ULTRASOUND-PROMOTED SYNTHESIS OF INDOLE APPENDED HEYEROCYCLES

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ABSTRACT

Ultrasound-assisted synthesis is a green synthetic approach used to accelerate the rate of reaction. This review provides a comprehensive survey relating to syntheses of indole coupled heterocycles with diverse pharmacological activities by ultrasound irradiation. This method is advantageous in simple operative procedures, improvement in the yield, easiness of the recovery of the product and solvent free reaction conditions.

Keywords: Ultrasound, Indole appended heterocycles, Synthesis.

1. INTRODUCTION

Sonochemistry can be defined as a study of chemical reactions under the influence of ultrasound [1]. Sonochemistry operates in the region of 20 kHz to 1 MHz and has many applications due to its high energy and the ability to disperse reagent in small particles and promotes reactions. A process of acoustic cavitation usually occurs (formation, growth and implosive collapse of bubbles irradiated with sound) due to irradiation of high intensity ultrasound. The temperatures of the bubbles are nearly 5000 K and pressures of around 1000 atm. These cavitations can create extreme physical and chemical conditions in otherwise cold liquids [2-5].

Sonochemistry enhances chemical reactions and causes mass transfer. It offers the potential reaction in small time cycles, cheaper reagents and less extreme physical conditions [6-8]. Ultrasonic-assisted organic synthesis as a green synthetic approach is a powerful technique that is being used more and more to increase reaction rate [9-11]. It can also be considered as
important tool for conservation of energy and minimization of waste as compared to the convectional techniques [12].

The literature reveals excellent review of Cella and Stefani used the available literature which clearly shows the importance of taking advantage of the unique features of ultrasound-assisted reactions to synthesize heterocyclic ring systems [13]. The indole moiety is probably the most well-known heterocycle found in a variety of natural products and medicinal agents [14]. Indole analogues were established as a potent antimicrobial, anti-inflammatory, analgesic, anticonvulsant, anti malarial, anticancer, antiulcer, anti leishmanial, contraceptive, antioxidant etc. Indole derivatives are also having agonistic effects on several receptors [15].

This review will therefore limit its coverage of the literature and focus on the use of ultrasound to promote the reactions employed to obtain amalgamation of various heterocyclic rings with indole. In this review, some reports for syntheses of various heterocycles coupled with indole under conditions of ultrasonic irradiation are reviewed.

2. SYNTHESIS OF BIS-INDOLE
In this context, synthesis of bisindoles 3 from indole 1 and substituted carbonyl compounds viz. aldehyde or ketones 2 are described. Sonar et al. [16] synthesized bis(indolyl)methanes 3 by the reaction of indole 1 with various aldehydes and ketones 2 under the influence of ultrasound in solvent-free condition by using alum. Alum (KAl(SO$_4$)$_2$.12H$_2$O) is an inexpensive, non-toxic and mild catalyst. Ghodrati et al. [17] developed a green and efficient procedure for the preparation of bis(indolyl)methanes 3 via the condensation of indoles 1 with various carbonyl compounds 2 in presence of catalytic amount of nanosilica gel under ultrasonic irradiation in solvent-free condition. The nanosilica gel was used as an inexpensive and readily available catalyst without any support of reagent or modification on it. Li et al. [18] synthesized bis(indolyl)methanes 3 by condensation of indole 1 with various carbonyl compounds (aldehydes/ketones) 2 in the presence of silico tungustic acid (SiO$_2$.12WO$_3$.24H$_2$O) as a catalyst under ultrasonic irradiation in good to excellent yields in ethanol. This method is advantageous in short reaction time, simplicity in operation and green aspects as compared to conventional methods. Joshi et al. [19] used 1-Hexenesulphonic acid sodium salt (C$_6$H$_{11}$SO$_3$Na) as catalyst for green synthesis of bis(indol-3-yl)methanes 3. The reaction of indole 1 with various aldehydes 2 in
water using ultrasound irradiation at ambient temperature for appropriate time using 1-hexenesulphonic acid sodium salt furnish the desired product in good to excellent yield.

Li et al. \(^{[20]}\) carried out ultrasound-promoted synthesis of bis(indolyl)methanes 3 catalyzed by ammonium bisulphate (ABS) via the reaction of indole 1 or N-methyldindole with aromatic aldehydes 2 in excellent yields in aqueous media at 23–25 °C.

Li et al. \(^{[21]}\) synthesized bis(indolyl) methanes 3 via electrophilic substitution reactions of indoles 1 with aromatic aldehydes and ketones 2 catalyzed by aminosulfonic acid (H\(_2\)NSO\(_3\)H) was in 23–96% yield at 30–38 °C in ethanol aqueous solution under ultrasound irradiation.

Heravia et al. \(^{[22]}\) synthesized bis(indolyl)alkanes 3 in excellent yields in the presence of catalytic amount of silica-supported Preyssler nano particles (H\(_{14}\)[NaP\(_5\)W\(_{30}\)O\(_{110}\)]/SiO\(_2\)) as green, reusable and efficient catalyst under ultrasonic irradiation.

Mo et al. \(^{[23]}\) presented ultrasound-promoted synthesis of bis(indolyl)methanes 3 catalyzed by acidic Ionic liquid [(CH\(_2\))\(_4\)SO\(_4\)HMIM][HSO\(_4\)].

Vahdat \(^{[24]}\) efficiently synthesized bis(indolyl)methanes 3 by the reaction of indole 1 with certain aldehydes and ketones 2 in water which afforded the corresponding bis(indolyl)methanes in excellent yields. This reaction has been carried out in the presence of 2 mol% of cerium (IV) trflate at room temperature.
3. SPIRO-INDOLE SYNTHESIS
3.1. Spiro (indole-pyridine)
Dabiri et al. [25] synthesized new and efficient method for synthesis of spirooxindoles. This procedure involves multi-component reaction of isatin 4, furan-2,4(3H,5H)-dione 5, 2-hydroxynaphthalene-1,4-dione 6 and ammonium acetate 7 to afford spirooxindoles 8 in presence of a catalytic amount of p-toluene sulphonic acid (p-TSA) as an inexpensive and available catalyst in ethanol under ultrasound irradiation (Scheme 2).

Bazgir et al. [26] reported a simple, one pot, efficient and three-component procedure for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4-b]pyridine]-2,6′(1′H)-diones 11 by the reaction of isatins 4, 4-hydroxycumarin 9, and 1H-pyrazol-5-amines 10 in water using p-toluene sulphonic acid (p-TSA) under ultrasonic irradiation. The use of water as a solvent is considered to be eco-friendly method (Scheme 3).

Ghahremanzadeh et al. [27] synthesized three-component, one-pot condensation reaction of isatins 4, 1H-pyrazol-5-amines 10 and barbituric acids 12 in aqueous media to afford a novel spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine]trione derivative 13 (Scheme 4).
3.2 Spiro(indole-pyrrolidine)

Chen et al. [28] published a study of reactions of isatin 4, α-amino acids 14 and 1,4-naphthoquinone 15 using ultrasound in methanol at about 40 °C to afford a series of 3-spiro[pyrrolidino-oxindole] derivatives 16 in good to excellent yields (Scheme 5).

Tabatabaei rezaei et al. [29] obtained synthetic route for the preparation of a novel class of dicyano-functionalised spiropyrrrolizidine 18 and spiropyrrrolidine 19 from the reaction of various arylidenedimalononitrile 17 Knoevenagel adducts with non-stabilized azomethine ylides generated from isatin 4 and α-amino acids 14 (sarcosine/N-phenylglycine/proline) (Scheme 6).

Ge et al. [30] synthesized a class of novel tetracyclic dispiropyrrrolizidines 21 via the 1,3-dipolar cycloaddition of azomethine ylide using isatin 4, α-amino acids 14 and 3-
benzylidene-3,4-dihydroquinolin-2(1H)-one **20** under ultrasound irradiation conditions (Scheme 7).

![Scheme 7.](image)

Hu et al. and Liu et al. \(^{[31]}\) worked on catalyst-free 1,3-dipolar cycloaddition reactions to yield compounds **23** and **24** by using 5-benzylidenethiazolidine-2,4-dione **22** and isatin **4** promoted by ultrasound \([31-a]\). H. Liu et al. investigated use of sarcosine and proline in this reaction \([31-b]\) (Scheme 8).

![Scheme 8.](image)

### 3.3 Spiro(indole-thiazolidinone)

Dandia et al. \(^{[32]}\) developed a straightforward aqueous-mediated ultrasound-promoted synthesis of spiro [indole-thiazolidinone] libraries **27** from isatin **4**, substituted amines **25** and thioglycolic acid **26** by using cetyl trimethyl ammonium bromide (CTAB) as a phase transfer catalyst. The method is more convenient and efficient as compared to multistep conventional processes and it obviates the azeotropical removal of water and use of carcinogenic solvents and dehydrating agents (Scheme 9).

![Scheme 9.](image)
3.4 Spiro (indole-pyranopyrazole)

Zou et al. [33] reported an efficient one-pot synthesis of spiroydol-3,4'-pyrano[2,3-c]pyrazole] derivatives 31 by four-component reaction of isatin 4, β-keto ester 28, hydrazine 29 and malononitrile or ethyl cyanoacetate 30 catalyzed by piperidine under ultrasound irradiation (Scheme 10).

![Scheme 10](image)

3.5 Spiro(indole-pyrazolo phthalazine)

Wang et al. [34] synthesized a series of 3'-aminospiro[indoline-3,1'-pyrazolo[1,2-b]phthalazine]-2,5',10'-trione derivatives 33 by a one-pot three-component reaction of isatin 4, malononitrile or ethyl cyanoacetate 30 and phthalhydrazide 32 using as a catalyst piperidine under ultrasound irradiation (Scheme 11).

![Scheme 11](image)

3.6 Spiro(indole-pyrazolo thiazepines)

Dandia et al. [35] carried out catalyst-free aqueous mediated multicomponent domino reaction of isatin 4, dimethyl pyrazole 34 and thioglycollic acid 26 affording novel spiroydol-3,4'-pyrazolo[3,4-e][1,4]thiazepines] 35 using sonication in excellent yield and shorter time. This method is catalyst-free advantageous over conventional method. The synthesized compounds were screened for their anti-hyperglycemic activity to inhibit the enzyme α-amylase (Scheme 12).
3.7 Spiro (indole-pyridothiazine)

Arya et al. [36] developed zeolite supported Brønsted-acid catalyst system (Ionic liquid supported on ZSM-5 zeolite) for the aqueous-mediated ultrasound-promoted synthesis of novel N-substituted spiro heterocycles 37 by the reaction of isatin 4, amines 25, and 2-mercaptanonicotinic acid 36 (Scheme 13).

3.8 Spiro (indole-quinazoline)

Rambabua et al. [37] designed a series of N-indolylmethyl substituted spiroindoline-3,2′-quinazolines 39 as potential inhibitors of SIRT1. These derivatives were synthesized in good yields by using Pd/C–Cu mediated coupling-cyclization strategy as a key step involving the reaction of N-substituted isatin 4 and 2-aminobenzamide 38. The synthesized derivatives have shown inhibition of SIR 2 protein (a yeast homologue of mammalian SIRT1) in vitro (Scheme 14).
3.9 Spiro (indole-oxirane)
Dandia et al. [38] an alternative and environmentally benign pathway for diastereoselective synthesis of fluorinated spiro[indole-3,2′-oxirane]-3′-benzoyl-2(1H)-ones is reported. The spiro[indole-3,2′-oxiranes] derivatives 42 were obtained in 90–97% yield exclusively via the epoxidation of 3-arylmethylene indole-2-ones 40 with 30% aqueous hydrogen peroxide 41 using cetyltrimethyl ammonium bromide as a phase transfer catalyst under ultrasound irradiation. The lead compounds have been tested for their antimicrobial activity and antioxidant properties (Scheme 15).

\[
\begin{align*}
\text{R} & \quad \text{H}_2\text{O}_2 & \quad \text{CTAB} & \quad \text{US, 90-97 %} \\
\text{R}_1 & \quad \text{41} & \quad & \text{42}
\end{align*}
\]

Scheme 15.

3.10 Spiro(indole-oxathiolane)
Dandia et al. [39] synthesized a aqueous mediated method for the preparation of 2′amino-4′benzoyl-2′-methyl spiro[indole 3,5′-[1,3]oxathiolane]-2(1H)-ones 44 from the reaction of spiro [indole-3,2′-oxiranes] 42 with thioacetamide 43 in the presence of Lithium bromide as catalyst (Scheme 16).

\[
\begin{align*}
\text{R}_1 & \quad \text{H}_2\text{C} & \quad \text{NH}_2 & \quad \text{LBF} & \quad \text{US} \\
\text{42} & \quad \text{43} & \quad & \text{44}
\end{align*}
\]

Scheme 16.

4. MICHEAL ADDITION (B-INDOLYLKETONES)
Fu et al. [40] developed a solvent free procedure for the synthesis of 3-substituted indole derivatives 47 from indole 1 and nitroalkanes 45 using 2-chloroethanol 46 as solvent under ultrasound irradiation. The use of 2-chlorethanol as a mild acidic promoter supports the practical utility of this procedure for a wide variety of indoles and nitroalkenes. The use of equimolar substrates, simplicity of operation, high efficiency of promoter, environmentally benign reaction conditions as well as facility of scale-up enable the advantages and potentials to this methodology (Scheme 17).
Shen et al. \cite{41} synthesized a novel base-catalysed approach for the synthesis of β-indolylketones. They developed a convenient, efficient and practical method for the one-pot synthesis of β-indolylketones 49 via a condensation of indole 1, aromatic aldehydes 2 and deoxybenzoin 48 under ultrasonic irradiation (Scheme 18).

Ji et al. \cite{42} carried out the synthesis of β-indolylketones. This p-TSA catalysed Michael addition of indole 1 to unsaturated carbonyl ketones 50 under ultrasonic irradiation to afford the corresponding product β-indolylketones 51 in excellent yields (up to 94\%) (Scheme 19).

Li et al. \cite{43} synthesized Silica sulfuric acid (SSA) catalyses the Michael addition of indole 1 to α,β-unsaturated ketones 50 under ultrasonic irradiation to afford the corresponding β-indolylketones 51 in 50-85\% yields at room temperature. (Scheme 20)
Baron et al. \[44\] synthesized β-indolylketones 47 using variety of nucleophiles 53 provided by activated methylenes have been added on 3-(2-nitrovinyl)-1H-indole 52 in very good to excellent yields, under sonication and solvent-free conditions, using solid potassium carbonate or sodium acetate as a base. Direct synthesis avoiding preliminary NH protection is reported and exemplified to 15 molecules (Scheme 21).

Li et al. \[45\] worked on synthesis of 2-((1H-indol-3-yl)(aryl)methyl)malononitrile 55 via the Michael addition of indole 1 with various arylmethylenemalononitriles 54 was carried out in good yields using anhydrous zinc chloride as the catalyst under ultrasound irradiation (Scheme 22).

Li et al. \[46\] reported Michael addition reaction of indole 1 with 1,5-diaryl-1,4-pentadien-3-ones 56 catalysed by AlCl₃ under ultrasonication at room temperature to give β-indolylketones i.e. monoaddition products 57 and bis-addition products 58 (Scheme 23).
5. EPOXIDE RING OPENING

Li et al. [47] synthesized synthesis of 3-aryl-3-hydroxy-2-(1H-indol-3-yl)-1-phenyl-1-propanone 60 by the cleavage of epoxides 59 with indole 1 by ultrasound irradiation in good yields catalyzed montmorillonite K10-ZnCl$_2$ within 2–5 h at room temperature (Scheme 24).

Khorshidi [48] used a recyclable catalyst Ruthenium-exchanged FAU-Y zeolite (RuY) for region selective ring-opening of epoxides 61 with indoles 1 under ultrasound irradiation to give compound 62. This method is solvent free and provides good yields of the desired products (Scheme 25).

6. INDOLE FUSED WITH IMIDAZOLE

Damavandi et al. [49] performed one-pot synthesis of 3,4-dihydro-2-arylimidazo[4,5-\textit{b}]indole 63 compounds through the three-component reaction of aromatic aldehydes 2, isatin 4 and ammonium acetate 7 using a catalytic amount of L-proline as catalyst under ultrasonic
irradiation. This method offers a several advantages including mild reaction conditions, high yields of products as well as a simple experimental and applicability (Scheme 26).

![Scheme 26](image)

Damavandi et al. [50] synthesized one-pot procedure for preparation of 3,4-dihydro-2-arylimidazo[4,5-b]indole 63 and 2-aryl-1H-imidazo[4,5-f][1,10]phenanthroline 64. The procedure proceeded by the multi-component reaction of aromatic aldehydes 2, indoline-2,3-dione 4 or 1,10-phenanthroline-5,6-dione 64 and ammonium acetate 7 catalyzed by L-proline under ultrasonic irradiation using different solvents viz. ethanol, methanol, acetonitrile, ethyl acetate (Scheme 27).

![Scheme 27](image)

7. MANNICH REACTION OF INDOLE (SYNTHESIS OF GRAMINE)

Li et al. [51] synthesized Mannich bases 68 related to gramine via Mannich reaction of secondary amine 67, formaldehyde 66 and indole or N-methylindole 1 in 69–98% yields in acetic acid aqueous solution at 35°C under ultrasound irradiation (Scheme 28).

![Scheme 28](image)
8. INDOLE FUSED WITH QUINAZOLINE

Avalani et al. [52] developed a simple and efficient one pot synthesis of isoindolo[2,1-a]quinazoline 71 catalyzed by *Saccharomyces cerevisiae* (baker's yeast) as a whole cell biocatalyst at room temperature under ultrasonication. This work also discussed about the synergetic effect of baker's yeast and ultrasound irradiation (Scheme 29).

![Scheme 29.](image)

9. INDOLE FUSED WITH QUINONE

Liua et al. [53] reported the synthesis of 3-indolylquinones 73 efficiently catalyzed by molecular iodine under ultrasonic irradiation to afford in good to excellent yields. The conjugate addition reactions of indoles 1 with quinones 72 which provided a novel, mild, convenient approach for the preparation of 3-indolylquinones 73 (Scheme 30).

![Scheme 30.](image)

10. PYRANOINDOLE

Demavandi et al. [54] found that ultrasound irradiation was the rapid and efficient method for synthesis of novel 2-amino-4,5-dihydro-4-arylpyrano[3,2-b]indole-3-carbonitriles 75 from indol-2-ol 74, aldehydes 2 and malononitrile 30 using the catalyst Potassium dihydrogen phosphate (KH₂PO₄) (Scheme 31).

![Scheme 31.](image)
11. CHROMENEINDOLE

Nia et al. [55] synthesized novel fused 1H-benzo[f]chromen-indole derivatives 78 regioselectively in good to high yields by triethyl amine catalyzed condensation of 3-cyanoacetylindoles 76, β-naphthol 77 and aldehydes 2 in methanol under ultrasounic irradiations. The synthesized derivatives were screened for antibacterial activity against gram positive and gram negative micro-organisms. Some of the compounds showed significant antibacterial activity (Scheme 32).

![Chemical Structure Image](https://example.com/structure.png)

Scheme 32.

12. DI SUBSTITUTED INDOLE

Wang et al. [56] developed ceric ammonium nitrate efficiently catalyzed the reaction of isatin 4 with indoles 5 under sonic waves to afford symmetrical 3,3-di(indolyl)indol-2-ones 79 and reaction of 3-hydroxy-3-indolylindolin-2-ones 80 with indoles 1 to afford the corresponding adducts 81 in excellent yields. This methodology provides an efficient route to the synthesis of symmetrical and unsymmetrical 3,3-di(indolyl)indol-2-one derivatives (Scheme 33).

![Chemical Structure Image](https://example.com/structure.png)

Scheme 33.
13. MISCELLANEOUS REACTIONS

Khorshidi et al. [57] reported simple and efficient synthesis of 3-indolyl-3-hydroxyoxindoles 80 from indole 1 and isatin 4 by a simultaneous application of ultrasonic waves and Fe(III) as a catalyst which results in greater efficiency in terms of reaction time and yield. The synthesized compounds were mono indolylated isatins. The reusability of the catalyst and environmentally friendly conditions are also noticeable (Scheme 34).

Koulocheri et al. [58] prepared a series of 2,3-bis(4-hydroxyphenyl)indole derivatives 82 by ultrasound-promoted intra molecular cyclo dehydration of a polyphosphoric acid solution of α-anilinyl- (or 3-anisidyl)desoxyanisoinns and their optical spectroscopy and estrogen receptor (ER) binding properties were studied. Compounds give intense long-wavelength fluorescent emission, sensitive to solvent polarity and pH (Scheme 35).

14. CONCLUSION

Ultrasound-assisted synthesis is an important tool of green chemistry. As illustrated by the examples presented herewith, the reactions of indole appended heterocycles can be modified through new approaches related to green chemistry. In medicinal chemistry, these new approaches have been used in the development of more eco-friendly processes to get the drug products and chemical processes. As we have shown in the review, several convenient ultrasound-promoted synthetic methodologies have been established for the preparation of the title class of compounds. The main advantages of the use of ultrasound in the synthesis of various derivatives of indole are evident when compared with classical methodologies i.e., a
reduction in the reaction times and an improvement in the yields. Most of the literature covered by this review employed simple ultrasonic procedures in mild conditions.

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