Synthesis and Chemistry of Bis-imidazole Derivatives: A Review

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Abstract- Imidazole, an important heterocycle, having biological and therapeutic properties prompted various medicinal chemists to develop various synthetic methods to synthesize a large number of novel derivatives used in chemotherapy. This fascinating group of heterocyclic compounds has interesting biological activities such as antimicrobial, anticancer, antiviral, analgesic, anti-inflammatory, anthelmintic, anticonvulsant, antiulcer, and anti-allergic activity. Various bis-imidazole derivatives introduced a great contribution not only in the field of synthetic organic chemistry but also in the field of medicinal chemistry and chemotherapy. This article aims to review the work reported in the synthesis and chemistry of bis-imidazole derivatives during past years.

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GJSFR-B Classification: FOR Code: 039999

Strictly as per the compliance and regulations of:
Synthesis and Chemistry of Bis-imidazole Derivatives: A Review

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Abstract - Imidazole, an important heterocycle, having biological and therapeutic properties prompted various medicinal chemists to develop various synthetic methods to synthesize a large number of novel derivatives used in chemotherapy. This fascinating group of heterocyclic compounds has interesting biological activities such as antimicrobial, anticancer, antiviral, analgesic, anti-inflammatory, anthelmintic, anticonvulsant, antiulcer, and anti-allergic activity. Various bis-imidazole derivatives introduced a great contribution not only in the field of synthetic organic chemistry but also in the field of medicinal chemistry and chemotherapy. This article aims to review the work reported in the synthesis and chemistry of bis-imidazole derivatives during past years.

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I. INTRODUCTION

Imidazole 1, a histidine 2 component, is five membered heterocyclic compound containing nitrogen atoms in 1 and 3 positions. It has fascinating biological activities such as antibacterial [1, 2, 3], anticancer [4], antiviral [5], anti depressant [3, 6]. Bis-imidazole is an important moiety in therapeutic chemistry due to its versatile synthesis methods and biological activities.

Imidazole is a five membered aromatic heterocyclic compound, categorized as diazole having two nitrogen atoms. Many important drugs contain imidazole ring, such as antifungal drugs, Nitroimidazole [7-12], and Purine 3 which is the most widely occurring nitrogen-containing heterocycle in nature consist of imidazole fused to pyrimidine [3]

Due to the significant biological activity of bis-imidazole derivatives and the rise of practical, safe, and environmentally friendly procedures for the synthesis of bis-imidazoles, [13-15] organic chemists become interested in the development of novel bis-imidazole derivatives.

The synthesis of bis-imidazole derivatives in literature does not fit with their increasing biological importance. Herein we try to put in front of organic synthesis community the few novel bis-imidazole derivatives that were synthesized and found a unique application in the last years.

II. GENERAL METHODS OF SYNTHESIS

Imidazole moieties and substituted imidazoles can be formed through various methods. Different synthesis methods include Debys synthesis, Radiszewski synthesis, dehydrogenation of imidazolines, imidazole from alpha halo ketones, Wallach synthesis, from aminonitrile and aldehyde and Marckwald synthesis [12, 16]. Herein we introduce the various methods applied for the synthesis of bis-imidazole derivatives.

III. SYNTHESIS OF BIS (IMIDAZOLE)

Zhou et al. proposed a simple, convenient and efficient method for synthesis of ether bis-imidazoles and their derivatives [17] from oligo-ethyleneglycols, imidazole, and 2-methylimidazole. The synthetic approach is shown in scheme (1).

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Bis-imidazole also synthesized by Asiri et al. [18]. He and his coworkers synthesized firstly imidazole from benzyl, ammonium acetate, and one of the three isomers of chlorobenzaldehyde. Then new bis-imidazoles was synthesized by dissolving the imidazole derivative and cooling in ice bath, then adding potassium ferricyanide to the cooled imidazole, the synthesis route is shown in scheme (2).

Ghazvini et al. reported an efficient one-pot synthesis for some novel bis imidazole from 4,4′-(2-oxocycloalkane-1,3-diylidene) bis(methan-1-yl-1-ylidene) dibenzaldehydes derivatives with benzyl and ammonium acetate [15]. The reaction conditions were optimized by changing the type and amount of catalyst, and adjusting reaction temperature. The key advantages of this procedure are environmentally friendly conditions and good yield of products. The synthetic pathway is shown in scheme (3).
Nassir et al. synthesized some novel bis-imidazole sulfonamide compounds [19]. The bis-imidazole sulfonamides compounds were obtained by treating imidazole with tris-(4-substituted benzensulfonate)-diethanolamine under basic conditions to form the corresponding bis-imidazole as shown in scheme (4).

Jasinski et al. afford an interesting method for synthesis of some novel bis-imidazoles [20]. The synthesis procedure involved the formation of bis-imidazole oxide compounds that were converted finally to bis-imidazole. The bis-imidazole oxide derivatives synthesis step was carried out according to scheme (5).
The prepared bis[imidazole 3-oxides] was isomerized with Ac₂O to give the bis[2H-imidazol-2-one] as shown in scheme (6). Finally bis[imidazole 3-oxides] derivatives was converted to 2H-imidazole-2-thiones and bis-imidazole derivatives using 2,2,4,4-tetramethylcyclobutane-1,3-dithione and Raney-Ni respectively according to scheme (7).

Scheme (5)

Scheme (6)

Scheme (7)
Bhalla et al. studied the coordination ability bis-imidazole, to achieve their goal they prepared Bis(1-methyl-4,5-diphenylimidaz-2-oyl) (benzyloxy) methane ligand [21, 22] using the conditions followed in scheme (8).

Due to presence of donor nitrogen atoms, imidazole heterocycle is of great interest in the coordination chemistry. To be used as a proligands, Higgs et al. reported the synthesis of new sterically hindered bisimidazole. The authors followed a multi step synthesis as shown in scheme (9), which lead to the formation of 1,2-bis-(4-phenylimidazol-2-yl)ethane [23]. The first step involves dissolving succinic acid in MeOH and neutralised to pH 7.5 using [NMe2(CH2Ph)][OMe] (40% solution in MeOH). In the following step Formamide was then added to the reaction mixture and the solution stirred for 5 min before bromoacetophenone was added. In the third step ammonium acetate is introduced to the reaction liquor and refluxed for 48 hours. Here we have prepared Dimethylbis(4-phenylimidazol-2-yl)lmethan. The authors extended their work to another final step which involves the use of sodium hydride to achieve deprotonation of the obtained bisimidazole.

New bis-imidazole derivatives have been synthesized by Zampieri et al. [24]. The synthesis was achieved using via a Michael type reaction by nucleophilic attack of imidazole to 1-Aryl-2-[(dialkylamino)methyl]-propenone hydrochlorides or and 2-[(dimethylamino)methyl]-1-(thiophene-2-yl)-propenones under microwave (MW) irradiation of the reagent mixture in EtOH–H2O at room temperature.
Wiznycia et al. prepared a series of symmetric bis(imidazole-4,5-dicarboxamides) with amino acid esters and a variety of linker groups [25]. The bis-imidazole derivatives in this study were obtained by reacting a symmetric pyrazine derivative bearing reactive acid chloride and acyl imidazole functionalities with 2 equiv of an amino acid salt along with a base scheme (11).

Zhang et al. reported a scheme involves the synthetic procedure for the synthesis of bis-imidazole compounds according to previous studies [26, 27, 28] as illustrated in scheme (12). In this study, the authors synthesized one symmetrical structure called 1,4-bis(4,5-diphenyl-1H-imidazol-2-yl)benzene and two
asymmetrical structures, namely 2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-1H-phenanthro (9,10-d) imidazole and 2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-1H-imidazo(4,5-f)(1,10)phenanthroline. The synthetic route of bis-imidazole compounds begins with terephthalaldehyde, benzyl, and ammonium acetate in presence of glacial acetic acid.

**Scheme (12)**

**IV. Conclusion**

Bis-imidazoles are an important heterocycles having great biological activities and used as an important precursor for the synthesis of various other bioactive compounds. Several synthetic routes and methods have been introduced to achieve the synthesis of these compounds. This review highlighted the strategies and synthetic routes for the bis-imidazole synthesis.

*Conflict of Interest*

The authors confirm that this article content has no conflict of interest.

**References Références Referencias**
