AN UPDATE ON THE SYNTHESIS OF BENZOXAZOLES

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ABSTRACT

Benzoxazoles being structurally similar to bases adenine and guanine interact with biomolecules present in living systems. These compounds possess antimicrobial, central nervous system activities, antihyperglycemic potentiating activity, analgesic, and anti-inflammatory activity. It can also be used as starting material for other bioactive molecules. Modifications in structure and the biological profiles of new generations of benzoxazoles were found to be more potent with enhanced biological activity. Considering all these, we have prepared this review and discussed the synthesis and biological activities of benzoxazoles.

Keywords: Benzoxazoles, Chemistry synthesis, Biological activities.

INTRODUCTION TO CHEMISTRY

Benzoxazole (1) (m.p. 27-30°C; b.p. 182°C), is a planar molecule with aromatic chemical properties [1].

Benzoxazoles tend to react mainly at C-6 in electrophilic substitutions and to a lesser extent at C-5. Nitration of benzoxazole affords the 6-nitro products (2).

Halogenobenzoxazoles (5) undergo a range of nucleophilic displacements which are summarized in the scheme.

Benzoxazole quaternizes to give the methiodide (6), but under more vigorous conditions may suffer ring cleavage.

The 2-amino benzoxazole (7) exists as the amine tautomers (8). The amino benzoxazole (7) protonate on the ring nitrogen and reacts with methyl iodide at 100°C to give the N^3-alkylated product (9). The reaction
of 2-aminobenzoxazole with aryl isothiocyanates gives N-aryl-N'-(benzoxazo-2-yl) thioureas (10) [2]. The product (11) obtained on reaction with PCl₅ in POCl₃ and with oxidizing agents have been identified as 3-aryliminobenzoxazo [3,2-b][1,2,4]-thiazolidines.

The reaction o-aminobenzoxazoles with benzonitriles gives N-(benzoxazol-2-yl) benzamidines in high yields. Lead (12) acetate affords 2-aryl[1,2,4]triazolo[5,1-b]benzoxazoles (13) in good yields when cyclodehydrogenation takes place [3].

A new series of 5 (or 6) methyl-2-substituted benzoxazoles (14) were described by Oren et al. [4]. Some of these compounds showed significant activity against Pseudomonas aeruginosa having MIC 2.5 mg/ml, providing higher potencies than the reference drugs.

The in vitro antibacterial and antifungal activities of six benzimidazole and benzoxazole derivatives (15) were tested on clinical isolates where two of the benzoxazoles were found to be active [5].

Some 2-(N-Aryl-carboxamidomethylthio)benzoazoles (16) and corresponding sulfones (17) were prepared, and their antimicrobial activity was assayed against some bacteria and fungi and was found to exhibit 20-70% inhibition at a concentration of 0.1 mg/ml [6].

Sarangapani and Reddy [7] synthesized some new isatin-[N-(2-alkylbenzoxazol-5-carbonyl)]hydrazones (18) from our laboratory and found them to exhibit a moderate antibacterial activity against Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Proteus vulgaris and mild antifungal activity against Aspergillus niger, and Cola verticillata.

Bahadur and Pandey [8] reported the synthesis and antiviral activity of p-(2-benzoxazolyl) phenoxy acetic acid hydrazides (19) and corresponding arylidene hydrazides (20). These compounds were found to exhibit a significant antiviral activity in vitro but not in vivo.

Katsura et al. [9] reported the synthesis and antilulcer activity of compounds (21).

2-Mercaptobenzoxazoles (22) exist predominantly in the thione form (23). Alkylation can occur at sulfur to yield compound (24).

Reaction of Z-X-Z (ex; X = CH₂, Z = Cl), with 2-mercaptobenzoxazole.
(14) Affords the corresponding thioether linked bis heterocycles [10] [25].

Reactions of piperazines with 2-chlorobenzoxazole (26) result in the formation of compounds (27) and (28) [11]. Alkylation (28) with methyl iodide results in the quaternary salt (29).

\[
\text{N} \quad \text{N} \quad \text{N} \quad \text{R} \quad \text{CH}_3
\]

(28)

\[
\text{N} \quad \text{N} \quad \text{R} \quad \text{+CH}_3 \quad \text{DMF}
\]

(29)

Similarly, compound (28) on alkylation with allyl iodide in dimethyl formamide results in the corresponding quaternary salt (30). Benzoxazoles react with two moles of diphenyl keten in a [2+2+2] cycloaddition involving the C=N double bond, affording an oxazine-fused benzoxazole. Benzoxazoles are resistant to alkaline hydrolysis but are readily cleaved by acids, probably because of nucleophilic attack.

\[
\text{N} \quad \text{N} \quad \text{R} \quad \text{CH}_3
\]

(30)

Benzoazole hydrolysis is relatively easy, 2-methyl benzoazole giving o-acetamido phenol in hot water, although the reaction is more rapid in dilute acid.

\[
\text{N} \quad \text{N} \quad \text{H} \quad \text{CH}_3
\]

(31)

Quaternary salts are hydrolyzed more readily as shown by the hydrolysis of N-methyl benzoazole (32).

\[
\text{N} \quad \text{N} \quad \text{Me} \quad \text{+H}_2\text{O} \quad \text{OH}
\]

(32)

Although 2-methylbenzoazole (31) can be cleaved by methoxide at 120°C to give o-amino phenol (34).

\[
\text{N} \quad \text{O} \quad \text{CH}_3 \quad \text{OCH}_3 \quad \text{N} \quad \text{H}_2
\]

(34)

Quaternization of benzoazole (35) with methyl iodide at 120°C leads to 2-hydroxytrimethyl aniline.

\[
\text{N} \quad \text{CH}_3
\]

(35)

Benzoxazole affords an excellent synthetic route to w-nitrilo acids (38).

\[
\text{N} \quad \text{N} \quad \text{O} \quad \text{CH}_3 \quad \text{CN} \quad \text{COOH}
\]

(38)

6-Chloro-2-phenoxybenzoxazole (39) reacts smoothly with a series of aliphatic primary amines to give 6-chloro-2-(substituted amino) benzoxazoles (40), at room temperature, in the presence of an excess of amines [12]. Thus, 2-phenoxy group of the benzoxazole system nucleophilically moves susceptible than its 6-chloro group.

\[
\text{Cl} \quad \text{N} \quad \text{O} \quad \text{R} \quad \text{NH} \quad \text{R}
\]

(39)

\[
\text{Cl} \quad \text{N} \quad \text{O} \quad \text{NH} \quad \text{R}
\]

(40)

2-Methylbenzoazole (31) reacts with benzaldehyde in the presence of zinc chloride to give the 2-benzylidene derivative (41) indicating the reactivity of the methyl group linked to azomethine system.
2-Benzylbenzoxazole (42) is reactive enough to couple with diazonium salts and reacts at the 2-methylene group with aldehydes, nitroso compounds, and amyl nitrite.

Benzoxazoles with acyl substituents at C-2 may undergo Grignard reactions.

Benzoxazoles react with two moles of diphenyl keten in a [2+2+2] cycloaddition involving the C=N double bond, affording an oxazine-fused benzoxazole.

**Synthesis**

Benzoxazoles (44) have been obtained by heating o-aminophenol and carboxylic acids in the presence of PPA [13].

The condensation of carbon disulfide or cyanogen bromide with o-aminophenol leads to benzoxazole thione (45) or 2-aminobenzoxazole (46), respectively.

Thermal cyclization with acid catalysts is commonly employed to synthesize benzoxazoles (1).

Thermal dehydration [14] of o-(acylamino) phenols is most widely used for the preparation of these compounds (47).

Beckmann rearrangement of oximes of o-hydroxybenzophenones leads to the formation of benzoxazoles (48).

Benzoxazoles (49) can also be prepared by the action of potassium amide in liquid ammonia.

Benzoxazoles (47) are obtained by the oxidative ring closure of some Schiff’s bases. E.g., phenanthro-oxazoles (50) formation.

The synthesis of benzoxazoles (1) by the cyclocondensation reaction of o-aminophenol with S-methyl isothioamide hydroiodides on silica gel under microwave irradiation and also in a solvent under reflux [15].

Different substituted benzoxazoles (51) are synthesized [16] by distillation of aminocresol hydrochlorides with sodium formate.
An advanced method involves cyclization of a 2-aminophenol with s-triazines, triethyl orthoformate or isonitriles and 2-hydroxybenzonitrile, photochemically to yield benzoxazole (1) [17-22].

Bhawal et al. [23] reported the mild and simple method (52) via Beckmann rearrangement of o-acyl phenol oximes.

1,2-benzoxazoles (53) are also prepared from salicylaldoximes and ortho-hydroxy phenyl ketoximes via intramolecular Mitsunobu reaction [24].

However, the reaction with o-hydroxyphenyl ketoxime led to a 7/3 mixture of 1,2-benzoxazole and 1,3-benzoxazole (54).

The one-pot thermal reaction of 1,3-bis(o-acylaminoxyphenoxy)-2-methylene propane derivatives gave the bis(benzoxazole) derivatives (55) in good yields [25].

2-Amino-4-methyl phenols, when treated with the corresponding acid chlorides, gave bis(o-acylaminoxyphenoxy)-2-methylene propane (55). The thermal bulk reaction of (55) gives the corresponding bis(benzoxazoles) [26] (56).

Synthesis of some new spiro-(pyran-4,2'-benzoxazole) derivatives are reported by El-Saghier and Khodairy [27] Ketene S,S-acetal reacts with 2-aminophenol to afford 2-(1-acetyl-2-oxopropylidene) benzoxazole (57), which was allowed to react with a variety of active methylene having an α-cyano of α-keto group to give spiro(pyran-4,2'-benzoxazole) derivatives.

Synthesis of 2-(4-aryl-2-thiazolylamino) benzoxazoles is reported by Khan and Rastogi [28]. The reaction of 2-amino-4-arylthiazoles with CS₂ and MeI in DMF in the presence of strong sodium hydroxide solution gives the corresponding dimethyl N-(4-aryl-2-thiazolyl) dithiocarbonimidodithioates. These compounds on reaction with 2-aminophenol in refluxing DMF, in the presence of one equivalent sodium hydroxide affords the 2-(4-aryl-2-thiazolylamino)-benzoxazoles (58).

New synthesis of naphtho- and benzoxazoles (59) was reported by Saltz et al. [29]. The method consists of a decomposition of naphtho and benzoxazinones with KOH.
Synthesis of aromatic benzoxazoles containing allyl ether groups (60) reported by Dang et al. [30].

Piperidine-4-carboxylic acid and o-aminophenol were heated with polyphosphoric acid to afford [31] (61).

The compounds (62) prepared by direct condensation of suitable aminophenol with substituted phenyl acetic acid [32].

A simple and convenient synthesis of 5-substituted benzoxazoles has been reported by Kunz et al. [33]. 5-Substituted benzoxazoles (63) are prepared from 4-substituted 2-aminophenols by the treatment with trimethyl orthoformate and concentrated aqueous hydrochloric acid.

New bis(benzoxazoles) (64, 65) have been synthesized in excellent yield from the corresponding bis(o-aminophenol) by refluxing with triethyl orthoformate [34].

The oldest method in the synthesis of benzoxazoles [35] (66) is heating or distilling 2-formamidophenols at elevated temperatures.

Benzoxazole (1) is also obtained from the dry distillation of formamide and 2-aminophenol [36].

Solid phase synthesis of benzoxazoles was reported by Wang and Hauske [37]. 2-Aminophenol attached to a solid support can be converted to the corresponding benzoxazole (67) by the treatment with triphenylphosphine and diethyl azodicarboxylate in THF at room temperature, in high yield and purity.
Phosphoryl methyl benzoxazoles (68) were prepared in three steps from o-aminophenols by: (i) Chloroacetylation with chloroacetyl chloride in the presence of NaHCO$_3$, (ii) oxazole formation by treatment with ethyl polyphosphate, and (iii) Arbuzov reaction with triethyl phosphate [38].

A novel series of 2-Aryldienylbenzoxazoles were prepared by Kosaka et al. [39]. The compounds (69) were prepared from o-aminophenols which were chloroacetylated, cyclized by ethyl polyphosphate and subjected to the Arbuzov reaction to give phosphonates. The condensation of an aldehyde with phosphates by Hormer-Wadsworth-Emmons reaction and compounds were deprotected under acid conditions.

A one-pot synthesis of benzoxazoles by chromium-manganese redox coupled reactions reported by Hari et al. [40]. The reaction in which a chromium-manganese redox couple is employed both to catalytically reduce an o-hydroxy nitroarene and to oxidatively cyclize a subsequently formed imine (70).

2-Hetero aromatic substituted isothiocyanato benzoxazoles were synthesized by Haugwitz et al. [41]. The intermediates of 5 and 6-nitrobenzoxazoles were prepared by the following routes:

a. PPA-catalyzed ring closure of o-aminophenols with the appropriate carboxylic acids followed by nitration of benzoxazoles
b. Acylation of nitroaminophenols with carboxylic acid chlorides and subsequent thermally induced cyclodehydration of the amides c. Oxidation cyclization of Schiff bases using lead (IV) acetate and d. Reaction of imino ethers derived from 2-cyanopyrazine or cyanonitropyridine with o-aminophenols and nitration of corresponding benzoxazoles.

Followed by thiocarbonylation of resulting amines using thiophosgene, completed the synthesis of 5 and/or 6-isothiocyanato benzoxazoles (71).

Salome Rodriguez Morgade Gouloumis et al. [42] reported the synthesis of benzoxazole derivatives. Theaza-Wittig reaction of the triphenyl phosphoranylidene amino-1,4-benzoquinone with aryl isocyanates and aryl chlorides allows the preparation of benzoxazole derivatives (72). The same reaction using aminophosphorano-quinone provides substituted benzoxazoles (73).

Qian et al. [43] reported, yellow HgO as an efficient cyclodesulfurizing agent in the synthesis of 2-(substituted amino) benzoxazoles from N-(2-hydroxy phenyl)-N'-phenylthioureas. 2-(Substituted amino) benzoxazoles (74) (R$_1$, R$_2$= H, F; R$_3$, R$_4$= H, Cl, F; R$_5$= H, F, OH) were prepared in good yields by cyclodesulfurization of N-(2-hydroxyphenyl)-N'-phenyl thioureas with yellow HgO.

Facile synthesis of 2-substituted benzoxazoles via ketenes reported by Olágbemiro et al. [44]. The generation of diphenyl, phenyl, phenoxy, and chloroketenes by the treatment of corresponding acid chlorides with triethylamine in the presence of 2-aminophenol resulted in good yields of 2-substituted benzoxazoles (75).
Ruthenium complex-catalyzed facile synthesis of 2-substituted benzoxazoles (77) reported by Kondo et al. [46] RuCl$_3$(PPh$_3$)$_3$ shows high catalytic activity for the reaction of o-aminophenol.

$$\text{OH} + \text{NH}_2 + \text{ROH} \rightarrow \text{RuCl}_3(\text{PPh}_3)_3 \rightarrow \text{R} = \text{Bu, Aralkyl}$$

With ROH (R = Bu, aralkyl) to give the corresponding benzoxazoles. Benzoxazoles being structurally similar to bases adenine and guanine possess significant biological activities [47-49] and structural modifications can result in molecules with enhanced biological activity.

CONCLUSIONS

Considering the biological and pharmacological importance of these molecules, the synthetic strategies of various benzoxazoles were discussed and reviewed in this article.

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