A Review on Various Synthetic Methods of Benzoxazole Moiety

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Abstract
In this review an attempt has been made to provide different available methods to synthesize Benzoxazole molecule not only through the traditional synthetic approach but also by using different catalysts, nanoparticles, and green synthesis. The present research work mainly focused on synthesis of benzoxazole derivatives from year 2010 onwards has been extracted from reputed journals and compiled into the review article.

Keywords
Benzoxazole, Catalysts, Green Synthesis, Nano Catalyst.

INTRODUCTION:
Among all the heterocyclic compounds, Benzoxazole is one of the most significant heterocycle showing remarkable pharmacological activities. As a result of deep research in the field of synthesis and modifications involving the benzoxazole nucleus has generated large number of molecules having diverse applications in the field of medicinal chemistry. The structural study and biological activities of benzoxazole derivatives has been a research interest, due to potential biological and pharmacological activities exhibited by them. Literature survey revealed that the benzoxazole moiety possesses most remarkable and a wide range of biological activities. Benzoxazole is common heterocycles in the field of drugs. Previous reports have revealed that substituted benzoxazole possess diverse chemotherapeutic activities including antimicrobial¹,²,³, antiviral⁴, antibiotic⁵, and antitumor activities⁶. Study has revealed that substituted benzoxazoles and related heterocycles are biologically active with lower toxicities⁷. Benzoxazoles are interesting fluorescent compounds and they are studied as potential bleaching herbicides⁸. They have also shown low toxicity in warm-blooded animal⁹.

Chemistry:
Benzoxazole is a planar molecule of the cyclic system having conjugated π electrons. The weak basic property of benzoxazole is because of the nitrogen lone pair of electrons which is coplanar with heterocyclic ring hence it is not involved in delocalization.
2-Heteroatom-substituted benzoxazoles may exist in two tautomeric forms 2 and 3. The X-ray analysis of such compounds shows that benzoxazol-2(3H)-one 2 (X = O), benzoxazole-2(3H)-thione 2 (X = S), and N-benzylbenzoxazol-2(3H)-imine 4 (R = Bn) exist with an exocyclic double bond in the crystalline form. In benzoxazole, C-2 atom is the only electrophilic reactive site of the molecule.

**Synthetic Approach:**
Benzoxazole moiety is synthesized in different ways. In which most of the synthetic procedure includes addition of CS₂/KOH and by means of PPA. There are various other synthetic methods too, which includes by the addition of CNBr, by means of aldehydes and some chemical agents like DDQ, IBD etc. Most of the synthetic methods used aminophenol as one of the major reactant to synthesize benzoxazole moiety. Condensation of o-aminophenol by means of carbon disulfide in the presence of base like potassium hydroxide or sodium hydroxide gave the required benzoxazole in good yield (Scheme 1).

4-Carbomethoxy-2-aminophenol (6, R: COOCH₃) was treated with Cyanogen bromide to give 2-aminobenzoxazole (7) in good yield (Scheme 2)²⁹,²⁰ methoxy-aminophenol (6, R:OCH₃) with CNBr gives 2-aminobenzoxazole (7)³¹.
According to literature cyclizing agent like PPA is used for benzoxazole synthesis, 2,4 diaminophenol (8) and 1,4- naphthalene dicarboxylic acid (9) were dissolved in poly(phosphoric acid) (PPA) under nitrogen atmosphere to produce a thick paste of 1,4-di(5-aminobenzoxazol-2-yl)naphthalene \(^{22}\) (Scheme 3).

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\[
\begin{align*}
\text{ClH}_2\text{N} & \quad \text{NH}_2\text{HCl} \quad + \\
& \quad \text{HOOC} \quad \text{COOH} \\
& \quad \text{PPA} \\
& \quad \text{H}_2\text{N} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

Scheme 3

5-amino-2-(4-tert-butyl-phenyl)-benzoxazole (13a) synthesized by taking 2,4-diaminophenol (11a) with p-tert-butyl benzoic acid (12a) in polyphosphoric acid\(^ {23}\), o-aminophenol (11b) reacted with aminobenzoic acid (12b) in the presence of PPA gives 3-(benzo[d]oxazol-2-yl)aniline (13b)\(^ {24,25}\), Synthesis of 2-(20-Hydroxyphenyl)benzoxazole (13c) by 5-Formylsalicylic acid (12c) and 2-aminophenol (11c) in polyphosphoric acid stirred at 180°C for 5 hour\(^ {26}\) and 2,4-Dihydroxybenzoicacid (12d) with o-aminophenol (11d) in polyphosphoric acid forms dark brown precipitate which is (1H-benzo[d]oxazole-2-yl) benzene-1,3-diol (13d)\(^ {27}\). 2-(3,4-Diethoxyphenyl) benzoxazol-5-amine (13e) was prepared by heating 2,4-diaminophenol (11e) and 3,4-dimethoxybenzoic acid (12e) in presence of cyclizing agent PPA\(^ {28}\). 5-amino-2-(20-hydroxy-40-methylphenyl) benzoxazole (13f) was synthesized by the reaction of 2,4-diaminophenol (11f) and 4-methylsalicylic acid (12f) in polyphosphoric acid (PPA) at 150°C (Scheme 4)\(^ {29}\).

A mixture of 2-amino-4-bromophenol (14) and 5-(trifluoromethyl) pyridin-2-amine (15) in 1 M NaOH was stirred at 85°C for 3 h to get 5-(5-}

\[
\begin{align*}
11a: R=\text{NH}_2 & & 12a: 4-(\text{CH}_3)_3 \\
11b: R=\text{H} & & 12b: 3-\text{NH}_2 \\
11c: R=\text{H} & & 12c: 2-\text{OH}, 5-\text{CHO} \\
11d: R=\text{H} & & 12d: 2-\text{OH}, 4-\text{OH} \\
11e: R=\text{NH}_2 & & 12e: 2-\text{OH}, 4-\text{OH} \\
11f: R=\text{NH}_2 & & 12f: 3-\text{OCH}_3, 4-\text{OCH}_3 \\
& & 13a: R_1=\text{C}(\text{CH}_3)_3, R=\text{NH}_2 \\
& & 13b: R_1=\text{NH}_2, R=\text{H} \\
& & 13c: R_1=\text{OH}, \text{CHO}, R=\text{H} \\
& & 13d: R_1=\text{OH}, \text{OH}, R=\text{H} \\
& & 13e: R_1=\text{OH}, \text{OH}, R=\text{NH}_2 \\
& & 13f: R_1=\text{OCH}_3, \text{OCH}_3, R=\text{NH}_2
\end{align*}
\]

Scheme 4
A mixture of 2-aminophenol (17) and 4-benzyloxy benzaldehyde (18) was refluxed in ethanol followed by oxidative cyclization with lead tetra acetate gives 2-[4-(Benzyloxy)phenyl]-1,3-benzoxazole compound (20a) (Scheme 6)\(^{31}\). A mixture of schiff base compound (19) and manganese(III) acetate in DMSO was kept at 140 °C for 24 h to get 3-Benzoxazole-N-Ethyl Carbazole (20b) (Scheme 6)\(^{32}\).

Lead tetra acetate also used in the synthesis of 2-(4-nitrophenyl)-6-(tetradecyloxy)benzo[d]oxazole molecule (22a)\(^{33}\), Dess–Martin periodinane (DMP), a highly versatile hypervalent iodine(V) reagent, was found to efficiently mediate the intramolecular cyclization of phenolic azomethines/Schiff bases at ambient temperature leading to the rapid and expeditious synthesis of substituted benzoxazoles (22b) (Scheme 7)\(^{34}\).

The Diversity-oriented synthesis of substituted benzoxazole via potassium persulfate - CuSO\(_4\) mediated oxidative coupling reactions of aldehydes in aqueous micelles (Scheme 8)\(^{35}\), 2-arylbenzoxazoles (25b) were directly synthesized from substituted 2-aminophenols (23b) and aldehydes in the presence of activated carbon in xylene under an oxygen atmosphere (Scheme 8)\(^{36}\).
The elemental sulfur was good oxidant in the presence of N-methyl piperidine for rearranging oxidative coupling between o-aminophenol (26) and ketones (27) to give 2-alkylbenzoxazoles (28) (Scheme 9).
Potassium ethylxanthate and 2-amino-5 nitrophenol (34) in dry pyridine was kept for stirring for 6 hour at 120°C, followed by keeping the same reaction mixture for another 16 hour at room temperature and added 2M HCl solution to adjust the pH value to 6 to get 6-nitrobenzo[d]oxazole-2-thiol (35) (Scheme 12).

The mixture of substituted anilines (36) and substituted orthoesters (37) in the presence of BF₃OEt₂ at room temperature gives substituted benzoazole (38) (Scheme 13).

A mixture of di-(imidazole-1-yl)-methanimine and compound 2-amino-5(trifluoromethoxy)phenol (39) in DMF was refluxed overnight under nitrogen atmosphere to get 2-amino-6(trifluoromethoxy)benzoxazole (40) (Scheme 14).

A direct base-mediated intramolecular reaction without a transition-metal catalyst by using K₂CO₃ in DMSO at 140 °C forms benzoxazole derivative (42) (Scheme 15).
Benzoylthioureas (43) were reacted using diacetoxyiodobenzene (DIB) in presence of base, the expected benzothiazoles (44') were not obtained, unexpected benzoazoles (44) were found (Scheme 16). 

Azido complexes in nitrogen extrusion reaction used for synthesis of benzoazole by taking o-hydroxy aryl ketones (45), the benzoazole (46 & 47) formed was by the nitilium ion of an aryl migration because of rearrangement of the initial azido intermediates (Scheme 17).

Phosphonated Benzoazole Derivatives (49) synthesized by using 2-amino-3-hydroxy-1-benzenephosphonic acid (48) and Methyl cyanide (Scheme 18).

2-isocyanophenylxyacrylate (50) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (51) used to synthesize (E)-methyl 3-(2-(benzo[d]oxazol-2-yl)phenyl)acrylate (52) (Scheme 19).
Synthesis by using Catalyst:
As every synthetic chemical reaction require activation energy to proceed, catalysts which lowers that energy barrier and begins the reaction without involving themselves in the chemical changes.

The several synthetic methods of benzoxazole discussed above suffer from one or more of the drawbacks such as requirement of lengthy reaction times, high consumption of energy, very high temperature, lesser yields, tedious process etc., Thus, there is a strong demand for a highly efficient catalyst for the synthesis of heterocycles. Several methods have been developed to access this framework, in which eco-friendly and cost-effective catalyst has been attracting research interest from chemists. Following is the compilation of the catalytic approach for synthesis of benzoxazoles.

![Chemical Structure](image)

**Scheme 19**

The condensation of aromatic aldehyde (53a) with 2-aminophenol (54a) catalyzed by NH₃(CH₂)₂NH₃BiCl₅ as heterogeneous and recyclable catalyst was reported for the synthesis of 2-phenyl-1H-benzo[d]imidazole (55a)⁴⁸, Phenylboronic acid catalyzed-cyanide promoted reaction followed by addition of KCN gives one-pot synthesis of 2-(2-hydroxyphenyl)benzoxazole derivatives (55b)⁴⁹, Zinc triflate-catalyzed synthesis of 2-substituted benzoxazoles (55c) from 2-aminophenols (54c) and aldehydes (53c)⁵⁰, Silica supported ferric chloride (SiO₂-FeCl₃) is used for the Synthesis of Benzoxazole (55d)⁵¹, Synthesis of benzoxazole (55e) in high yields by coupling of o-aminophenol (54e) with aldehydes (53e) by using TiCl₃OTf in ethanol at ambient temperature (Scheme 20)⁵².

![Chemical Structure](image)

**Scheme 20**

The various 2-aminobenzoxazoles (58) and other benzoxazole derivatives prepared using a catalytic amount of poly (ethylene glycol)-bound sulfonic acid (PEG-SO₃H) (Scheme 21)⁵³.
Synthesis of 2-phenyl benzoxazole (61) (scheme 22) by means of various catalysts, R (% yield): Al-Cu-Cl$^-$ (99%), Al-Zn-PO$_4^-$ (76%), Mg(OH)$_2$ (63%), Al$_2$O$_3$ (61%), Ca(OH)$_2$ (59%), Al-Zn-Cl$^-$ (56%), SiO$_2$ (56%), MnO$_2$ (51%), Al(OH)$_3$ (42%), AlCl$_3$ (41%$^4$).

Propylsulfonic acid functionalized SBA-15 (SBA-Pr-SO$_3$H) was used as catalyst for 2-arylbenzoxazoles (64) synthesis from benzoyl chloride derivatives and 2-aminophenol (62) (Scheme 23)$^{55}$.

Indion 190 resin used as efficient, environmentally friendly, and reusable catalyst for synthesis of benzoxazoles (67a)$^{56}$, nickel supported silica$^{57}$ and Samarium triflate [Sm(OTf)$_3$]$^{58}$ used for the synthesis of benzoxazole derivatives from aminophenol and aldehyde, also synthesis of 2 aryl benzoxazoles catalyzed by KCN/MWCNT using ultra sound (67d) (Scheme 24)$^{59}$.
The reaction between substituted 2-aminopenol and 1H-1,2,3-triazole-4-carbaldehyde (68) gives 1,2,3-triazole moiety of benzoxazole (69) by using copper (II) acetylacetonate as catalyst (Scheme 25).

![Scheme 25]

Ruthenium-Catalyzed Synthesis of 2-phenylbenzo[d]oxazole (72) Using acceptorless dehydrogenative coupling (ADC) Reaction of Primary Alcohols like phenyl methanol (71) with 2-aminophenol (70) (Scheme 26).

![Scheme 26]

The synthesis of benzoxazole linked with benzimidazole (74) was achieved by copper catalyzed reaction carried in sealed tube for 12 hours at 190°C (Scheme 27).

![Scheme 27]

Palladium catalyzed reaction between o-aminophenol (75) and Isocyanides (76) gives 2-aminobenzoxazoles (77) in the presence of dioxane (Scheme 28).

![Scheme 28]

Combined Catalyst of Bronsted Acid and Copper Iodide is used for synthesis of 2-methylbenzoxazole (80) from 2-aminophenols (78) and β-Diketones (79) (scheme 29).
Palladium used as catalyst for (E)-2-(4-methoxystyryl) benzo[d]oxazole (83) synthesis by aminocarbonylation method in the presence of 2-aminophenol (81) and (E)-1-(2-bromovinyl)-4-methoxybenzene (82) (Scheme 30)\(^6\).

2-aryl substituted benzoxazole (86) prepared by the reaction of substituted 2-aminophenol (85) and heterocyclic aldehydes (84) in the presence of composite catalyst as TiO\(_2\) – ZrO\(_2\) at moderate temperature (Scheme 31)\(^6\).

\[^{65}\] N-(2-iodo/bromophenyl) benzamides used for CuI-catalysed synthesis of benzoxazoles (88) from methyl-2-methoxybenzoate as the ligand (Scheme 32)\(^6\).

**Synthetic approach via Nanotechnology:**
Although the synthesis of substituted benzoxazole by using some catalyst, ultrasound irradiation, and microwave irradiation methods have their own advantages, it also possesses certain disadvantages like highly toxic reagents or severe reaction conditions, strong acids, unapproachable materials, costly instruments, non-recyclable and non-selectivity, and so forth. To overwhelmed these, the nanocatalyst plays an important role.

The nanocatalysts are highly selective, stable and reactive; thereby it overtakes the conventional catalyst. The nanoparticle catalytic activity is depends on size, hence altering the particle size the
relative ratio of surface atom also changes. Size and surface of the nanocatalyst play a major part because it is the reason for its selectivity and reactivity. The synthesis of benzoxazole using Fe(III)–Schiff 5 base/SBA-15 as a nanocatalyst in water along with aminophenol and 4-(dimethylamino)benzaldehyde (90a), ZnO nanoparticles used as a green efficient catalyst in the room temperature for the synthesis of 2-aryl1,3-benzoxazole derivatives (91b)\textsuperscript{49}, A series of substituted benzoxazoles (91c) synthesized by combining 2-aminophenol (89c) with aryl, heteroaryl, aliphatic aldehydes in the presence of nano ceria (CeO\textsubscript{2}) as an efficient heterogeneous catalyst\textsuperscript{70}, An efficient and one-pot synthesis of 2 aryl benzoxazole (91d) catalyzed via nano-solid acid catalysts like nanosulfated zirconia, nano-structured ZnO, nano-γ-alumina and nano-ZSM-5 zeolites (Scheme 33)\textsuperscript{71}.

![Scheme 33](Image)

Ag@TiO\textsubscript{2} nanocomposite used for one-pot synthesis of 2 aryl benzoxazole (93) derivatives in aqueous media (Scheme 34)\textsuperscript{72}.

![Scheme 34](Image)

Synthesis of 2-aryl benzoxazole (96) by the mechanism of redox reaction using one of the effective nano copper ferrite at 130°C (Scheme 35)\textsuperscript{73}.

![Scheme 35](Image)
A one-pot synthetic approach for 2-aryl benzoxazole (99) was developed by using copper nanoparticles as a catalyst with o-bromoanilines (97) and acyl chlorides (98) as starting materials (Scheme 36).

**Scheme 36**

Green synthesis:

It has been revealed that for the purpose of protecting our environment and human health from various unsafe hazardous chemical reactions and their effects, the concept of eco-friendly reactions are very important. In recent years to achieve the scientific target of safe, nontoxic and nonhazardous chemical reactions green chemistry took major place in research. Most trusted part in the green chemistry is to develop alternative safe reaction conditions and to undertake the required chemical conversion with almost negligible waste generation and less by-products as well as avoiding the use of toxic and volatile organic solvents. Therefore it is most important to have effective and safe approach for the chemical transformations that comes under green chemistry.

The green chemistry methodology which applied for the synthesis of benzoxazole moiety is mainly by using water as solvent, by green solvents, by sound waves and reactions carried out without any solvents.

Synthesis of 2-aryl benzoxazole (102) derivatives comprising the reaction of corresponding 2-aminophenol (100) with aromatic aldehyde (101) by Phospho sulfonic acid (PSA) catalyst as green synthesis, by using glycerol as green solvent, using Cu(II)-DiAmSar/SBA-15 as a non-leaching heterogeneous nanocatalyst under solvent-free conditions, and also a ball-milling strategy of convenient solvent-free method for the synthesis of 2-aryl benzoxazole (102) has been developed using recyclable ZnO-NPs (Scheme 37).

**Scheme 37**

Synthesis of substituted benzoxazoles by using the catalyst p-TsOH in the presence of ethyl 2-cyano-2-(2-nitrobenzene-sulfonyloxyimino)acetate and keeping in microwave irradiation. Ultrasound as green process as the environmental friendly synthesis of novel benzoxazole by the reaction of azo-linked salicylic acid derivative (104b) and 2-amino-4-chlorophenol (103b), Propylphosphonic anhydride in microwave irradiation helps cyclization of o-aminophenol (103c) with carboxylic acid (104c) (Scheme 38).
Carboxylic acid (106) used for synthesis of various substituted benzoazoles (109) based on the method of TCT (cyanuric chloride)/microwave acid activation (Scheme 39).^82^

One pot green synthetic method for the synthesis of marcapto benzoxazole (112) by the treatment of aminophenol (110) with tetramethylthiuram disulfide (TMTD) (111) using H$_2$O as solvent (Scheme 40).^83^

A sonochemical method for the synthesis of 2-aminobenzoxazole (115) has been reported (Scheme 41).^84^
A green synthesis of 2-aryl benzoxazole (117) obtained by means of electrochemical pathway by supplying 10mA (Scheme 42).

![Scheme 42](image)

2-aryl benzoxazole derivatives (119) synthesized by a green route catalyzed by Al$^{3+}$-exchanged K10 clay (Scheme 43).

![Scheme 43](image)

Synthesis of 2-aryl benzoxazole (122) using benzyl alcohol (121) and 2-aminophenol (120) catalyzed by (FeL$^{APIP}$)$_2$O complex (Scheme 44).

![Scheme 44](image)

CONCLUSION:
This review is attempted to summarize the various updated synthetic, catalytic, nanocatalytic as well as green chemistry methods. The majority of benzoxazole synthesis used aminophenol as a starting material along with different reagents, solvents and catalysts. The synthesis of these substituted benzoxazole compounds described in this review includes building of hydrazido benzoxazole moiety starting with substituted aminophenol using different reagents like Cyanogen bromide (CNBr), Poly phosphoric acid (PPA), 5-(trifluromethyl)pyridin-2-amine in base, electrophilic cyanating agent like (NCTS) system of them were indicated. Likewise, a number of benzoxazole derivatives were reported to exhibit interesting biological and pharmacological activities as well as industrial applications. We hope this review is to be beneficial for researchers in the field of heterocyclic synthesis. Also, it can help them for the easiest and efficient method to synthesize novel benzoxazole heterocycles, which can lead to promising medicinal activities.

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