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SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES: A BRIEF REVIEW

Chandrakant D. Bhenki*

Department of Chemistry, Shri S. H. Kelkar College, Devgad, Sindhudurg, (M.S.), India.

ABSTRACT: Benzimidazole has been a popular heterocycle in medicinal and pharmaceutical chemistry with diverse bioactivities viz. antiviral, antifungal, antihypertensive and anticancer etc. In this review diverse synthetic pathways to prepare functionalized derivatives of benzimidazoles are described. The present review helps in the further development of novel benzimidazoles for future drug discovery and provides an in depth view of synthetic routes for preparation of benzimidazoles. In this review recent reports from on various routes of synthesis of benzimidazole scaffolds are discussed.

Keywords: benzimidazoles,heterocycles, pharmaceutical chemistry, greener approach etc.

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Corresponding Author: Dr. Chandrakant D. Bhenki* Ph.D.

Department of Chemistry, Shri S. H. Kelkar College, Devgad, Sindhudurg, (M.S.), India.

Email Address: cdbhenki@gmail.com

1.INTRODUCTION

Organic molecules bearing different heterocyclic ring systems have attracted a great deal of attention in now a day, both in chemical and medicinal research that could be attributed to their different pharmacological applications. Benzimidazoles represent a class of nitrogen heterocyclic which possesses biological and pharmacological activities. Synthetically produced heterocycles designed by organic chemists are used as pharmaceuticals, dyestuff, agrochemicals and are of increasing importance in many other areas including adhesives, molecular engineering, polymers etc. In biological processes naturally occurring heterocyclic moieties played a vital role. They are broadly found in naturally in plant alkaloids, nucleic acids, and anthocyanins and flavones as well as in chlorophyll. Additionally several proteins, hormones, vitamin's contain aromatic heterocyclic ring system[1-3]. Heterocycles act as drugs because they have specific chemical reactivity and they

provide convenient building blocks to which pharmacologically active substituent can be attached. Thus, we needed the development of innovative methodology for bioactive heterocyclic in synthetic organic and medicinal chemistry with some advantages including its simplicity of operation, greener approach, easy workup procedure, selectivity, higher yields, and high-atom economic [4]. Nitrogen heterocyclic compounds are among the most privileged and significant structural components of pharmaceuticals [5,6]. A recent analysis of the nitrogen heterocyclic composition of U.S. FDA (Food and Drug Administration) approved drugs has revealed the relative frequency by which various nitrogen heterocyclic compounds have been incorporated into approved drugs architecture[7].Benzimidazole is an aromatic *N*-heterocyclic formed by the fusion of benzene and imidazole ring **(Fig. 1)**.

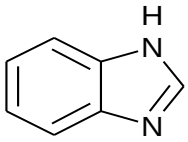


Fig. 1: Structure of Benzimidazoles

Nitrogen containing heterocycles, are present in vitamins, proteins and nucleic acids. Benzimidazole is a heterocyclic aromatic organic compound. The most prominent compound available in the nature containing benzimidazole skeleton is Nribosyl dimethyl benzimidazole, which serves as axial ligands for cobalt in vitamin B_{12} [8]. Benzimidazole moieties are very important class of heterocyclic compounds that have many applications in pharmaceutical industry. Benzimidazole derivatives have attracted a significant attention in recent years because of their medicinal applications as antiviral , antifungal [9] ,antihypertensive[10] , and anticancer [11], compounds. Apart from therapeutic applications, benzimidazoles formed as intermediates in different organic reactions. In addition to this benzimidazoles are used as fluorescent whitening agent, dyes, organic ligands and functional materials [12-14]. Pharmacologically active molecules such as albendazole/ mebendazole/ thiabendazole (antihelmentic), omeprazole (antiulcer), astimizole(antihistaminic) etc. contains the substituted benzimidazoles and display a broad spectrum of potential pharmacological activities.Benzimidazole derivatives also show cytotoxic activity. Substituted benzimidazole derivatives is evaluated by their ability to inhibit gastric H+ /K+ ATPase and by blocking the gastric acid secretion [15] . Some of the benzimidazole derivatives such as Albendazole, Mebendazole were widely used in treatment of parasitic worm infestations **(Fig.2)**.

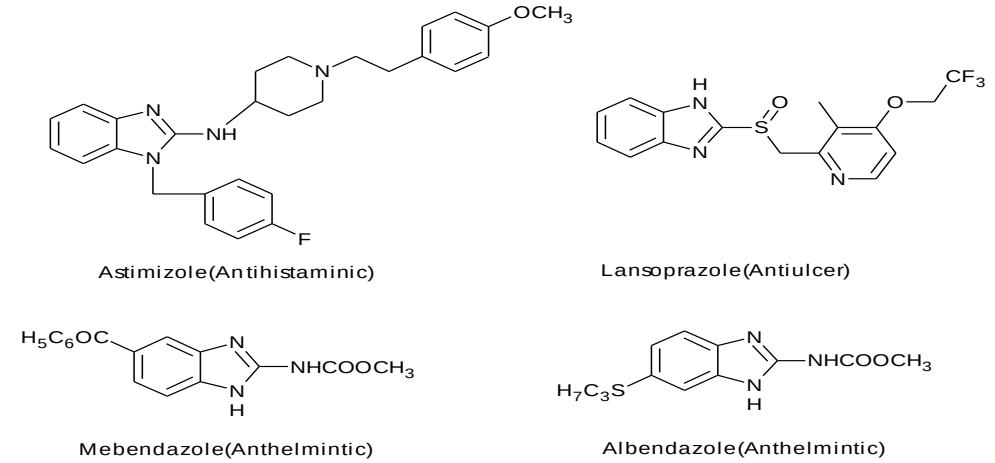


Fig. 2 : Marketed drug product having phthalazine skeleton

SYNTHETIC ASPECTS

Recent advances have been dominated by the development of improved procedures in terms of operational simplicity,atom economy, and ecofriendly viability, which selectively lead to either 2-substituted benzimidazoles or 1,2-disubstituted benzimidazoles as the sole product [16]. A plethora of catalysts were reported for the synthesis of 2-substituted benzimidazoles.

Historically, the first benzimidazole was prepared in 1872 by Hoebrecker [17]. **(Fig. 3)**.

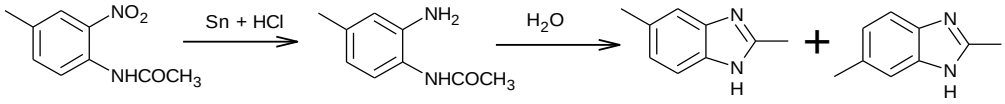
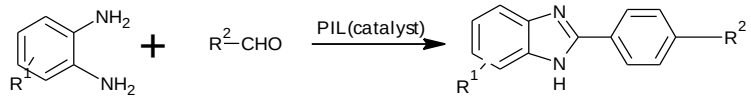


Fig. 3 : Synthesis of Benzimidazole by Hoebrecker

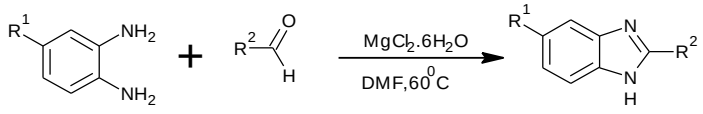
Numerous methods have been developed for the construction of benzimidazoles, in the literature.

Majumdar and co-workers [18] described green synthesis of 2-substituted benzimidazoles through grinding a mixture of *o*-phenylenediamine with suitable aldehydes and an imidazolium trifluoroacetate protic ionic liquid catalyst (**Scheme 1)**



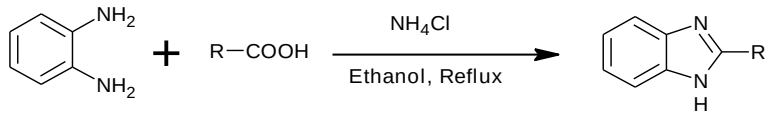
Scheme 1

Ghosh *et al* [19] prepared the series of substituted benzimidazoles by combining *o*-phenylenediamine with aryl, heteroaryl aldehydes in the presence of catalytic amount of $MgCl_2.6H_2O$ **(Scheme 2).**



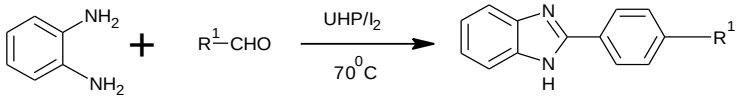
Scheme 2

Rithe and co-workers [20] employed successfully ammonium chloride for the synthesis of various2-substituted benzimidazole derivatives in moderate to good yield by condensation of o-phenylenediamine and different aromatic acid in ethanol at reflux condition **(Scheme 3).**



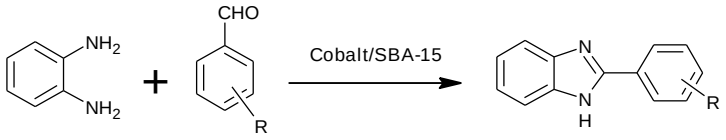
Scheme 3

Alapati, and associates [21] described a simple and efficient one-pot synthesis of 2-substituted benzimidazoles from *o*-phenylene diamine and aryl aldehydes using UHP and I_2 in DMSO **(Scheme 4)**.



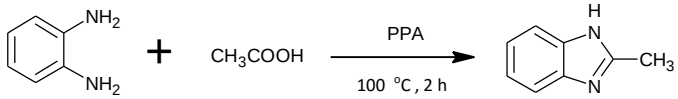
Scheme 4

Rajabi *et al* [22] reported the one-pot synthesis of benzimidazol derivatives *via* oxidative condensation of aromatic aldehydes with *o*-phenylenediamine under mild conditions using a cobalt(II) supported on mesoporous silica-type material **(Scheme 5)**.



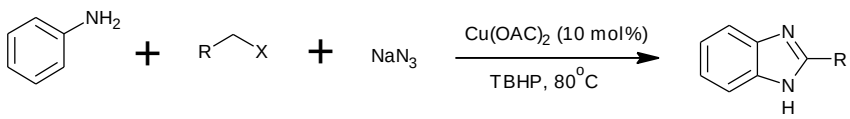
Scheme 5

Saini *et al* [23] reported the polyphosphoric acid is an efficient catalyst for the synthesis of 2-methylbenzimidazole from *o*-phenylenediamine and acetic acid.2-methyl benzimidazole is a heterocyclic organic compound having an important pharmacophoric group which is used in medicinal industry **(Scheme 6)**.



Scheme 6

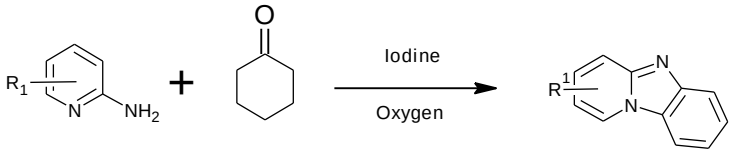
Mahesh and co-workers [24] investigated the synthesis of 2-substituted benzimidazoles in presence of Cu(II) as catalyst. The targeted molecules were prepared by the reaction of aniline, primary alkyl halides and sodium azide(**Scheme 7)**.



Scheme 7

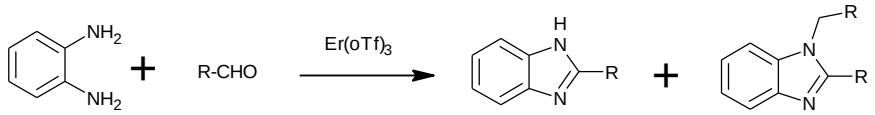
Xie and co-workers [25] developed the novel approach for synthesis of pyrido[1,2-*a*]benzimidazoles

from 2-aminopyridines and cyclohexanone. Iodine easily catalyzes this transformation in presence of oxygen as oxidant.Non-aromatic cyclohexanones were used as aryl source *via* dehydrogenation-aromatization process using molecular oxygen as the green oxidant **(Scheme 8).**



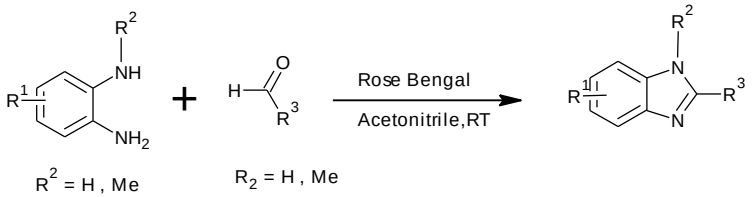
Scheme 8

Cano *et al* [26] developed an efficient protocol for the synthesis of benzimidazole derivatives, starting from *o*-phenylenediamine with diverse aryl aldehydes using $Er(OTf)_3$ as the catalyst **(Scheme 9)**.



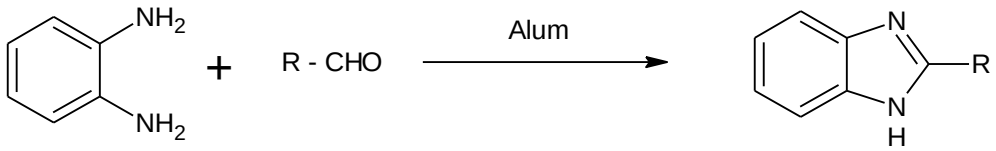
Scheme 9

Kovvuri*et al* [27] developed photocatalytic method for the synthesis of functionalized benzimidazoles *via* photocatalytic condensation of *o*-phenylenediamine and aldehydes using the Rose Bengal as photocatalyst (**Scheme 10) .**



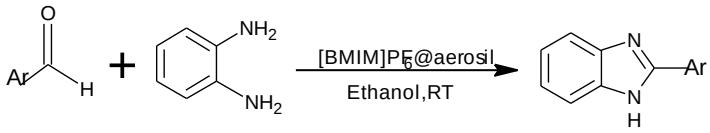
Scheme 10

Gurumeet C. Wadhawa *et al* [28] reported the synthesis of 2-substituted benzimidazoles and 1,5-disubstituted benzodiazepines using alumby thecondensation reaction between *o*-phenylenediamine and an aldehyde or a ketone to synthesizes 2-substituted benzimidazole and 1,5-disubstituted benzodiazepines Respectively **(Scheme 11)**.



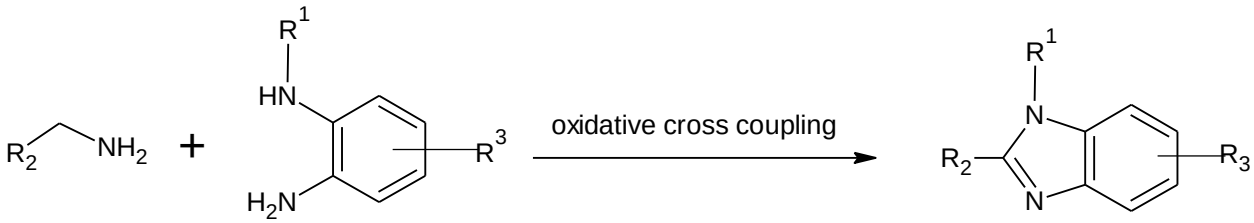
Scheme 11

Sonawane *et al* [29] reported synthesis of biologically relevant 2-substituted benzimidazoles from *o*-phenylenediamine and aryl aldehydes in high yields under mild reaction conditions by using aerosol supported ionic liquid phase (ASILP) as a catalyst **(Scheme 12)**.



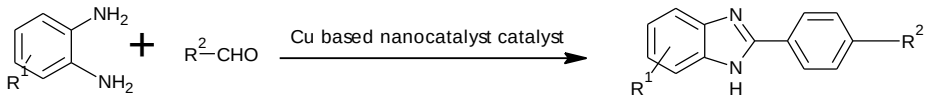
Scheme 12

Martine Larger on and co-workers [16] reported recent advances in the synthesis of Benzimidazole Derivatives from the Oxidative Coupling of Primary Amines. **(Scheme 13)**.



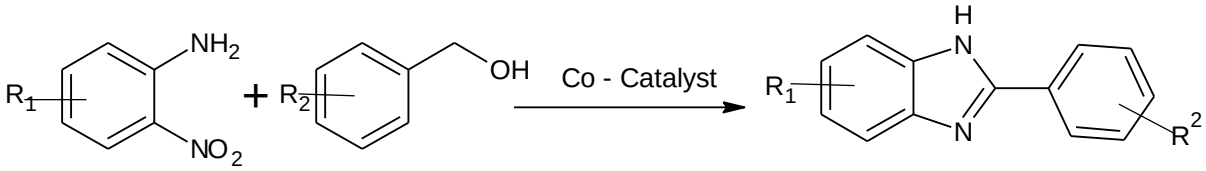
Scheme 13

Sugandha Singhal, *et al* [30] described Recent trends in the synthesis of benzimidazoles from*o*-phenylenediamine *via* nanoparticles and green strategies using transition metal catalysts. (**Scheme 14) .**



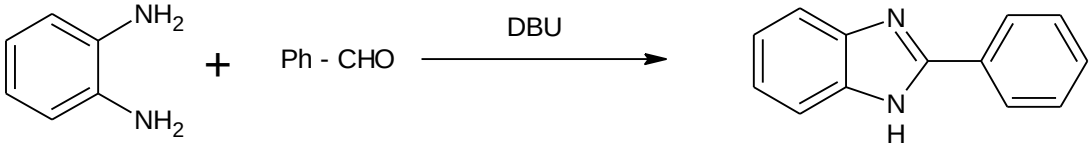
Scheme 14

Sanju Das, *et al* [31] described Cobalt-Catalyzed Sustainable Synthesis of Benzimidazoles by Redox-Economical Coupling of o-Nitroanilines and Alcohols **(Scheme 15)**.



Scheme 15

Sarah John, reported [32] a mild and effective protocol for benzimidazole synthesis from o-phenylenediamine and aromatic aldehydes catalysed by DBU. **(Scheme 16)**.



Scheme 16

2. CONCLUSION

Synthesis of benzimidazole derivatives has long been an area of intense development due to the great synthetic and medicinal importance of this heterocyclic core and still constitutes an active domain from academic and industrial points of view. This review has attempted to summarize the various synthetic routes for the synthesis of benzimidazoles. Numbers of benzimidazoles were synthesized by different reaction conditions including greener protocols. Finally, In conclusion, this review helps to find potential future directions on the development of new effective Benzimidazole derivatives through greener approach and for different biological targets.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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