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SYNTHETIC ROUTES FOR A VERSATILE NUCLEUS: BENZIMIDAZOLE – A REVIEW

Sivakumar. R*, Kumar Nallasivan, P, Sivaraj .S, Venkatanarayanan. R

Department of Pharmaceutical Chemistry, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore- 641 402, Tamilnadu. India.

**** For correspondence***
R.Siva kumar, Department of Pharmaceutical Chemistry,
RVS College of Pharmaceutical Sciences,
Sulur, Coimbatore - 641 402. Tamilnadu, India.
E-mail: andrilan@rediffmail.com, Mobile: 09791903606

Abstract: Benzimidazoles of both natural and synthetic sources are the key components of many bio-active compounds. A number of synthetic methods have been developed in recent years to uncover a variety of new reagents for the synthesis of 2-substituted benzimidazoles. The present review focus on synthesis of 2-substituted benzimidazole derivatives by cyclizing the o-phenelendiamine and substituted carboxlic acid or aldehyde with the help of different catalysts or agents.

Key words: Benzimidazole, synthetic method, anti microbial activity.

Introduction:

Benzimidazole derivatives have been found to possess varied pharmacological activities. A large number of benzimidazole derivatives were synthesized which have exhibited potent anthelmentic [1], antimicrobial [2-4], *in vitro*-anti-HIV [5], anti-fungal [6], anti-tubercular [7], anticancer [8-9], and anti-oxidant [10-11]. Current clinical examples include the antihistamine astemizole (1), the antiulcerative esomeprazole (2) and albendazole (3) which is used to treat parasitic diseases.

A variety of methods have been developed for the preparation of

substituted benzimidazoles [12-13]. The traditional synthesis of benzimidazoles involves the reaction between a phenylenediamine and a carboxylic acid or its derivatives (4} under harsh dehydrating reaction conditions [14-17].

Subsequently, several improved protocols have been developed for the synthesis of benzimidazoles via the condensation of o-phenylenediamines with aldehydes in the presence of acid catalysts under various reaction conditions.

Byeong Hyo Kim et al [18] described Indium-mediated Reductive Inter-molecular Coupling Reaction of 2-Nitroaniline with Aromatic Aldehydes to Benzimidazoles. (5)

Takashi Itoh et al [19] synthesized 2-arylbenzothiazoles and imidazoles using scandium triflate as a catalyst for both a ring closing and an oxidation steps. (6)

Donglai Yang et al [20] reported a highly efficient and versatile method for the synthesis of benzimidazoles in one step via the $Na_2S_2O_4$ reduction of o-nitroanilines by heating a solution of o-nitro aniline and an aldehyde in EtOH or another appropriate solvent, in the presence of aqueous or solid $Na_2S_2O_4$, provided facile access to a series of 2-substituted N-H benzimidazoles containing a wide range of functional groups not always compatible with the existing synthetic methods. (7)

Khodabakhsh Niknam et al [21] developed a highly selective synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles from the reaction of o-

phenylenediamines and aromatic aldehydes in the presence of metal hydrogen sulfates [M(HSO4)n] in water and also under solvent-free conditions in good to excellent yields.(8)

Robert J. Perry et al [22] described the preparation of 2-aryl benzimidazoles based on the palladium-catalyzed carbonylation, coupling, and cyclization of haloaromatics and o-phenylenediamines in the presence of 2,6-lutidine. This route is tolerant of a variety of functional groups and nicely complements the classical route where the desired benzoic acid derivatives are unavailable. (9)

Meihua Shen et al [23] also reported the synthesis of benzimidazoles from aryl azides using iron (II) bromide as a catalyst. The identity of the ortho-substituent of an aryl azide influences its reactivity toward transition metals. Substitution of a vinyl group with an imine disables rhodium (II)-mediated C−H amination and triggers a Lewis acid mechanism catalyzed by iron (II) bromide to facilitate benzimidazole formation. (10)

Han Xiangming [24] reported an efficient procedure for the preparation of synthesis of 2-arylsubstituted benzimidazoles using p-TsOH as a catalyst. The advantageous features of this method are simple and convenient procedure, easy purification and shorter reaction time. (11)

Sapkal et al [25] have done acidic ionic liquid catalyzed environmentally friendly synthesis of benzimidazole derivatives. In this study an efficient synthesis of benzimidazole derivatives

from o-phenylenediamine and substituted aromatic aldehyde catalyzed by 1-benzyl-3-methyl-imidazolium hydrogen sulphate [bnmim] HSO4 ionic liquid in high yield under microwave irradiation is reported. The remarkable advantages offered by this method are much faster reaction, excellent yields, environmentally benign catalyst and simple workup procedure. (12)

Y.C.Joshi et al [26] reported a mild and efficient one pot synthesis of imidazolines and benzimidazoles from aldehydes using and 1,2-diamines in the presence of cerric (IV) ammonium nitrate (CAN). (13)

Nagawade et al [27] reported preparation of 2-substituted benzimidazoles in solvent-free conditions from o-phenylenediamine and aldehydes in the presence of $BF_3 \cdot OEt_2$ as a catalyst. The method is applicable to aromatic, unsaturated and aliphatic aldehydes and to substituted o-phenylenediamines without significant differences. (14)

Pawar et al [28] used glyoxylic acid at 5 mol % as a novel highly water-soluble catalyst for the synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles from a wide range of substituted o-phenylenediamines and various substituted aldehydes using water as solvent at ambient temperature. The remarkable advantages offered by this method are easily and inexpensive available catalyst, simple procedure, mild conditions, much faster reactions and excellent yields of products.

Ganesh R. Jadha et al [29] used ammonium metavanadate at 10 mol% used as a catalyst for the synthesis of

various 2-substituted aryl benzimidazoles. It was used as an oxidizing agent for the condensation of o-phenylenediamine with different substituted aryl aldehydes at room temperature in ethanol. The method was proved to be simple, convenient and the product was isolated with good yields.

Ma H et al [30] reported a simple $KHSO_4$ promoted synthesis of 2-arylsubstituted benzimidazoles by oxidative condensation of aldehydes with o-phenylenediamine. (15)

Nagawade et al [31] described a fast procedure for the synthesis of various biological important benzimidazoles in the presence of a catalytical amount of zirconly (IV) chloride using o-phenylenediamine and substituted aldehydes. (16)

Wang shen et al [32] reported a mild and efficient method for the preparation of substituted benzimidazoles from 1, 1-dibromoethenes and o-diaminobenzenes. The reaction employs 1,4-Diazabicyclo[2.2.2]octane as the base and N-methylpyrrolidone as the solvent. (17)

Fatemeh F. Bamoharram et al [33] synthesized 2-substituted benzimidazoles in good to excellent yields in the condensation reaction between 1, 2-phenylenediamine and benzoyl chloride derivatives in refluxing xylene in the presence of a catalytic amount of Keggin type heteropolyacids. (18)

Chan Sik Cho et al [34] also reported Ruthenium-Catalyzed Synthesis of Benzimidazoles from N-Alkyl-1,2-

diaminobenzenes via Alkyl Group Transfer. (19)

Cecilia D et al [35] reported a one-pot procedure for preparing 2-substituted benzimidazoles directly from activated alcohols in good to excellent yields using a new Tandem Oxidation Process (TOP). (20)

A microwave-assisted method for the synthesis of 2-substituted benzimidazoles in the presence of alumina-methanesulfonic acid (AMA) is reported by K. Niknam et al [36]. In addition, by this method some new bis-benzimidazoles from the direct reaction of o-phenylenediamine and dicarboxylic acid under microwave irradiation in good to excellent yields are described. (21)

Similarly, 2-substituted benzimidazoles are also synthesized readily by the ruthenium catalyzed reaction of 1,2-phenylenediamine with primary alcohols as stated by Teruyuki Kondo et al [37]. It was reported that primary alcohols are oxidatively cyclized with 1,2-phenylenediamines in the presence of $RuCl_2(PPh_3)_3$ to give 2-substituted benzimidazoles.

Elba I. Bujan et al [38] reported the synthesis of Several benzimidazole N-oxide derivatives by heating at reflux the corresponding N-alkyl-2-nitroaniline derivative with NaOH in 60% 1,4-dioxane–water in vary good yield.

Conclusion:

However many of these methods have several drawbacks such as low yields,

use of expensive reagents, long reaction time, tedious work-up procedure, and harsh reaction conditions. Therefore, the search continues for a better catalyst for synthesis of benzimidazole derivatives in term of operational simplicity, economic valiability and in particular greater selectivity.

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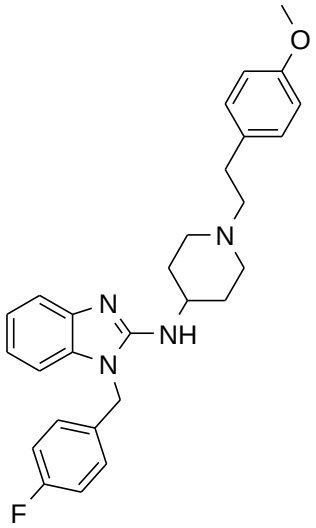

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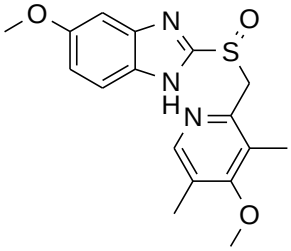

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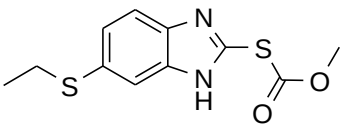

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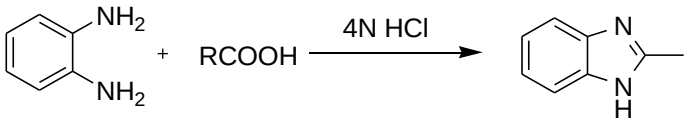

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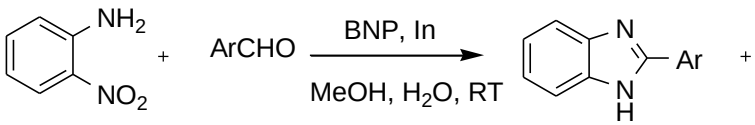

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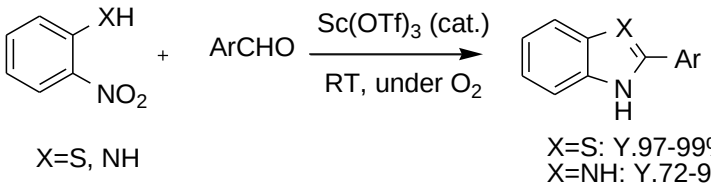

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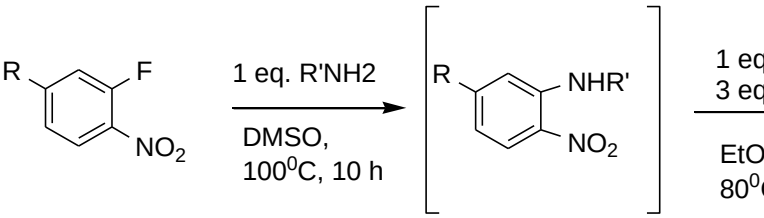

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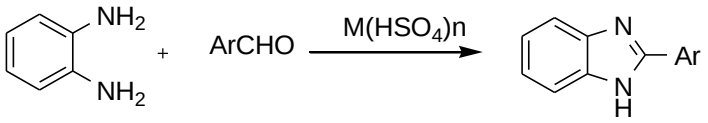

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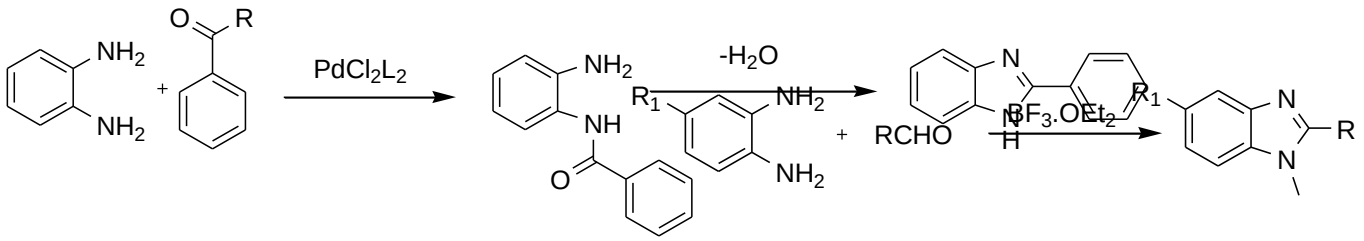

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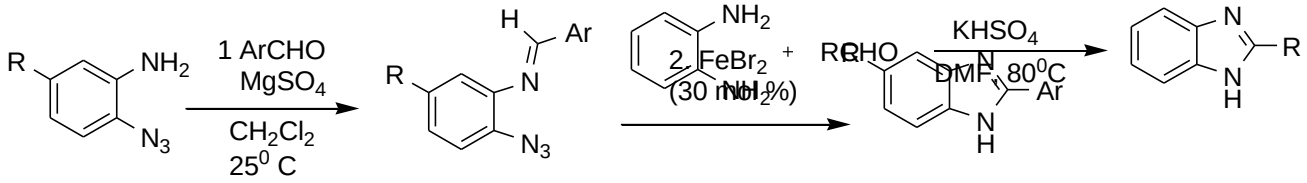

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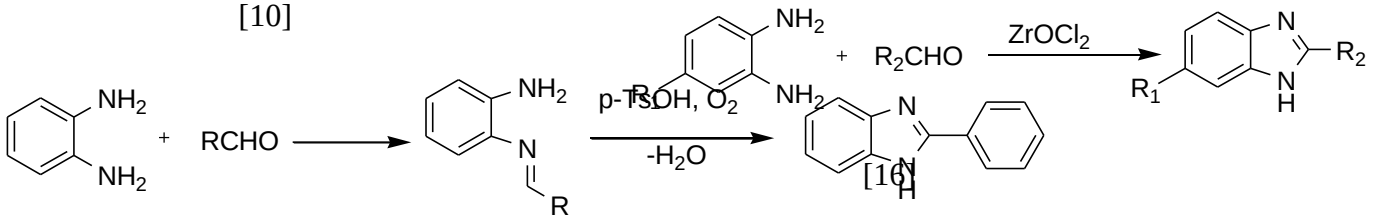

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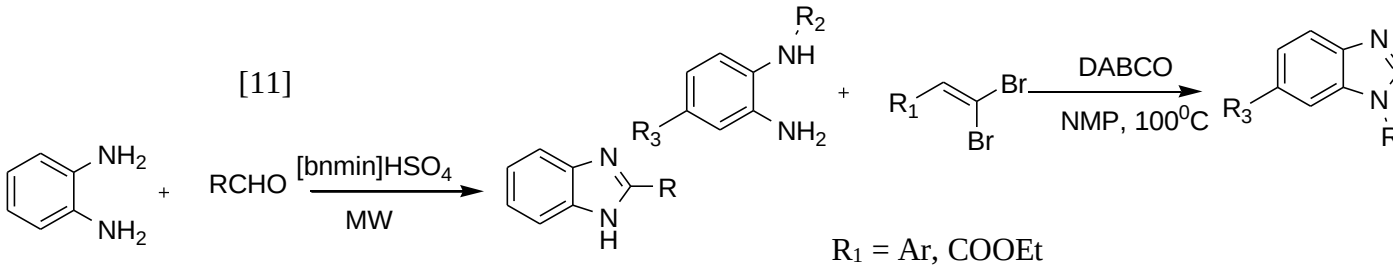

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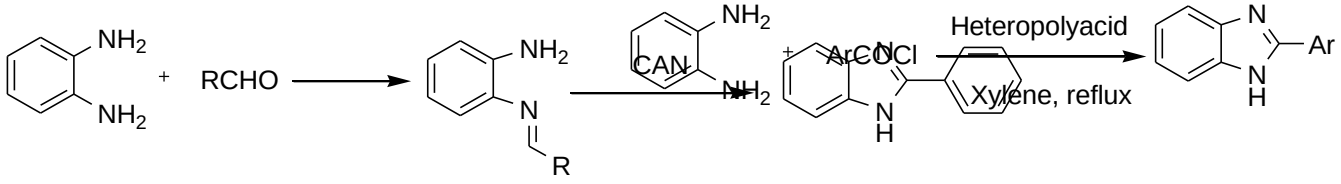

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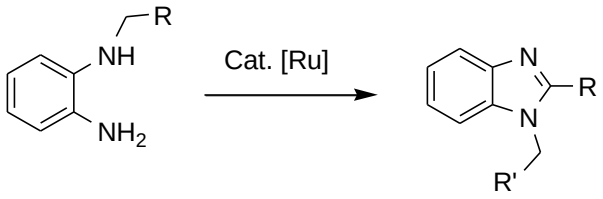
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R'

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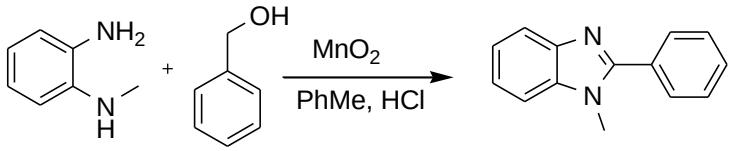
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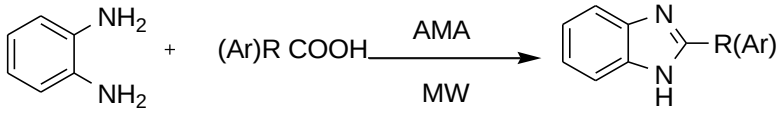
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H

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