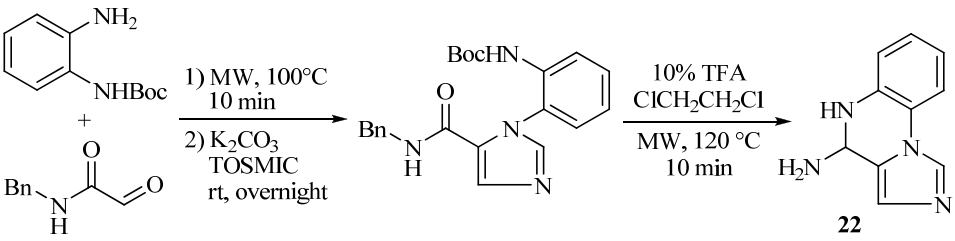
Traditionally, benzothiadiazin-3-one 1,1-dioxides have been synthesized in a number of linear protocols. However, Rolfe and Hanson [21] have developed a MW-assisted, copper-catalyzed, sequential, one-pot synthesis of these compounds. A variety of derivatives of benzothiadiazin-3-one 1,1-dioxides **21** can be rapidly accessed by combining an initial copper-mediated *N*-arylation and a cyclization with carbonyldiimidazole (CDI) in DMF under MW irradiation.

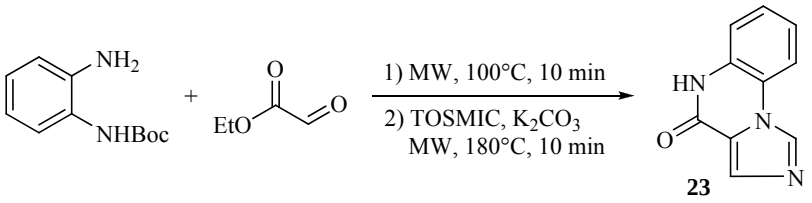


R = H, F; R^1 = allyl, aryl; R^2 = alkyl, OBn

Isonitriles and isocyanates

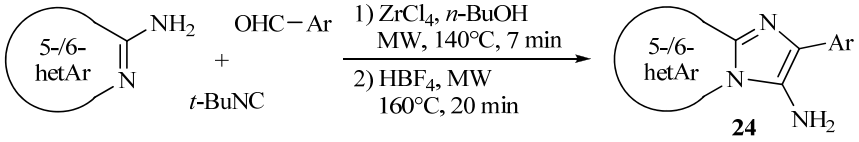
Multicomponent reactions (MCRs), especially isocyanide-based protocols, are an excellent tool for the generation of libraries of N-heterocycles. Tosylmethylisocyanides (TOSMICs) are a valuable and versatile class of synthons and one which is used for the preparation of several families of heterocycles, such as oxazoles, pyrroles, imidazoles, benzofurans, quinoxalines, and pyrrolopyrimidines. De Moliner and Hulme [22] have reported the concise synthesis of two pharmacological compounds that bear an imidazoquinoxaline core **22** and **23**. The protocol involves the use of 1,2-phenylenediamines and ethyl glyoxylate or benzylglyoxamide along with tosylmethylisocyanides in a MW-assisted three-component Van Leusen condensation. An internal aminonucleophile promotes deprotection and cyclization under MW irradiation after the imidazole intermediate is isolated.





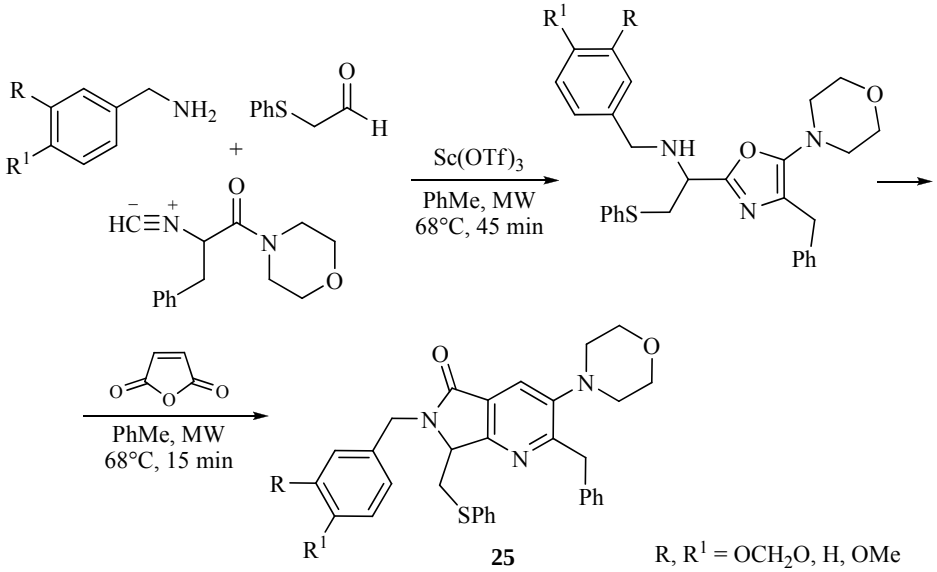
23

The problematic removal of alkyl amine (or aryl amine), which comes from the isocyanide component in the Ugi-MCR product, has led to the development of several convertible isonitriles. The isonitrile component requires a particular alkyl group, which in post-MCR protonolytic dealkylation can generate a highly stable carbocation. The use of *t*-butyl isocyanide as a convertible isonitrile has been attempted for the synthesis of *N*-fused imidazoles. An example of its application can be found in Guchhait and Madaan [23] in their tandem one-step dealkylation of *t*-butylamine in an Ugi-MCR product to afford *N*-fused heterocycles **24**. MW irradiation strongly promoted de-*t*-butylation and gave a much higher product yield.



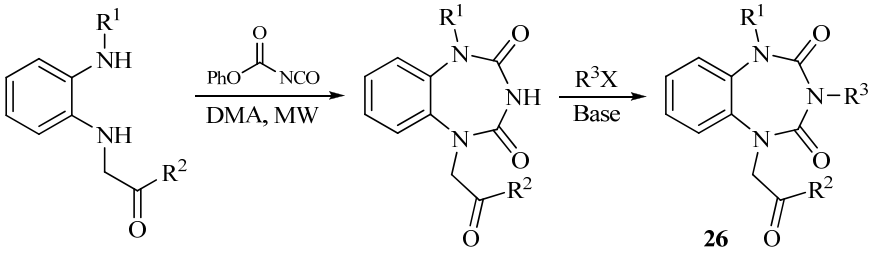
24

Islas-Jácome *et al*. [24] used a multicomponent domino process under MW irradiation, namely a sequence of Ugi-3CR, aza-Diels–Alder cycloaddition, *S*-oxidation and a Pummerer-type cyclization. In the assembling of the three fused rings, seven new covalent bonds were formed with the simultaneous loss of water and CO_2. The use of metal triflates as catalysts promoted the Ugi reaction by activating the imine prior to the isonitrile nucleophilic attack. The use of $Sc(OTf)_3$, in particular, gave the highest yield. In spite of the molecular complexity of such pyrrolopyridinone nuclei **25**, yields were good in all cases. The versatility of this polyheterocycle synthesis is well suited to diversity-oriented approaches.



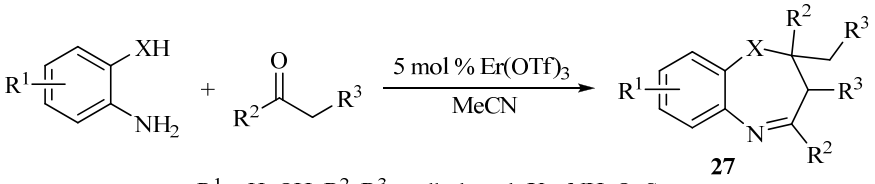
25

Chuckowree *et al*. [25] have published a MW-assisted synthesis of a novel library of 1,3,5-benzotriazepine-2,4-diones (1,3,5-BZT) **26**, using amide coupling reactions. The synthesis of the 1,3,5-BZT scaffold was achieved as shown below.

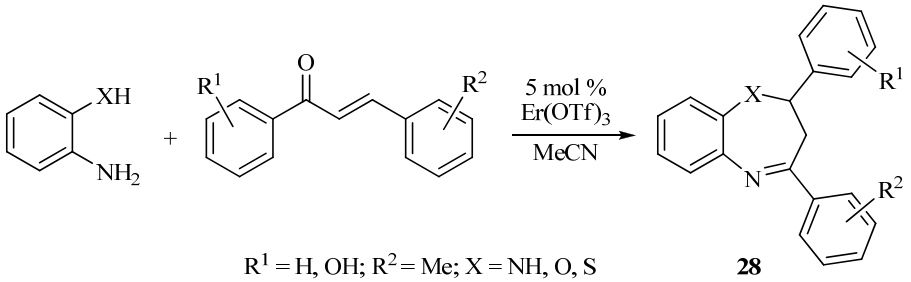


R^1 = aryl; R^2 = OBn, O-*t*-Bu; R^3 = H, alkyl

Procopio *et al*. [26] have reported a green synthetic protocol that uses lanthanide(III) derivatives and MW irradiation to synthesize substituted benzoheteroazepines **27** and **28** in very mild conditions. They identified $Er(OTf)_3$ as an effective catalyst for the MW-assisted condensation of *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol with several ketones or chalcone derivatives and products were obtained in good yields.

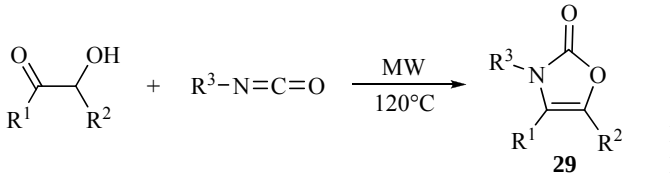


R^1 = H, OH; R^2, R^3 = alkyl, aryl; X = NH, O, S



R^1 = H, OH; R^2 = Me; X = NH, O, S

Santoyo *et al*. [27] have reported a new method for the synthesis of 4-oxazolin-2-ones **29** *via* the one-pot MW-promoted condensation of α-ketols and isocyanates. In contrast to the previously reported two-step methods, this was a single-step solvent-free procedure which provided much higher yields (ca. 77%) and a very simple isolation procedure.

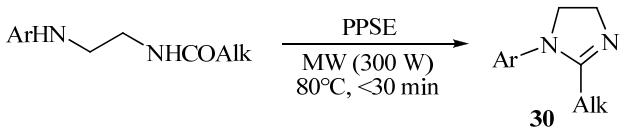


R^1, R^2 = H, alkyl;
R^3 = alkyl, aryl

Other examples

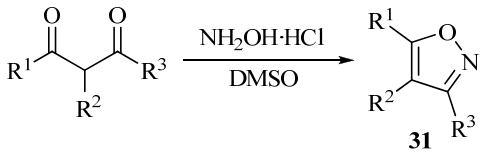
The classical method for the synthesis of imidazoline nucleus is the condensation of substituted 1,2-diaminoethane derivatives with carboxylic acids or derivatives such as esters, orthoesters, and nitriles at high temperatures. 2-Imidazolines have also been obtained *via* the [3+2]-cycloaddition of aziridines and nitriles as well as *via* multicomponent synthesis. MW irradiation strongly accelerates all these reactions and minimizes product thermal decomposition. The

MW-assisted synthesis of 2-alkyl-1-aryl-4,5-dihydro-1*H*-imidazoles **30** involves the ring closure of *N*-acyl-*N'*-arylethylenediamines by trimethylsilyl polyphosphate (PPSE). Reverdito *et al.* [28] optimized this cyclization using a MW oven at 80°C (300 W) achieving 78–98% yields in less than 30 min.



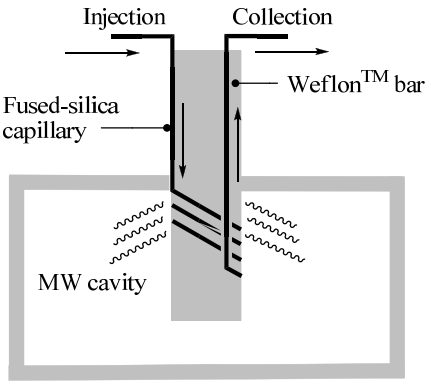
30

3,5-Disubstituted and 3,4,5-trisubstituted 1,2-isoxazole derivatives **31** have been efficiently prepared using MW by Rodriguez *et al.* [29]. The method involved the use of a continuous-flow microreactor, under MW irradiation, that gave complete conversion in just a few minutes at moderate temperatures (Figure).



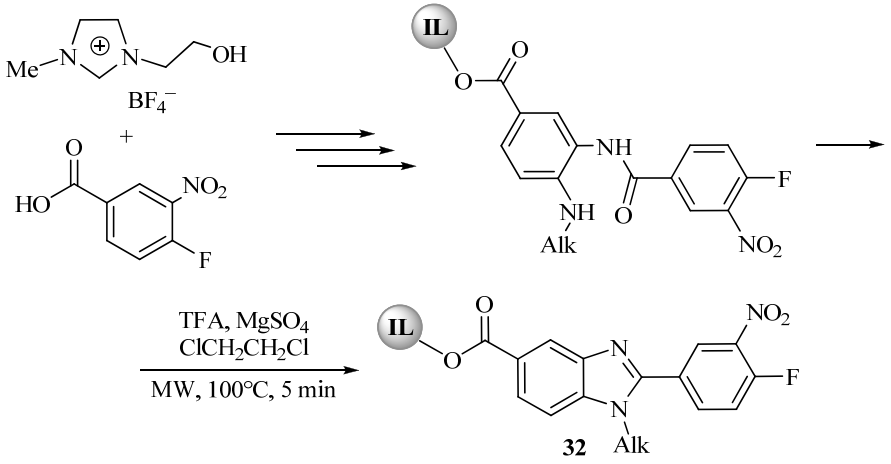
31

R^1, R^3 = alkyl, Ph; R^2 = H, alkyl



Continuous-flow MW microreactor

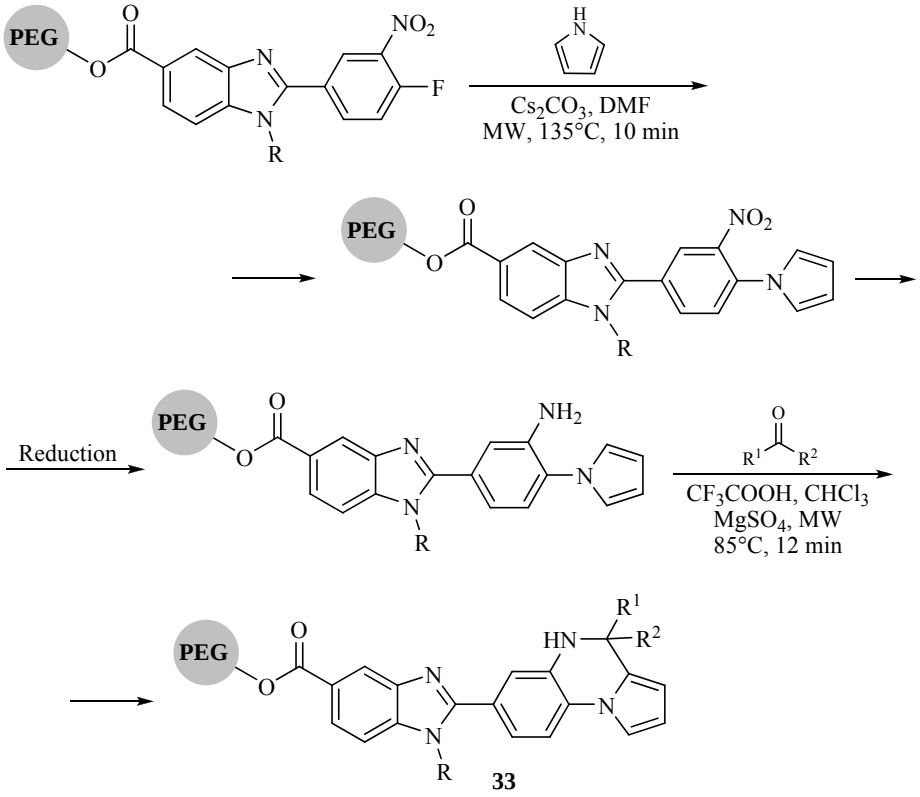
Thummanagoti *et al.* [30] have successfully developed a rapid MW-assisted procedure for the synthesis of benzimidazole-linked pyrrolo[1,2-*a*]benzimidazolones, pyrido[1,2-*a*]benzimidazolones and isoindolo[1,2-*a*]benzimidazoles. The cascade reactions of ionic liquid-bound substrates were used for the preparation of skeletally diverse biheterocyclic molecular libraries.



32

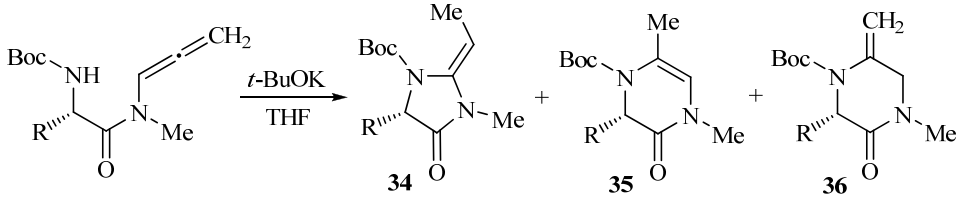
Maiti and Sun [31] have successfully developed a novel application of the Pictet–Spengler reaction and have used it for the efficient synthesis of biologically promising derivatives of benzimidazolylpyrrolo[1,2-*a*]quinoxaline **33**. The MW-

assisted reaction was carried out in soluble PEG. A linear sequence of nucleophilic aromatic substitution, nitro-reduction and the Pictet–Spengler cyclization were used to create easier access to benzimidazole linked pyrroloquinoxalines. The combination of less active aromatic amine functionality and pyrrole or indole moieties with ketones are the key features of this unconventional Pictet–Spengler cyclization. The variety of ketones used brought additional diversity into the targeted skeleton along with the introduction of a spiro junction. The use of this MW-promoted Pictet–Spengler cyclization on a soluble polymer support opens up a new pathway to the efficient synthesis of related, diversified biheterocycles. This is the first example of a pyrrole ring nucleophilic aromatic substitution reaction directly on an aromatic substrate that is followed by a Pictet–Spengler type reaction.



R = H, Me; R^1, R^2 = alkyl or R^1+R^2 = cycle

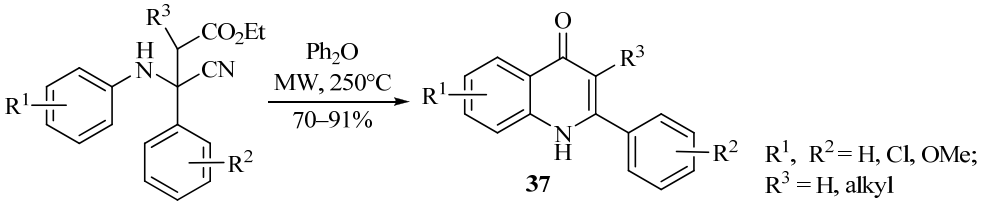
The peculiar reactivity of allenes has set them out as optimal starting materials for this field, a fact that has been well shown by Broggini *et al*. [32] in the cyclization of allenylamides derived from the *N*-propargylamides of α-aminoacids. These *N*-allenylamides give heterocycles **34**–**36** *via* the NH group attack on the inside C–C double bond of the 1,2-diene moiety in a basic medium.



R = *i*-Pr, *i*-Bu, Bn

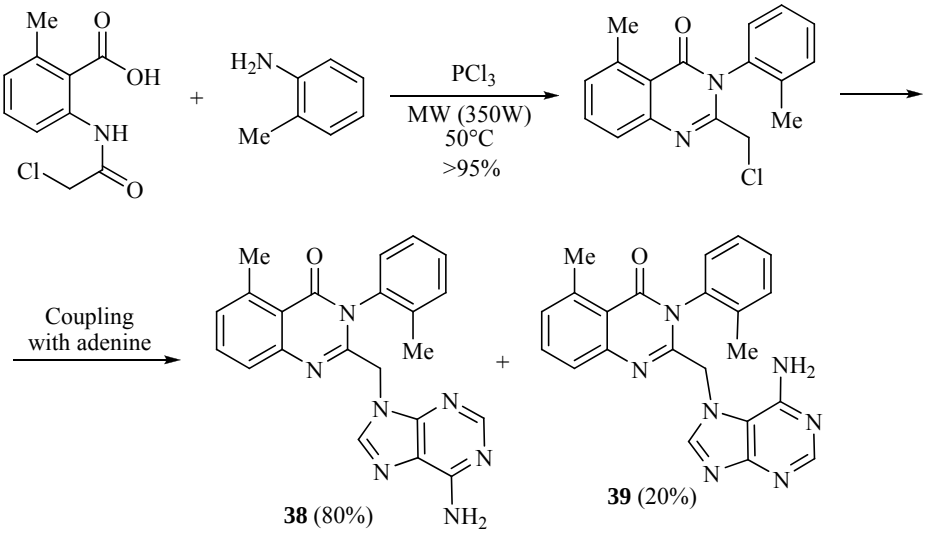
Reactions carried out at room temperature gave a complex product mixture with a moderate yield (60%), while under MW irradiation the heterocyclization processes was faster and cleaner, exclusively affording the six-membered ring products .

A number of protocols have been developed for the preparation of 4-quinolones. A classic and widely employed approach is the Conrad–Limpach synthesis from anilines and β-ketoesters. Romek and Opatz described the MW-assisted synthesis of 4-quinolones **37** by cyclization of α-alkylated *N*-arylaminonitrile derivatives [33].



Under MW irradiation, complete conversion occurred in 10–30 min instead of the possible 12 h needed with traditional heating.

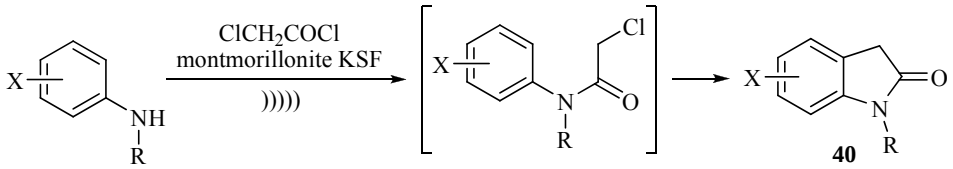
Quinazolinones are a class of heteroaromatic compounds that have drawn a great deal of attention because of their biological and pharmacological properties. Sawant *et al*. [34] prepared the quinazolinone ring, and thereafter, subsequent conjugation with adenine in the same pot gave purine quinazolinone compounds **38** and **39** in excellent total yield under MW irradiation.



CYCLIZATION UNDER ULTRASOUND

Clays

Dandia *et al*. have reported an efficient one-pot clay-catalyzed synthesis of 3-unsubstituted oxindoles under sonochemical conditions [35]. The reaction of substituted anilines with chloroacetyl chloride, and the intramolecular Friedel–Crafts reaction of the α-chloroacetanilide generated *in situ*, lead to a facile synthesis of a wide variety of substituted oxindoles **40**, while avoiding typical harsh reaction conditions.



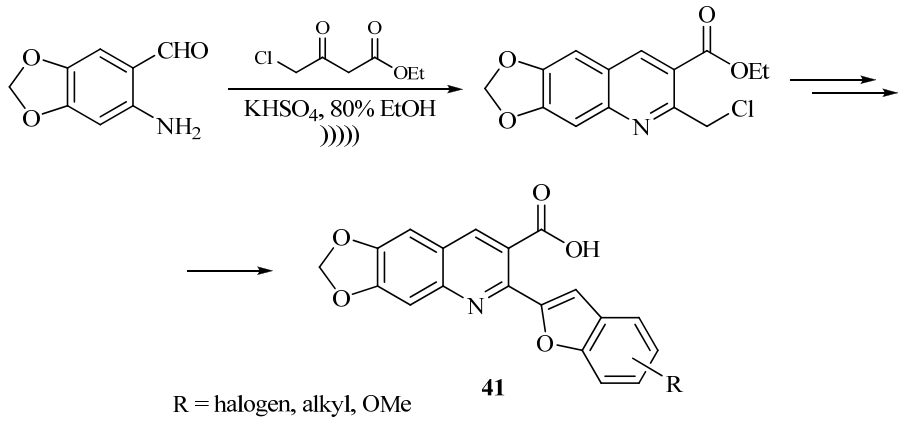
R = H, alkyl; X = alkyl, halogen, NO_2;
))))) = ultrasound

Various inorganic supports such as acidic alumina, silica gel and montmorillonite KSF have all been investigated. The latter was found to be the catalyst of choice and thus the use of classic Lewis acids in solution was avoided. This rapid US-assisted reaction gave excellent yields (93%). The KSF clay was also recovered, washed with methanol and reused several times without any significant loss in activity. This method tolerates both electron withdrawing and electron donating substituents.

The model reaction carried out under plain stirring in silent conditions failed and afforded only the α-chloroacetanilide intermediate without any cyclization, even after prolonged heating. Thus, US irradiation not only facilitated the reaction to completion, but also significantly increased the yield of the required oxindole derivatives.

Other examples

Gao *et al.* [36] have reported a facile procedure under mild conditions for the preparation of 2-(benzofuran-2-yl)-6,7-methylenedioxyquinoline-3-carboxylic acid derivatives **41** under ultrasound in a thermostated cleaning bath (40 kHz, 250 W).

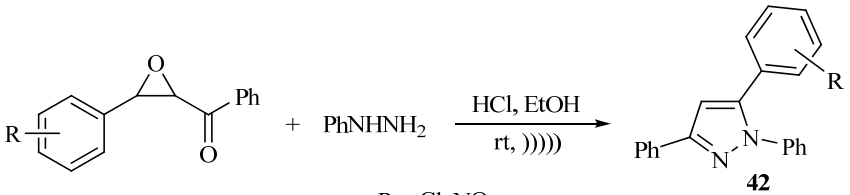


R = halogen, alkyl, OMe

The targeted derivatives were synthesized in a two-step procedure starting from ethyl 2-chloromethyl-6,7-methylenedioxyquinoline-3-carboxylate which was obtained from the Friedländer condensation of 2-amino-4,5-methylenedioxybenzaldehyde and ethyl 4-chloro-3-oxobutanoate, as outlined above for synthesis of oxindoles **40**. The Friedländer condensation was carried out under US irradiation at 80°C using a $KHSO_4$ catalyst in a 80% EtOH solvent (yield 74%).

The final products were obtained in the second step of the synthetic procedure by reaction with variously functionalized aldehydes heated under reflux.

The sonochemical synthesis of 5-aryl-1,3-diphenylpyrazole **42** was reported by Li *et al.* [37].



The reaction was carried out by irradiating the phenylhydrazine in a cleaning bath in the presence of 2,3-epoxy-1,3-diphenyl-1-propanone that had previously been prepared in accordance with the literature. The yield was optimized with a 2,3-epoxy-1,3-diphenyl-1-propanone to HCl molar ratio of 5:1 (89%).

A practical procedure for the synthesis of a number of 5-aryl-1,3-diphenyl-pyrazoles under US irradiation at room temperature was described by the same authors. This was carried out by reacting 3-aryl-2,3-epoxy-1-phenyl-1-propanone with phenylhydrazine in acidic ethanol (0.2 equiv HCl).

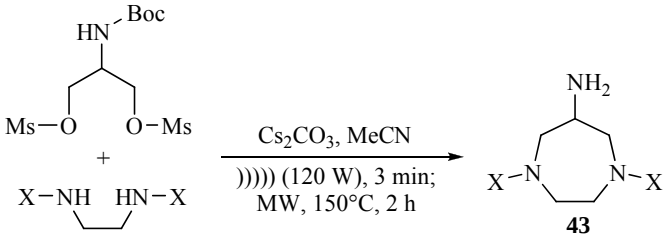
CYCLIZATION UNDER COMBINED MICROWAVE AND ULTRASOUND IRRADIATION

Microwaves and ultrasound can be used alone or combined in either a sequential or simultaneous fashion; these variations can lead to significantly differing results. The existence of synergic or additive effects resulting from their combined use has been widely demonstrated over the last decade [38]. Due to the optimal heat and mass transfer the technique provides, simultaneous MW/US irradiation strongly improves the kinetics and yields of chemical modifications in the heterogeneous phase [2].

For simultaneous irradiation, US can be conveyed inside a modified MW oven by inserting a non-metallic horn, made of quartz, Pyrex®, ceramic, *etc.*, through its wall and down into the reaction vessel [39].

Combined irradiation can also be achieved by sequential MW/US treatment in flow reactors that do allow the use of commercially available metallic horns. In these reactors, a pump circulates the reacting mixture through two separate reaction cells, one standing inside the MW oven and the other (fitted with a US probe) standing outside it [40].

Seven-membered heterocycles with two heteroatoms in the positions 1 and 4 provide interesting scaffolds for combinatorial chemistry because of their unique pharmacological activity on the central nervous system for which 1,4-benzo-diazepines is frequently mentioned [41]. Several substituted analogues of 6-amino-perhydro-1,4-diazepine are well-known serotonin and dopamine receptor antagonists [42]. The few published procedures for the preparation of 6-aminoperhydro-1,4-diazepines have involved several steps, required long reaction times, and afforded low yields [43]. A very efficient and rapid synthesis of the 6-aminoperhydro-1,4-diazepine scaffold **43** under sequential US/MW irradiation in acetonitrile was reported by Barge *et al.* [44]. Protected ethylenediamine derivatives and *N*-Boc-serinol dimesylate underwent rapid cyclization to give 6-aminoperhydro-1,4-diazepine derivatives in excellent yields and with high selectivity, whereas the same reaction failed or gave negligible yields under conventional heating. Using the present method, access to this scaffold became much easier and faster.



Thus, rapid and green cyclizations to *N*-heterocycles are possible thanks to the enabling technologies we have outlined above although they would be impossible under conventional heating. The unique environments obtained under US or MW, used separately or in a combined fashion, make these energy sources an irreplaceable tool in heterocyclic chemistry. The scale-up of synthetic protocols will require the use of sequential-flow reactors and, of course, a careful analysis of costs, including energy consumption.

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