Recent developments on ultrasound-assisted organic synthesis in aqueous medium

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Abstract: In the recent past, a number of methods were reported on the application of ultrasound in organic reactions for the synthesis of diverse organic scaffolds. On the other hand, as far as green chemistry is concerned, water is the safest of all solvents. Thus, a “strong collaboration” between ultrasonic irradiation and aqueous medium holds the key to the development of an environmentally sustainable protocol. The present review summarizes the latest developments in ultrasound-assisted and water-mediated organic synthesis reported to date.

Keywords: ultrasonic irradiation; sonochemistry; aqueous medium; organic synthesis; heterocyclic chemistry; sustainable chemistry.

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1. INTRODUCTION

Sustainable organic methodologies are in high demand in the chemical industry to produce various organic scaffolds in the form of fine chemicals, medicinal and pharmaceutical agents, agrochemicals, and many others. The people of the twenty-first century are well aware about the side effects of the hazardous substances used or generated in chemical processes. It is high time to take the steps necessary to protect our “Mother Nature” from ever increasing chemical pollution associated with synthetic organic processes. Thus, today’s methodologists are trying to make their protocols more environmentally friendly and sus-
tainable by avoiding the extensive use of harsh reaction conditions, hazardous reagents and solvents.5–8 As a result, the last decade has seen a tremendous outburst in the modification of chemical processes to make them ‘sustainable’ for the betterment of the environment.

The involvement of ultrasound in organic synthesis sometimes fulfills this goal. Ultrasound irradiated reactions are much more advantageous over traditional thermal methods in terms of reaction rates, yields, purity of the products, product selectivity, etc.9–14 Ultrasonic waves cause molecules to oscillate around their mean position, which increases the average distance between the molecules.15 Thus, under suitable conditions, a huge number of cavitation bubbles are generated in reaction mixture, which grow rapidly and subsequently undergo vigorous collapses that results in the formation of micro-jets that can produce fine emulsions between the reactants.16 In addition, the local temperature within the reaction mixture is also increased by the violent collapse of the cavitation bubbles, which eventually lead to the activation energy barrier being crossed.17 Sometimes the application of ultrasound can avoid the use of catalysts in organic reactions.18–22 On the other hand, last decades have shown a tremendous outburst of chemical reactions performed under “in-water” conditions23 to make them “sustainable” for the betterment of the environment. Scientists are choosing water as a solvent not only because of its environmental friendliness but also because it is cheap, non-flammable, and abundantly available. Water as a solvent activates the functional groups by forming hydrogen bonds. Due to high surface tension and hydrophobic nature,24 the reactants in aqueous medium are bound to form aggregates in order to decrease the exposed organic surface area,25–27 which increases the rate of the reaction. Thus, a “strong collaboration” between ultrasonic irradiation and aqueous media holds the key to the development of an environmentally sustainable protocol.

Such beneficial features in terms of sustainability have motivated organic chemists to explore aqueous-mediated organic synthesis employing ultrasonic irradiation in more depth and as a result, in the recent past, there were immense applications of ultrasound in organic reactions for the synthesis of various heterocyclic as well as non-heterocyclic scaffolds in aqueous media. The present review summarizes the latest developments in ultrasound-assisted and water-mediated organic synthesis reported to date.

2. ULTRASOUND-ASSISTED SYNTHESIS OF HETEROCYCLES IN AQUEOUS MEDIUM

More than half of the known organic compounds are containing heterocyclic ring.28–33 These spectacular classes of compounds are important because they represent a “privileged” structural subunits well distributed in naturally occurring compounds with immense biological activities such as anticancer,34 cytotoxic,35 anti-HIV,36 anti-malarial,37 anti-inflammatory,38 anti-microbial39 and many
more. To realize the importance of heterocycles, in the recent past, a number of synthetic protocols are being reported in the literature almost in every month. But in generally these protocols are not satisfying the sustainability issues as in many occasions toxic solvents, harsh reaction conditions are being used. Therefore, now-a-days it is the thrusting area of research to synthesize biologically relevant heterocycles using sustainable pathways.

2.1. Ultrasound-assisted synthesis of N-heterocycles in aqueous medium

2.1.1. Synthesis of dihydroquinolines

Quinolines are very common naturally occurring compounds. Many synthetic scaffolds containing the quinoline moiety possess significant biological efficacies that include anti-fungal, anti-malarial, anti-protozoal, analgesic activity. Therefore a large numbers of methods employing various catalysts are already available in the literature for the synthesis of quinolines and dihydroquinolines. Although these reported methods have their own merits, they still suffer from some disadvantage, such as the use of toxic solvents, drastic reaction conditions, long reaction times, etc. Pagadala et al. (Scheme 1) developed a simple, efficient, ultrasound-assisted, catalyst-free, one-pot, four-component protocol for the synthesis of a series of biologically promising dihydroquinoline derivatives (6 and 7) from the reactions of various aldehydes (1), malononitrile (2), ammonium acetate (3) and 2-naphthol (4)/resorcinol (5) in aqueous medium at 60 °C. The ultrasonic-irradiated method was found to be superior as compared to the conventional method with respect to reaction time and yields.

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Scheme 1. Ultrasound-promoted catalyst-free synthesis of dihydroquinolines in water.
2.1.2. Synthesis of pyrroles and pyridazines

Pyrroles and pyridazines are very common in natural products, pharmaceuticals, and various bioactive molecules. Thus, a number of methods are already available in the literature for the synthesis of these important classes of heterocycles employing various reaction conditions. However these reported methods suffer due to the use of hazardous solvents, harsh reaction conditions, long reaction times, etc. In this context, an efficient, ultrasound-assisted, catalyst-free protocol was developed by Eftekhari-Sis and Vahdati-Khajeh (Scheme 2) for the synthesis of 6-aryl-3-methylpyridazine-4-carboxylic acid esters (11) and 5-aryl-4-hydroxy-2-methyl-1H-pyrrole-3-carboxylic acid esters (12) via three-component reactions of arylglyoxal hydrates (8), β-dicarbonyl compounds (9) and hydrazine hydrate (10) or ammonium acetate (3), respectively, in aqueous media at room temperature.

![Scheme 2. Ultrasound promoted, catalyst-free synthesis of pyrroles and pyridazines in water.](image)

2.1.3. Synthesis of N-substituted 1,8-dioxodecahydroacridines

N-Aryl-1,8-dioxodecahydroacridine moieties are important in drug design and discovery as they possess potential pharmacological activities, such as antimicrobial, anticancer and enzyme inhibitory properties. A large number of methods are already available in the literature for the synthesis of these important scaffolds employing various catalysts such as 1-methylimidazolium trifluoroacetate, silica-supported N-propylsulfamic acid, amberlyst-15, ZnO nanoparticles, LiBr and NH4Cl. Although these available methods possess notable merits they suffer from some drawbacks, such as, use of organic solvents, longer reaction times, etc. In this context, Chate et al. (Scheme 3) developed a practical ultrasound-assisted, one-pot method for the synthesis of N-substituted 1,8-dioxodecahydroacridines (16 and 17) via three-component reactions between aldehydes (1), dimerone (13) and isoniazid (15)/aromatic amines.

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(14) in the presence of β-cyclodextrin as a supramolecular, biodegradable, reusable catalyst in aqueous medium. Use of organic solvents such as CH$_3$CN, THF, DMF and EtOH gave inferior results in terms of both reaction time and yield.

![Scheme 3. Ultrasound-promoted synthesis of N-substituted 1,8-dioxodecahydroacridines in water.](image)

2.1.4. Synthesis of pyrazolo[3,4-b]pyridine derivatives

Many anxiolytic drugs, such as cartazolate, etazolate and tracazolate, contain the pyrazolopyridine moiety.\textsuperscript{65–68} A simple, ultrasound-assisted, high-yielding, environmentally benign protocol was developed for the synthesis of pyrazolo[3,4-b]pyridine derivatives (19) via one-pot, three-component reactions of aldehydes (1), ethyl cyanoacetate (2a), and 3-amino-5-methylpyrazole (18) using sodium chloride as the catalyst in aqueous media at room temperature (Scheme 4).\textsuperscript{69} The ultrasonic-irradiated method was found to be advantageous as compared to the conventional heating method. The use of organic solvents, such as acetonitrile, toluene, dichloromethane, tetrahydrofuran, ethanol and methanol, gave inferior results in terms of both reaction times and yields.

2.1.5. Synthesis of spiro[indoline-3,4′-pyrazolo[3,4-b]pyridine]-2,6′(1′H)-diones

A simple, facile, environmentally benign, aqueous-mediated, ultrasound-assisted, three-component protocol was developed for the synthesis of medicinally important spiro[indoline-3,4′-pyrazolo[3,4-b]pyridine]-2,6′(1′H)-diones (23) from the reaction of 4-hydroxytocoumarin (20), isatins (21) and 1H-pyrazol-5-amines (22) using p-toluenesulfonic acid (p-TSA) as catalyst at 60 °C (Scheme 5).\textsuperscript{70}

Scheme 5. Ultrasound-promoted synthesis of spiro[indoline-3,4′-pyrazolo[3,4-b]pyridine]-2,6′(1′H)-diones in water.

2.1.6. Synthesis of highly substituted pyrimidine-5-carboxylic acid derivatives

Dihydropyrimidinones (25) possess immense biological efficacies, such as antiviral, antibacterial, antihypertensive, antitumor and many more activities. In 1893, Biginelli first reported the synthesis of dihydropyrimidinones (25) with only 20–50 % yields. In 2003, Li et al. (Scheme 6) employed ultrasound for the synthesis of bioactive dihydropyrimidinones (25) by one-pot, three-component reactions between various aldehydes (1), urea (24a) and ethyl acetoace-
tate (9) using sulfamic acid as catalyst in ethanol at room temperature. Later, Gholap et al. (Scheme 6)\(^7\) used 1-butylimidazolium tetrafluoroborate \([\text{Hbm}]\text{[BF}_4\text{]}\) as an efficient ionic liquid for the synthesis of dihydropyrimidinones (25) under the influence of ultrasound at ambient temperature. Zirconium chloride (10 mol %) was used by Kumar and Parmar (Scheme 6)\(^7\) as catalyst in ethanol for the same batch of the reactions under ultrasonic irradiation at room temperature.


Recently, in 2010, Mandhane et al. (Scheme 6)\(^7\) developed a simple, efficient, environmentally friendly, aqueous-mediated, ultrasound-assisted method for the synthesis of dihydropyrimidinones (25) at room temperature using a catalytic amount of thiamine hydrochloride as an efficient organo-catalyst.

2.1.7. Synthesis of pyrimidine fused heterocycles

Heterocycles containing a pyrimidine moiety are very common in naturally occurring compounds. They possess numerous biological efficacies that include antitumor,\(^7\) antiviral\(^7\) and antioxidant\(^7\) activity. Owing to the attractive pharmacological properties of these scaffolds, several methods are available for the synthesis of various pyrimidine fused heterocycles.\(^8\)–\(^8\) Again these methods suffer disadvantages due to the use of hazardous solvents, long reaction times and harsh reaction condition. Recently, in 2010, Mosslemin and Nateghi (Scheme 7)\(^8\) synthesized a series of pyrimidine annulated fused heterocycles (28, 29 and 31) in high yields via an ultrasound-assisted, one-pot, three-component condensation reaction of barbituric acid (26a) or 2-thiobarbituric acid (26b), aldehydes (1) and a series of enamines (27a, 27b, 18a and 30) using piperidine as catalyst in water at 60 °C. Another simple, convenient, environmentally friendly, ultrasound-assisted, facile one-pot, four-component protocol was developed by Naeimi and Didar (Scheme 8)\(^8\) for the synthesis of pyrido[2,3-d:6,5-d’]dipyrimidines (28a) from the reactions of aldehydes (1), 2-thiobarbituric acid (26b) and ammonium acetate (3) using magnetically separable nano copper ferrite as a heterogeneous catalyst in water.
ULTRASOUND-ASSISTED ORGANIC SYNTHESES IN AQUEOUS MEDIUM

Scheme 7. Ultrasound-promoted synthesis of pyrimidine fused heterocycles in water.

Scheme 8. Ultrasound promoted synthesis of pyrido[2,3-\(d\):6,5-\(d\)]dipyrimidines in water.

2.1.8. Synthesis of 2-amino-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles

Quinoline and its derivatives are an important class of pharmaceutical compounds that occur predominately in natural products, exhibit a broad spectrum of biological activities, and act as antivirals,\(^8^9\) antiperterpts,\(^9^1\) antidepressants,\(^9^2\) anti-
-oxidants,\textsuperscript{93} and anti-inflammatory,\textsuperscript{94} antiproliferation\textsuperscript{95} and anticancer\textsuperscript{96} agents. In particular, hexahydroquinolines also possess antioxidant\textsuperscript{97} and cytotoxic\textsuperscript{98} activities. A series of highly substituted 2-amino-1,4,5,6,7,8-hexahydroquinolines-3-carbonitriles (32) were synthesized \textit{via} ultrasound-assisted, one-pot, four-component condensations of aromatic aldehydes (1), dinedone (13), malononitrile (2) and ammonium acetate (3) using K\textsubscript{2}CO\textsubscript{3} as a catalyst in aqueous medium at ambient temperature (Scheme 9).\textsuperscript{99}

![Scheme 9. Ultrasound-promoted synthesis of 2-amino-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles in water.](image)

### 2.1.9. Synthesis of 2-amino-4,6-diphenylnicotinonitriles

Safari \textit{et al.} (Scheme 10)\textsuperscript{100} reported a simple ultrasound-promoted catalyst-free, high yielding, convenient, environmentally benign approach to the synthesis of 2-amino-4,6-diphenylnicotinonitriles (34) \textit{via} four-component reactions of aromatic aldehydes (1), malononitrile (2), acetophenones (33) and ammonium acetate (3) in water. The ultrasonic-irradiated method was found to be advantageous as compared to the conventional stirring method at 50 °C. The use of organic solvents, such as ethanol, methanol, acetonitrile, dichloromethane or tetrahydrofuran, gave inferior results in terms of both reaction times and yields.

### 2.1.10. Synthesis of tetrahydrodipyrazolopyridines

Shabalala \textit{et al.} (Scheme 11)\textsuperscript{101} demonstrated a simple, convenient, ultrasound-promoted, catalyst-free, environmentally benign protocol for the one-pot, four-component syntheses of tetrahydrodipyrazolopyridines (35) from the sequential reactions of ethyl acetoacetate (9), hydrazine hydrate (10), aromatic aldehydes (1) and ammonium acetate (3) in water at 50 °C. The ultrasonic-irradiated method was found to be advantageous when compared to the conventional method with respect to reaction times and yields.
ULTRASOUND-ASSISTED ORGANIC SYNTHESSES IN AQUEOUS MEDIUM

Scheme 10. Ultrasound-promoted synthesis of 2-amino-4,6-diphenylnicotinonitriles in water.

\[
R-CHO + \text{2-aminophenol} + CH_3COONH_4 \xrightarrow{\text{ultrasonic irradiation}} NC-R + \text{H}_2\text{O}
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Scheme 11. Ultrasound-promoted synthesis of tetrahydrodipyrrozolopyridines in aqueous medium.

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H_2C-C\text{O}_2\text{H} + NH_2\text{NH}_2\text{H}_2\text{O} + R-CHO + CH_3\text{COONH}_4 \xrightarrow{\text{ultrasonic irradiation}} H_2\text{O}, \text{Catalyst free} \to \text{50°C, 1-2.5 h} \to NC-R
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2.1.11. Synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-ones

A series of 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-one derivatives (37) were synthesized with excellent yields in the one-pot, three-component condensations between aromatic aldehydes (1), isatoic anhydride (36), and various amines (14) in the presence of a catalytic amount of p-dodecylbenzenesulfonic acid (DBSA) in water under the influence of ultrasound irradiation at 40–42 °C (Scheme 12). The ultrasonic-irradiated method was found to be superior to the conventional method with respect to reaction times and yields.

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Scheme 12. Ultrasound-promoted synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-ones in water.

2.2. Ultrasound-assisted synthesis of O-heterocycles in aqueous medium

2.2.1. Synthesis of 2-amino-4H-chromenes

2-Amino-4H-chromenes (38) belong to the class of privileged medicinal scaffolds having highly pronounced anticoagulant, diuretic, spasmolitic and anti-anaphylactic activities. After realizing the importance of this moiety, Safari and Javadian (Scheme 13) demonstrated an efficient, environmentally benign,
aqueous-mediated, ultrasound-assisted, one-pot, three-component condensation of aldehydes (1), malononitrile (2) and resorcinol (5) in the presence of a catalytic amount of magnetically-separable Fe$_3$O$_4$-chitosan nanoparticles to afford the corresponding 2-amino-4$H$-chromenes (38) in high yields. Later, Datta and Pasha (Scheme 13)$^{107}$ also developed an ultrasound-assisted protocol for the synthesis of 2-amino-4$H$-chromenes (38) by the same sequence of reactions using glycine as an efficient organo-catalyst in aqueous medium at ambient temperature.

![Scheme 13. Ultrasound-promoted synthesis of 2-amino-4$H$-chromenes in aqueous media.](image)

2.2.2. Synthesis of spiro[oxindoles]

A simple, efficient, environmentally benign, ultrasound-assisted, one-pot three-component protocol was developed for the synthesis of a series of medicinally important spiro[indoline-3,4$'$-pyrano[3,2-c]quinolines (40) in the reactions between isatins (21), malononitrile (2) or ethylecyanoacetate (2a) and 4-hydroxy-2$H$-quinolin-2-one (39) using a small amount of piperidine as a base catalyst in aqueous medium at 50 °C (Scheme 14).$^{108}$ Another novel, efficient, convenient, ultrasound-assisted, environmentally-friendly protocol was developed by Dandia et al. (Scheme 15)$^{109}$ for the synthesis of a series of biologically relevant spiro[chromene-4,3$'$-indolines] (42) and spiro[indoline-3,4$'$-pyrano[2,3-c]pyrazoles] (43) via one-pot, three-component reactions between substituted isatins (21), malononitrile (2) or ethyl cyanoacetate (2a), and dimedone (13) or 3-methyl-1-phenyl-2-pyrazolin-5-one (41) using sodium chloride as a catalyst in water.

2.2.3. Synthesis of pyrano-chromenes and benzopyrano-chromenes

A simple, convenient, ultrasound-assisted, one-pot, three-component protocol was developed by Gohil et al. (Scheme 16)$^{110}$ for the synthesis of a series of biologically relevant 2-amino-3-cyano-pyrano[4,3-b]pyrans (47 and 48) and 2-amino-3-cyano-pyrano[3,2-c]chromenes (49,50) from the reaction between 2-(triazolium(tetrazolium-amino)quinoline-3-carbaldehydes (44/45), malononitrile
(2)/methyl cyanoacetate (2a) and 4-hydroxy-6-methyl-2H-pyran-2-one (46) or 4-
-hydroxy-coumarin (20), respectively, in the presence of a catalytic amount of
L-proline in water at 50 °C.

Representatives

Scheme 14. Ultrasound-promoted synthesis of spiro[indoline-3,4′-pyrano[3,2-
c]quinolone] in aqueous media.

2.2.4. Synthesis of 2-aminobenzo[b]pyran
Recently, a series of synthetic 2-amino-4H-pyrans was evaluated to possess
potent anticancer, antibacterial, and antifungal properties. Such a
handful of diverse applications of 2-amino-4H-pyrans has resulted in a good
number of synthesis methods being available in the literature using various catalysts

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that include urea,\textsuperscript{115} sodium formate,\textsuperscript{116} trisodium citrate,\textsuperscript{117} TBAB,\textsuperscript{118} DBU,\textsuperscript{119} nano ZnO\textsuperscript{120} and MgO.\textsuperscript{121} Although these reported protocols find certain merits of their own, they still suffer from a number of demerits such as the use of toxic organic solvents, long reaction times, heating and harsh reaction conditions. A simple, straightforward, environmentally benign, ultrasound-assisted, one-pot, three-component protocol was reported for the synthesis of a series of bioactive 2-aminobenzo[\textit{b}]pyrans (51) with excellent yields from the reaction of various aromatic aldehydes (1), cyanoacetic esters (2\textit{a}) and dimesone (13) using KF/basic Al\textsubscript{2}O\textsubscript{3} as catalyst in water at room temperature (Scheme 17).\textsuperscript{122}
2.2.5. Synthesis of 1,8-dioxooctahydroxanthenes

In 2006, Jin et al. (Scheme 18) demonstrated a simple, facile, environmentally benign, aqueous-mediated, ultrasound-assisted protocol for the synthesis of bioactive 3,3,6,6-tetramethyl-9-aryl-1,8-dioxooctahydroxanthenes (52) via a pseudo three-component reaction between various aldehydes (1; 1 equiv.) and dimedone (13; 2 equiv.) using 10 mol% p-dodecylbenzenesulfonic acid (DBSA) as catalyst at ambient temperature. Later, in 2010, Rostamizadeh et al. (Scheme 18) developed another efficient ultrasound-irradiated method for the same series of reactions using MCM-41-SO3H as catalyst in water at room temperature.

![Scheme 18. Ultrasound-promoted synthesis of 1,8-dioxooctahydroxanthenes in aqueous media.](CC) 2017 SCS. All rights reserved.

2.2.6. Synthesis of benzo[f or h]chromene

Jin et al. (Scheme 19) described a simple, efficient, mild, water-mediated, ultrasound-assisted, practical procedure for the synthesis of 2-amino-3-cyano-benzo[f]chromenes (6) as well as benzo[h]chromenes (53) by one-pot, three-component reactions between aromatic aldehydes (1), malononitrile (2) and 2-napthol (4) or 1-naphthol (4a), respectively, using a catalytic amount of CTABr as catalyst at room temperature.

2.2.7. Synthesis of various aryl-14H-dibenzo[a,j]xanthenes

A simple, facile, environmentally benign, ultrasound-assisted protocol was reported for the synthesis of various biologically promising benzo[a,j]xanthenes (54) via pseudo three-component reactions between various aldehydes (1; 1 equiv.) and 2-naphthol (4; 2 equiv.) using silica-supported ammonium dihydrogen phosphate (NH4H2PO4/SiO2) as catalyst in water at 40 °C (Scheme 20).
2.2.8. Synthesis of dihydropyrano[2,3-c]pyrazoles

A simple, mild, efficient, sustainable, catalyst-free, water-mediated protocol was developed by Zou et al. (Scheme 21)\(^{127}\) for the synthesis of dihydropyrano[2,3-c]pyrazoles (55) via one-pot, four-component reactions of hydrazine hydrate (10), ethyl acetoacetate (9), various aldehydes (1), and malononitrile (2) under ultrasound irradiation at 50 °C. Ultrasonic irradiation enhanced the rate of the reaction as compared to the conventional stirring method.

2.2.9. Synthesis of 2-aminopyrano[3,2-b]pyrans

A simple, mild, ultrasound-assisted, catalyst-free, green and convenient approach to the synthesis of biologically important 2-aminopyrano[3,2-b]pyrans (57) via one-pot, three-component reactions between various aldehydes...
(1), malononitrile (2) and kojic acid (56) in water was described by Banitaba et al. (Scheme 22). The ultrasonic-irradiated method was found to be advantageous as compared to the conventional stirring method.

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2.2.10. Synthesis of 2-amino-3-cyano-4H-pyran derivatives

A simple, mild, efficient protocol was developed for the synthesis of a series of novel 2-amino-3-cyano-4H-pyran derivatives (59) via one-pot, three-component condensations of aldehydes (1), malononitrile (2) and various active 1,3-dicarbonyl compounds (58) using molecular iodine as a catalyst in aqueous medium under ultrasonic irradiation (Scheme 23). During the optimization for the synthesis of 59a, it was found that the ultrasound (US)-irradiated pathway was more advantageous even than the microwave (MW)-irradiated pathway. Among the various solvents tested, water was found to be the most suitable for these reactions.

2.3. Ultrasound assisted synthesis of S-heterocycles in aqueous media

2.3.1. Synthesis of spiro[indole-3,4'-pyrazolo[3,4-e][1,4]thiazepines]

1,4-Thiazepine derivatives are important because of their significant therapeutic and biological activities. Dandia et al. (Scheme 24) developed a simple, straightforward, efficient, ultrasound-assisted, catalyst-free, one-pot, three-component protocol for the synthesis of biologically relevant spiro[indole-3,4'-pyrazolo[3,4-e][1,4]thiazepines] (61) by the domino reactions of isatins (21), 3-amino-5-methylpyrazoles (18a) and 2-mercaptoacetic acid/2-mercaptopyruvic acid (60) in water at room temperature.
2.3.2. Synthesis of rhodanines

Rhodanines (64), in particular, have immense pharmacological efficacies that include the inhibition of targets such as HCV NS3 protease\textsuperscript{134} and β-lactamase.\textsuperscript{135} Rostamnia and Lamei (Scheme 25)\textsuperscript{136} demonstrated a facile, straightforward, environmentally benign, catalyst-free, ultrasound-assisted, aqueous-mediated protocol for the synthesis of rhodanines (64) from the reactions of various primary amines (14), carbon disulfide (62) and dialkyl but-2-ynedioate (63) at room temperature.

2.3.3. Synthesis of spiro[indole-thiazolidinones]

Dandia et al. (Scheme 26)\textsuperscript{137} reported other simple, convenient, one-pot, three-component tandem reactions of isatins (21), various amines (14) and 2-mercaptoacetic acid/2-mercaptopropionic acid (60) to afford a series of pharmaceutically important spiro[indole-thiazolidinones] (65) using cetyltrimethylammonium bromide [CTAB] as a phase transfer catalyst in water under ultrasound-irradiation at room temperature.

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ULTRASOUND-ASSISTED ORGANIC SYNTHESES IN AQUEOUS MEDIUM

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Scheme 24. Ultrasound-promoted synthesis of spiro[indole-3,4′-pyrazolo[3,4-e][1,4]thiazepines] in water.

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2.3.4. Synthesis of spiro[indole-pyrido[3,2-e][1,3]thiazines]

Arya and his group (Scheme 27)\textsuperscript{138} successfully employed their synthesized ZSM-5 zeolite-supported Brønsted-acid ionic liquid as a catalyst for the synthesis of novel biologically interesting spiro[indoline-3,2'-pyrido[3,2-e][1,3]thiazine]-2,4'(3'H)-diones (67) from one-pot, three-component reactions of isatins (21), various amines (14) and 2-mercaptanonic acid (66) in water under ultrasonic irradiation at room temperature. It was found that for the same catalytic system,
the ultrasound-assisted pathway was much more efficient than the conventional and MW irradiated pathway for this particular synthesis with respect to yield and time.

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<td>4-OCH₃</td>
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<td>88</td>
<td>11</td>
<td>75</td>
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<tr>
<td>9</td>
<td>H</td>
<td>COCH₃</td>
<td>4-CH₃</td>
<td>15</td>
<td>80</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>CH₃</td>
<td>4-CH₃</td>
<td>15</td>
<td>85</td>
<td>12</td>
<td>70</td>
</tr>
</tbody>
</table>

Scheme 27. Ultrasound-promoted synthesis of spiro[indoline-3,2′-pyrido[3,2-ε][1,3]thiazine]-2,4′(3′H)-diones in aqueous media.

2.3.5. Synthesis of 2-aminothiophenes

2-Aminothiophenes are very common in naturally occurring compounds having various pharmaceutical efficacies. In 1976, Gewald first synthesized these scaffolds in a one-pot cyclocondensation of ketones or aldehydes, β-substituted acetonitriles and elemental sulfur. Recently, Mojtahedi et al. (Scheme 28) synthesized a number of substituted 2-aminothiophenes (70) via one-pot, three-component condensations of carbonyl compounds (68), malononitrile (2) or ethyl cyanoacetate (2a) and elemental sulfur (69) in the presence of diethylamine as base in water under ultrasonic irradiation at room temperature.

2.3.6. Synthesis of spiro[indole-3,5′-[1,3]oxathiolanes]

Novel ultrasound-assisted syntheses of substituted spiro[indole-3,5′-[1,3]-oxathiolane]-2(1H)-ones (73) were achieved in the reactions of spiro[indole-3,2′-oxiranes] (71) with thioacetamide (72) using LiBr as catalyst in water at room temperature (Scheme 29). The same reactions were also performed using both microwave and conventional pathways. Interestingly, it was observed that for these particular syntheses, the ultrasonic-irradiated process was superior in comparison to microwave irradiation or the conventional method in terms of reaction rates and yields.
2.3.7. Synthesis of N-(4-arylthiazol-2-yl)hydrazones

Zhang et al. (Scheme 30)\textsuperscript{146} demonstrated a simple, mild, catalyst-free, ultrasound-assisted, high-yielding, one-pot, three-component protocol for the synthesis of N-(4-arylthiazol-2-yl)hydrazones (77) in the reactions of various carbonyl compounds (74), hydrazinecarbothioamide (75) and 2-bromo-1-phenylethanones (76) in water at room temperature. The ultrasonic-assisted pathway was found to be advantageous as compared to the conventional stirring method in terms of reaction times and yields.

3. ULTRASOUND-ASSISTED SYNTHESIS OF OTHER VARIOUS SCAFFOLDS IN AQUEOUS MEDIUM

3.1. Synthesis of bis-coumarins

Bis-coumarins (78) are found to exhibit significant phytochemical efficacies, such as antimicrobial\textsuperscript{147} cytotoxic\textsuperscript{148} and potent HIV-1 integrase inhibitor\textsuperscript{149,150}
activities. The many diverse applications of bis-coumarins have drawn considerable interest of synthetic chemists during the last several years to develop useful synthetic routes to this scaffold of potential interest; as a result, many methods have already been reported.\textsuperscript{151–160} Although these methods possess notable merits, they still suffer from drawbacks, such as the use of toxic organic solvents, harsh reaction conditions, expensive catalysts, longer reaction times, etc. Therefore, in 2012, Al-Kadasi and Nazeruddin (Scheme 31)\textsuperscript{161} developed a simple, efficient, environmentally-friendly, ultrasound-assisted, catalyst-free, one pot, three-component protocol for the synthesis of bis-coumarins (78) by condensing 4-hydroxycoumarin (20) with various aromatic aldehydes (1) in water at ambient temperature.

### 3.2. Aza-Michael addition reaction

Banik and his group (Scheme 32)\textsuperscript{162} described a rapid, simple, straightforward, ultrasound-assisted, catalyst-free reaction between several amines (79) and \(\alpha\)-, and \(\beta\)-unsaturated carbonyls or nitriles (80) to afford the corresponding aza-Michael addition products (81) in water at room temperature. During optimization, the effect of various solvents was tested and water was found to be the superior under ultrasonic-irradiated condition.

### 3.3. Synthesis of dithiocarbamates

Organic dithiocarbamates are important synthetic intermediates of various biologically promising compounds.\textsuperscript{163} Azizi \textit{et al.} (Scheme 33)\textsuperscript{164} reported a simple,
Ultrasonic-assisted organic syntheses in aqueous medium

Scheme 31. Ultrasound-promoted, catalyst-free synthesis of bis-coumarins in an aqueous medium.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time, min</th>
<th>Yield of 81a, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tetrahydrofuran</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>Dichloromethane</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>Acetone</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>Acetonitrile</td>
<td>60</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>Water</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>Solvent-free</td>
<td>15</td>
<td>93</td>
</tr>
</tbody>
</table>

Scheme 32. Ultrasound-assisted synthesis of β-amino carbonyl and related compounds in water.

3.4. Synthesis of β-aminoalcohols

β-Aminoalcohols (86) are useful building blocks of various biologically active natural products,165 unnatural amino acids,166 and chiral auxiliaries.167 A simple, straightforward, environmentally benign, ultrasound-assisted, catalyst-free protocol was reported for the synthesis of β-aminoalcohols (86) from the reactions of epoxides (85) with various primary or secondary amines (79) in water at room temperature (Scheme 34).168
3.5. Synthesis of substituted thiourea

A simple, ultrasound-assisted, catalyst-free, one-pot pseudo three-component condensation of primary (14) or secondary amines (79) with carbon disulfide (62) was described by Azizi et al. (Scheme 35) for the rapid synthesis of various thiourea derivatives (87 and 88) in water at room temperature. Under the same optimized conditions, the reactions also proceeded smoothly in poly(ethylene glycol) (PEG).

3.6. Synthesis of bis(indol-3-yl)methanes

Joshi et al. (Scheme 36) reported an efficient, simple, rapid, ultrasound-promoted protocol for the synthesis of bis(indol-3-yl)methanes (90) in the reactions of indoles (89) with various aldehydes (1) in water using 1-hexenesulphonic acid sodium salt as a catalyst at room temperature.
3.7. Synthesis of 2,2′-(arylmethylene)bis[3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one] derivatives

A simple, straightforward, efficient, ultrasound-assisted protocol was developed for the synthesis of 2,2′-(arylmethylene)bis[3-hydroxy-5,5-dimethyl-2-cyclohexen-1-ones] (91) from the condensations of dimedone (13) with various aldehydes (1) using urea as the catalyst in water at 50 °C (Scheme 37).\textsuperscript{172}

3.8. Synthesis of thioethers

Song \textit{et al.} (Scheme 38)\textsuperscript{173} synthesized 2-[aryl(arylthio)methyl]-3-hydroxy-5,5-dimethylcyclohex-2-enones (93) via simple, efficient, ultrasound-assisted,
one-pot, three-component reactions between aromatic aldehydes (1), substituted thiophenol (92) and dimedone (13) using p-dodecylbenzenesulfonic acid (DBSA) as a catalyst in water at ambient temperature. It was observed that the use of ultrasonic irradiation greatly enhances the rate of the reaction.


Scheme 38. Ultrasound-promoted synthesis of 2-[aryl(arylthio)methyl]-3-hydroxy-5,5-dimethylcyclohex-2-enone in water.

3.9. Synthesis of 1-(amidoalkyl)-2-naphthylamines

A straightforward, efficient, ultrasound-assisted protocol was developed for the synthesis of 1-(amidoalkyl)-2-naphthylamines (96) via one-pot, three-component
condensations of aldehydes (1), acetamide (94) and 2-naphthylamine (95) using silica chloride as a catalyst in aqueous medium at ambient temperature (Scheme 39). Use of organic solvents, such as CH$_3$CN, CHCl$_3$, DCM, DCE and EtOH, gave inferior results in terms of both reaction times and yields. It was also observed that ultrasonic irradiation has a distinct effect on the rate of the reaction.

Scheme 39. Ultrasound-promoted synthesis of 1-(amidoalkyl)-2-naphthylamines in water.

3.10. Synthesis of 2-[3-aryl-1-(2-arylethyl)-2-propen-1-ylidene]hydrazinecarboximidamide hydrochloride

Li et al. (Scheme 40) developed a simple, facile, ultrasound-assisted method for the synthesis of various biologically promising 2-[3-aryl-1-(2-arylethyl)-2-propen-1-ylidene]hydrazinecarboximidamide hydrochlorides (99) by the condensation between 1,5-aryl-1,4-pentadien-3-one (97) and aminoguanidine hydrochloride (98) using p-dodecylbenzenesulfonic acid (DBSA) as the catalyst in water at ambient temperature. It was well demonstrated that the application of ultrasonic irradiation enhances the reaction rate.

3.11. Synthesis of highly substituted propanamide derivatives

A mild, simple, rapid, ultrasound-assisted, one-pot, three-component, catalyst-free approach to the synthesis of highly substituted propanamide derivatives (104) from the reactions of 2-oxopropyl benzoate (100), isocyanide (101) and carboxylic acid (102) or cinnamic acid (103) derivatives in water at room temperature was developed by Ramazani et al. (Scheme 41).

4. CONCLUSIONS

It is the cutting edge for today’s methodologists to develop protocols in greener pathways by avoiding the extensive use of hazardous reagents and solvents,
Entry  | R<sup>1</sup>  | R<sup>2</sup>  | With sonication | Without sonication |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>2-Cl</td>
<td>2-Cl</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<td>3-Cl</td>
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<tr>
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<tr>
<td>12</td>
<td>H</td>
<td>4-Cl</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>


Scheme 41. Ultrasound-promoted synthesis of highly substituted propanamide derivatives in water.

harsh reaction conditions, etc. For this reason, in recent time, aqueous-mediated syntheses are in high demand. Again, it is well established that the application of ultrasonic irradiation in organic synthesis is very advantageous in comparison to the conventional methods. Sometimes it is also more advantageous than a microwave irradiated pathway. Harsh reaction conditions could be avoided by application of ultrasonic irradiation. Therefore, it is not necessary to mention that ultrasound-assisted chemical synthesis in aqueous medium is one of the greenest approaches towards sustainability. As a result, in the recent past, there have been...
an immense number of applications of ultrasound in organic reactions for the synthesis of diverse organic scaffolds in aqueous media. The present review summarizes the latest developments on ultrasound-assisted and water-mediated organic synthesis reported to date.

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