



Sonochemistry (Applications of Ultrasound in Chemical Synthesis and Reactions): A Review Part III

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

As the need for friendly environment increasing the need for Sonochemistry increasing. Sonochemistry has become an important field of research for organic synthesis of diverse types of reactions, that decrease environmental hazardous and increase the yield of those reactions. The aim is to continue reviewing applications of ultrasound in chemical synthesis and reactions as reported in part I [1] and part II [2]. In this article I am trying to illustrate green sonochemical approaches for organic synthesis as one of the applications of ultrasound that minimize or eliminate the use and generation of hazardous substances and reduce environmental pollution.

Keywords: *Ultrasound; chalcones; heterocyclic compounds.*

1. INTRODUCTION

Sonochemistry is a powerful field of research in organic synthesis and pharmaceutical industry [3-5], where sonochemical effects are derived

from a phenomenon known as acoustic cavitation (formation, growth and implosion of microbubbles inside a liquid) that induce high temperature (near 5000 K) and high pressure (around 1000 atm.) [6].

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Sonochemistry is used for synthesis of different types of compounds with versatile applications. one of those applications is the green approach which is being used to accelerate synthesis of organic compounds and reduce the environmental pollutions which is a complaint from a traditional methods for synthesis of organic compounds. The green chemistry tools include using alternative material such as reagents, solvents and catalysts [7].

2. GREEN SONOCHEMICAL APPROACHES FOR ORGANIC SYNTHESIS

2.1 Solvent-free Sonochemical Protocols

2.1.1 Synthesis of licochalcones A-like structure

The literature offers several interesting examples of ultrasonic activation in "neat reactions," which have been an attractive option since the dawning of synthetic chemistry. Chalcones, important intermediates in the synthesis of many pharmaceuticals, are commonly synthesized via the Claisen-Schmidt condensation between acetophenone and benzaldehyde, principally under homogeneous acid or base catalysis. Martin-Aranda [8] have described a heterogeneous condensation reaction that is catalyzed by amino-zeolites (solid phase) in which both catalyst preparation and the reaction were performed under ultrasound. In this green, solvent-free procedure, chalcones were selectively produced in high yields (>95%). A combination of sonocatalysis and NH₂-zeolites was applied for the synthesis of commercial

chalcones with a Licochalcone A-like structure which exhibit pharmacological activity against *Staphylococcus aureus*. As shown in Fig. 1.

2.1.2 Synthesis of chalcones

Na- and Cs-Norit activated charcoal have been successfully used as catalysts in sonochemical chalcone preparation as a valid green alternative to the traditional use of NaOH (Carlos Javier Dura'n-Valle, et al. [9]. As shown in Fig. 2.

2.1.3 Synthesis of N-substituted imidazoles

Lo'pez-Pestana, et al. [10] to the ultrasound-assisted synthesis of N-substituted imidazoles via alkylation with 1-bromobutane and propargyl bromide. Under heterogeneous catalysis, ultrasonic irradiation plays a pivotal role in surface cleaning, particle size reduction, and metal activation, explaining the much higher yield in N-substituted imidazole synthesis. There is also a reduction in energy consumption and waste generation. As shown in Fig. 3.

2.1.4 Synthesis of α -aminophosphonates

Niralwad, et al. [11] have reported the first ever use of a 1-hexanesulfonic acid sodium salt for the synthesis of α -aminophosphonates under ultrasound irradiation in solvent-free conditions. A versatile method was described, which enables the reaction to be carried out with variously substituted aryl/heteroaryl aldehydes/ketones, amines, and triethyl phosphates, giving faster conversion, higher selectivity, and an easier workup. As shown in Fig. 4.

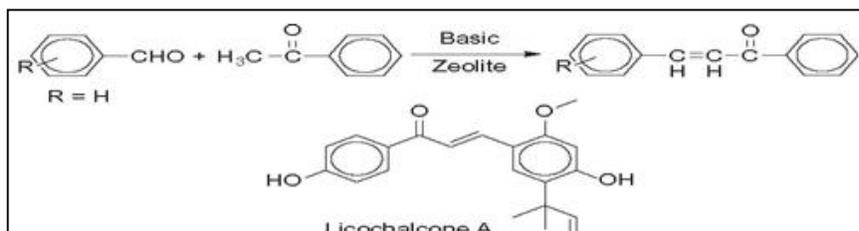


Fig. 1. Synthesis of Licochalcone A-like structure

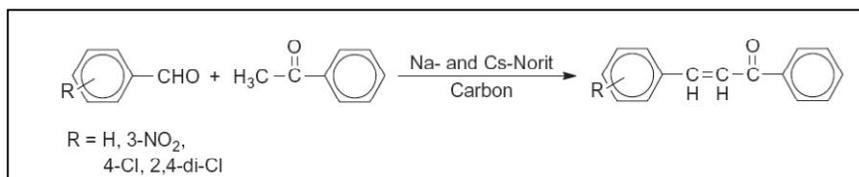


Fig. 2. Synthesis of chalcones

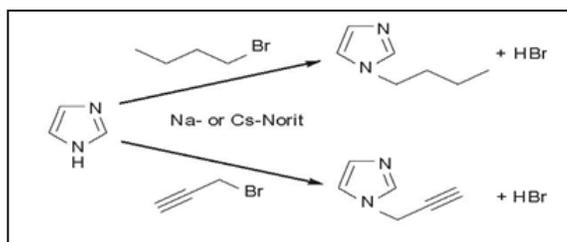
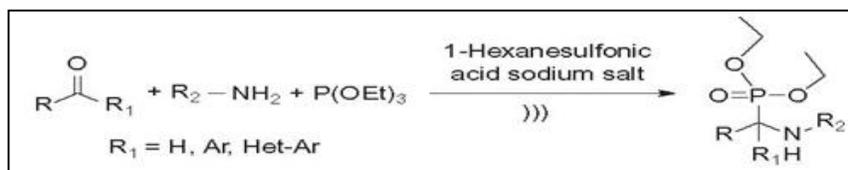


Fig. 3. Synthesis of N-substituted imidazoles

Fig. 4. Synthesis of α -aminophosphonates

2.2 Heterogeneous Catalysis in Organic Solvents and Ionic Liquids

2.2.1 Epoxidation reactions

The catalytic epoxidation of C=C double bonds is a versatile transformation in synthetic organic chemistry due to the synthetic utility of the ensuing epoxides and their further functionalization. Increased environmental concerns and awareness have resulted in a greater demand for environmentally friendly protocols that use relatively benign oxidants such as molecular oxygen and hydrogen peroxide in combination with reusable and recyclable solid catalysts. Hydrotalcites or anionic clays are homogenous basic mixed hydroxides with a brucite-like layer structure. They are known to be highly active catalysts in the H_2O_2 based epoxidation of olefins in the presence of a nitrile. An efficient and environmentally friendly epoxidation protocol for olefins and α,β -unsaturated ketones using hydrotalcite catalysts in the presence of acetonitrile and H_2O_2 under ultrasound has been proposed by Pillai, et al. [12]. The main advantages of the sonochemical method include a significant reduction in catalyst amount and reaction time, with a similar or improved product yield as that of conventional heating and stirring. The protocol is equally efficient for the selective epoxidation of α,β -unsaturated ketones. As shown in Fig. 5.

2.2.2 Imines formation

Authors have investigated greener synthetic protocols that make use of alternative energy

sources. Karla, et al. [13] screened a wide variety of promoters (alumina, silica, etc.) to imine synthesis under ultrasound irradiation using benzaldehyde and p-methoxyaniline as model compounds in ethanol. The reusability of the solid promoter was checked over several cycles and reactivation was achieved by heating in an oven for 4h. As shown in Fig. 6.

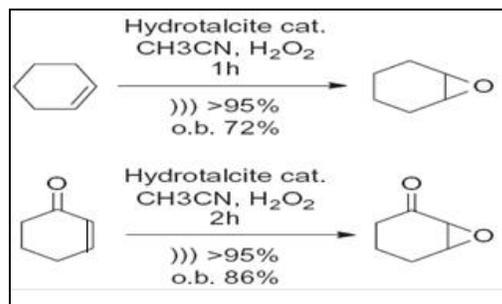


Fig. 5. Epoxidation reactions

2.2.3 Synthesis of 1,8-dioxo-octahydroxanthene

The use of non-aqueous room temperature ILs in organic transformations has gained considerable importance due to their negligible vapor pressure, reusability, and good thermal stability. An efficient methodology for the synthesis of 1,8-dioxooctahydroxanthene derivatives under ultrasonic irradiation at room temperature using carboxy-functionalized IL 1-carboxymethyl-3-methylimidazolium tetrafluoroborate, [cmmim][BF4], without any added catalyst, has been described by Dadhania, et al. [14]. The reaction

involves a condensation between 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and structurally diverse aldehydes. The resulting products were obtained in excellent isolated yields and high purity. The IL was recycled and its activity was largely retained for up to at least six cycles. The beneficial features of the reaction, such as its mild conditions, the absence of a catalyst, and the reusability of the IL are much more environmentally friendly than any conventional acid/base-catalyzed reaction. As shown in Fig. 7.

2.2.4 Isatins oxidation

Isatoic anhydrides are generally used as intermediates in organic synthesis and lead to a wide variety of compounds and building blocks, most often anthranilic acids. A novel, fast and environmentally friendly sonochemical procedure for the oxidation of isatins has recently been reported by Deligeorgiev, et al. [15]. The protocol entails the use of a urea-hydrogen peroxide complex in acetic or formic acid. As shown in Fig. 8.

2.2.5 Synthesis of polyurethanes

Naturally occurring oleic and undecylenic acids were used as raw materials in the synthesis of novel polyurethanes (PUs). Gonzalez-Paz, et al. [16] have described a novel route to diols from fatty acids. The application of environmentally friendly thiol-ene additions to 10-undecenoate and oleate derivatives was investigated with the goal of obtaining renewable diols. The application of thiol-ene additions to 10-undecenoate and oleate derivatives was carried out in order to obtain the required monomers. The resulting monomers were then polymerized with 4,4-methylene-bis(phenylisocyanate) in DMF solution, using tin (II) 2-ethylhexanoate as a catalyst, to produce the corresponding thermoplastic PUs (TPUs). Under sonochemical conditions TPUs were obtained in high yields (80–99%) with weight-average molecular weights in the 36–83 kDa range and characterized by good thermal and mechanical properties (Fig. 9). This means that PUs are excellent candidates for the substitution of petroleum-based materials. As shown in Fig. 9.

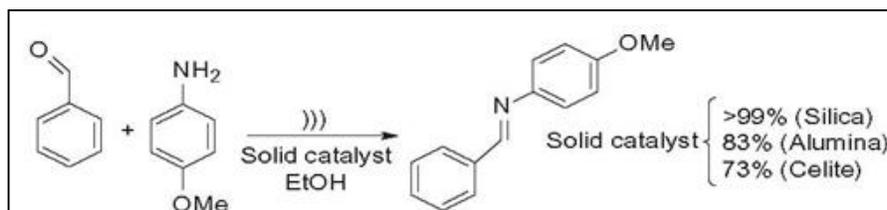


Fig. 6. Imines formation

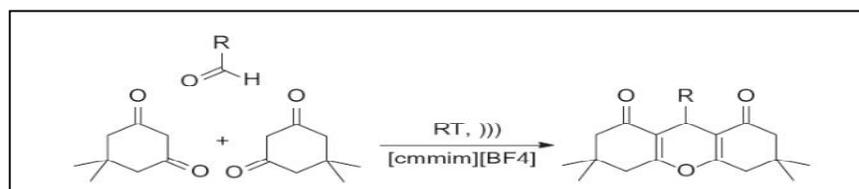


Fig. 7. Synthesis of 1,8-dioxo-octahydroanthene

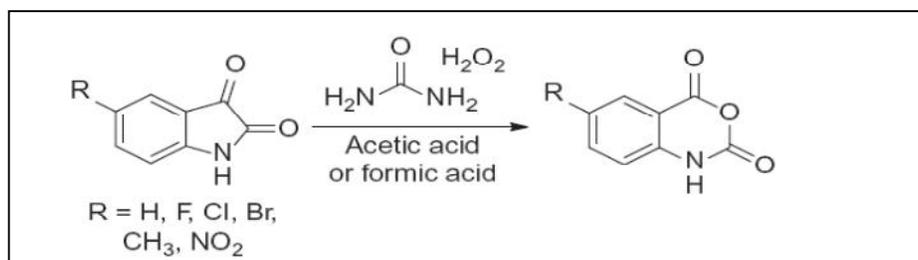


Fig. 8. Isatins oxidation

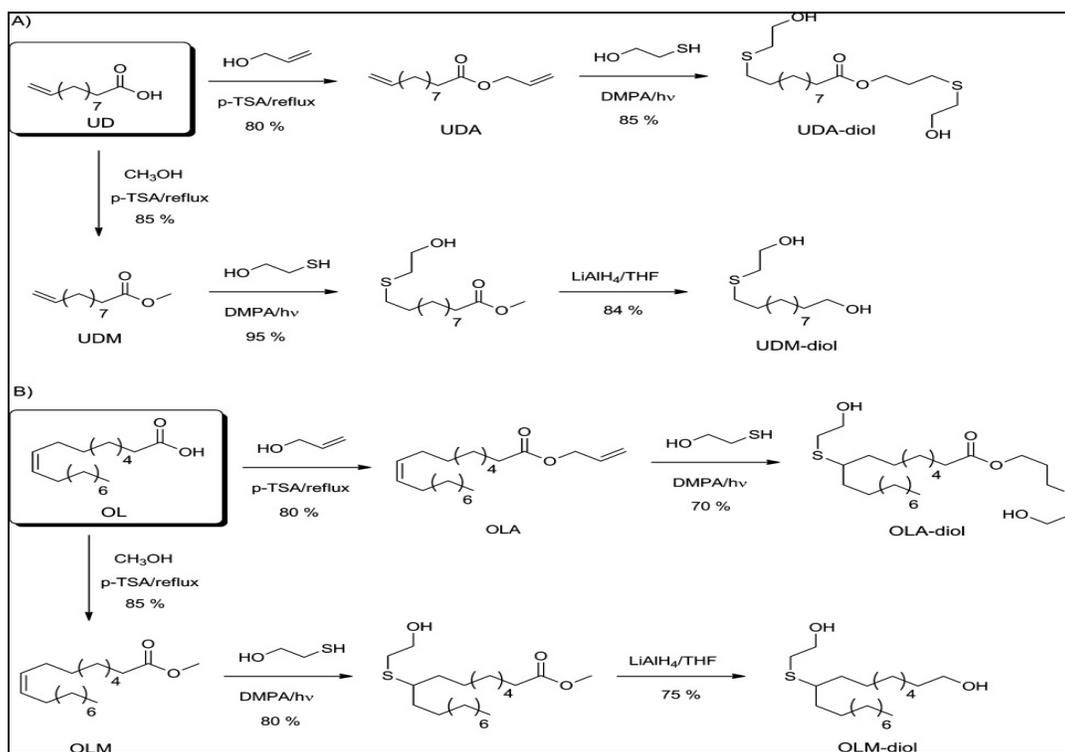


Fig. 9. Polyurethanes preparation

2.2.6 Synthesis of 8-C-glycosylflavanones

Santos, et al. [17] have described an efficient green route to C-glycosyl flavanones in one step via the direct glycosylation of an unprotected flavanone with unprotected and reducing sugars. Praseodymium triflate proved to be a suitable catalyst for the direct coupling reaction which leads to monoglycosylation products in yields ranging from 28% to 38% with complete regio- and stereo-selectivity for 8-C-glycosyl derivatives with an equatorial glycosidic bond. The efficiency of this method was significantly improved when the reactions were assisted by ultrasound irradiation (frequency of 45 kHz, power 80 W, temperature 80 C). This resulted in a threefold decrease in the reaction time over conventional heating for the monosaccharidyl derivatives and a fourfold decrease in the reaction time for disaccharidyl counterparts, with the target 8-C-glycosylflavanones obtained in yields of up to 56%. As shown in Fig. 10.

2.3 Heterocyclic Synthesis in Water

2.3.1 Synthesis of quinolone derivatives

Heterocycle synthesis includes several green sonochemical procedures in aqueous media,

some of which are routes to quinolines. Conventional Skraup, Döbner–von Miller, Conrad–Limpach, and Friedlaender homogeneous transition metal-catalyzed methods often suffer from hazardous organic solvents, long reaction times, low selectivity, and the need for excessive amounts of base. Kowsari and Mallak mohammadi, [18] have reported a green sonochemical protocol for the synthesis of quinolines in water which is catalyzed by basic ILs at room temperature. The reaction of isatin with acetophenone afforded substituted quinolines in high yield (90–95%). While the reaction under conventional heating required 8h, under ultrasonic irradiation the reaction occurred in only 2 h. As shown in Fig. 11.

2.3.2 Synthesis of 2-imidazolines

Sant' Anna Gda, et al. [19] have described a sonochemical synthesis of several 2-imidazolines via aldehyde and ethylenediamine condensation in the presence of N-bromosuccinimide. The reaction was performed in water, did not require the use of any catalyst, and can be considered extremely advantageous when compared with conventional procedures, giving faster reaction rates (12–18 min) and higher purity and yields (84–99%). As shown in Fig. 12.

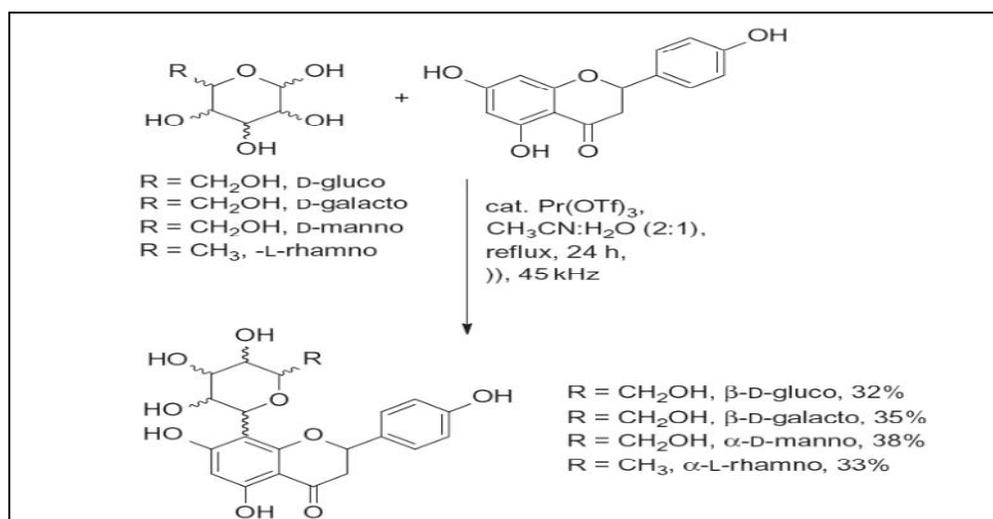


Fig. 10. Synthesis of 8-C-glycosylflavanones

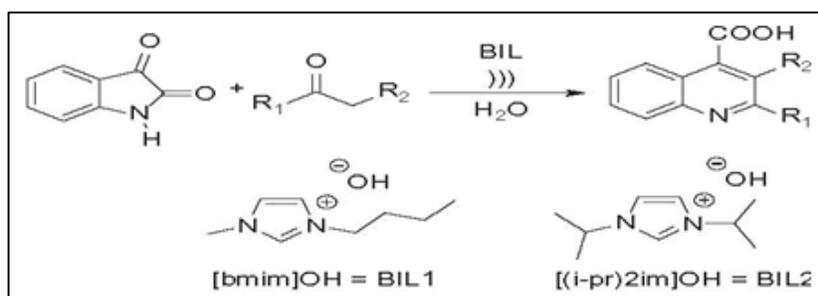


Fig. 11. Quinolines preparation

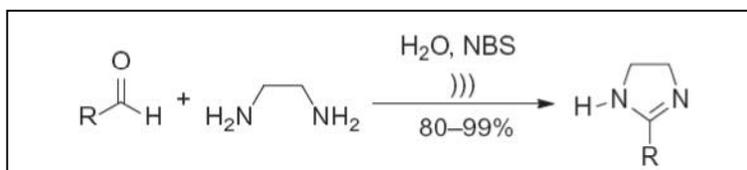


Fig. 12. Synthesis of 2-imidazolines

2.3.3 Four-component synthesis of dihydropyrano [2,3-c] pyrazoles

Zou, et al. [20] have developed a one-pot four-component synthesis of dihydropyrano [2,3-c]pyrazoles in water (over 88% yield in 30 min). This efficient and versatile ultrasound-assisted procedure was carried out with several substituted aryl or heteroaryl aldehydes, hydrazine, ethyl acetoacetate, and malononitrile. When the reaction was performed under conventional conditions, lower product yields were found in significantly longer reaction times. As shown in Fig. 13.

2.3.4 Synthesis of 1,8-dioxo-octahydroxanthens catalyzed by Si-MCM-41-SO₃H

New silica-based materials that can boast of a well-ordered structure, such as mesoporous Si-MCM-41, have been exploited as catalysts in recent years. Si-MCM-41-SO₃H was used by Rostamizadeh, et al. [21] in the synthesis of 1,8-dioxo-octahydroxanthens from dimedone and an aromatic aldehyde under ultrasonic irradiation. The combined use of MCM-41-SO₃H and ultrasound facilitates the intercalation of guest molecules (reactants) into host nanoreactors. The cavitation promotes the insertion of

reactants into nanocatalyst channels where they are accompanied by the inherent acidity of SO₃H groups that capable of bonding with the carbonyl oxygens of the aldehydes, thus assisting in the generation of ionic intermediates through reactant activation. As shown in Fig. 14.

2.3.5 One-pot synthesis of aryl-14-H-dibenzo[a,j]xanthenes.

The same authors have also used NH₄H₂PO₄/SiO₂ as a green catalyst Mahdavinia, et al. [22] for the one-pot synthesis of aryl-14-H-dibenzo [a,j] xanthene from aldehyde and β-naphthol mixtures in H₂O under sonication (25 kHz). The best results were obtained using 100mg of catalyst (yield of 92%). A wide range of aromatic aldehydes was employed and all benzoxanthenes were obtained in high to excellent yields in a general method that tolerated both electron-withdrawing and electron-donating constituents. As shown in Fig. 15.

2.3.6 Synthesis of highly substituted pyrroles

The ultrasound-assisted two-step synthesis of highly substituted pyrroles in aqueous media, in the absence of a catalyst, was described by Almeida and Faria [23]. The first step was the dimerization of a 1,3-dicarbonyl compound by ceric ammonium nitrate (CAN) under ultrasound to produce a tetracarbonyl derivative. This derivative was then combined with an amine in the absence of any catalysts to obtain the pyrrole via a Paal Knorr reaction. Electron-donating groups on the amines accelerated pyrrole formation. As shown in Fig. 16.

2.4 Solvent-free Reactions

2.4.1 Synthesis of 2H-chromen-2-ones

Coumarins are typically prepared via Pechmann reactions with substituted phenols and β-keto esters that usually require long reaction times and harsh conditions. An ecofriendly, efficient, and solventless example process has been described by Puri, et al. [24]. The reaction was catalyzed by copper perchlorate under ultrasound irradiation for the synthesis of 2H-chromen-2-ones. The best results were obtained at 45–50°C after 30–50 min of sonication (35 kHz) and 20 mol % of copper perchlorate. As shown in Fig. 17.

2.4.2 Synthesis of substituted coumarins

Khaligh and Shirini [25] have prepared a poly(4-vinylpyridinium) perchlorate [P(4-VPH)ClO₄], an innovative, solid, and reusable catalyst used for the synthesis of substituted coumarins via a solvent-free sonochemical Pechmann reaction at room temperature. All instances, except nitro- and chlorocoumarins, obtained good to excellent yields. As shown in Fig. 18.

2.4.3 Synthesis of substituted oxindoles

Most of the syntheses of oxindoles lead to 3-monosubstituted or 3,3-disubstituted oxindoles. It is, however, more difficult to prepare the less stable 3-unsubstituted oxindoles which require longer reaction times and harsh reaction conditions and give unsatisfactory yields. To combat these difficulties, a green, solvent-free procedure was described by Dandia, et al. [26] namely a one-pot clay-catalyzed reaction under sonication via Friedel–Craft cyclization. The reaction of substituted anilines with chloroacetyl chloride proceeds via the clay-catalyzed intramolecular Friedel–Craft cyclization of the α-chloroacetanilide, which is generated *in situ* under ultrasound irradiation and leads to several substituted oxindoles while avoiding harsh reaction conditions. As shown in Fig. 19.

2.4.4 Synthesis of 2-aminothiazole derivatives

In view of the importance of 2-aminothiazole and its derivatives, several synthetic methods have been developed over time, however, the Hantzsch reaction of α-halocarbonyl compounds with thioureas is the method of choice. Poor yields and difficult product recovery have often hampered this synthesis. An improved route to 2-(N-arylamino)-4-arylthiazoles under solvent-free conditions and physical activation, such as microwaves, grinding, or ultrasonication, has been reported by Gupta, et al. [27] Ultrasonication (in a cleaning bath) gave the highest yields (90–97%) in only 1 to 2-1/2h. As shown in Fig. 20.

2.5 Reactions in Organic Solvents

2.5.1 Synthesis of 1,5- Benzodiazepine derivatives

With the aim of improving the synthesis of 1,5-benzodiazepines, Guzen, et al. [28] have described the preparation of these heterocyclic compounds under milder conditions. 1,5-Benzodiazepines were synthesized via the

reaction of o-phenylenediamines with α -diketone or a ketone series under ultrasound irradiation. Of the several acidic catalysts used, the authors found the best results were obtained with p-toluene sulfonic acid (10 mol %) in dichloromethane, which gave the product in an 83% yield at room temperature in only 15 min. As shown in Fig. 21.

2.5.2 Synthesis of quinoxaline, benzoxazine and benzothiazine derivatives

Extending the application of ultrasound in the synthesis of heterocyclic compounds was the goal of Sadjadi, et al. [29] when they reported a general, efficient, and ecofriendly method for the synthesis of quinoxaline, benzoxazine, and benzothiazine that is catalyzed by nanocrystalline copper (II) oxide under ultrasonic irradiation. Of the several metallic catalysts used, the CuO nanoparticles showed the best activity and afforded the product in a 94% yield. The increased catalytic activity of nano-CuO over commercially available bulk CuO may be attributed to the higher surface area it provides as well as the higher surface reactive site concentration. Compared to reactions carried out in the presence of the same amount of CuO

nanoparticles under simple stirring in EtOH at room temperature, the reactions under ultrasound led to higher yields and shorter reaction times (15–20 min vs. 45–50 min). The nano-CuO catalyst was reused in three cycles with only a slight, gradual decrease in activity. As shown in Fig. 22.

2.5.3 Synthesis of 2-(3,5-dihydro- 1H- pyrazol-1-yl)-4-phenylthiazole derivatives

Although water is a particularly attractive choice, most organic compounds are not sufficiently soluble in it. A quite suitable alternative is the use of ethanol as the reaction medium, since as it is a bio-renewable product of low cost and low toxicity to human health and is relatively nonhazardous to the environment. Venzke, et al. [30] have reported a rapid and facile procedure for the synthesis of 2-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)-4-phenylthiazoles via a cyclization involving 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-1H-pyrazoles and phenacyl bromide in ethanol, used as a solvent, at room temperature under ultrasonic irradiation. The reaction afforded products in high yields in significantly shorter times than required under conventional reaction conditions. As shown in Fig. 23.

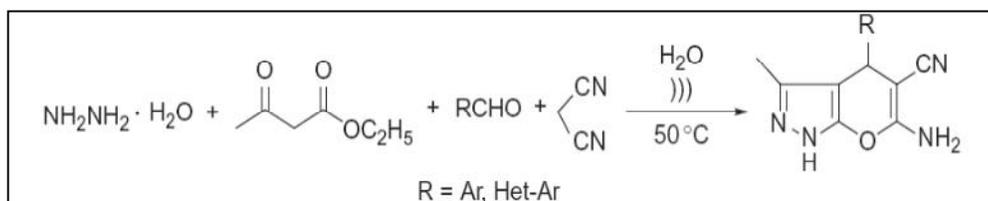


Fig. 13. Four-component synthesis of dihydropyrano[2,3-c]pyrazoles

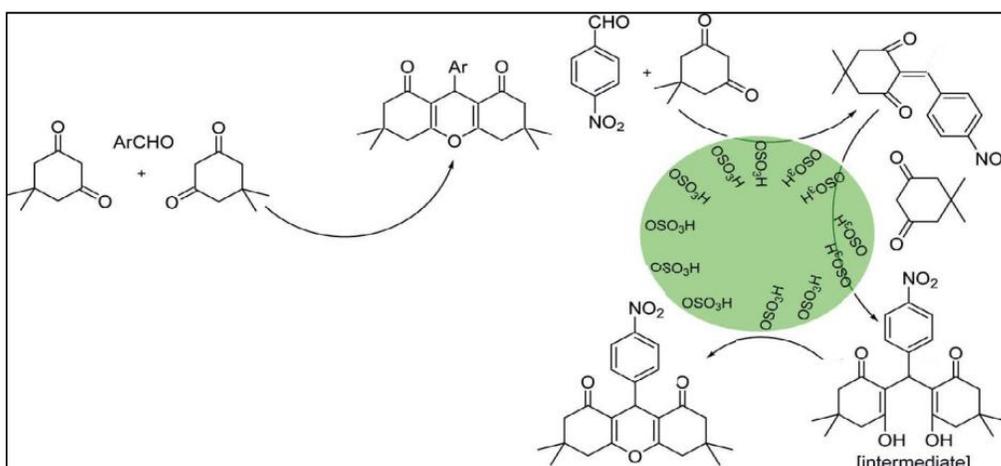


Fig. 14. Synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by Si-MCM-41-SO₃H

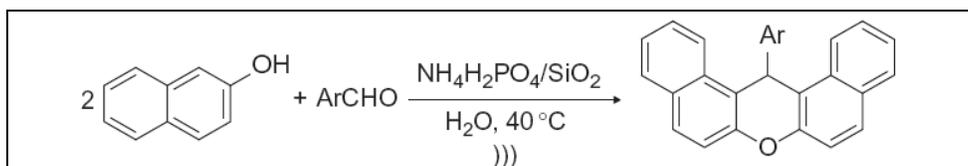


Fig. 15. One-pot synthesis of aryl-14-H-dibenzo[a,j]xanthenes

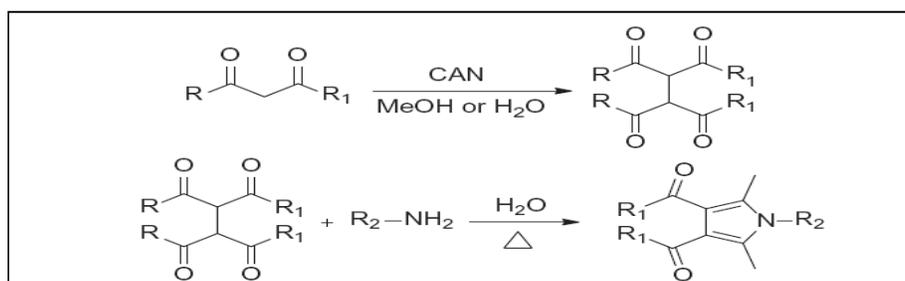


Fig. 16. Synthesis of highly substituted pyrroles

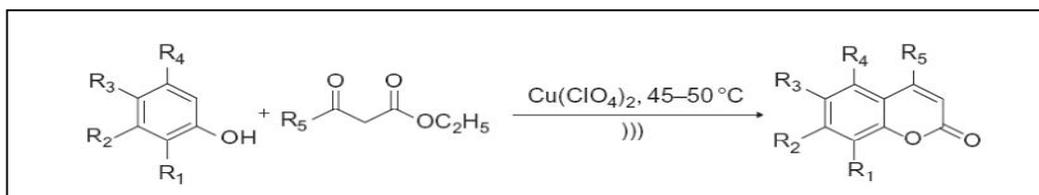


Fig. 17. Synthesis of 2H-chromen-2-ones

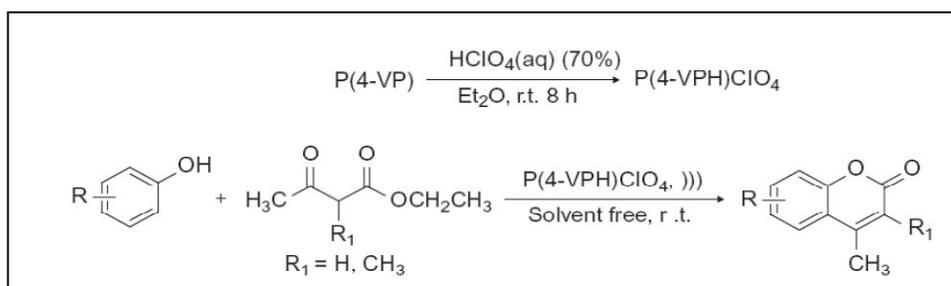


Fig. 18. Synthesis of substituted coumarins

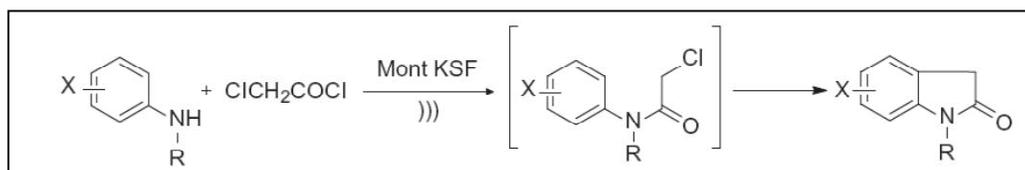


Fig. 19. Synthesis of substituted oxindoles

2.5.4 Synthesis of pyrazole derivatives

Pizzuti, et al. [31] have studied the applicability of ultrasound to the synthesis of novel pyrazole

derivatives via the ultrasound-assisted condensation of chalcones with hydrazines in the presence of KOH and ethanol. In detail, the authors described the synthesis of novel 3,5-

diaryl-4,5-dihydro-1H-pyrazole-1-carboxamide via the reaction of chalcones with aminoguanidine hydrochloride in KOH. The chalcone derivatives were obtained from acetophenone and the appropriate aldehydes by known methods. The mixture of reagents was sonicated with a probe for 30 min. The [2+3] cycloaddition of nitriles and azides is a common method for the synthesis of tetrazole derivatives. The "click" chemistry approach using zinc as a catalyst in aqueous solution still requires a tedious and time-consuming workup to remove the zinc salts. As shown in Fig. 24.

2.5.5 Synthesis of tetrazole derivatives

Chermahini, et al. [32] have proposed the reaction of a series of aromatic nitriles with sodium azide catalyzed by montmorillonite K-10 or kaolin clays in water or DMF as solvent. Conventional heating and ultrasonic irradiation were used to promote the reaction and compared. The versatility of this method was checked using various nitriles, which showed reasonable tetrazole yields. It was found that

using nitriles with electron-withdrawing groups results in both higher yields and lower reaction times. The catalysts were reused several times without significant loss in catalytic activity. Compared to conventional heating, ultrasonic irradiation reduced reaction times and increased catalytic activity. As shown in Fig. 25.

2.6 Heterocyclic Functionalization

2.6.1 Synthesis of spiro[indole-oxathiolanes]

Several authors have used water as the reaction medium in heterocyclic synthesis. An example was presented by Dandia, et al. [33] with the preparation of spiro [indole-oxathiolanes] via the reaction of spiro [indole-oxiranes] with thioacetamide in the presence of LiBr under ultrasound irradiation. The reaction was carried out in both a simple cleaning bath and a high-intensity probe system, and the two methods were compared with classical stirring. Under ultrasound, yields were higher (80–84% vs. 37% for stirring) and much faster (5 min vs.5h). As shown in Fig. 26.

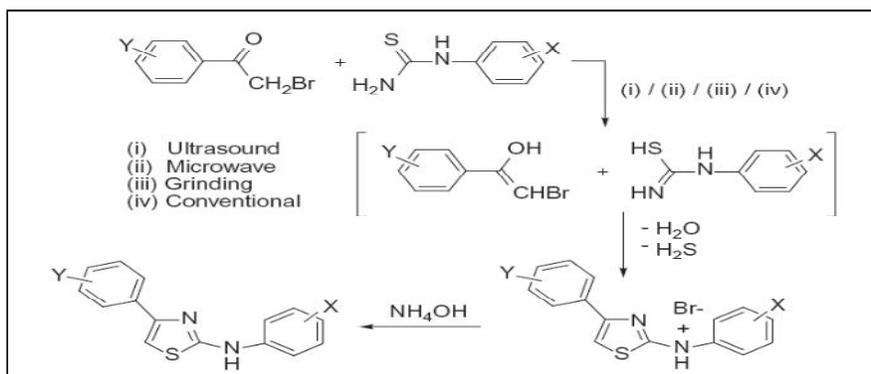


Fig. 20. Synthesis of 2-aminothiazole derivatives

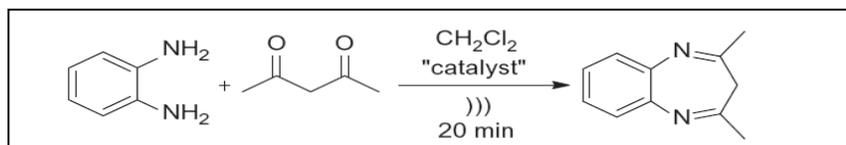


Fig. 21. Synthesis of 1,5- Benzodiazepine derivatives

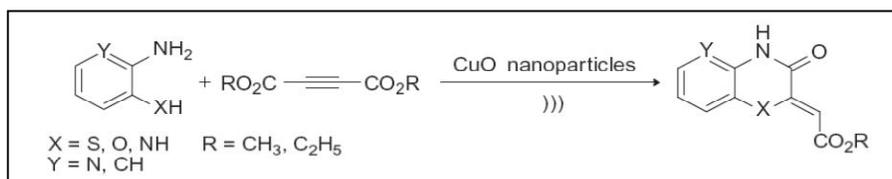


Fig. 22. Synthesis of quinoxaline, benzoxazine and benzothiazine derivatives

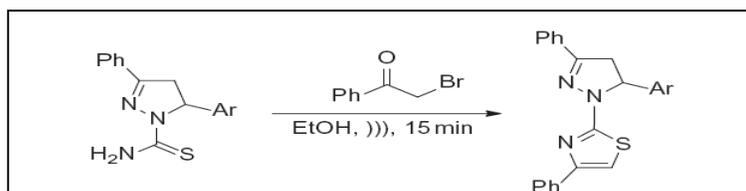


Fig. 23. Synthesis of 2-(3,5-dihydro-1H-pyrazol-1-yl)-4-phenylthiazole derivatives

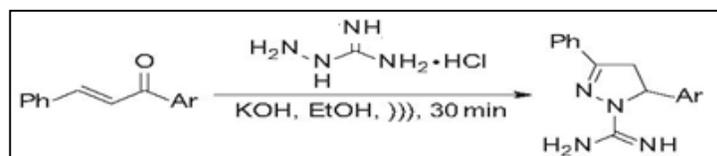


Fig. 24. Synthesis of pyrazole derivatives

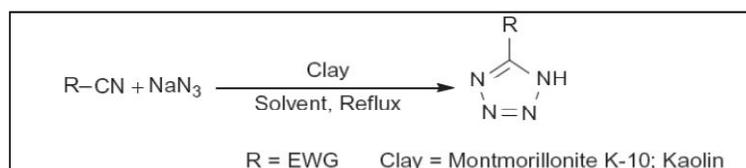


Fig. 25. Synthesis of tetrazole derivatives

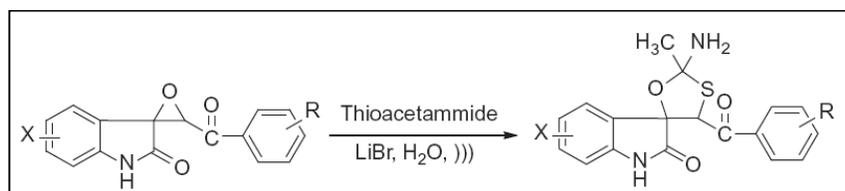


Fig. 26. Synthesis of spiro[indole-oxathiolanes]

2.6.2 Synthesis of bis(indolyl)methanes

In general, the synthesis of bis(indolyl)methanes is carried out via the reaction of indole with aldehydes (or ketones) and catalyzed using various catalysts, such as protic, Lewis, and solid acids. Dodecyl benzene sulfonic acid (ABS) was found to play the dual roles of proton acid catalyst and emulsifying agent in organic synthesis. Li, et al. [34] have reported the use of dodecyl benzene sulfonic acid as a highly effective catalyst for the green synthesis of bis(indolyl)methanes under ultrasound. The use of an aqueous medium and mild reaction conditions make this manipulation very interesting from an economic and environmental point of view. The synthesis of bis(indolyl)methanes carried out in water at room temperature under ultrasound (25 kHz) gave the product in high yield (85–98%). As shown in Fig. 27.

2.6.3 Synthesis of bis(indol-3-yl)methanes

Joshi, et al. [35] used the sodium salt of 1-hexenesulfonic acid as a catalyst in the synthesis of bis(indol-3-yl)methanes. A mixture of 1H-indole, aldehyde and 1-hexanesulfonic acid sodium salt (10 mol %) was dissolved in the minimum quantity of water possible with constant stirring. Furthermore, the reaction mass was irradiated under ultrasonic irradiation at ambient temperature for an appropriate time. This catalyst provides clean conversion (94%). Greater selectivity and an easy workup make this protocol practical and economically attractive. As shown in Fig. 28.

2.6.4 Synthesis of spiro[indoline-3,4-pyrzolo[3,4-b]pyridine]-2,6(10H)-dione

Bazgir, et al. [36] have reported a novel and clean synthesis of spiro[indoline-3,4-pyrzolo[3,4-

b]pyridine]-2,6(10H)-dione in a three-component condensation reaction of 4-hydroxycoumarin, isatines, and 1H-pyrazol-5-amines in the presence of p-toluene sulfonic acid (p-TSA) as an inexpensive catalyst in water under ultrasonic irradiation. The best result was obtained with p-TSA as a catalyst in water under ultrasonic irradiation for 6 h at 60°C. It was observed that a lower reaction temperature leads to a lower yield. As shown in Fig. 29.

2.6.5 Synthesis of 6-chloro-5-formyl-1,4-dihydropyridine derivatives

An efficient and environmentally friendly protocol for the synthesis of 6-chloro-5-formyl-1,4-dihydropyridine derivatives, which works via the convenient ultrasound-mediated reaction of

2(1H)pyridine derivatives with the Vilsmeier-Haack reagent, has been developed by Ruiz, et al. [37]. This method offers several practical advantages, including faster reaction rates, higher purity, and higher yields as well as cleaner conditions when compared with the conventional thermal method. To determine the influence of the ultrasonic irradiation source on the development of the process, the reactions were carried out and monitored using an ultrasonic cleaner and a sonic horn. Both methodologies worked better than the conventional method (reaction time of 18h and slightly lower yields (75–80%); they are more efficient, less time consuming, and more environmentally friendly, particularly when considering the basic green chemistry concepts. As shown in Fig. 30.

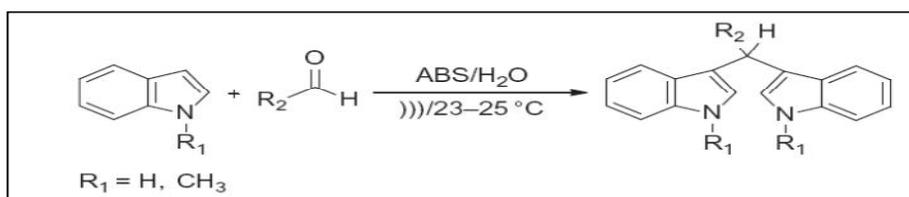


Fig. 27. Synthesis of bis(indolyl)methanes

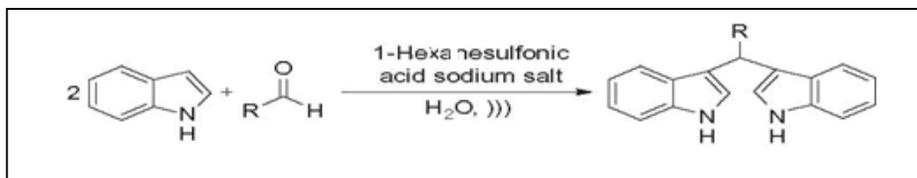


Fig. 28. Synthesis of bis(indolyl)methanes

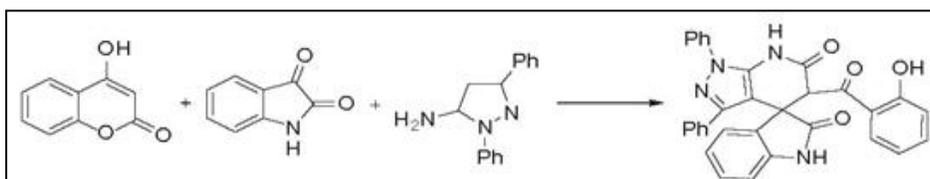


Fig. 29. Synthesis of spiro[indoline-3,4-pyrazolo[3,4-b]pyridine]2,6(10H)-dione

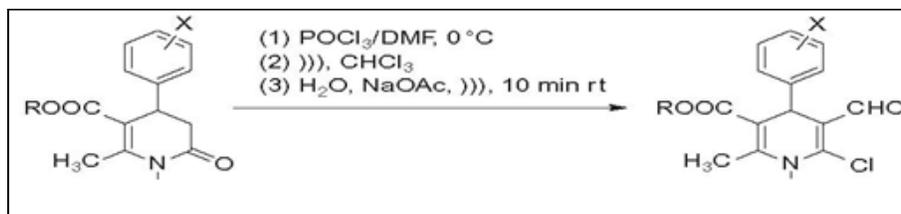


Fig. 30. Synthesis of 6-chloro-5-formyl-1,4-dihydropyridine derivatives

2.6.6 Synthesis of 3(4-oxo-4H-chromen-3-yl) acrylic acid hydrazides

It is well known that 3-formylchromones condense with compounds containing an active methylene group. Such condensation reactions are achieved using either an acid or base catalyst. Similarly, the condensation reactions of 3-formylchromones with hydrazine, mono substituted hydrazine, hydroxylamine, guanidine, and substituted pyrazoles have also been reported. Joshi, et al. [38] have reported the synthesis of 3(4-oxo-4H-chromen-3-yl)acrylic acid hydrazides via the simple Knoevenagel condensation of 3-formyl chromones and malonic acid in the presence of pyridine under reflux. This acid was clubbed with isoniazide using EDCI, HOBt in DMF under ultrasound irradiation at ambient temperature and furnished the desired products in excellent yields. When the reaction was carried out under conventional heating it gave a lower product yield even after a prolonged reaction time (150–180 min). However, the reaction was also carried out under ultrasonication and exhibited excellent product yields in short reaction times (35–40 min). As shown in Fig. 31.

2.6.7 Cu-catalyzed azide-alkyne cycloaddition (CuAAC)

Cintas, et al. [39] have presented a protocol for the ultrasound-assisted 1,3-dipolar cycloaddition reaction of azides and alkynes using metallic copper (Cu) as the catalyst. This protocol does not require additional ligands and proceeds with excellent yields. The Cu-catalyzed azide-alkyne cycloaddition (CuAAC) is generally recognized as the most striking example of “click” chemistry. Reactions involving metals are perhaps the favorite domain of sonochemistry, as ultrasound

favors mechanical depassivation and enhances both mass transfer and electron transfer from the metal to the organic acceptor. The reaction rate increases still further when simultaneous ultrasound and microwave irradiation are applied. The ultrasound-assisted click synthesis has been applied for the preparation of a wide range of 1,4 disubstituted 1,2,3-triazole derivatives starting from both small molecules and oligomers such as cyclodextrins (CDs). Using this efficient and green protocol, all adducts can be synthesized in 2–4h. As shown in Fig. 32.

2.7 Organometallic Reactions

2.7.1 Reactions in water

2.7.1.1 Allylindation of 1H-indole-3-carbaldehyde

Cintas, et al. [40] have provided a concise overview describing how ultrasound acts as a fundamental tool in improving the classical one-step coupling promoted by zero-valent metal species which are usually referred to as Barbier-like reactions. Sonication has allowed a widening of the applications of the Barbier reaction, facilitating its extension to other metals and enabling it to tolerate numerous sensitive functional groups, while also promoting the development of click reactions that use simply metallic copper as an efficient catalyst. The Barbier allylindation of 1H-indole-3-carboxaldehyde in the presence of azoles (e.g., pyrazoles and imidazole) under aqueous conditions has also been studied. The subsequent dehydration and nucleophilic addition were combined in a convergent, one-pot process for the synthesis of a variety of indole derivatives. Furthermore, the In-assisted Barbier-like reaction was exploited in the enantioselective synthesis of natural convolutamydin A in a

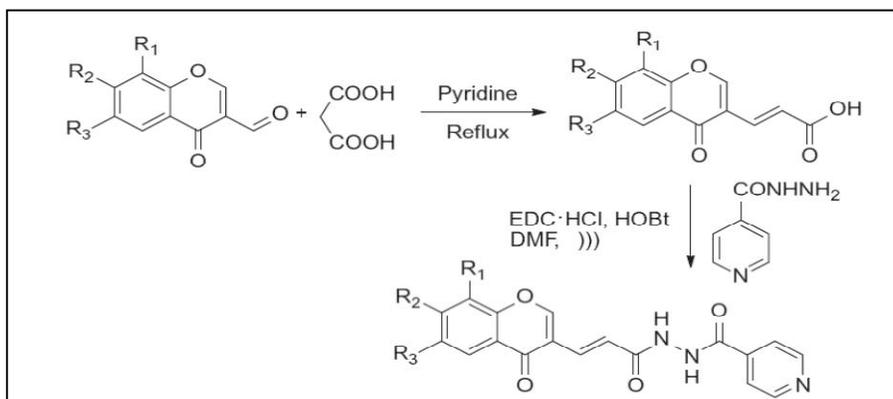


Fig. 31. Synthesis of 3(4-oxo-4H-chromen-3-yl)acrylic acid hydrazides

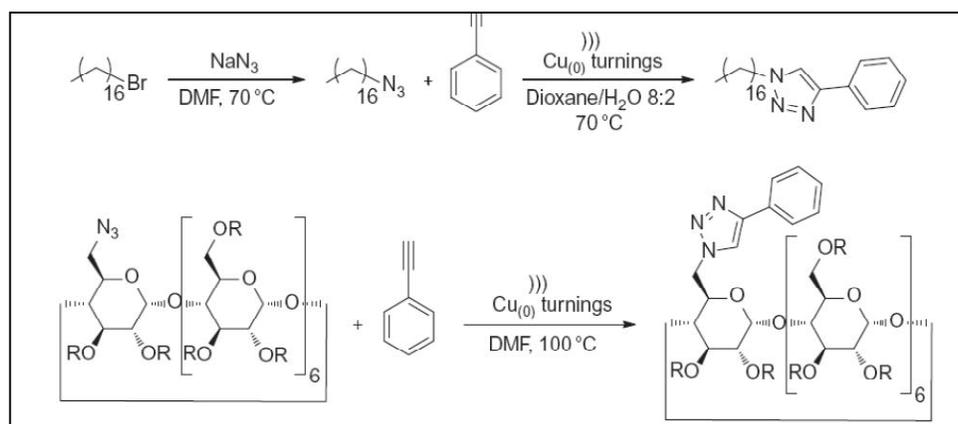


Fig. 32. Cu-catalyzed azide-alkyne cycloaddition (CuAAC)

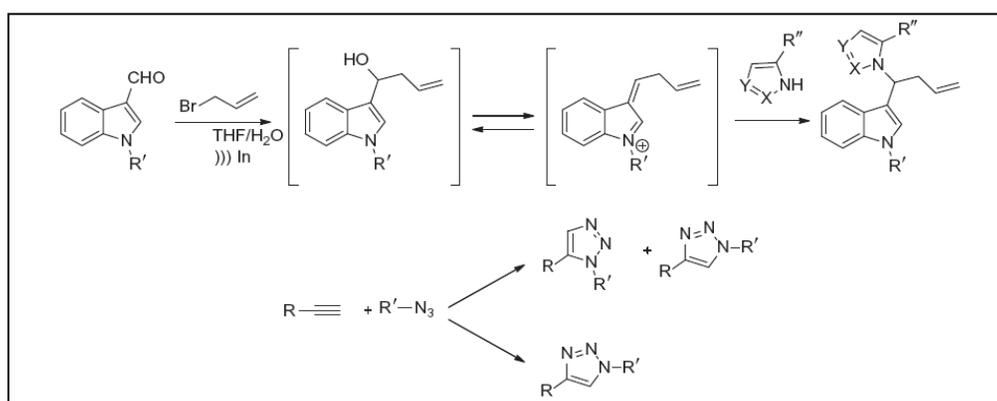


Fig. 33. Allylation of 1H-indole-3-carbaldehyde

three-component one-pot domino reaction, combining the allylation of 1H-indole-3-carbaldehyde with the dehydrative alkylation of stabilized C-nucleophiles (e.g., electron-rich heteroarenes, electron-rich aromatics, and stabilized enols) and N-nucleophiles (e.g., azoles) to generate a library of variously functionalized indolylbutenes. As shown in Fig. 33.

2.7.1.2 Synthesis of 2-amino-4H-chromenes

Conceptually, MCRs are potential candidates for the use of water as a solvent since the multiple hydrophobic reactants are brought into closer proximity by hydrophobic interactions. MCRs under ultrasonic activation have been used as simple, rapid atom economic and green methods in organic synthesis.

Datta and Pasha [41] have developed a one-pot sonochemical multicomponent synthesis of 2-amino-4H-chromenes from aromatic aldehydes,

malononitrile and resorcinol at 28–30 °C in water or aqueous mixtures using glycine as an organocatalyst. All chromenes were isolated in excellent yields within 9–45 min in the presence of water alone. To assess the general applicability of the protocol, a wide range of substituted aldehydes were allowed to undergo this three-component condensation. As shown in Fig. 34.

2.7.1.3 Synthesis of 2-amino-4,8-dihydropyrano [3,2-b]pyran-3-carbonitrile

Potential biological activity and high reactivity makes kojic acid an attractive molecule in MCRs. The combination of two important scaffolds, such as kojic acid and pyran, may lead to new compounds with improved pharmacological profiles. Banitaba, et al. [42] have described a green and simple approach to assembling of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile scaffolds via the three-component

reaction of kojic acid, malononitrile, and aromatic aldehydes in aqueous media under ultrasound irradiation. This methodology and the combinatorial synthesis were achieved by applying ultrasound irradiation, while making use of water as a green solvent. In comparison to conventional methods, experimental simplicity, good functional group tolerance, excellent yields, a short routine, and selectivity, without the need for a transition metal or base catalyst, are prominent features of this green procedure. As shown in Fig. 35.

2.7.1.4 Synthesis of β -amino carbonyl compounds

Kamble, et al. [43] have reported an environmentally benign synthesis of β -amino carbonyl compounds in aqueous hydrotropic solution under ultrasound irradiation. The term hydrotropes refers to a diverse class of water soluble surface active compounds that enhance the solubility of organic reactants in the aqueous phase (up to 200 times). Aqueous hydrotropic solutions provide an interesting approach to controlling the chemical contents of a bubble and work via a combination of low vapor pressure and increased aqueous hydrotropic solution viscosity relative to pure water. Chemical control of the vapor content of the collapsing bubble allows for a stronger collapse that leads to greater compressional heating of reactants, which, in turn, leads to reaction rate acceleration. Excellent results were obtained with sodium p-toluene sulfonate (50% w/v) aqueous solutions of selected hydrotropes, since this concentration was suitable for the maximum solubilization of organic compounds. The aqueous hydrotrop

solution was reused for the subsequent reactions. As shown in Fig. 36.

2.7.2 Reactions in organic solvents

2.7.2.1 Synthesis of 5-amino-7-aryl-7,8dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitriles.

Ablajan, et al. [44] have reported a one-pot synthesis of 5-amino-7-aryl-7,8dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitriles via three component reactions of 3-amino-1,2,4-triazole, aromatic aldehydes, and malononitrile in the presence of NaOH in ethanol under ultrasound irradiation at room temperature. Compared with the reflux reaction, no side products were detected in the sonochemical method. The suggested mechanism of the three-component, one-pot reaction is assumed to start with a condensation between aminotriazole and aldehyde. This intermediate then further reacts with malononitrile via an intramolecular Michael addition followed by isomerization. As shown in Fig. 37.

2.7.2.2 Synthesis of β -amino ketones

Sulfamic acid ($\text{NH}_2\text{SO}_3\text{H}$, SA) has emerged as a promising substitute for inorganic solvents conventional Bronsted- and Lewis-acid catalysts. It is a relatively dry, nonvolatile, non-hygroscopic, noncorrosive, and odorless crystalline solid with outstanding physical stability. It possesses distinctive catalytic features which are related to its zwitter ionic nature and displays excellent activity over a vast array of acid-catalyzed

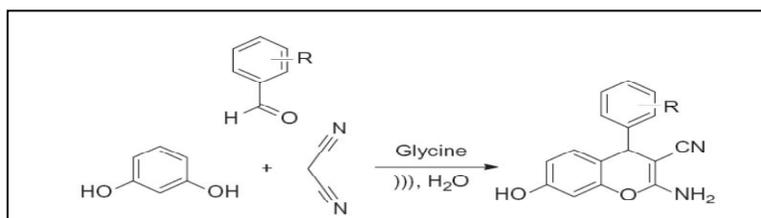


Fig. 34. Synthesis of 2-amino-4H-chromenes

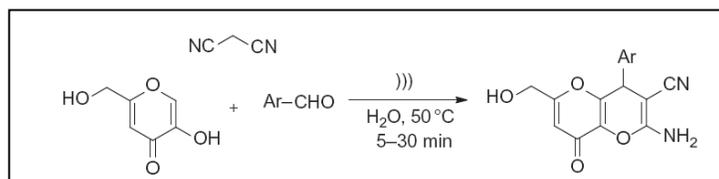


Fig. 35. Synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile

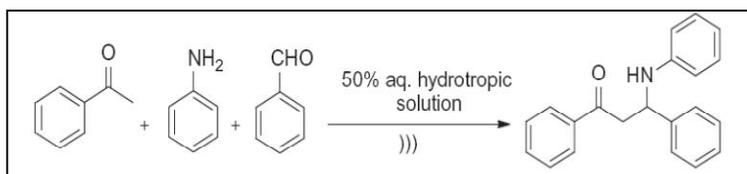


Fig. 36. Synthesis of β -amino carbonyl compounds

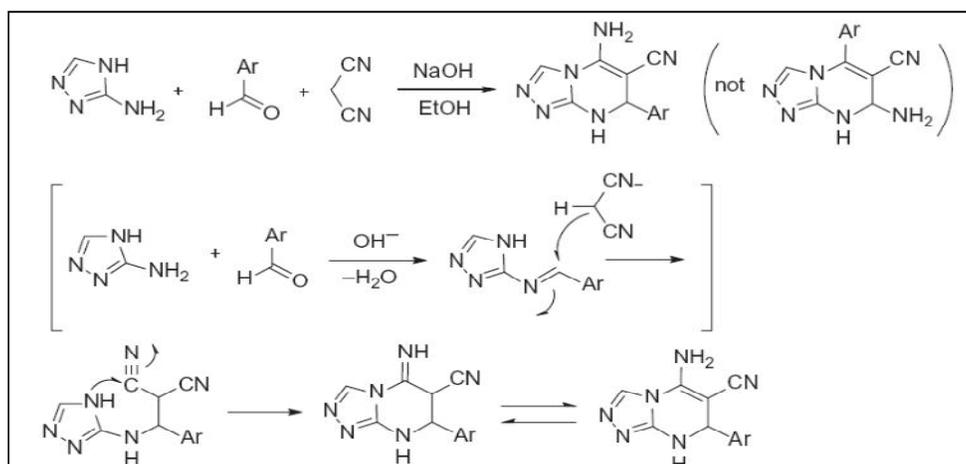


Fig. 37. Synthesis of 5-amino-7-aryl-7,8-dihydro-[1,2,4]-triazolo[4,3-a]pyrimidine-6-carbonitriles

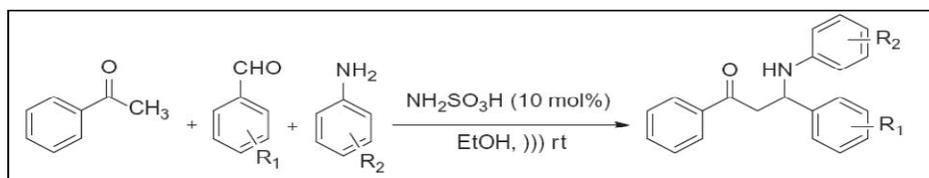


Fig. 38. Synthesis of β -amino ketones

organic transformations. Zeng, et al. [45] have reported an ultrasound-assisted one-pot approach to direct Mannich reactions of aldehydes, ketones, and amines in absolute EtOH, catalyzed by SA, which lead to the rapid and efficient synthesis of β -amino ketones under mild conditions. SA efficiently catalyzed the Mannich reaction which afforded the desired products in high yields (80–95%). Thus, in view of its excellent catalytic capacity, easy availability, cost effectiveness, outstanding stability, and ready recovery, SA was proven to be the best catalyst for such sonochemical Mannich reactions. As shown in Fig. 38.

3. CONCLUSION

The primary focus of my work is to give a light to a different types of sonochemistry applications, which becomes an interesting and pivotal for

industry specially pharmaceutical industry. The efficient synthesis of drugs with high yield and less environmental hazardous increases the need for future using ultrasound technologies in pharmaceutical preparations and drug delivery systems.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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