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Review

Ecofriendly Synthesis of Benzimidazole by Approaching Green chemistry Principles

Nasiruddin Ahmad Farooqui[1], Vishant Goel[*2], Praveen Kumar[3]

[1]Professor & HOD, Translam Institute of Pharmaceutical Education & Research, Mawana road Meerut, (UP.) India.
[2]Research Scholar, Translam Institute of Pharmaceutical Education & Research, Mawana road Meerut, (UP.) India.
[3]Associate Professor, Translam Institute of Pharmaceutical Education & Research, Mawana road Meerut, (UP.) India.

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Abstract:
Benzimidazoles and their derivatives play an extraordinarily significant role as therapeutic agents, e.g., antiulcer, analgesic, and anthelmintic drugs. The organic synthesis of benzimidazoles and derivatives to obtain active pharmacological compounds represents an important research area in organic chemistry. The use of non-environmental organic compounds and application high energy synthetic methods, the production of waste, and the application of conventional toxic processes are a problem for the pharmaceutical industry and for these important drugs' synthesis. The substituted benzimidazoles are summarized in this review to provide insight about their organic synthesis using ecofriendly methods, as well as their pharmacological activities.

Keywords: *benzimidazole; green chemistry; pharmacological activity*

***Corresponding Author**
Vishant Goel
Research Scholar, Translam Institute of Pharmaceutical Education & Research, Mawana road Meerut, (UP.) India.
Email id: vishantgoyal677@gmail.com

Introduction:

Since Woolley proposed in 1944 that benzimidazole may behave similarly to purines, stimulating various biological reactions, the therapeutic potential of benzimidazole nucleus has been known [1]. Some years later, Brink determined that 5,6-dimethylbenzimidazole is a vitamin B12 breakdown product and discovered that several of its derivatives had action similar to that of vitamin B12 [2,3]. Due to its presence in a variety of bioactive substances, including antihypertensives, anti-inflammatories, antivirals, analgesics, anticancer, proton pump inhibitors, anticonvulsants, antifungals, anticoagulants, antihistaminics, antiparasitics, and antiulcers, the development of the benzimidazole core has emerged over the recent years.

Thus, research on the synthesis of bioactive molecules from benzimidazole has significantly been accelerated over the last decade. Literature study shows that the different derivatives of benzimidazole have been synthesized for their pharmacological activities. The present review fits into this framework by discussing the literature existing in recent years on strategies for the reduction and replacement of hazardous solvents affording the preparation of benzimidazoles. Additionally, it discloses numerous benzimidazole derivatives with different pharmacological activities based on the substitution model around the nucleus.

Eco-Friendly Synthesis of Benzimidazoles and Derivatives

Due to synthetic importance and various bioactivities showed by benzimidazoles and their derivatives, a major effort has gone into generating libraries of these compounds. In the primary nineties, numerous benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline, and cyclized molecule, obtaining

compounds with superior stability and good biological activity [**3,4]**. Synthetic benzimidazole products containing electron donating group have been demonstrated to be effective antiulcer drugs [5,6], for example the Omeoprazole. Instead, other benzimidazole derivatives have shown healing activity in diseases such as ischemia-reperfusion injury or hypertension **[6,7**]. The initial synthetic methods described in the literature have shown o-phenylenediamine reacting with carboxylic acids or their derivatives [**8,9]**.

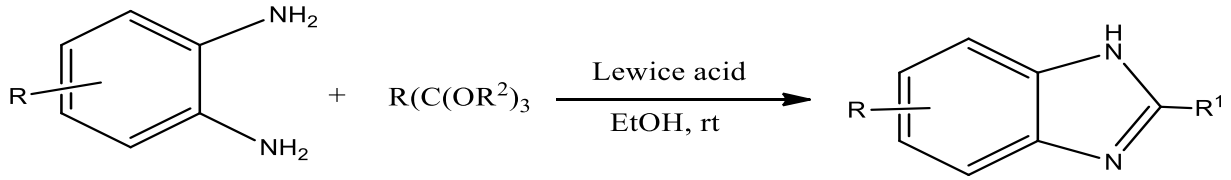
Mono acyl derivatives of *o*-phenylenediamine are converted into the corresponding benzimidazole under a temperature above the melting point of the starting compounds in an atmosphere of nitrogen to prevent oxidation [10]. Subsequently, synthetic methods replaced carboxylic acids with aldehydes obtaining 2-substituted and 1,2-substituted benzimidazoles. These synthetic procedures, however, showed different complications for long reaction times, under drastic conditions, and using toxic solvents [**11, 12, 13]**. Furthermore, waste production and non-recoverable and poorly green and selective catalysts are often used. The use of toxic solvents and the formation of a large amount of industrial waste are grave problems for the environment and human health.

Recently, green chemistry principles have inspired the activities of pharmaceutical industries, suggesting use of environmental solvents [14,15] reducing waste production by selective reaction methods and recyclable reagents[16] This circumstance has directed academia and industry to make substantial efforts towards the development of alternative synthetic routes.

Use of Catalysis for the Synthesis of Benzimidazoles

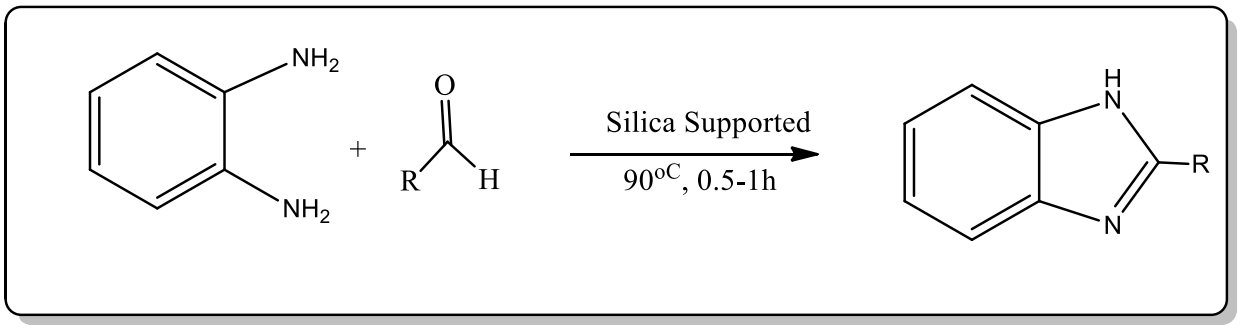
Since the development of innovative synthetic processes to obtain potential drug molecules has become a significant research field, the pursuance of more suitable and practical synthetic methods for benzimidazoles remains an active research area. Furthermore, the use of catalysts has become very important.

The use of Lewis acids as efficient catalysts in various transformations proved to be a greener alternative method for the synthesis of benzimidazole derivatives. A facile synthesis of benzimidazole derivatives using *o*-phenylenediamines and orthoesters at room temperature is the first example of the synthesis of these compounds **[17]**.



R= H,Me, Cl, NO_2
R_1= H, Me, Et, $CH_3(CH_2)_3$
R_2= Me, Et

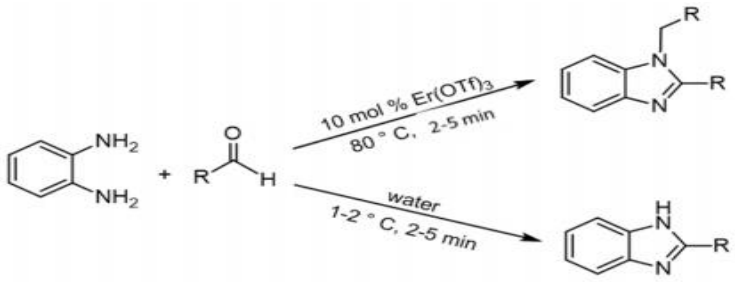
Synthesis of benzimidazole derivatives has been performed using arylaldehydes or arylmethylene-malononitriles as starting material under solvent and catalyst-free conditions, with silica gel used as a means of absorbing the starting materials [18]. The reaction was carried out by intermittent grinding or by a microwave-assisted technique .



Lanthanide triflates have been very successful in their application in the benzimidazoles catalytic synthesis as Lewis acid catalysts. Zn(OTf)2 has been used to synthesize novel benzimidazole-linked triazole derivatives [19]. In

addition to benzimidazoles, triazoles also exhibit various biological activities and are widely employed as pharmaceuticals and agrochemicals. In view of the biological importance of benzimidazole and 1,2,3-triazoles, to know the combined effect of the two moieties, it was considered worthwhile to synthesize certain new chemical products having benzimidazole and 1,2,3-triazole pharmacophores in a single molecule. The reaction performed by treatment of 2-(4-azidophenyl)-1H-benzo[d] imidazole (6) with different types of terminal alkynes in t-BuOH/H2O, sodium ascorbate, and Zn(OTf)2.

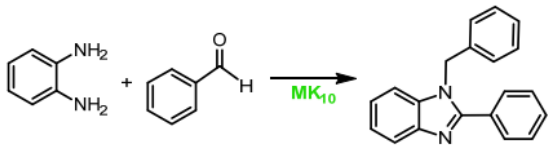
The use of Er(OTf)3 as a commercially available and easily recyclable catalyst promoted the synthesis of 1,2-disubstituted benzimidazoles [20]. Additionally, 2-substituted benzimidazoles were selectively obtained in high yield and short reaction times in water as solvent at 1–2 °C or at 80 °C (for electron-deficient aldehydes) (Scheme 4).



Next, catalytic applications of nanoporous materials in chemical synthesis have been highly successful. The use of zeolite as a hierarchical nanoporous material for the synthesis of benzimidazoles by the condensation of 1,2-phenylenediamine with aromatic aldehydes was investigated. The advantages of this procedure were high chemoselectivity and shorter reaction time, but the procedure was performed in a toxic solvent as acetonitrile. While numerous research studies have been conducted on the use of non-toxic solvents, adopting methods based on solvent-free or solid-state reaction conditions are also effective to reduce pollution. In this context, solid Lewis's acid catalysts are usually used [**21]**. In the last years, the use of heterogeneous catalysts in solvent-free, microwave-assisted reactions has been mainly important for industrial production. In this regard, Bonacci et al. found it useful to use this heterogeneous catalyst for the synthesis of cyclopentenone derivatives from furfural [**22**] and benzimidazole derivatives [**23**]. The reaction to obtain benzimidazoles is performed under MW irradiation and in solvent-free conditions (**Table 1)**

The reaction to optimize the conditions takes place between *o*-PDA (*o*-phenylenediamine) and benzaldehyde in a 1:1 or 1:2 molar ratio at different temperature and different wt (%) of MK10.

Table 1. Synthesis of benzimidazoles using MK10.



Entry	MK10 wt (%) [a]	Molar Ratio *o*-PDA:Benzaldehyde	Temp (°C)	Time (min)	Conversion (%) [b]	Selectivity (%) [c]
1	10	1:1	rt	120	19.3	12.0
2	10	1:2	rt	120	20.9	53.0
3	10	1:2	60	120	79.6	65.1
4	10	1:1	80	120	80.9	33.3
5	10	1:1	100	60	99.9	38.3
6	10	1:2	100	60	99.9	75.0
7	-	1:2	100	90	45.0	49.0
8 [d]	20	1:1	60	5	99.9	18.2
9 [d]	**20**	1:2	**60**	**5**	**99.9**	**98.5**

The complete conversion of *o*-phenylendiamine occurred using 20 wt% of MK10. The reaction was performed at 60 °C under MW irradiation. Furthermore, 2-phenyl-benzimidazole has been the principal product (81.2% yield). Using 2 mmol of benzaldehyde, 1-benzyl-2-phenyl-benzimidazole in 98.5% yield was obtained.

The essential benefit that is obtained in sustainability by using a heterogeneous catalyst is the catalyst recycling. To show this, after the complete conversion of the amine into the benzimidazole derivative, the final reaction mixture was treated with ethyl acetate to recover the MK10 by filtration, suitably washed, and dried. The recovered catalyst was used for the next run, adding fresh reagents following the procedures optimized.

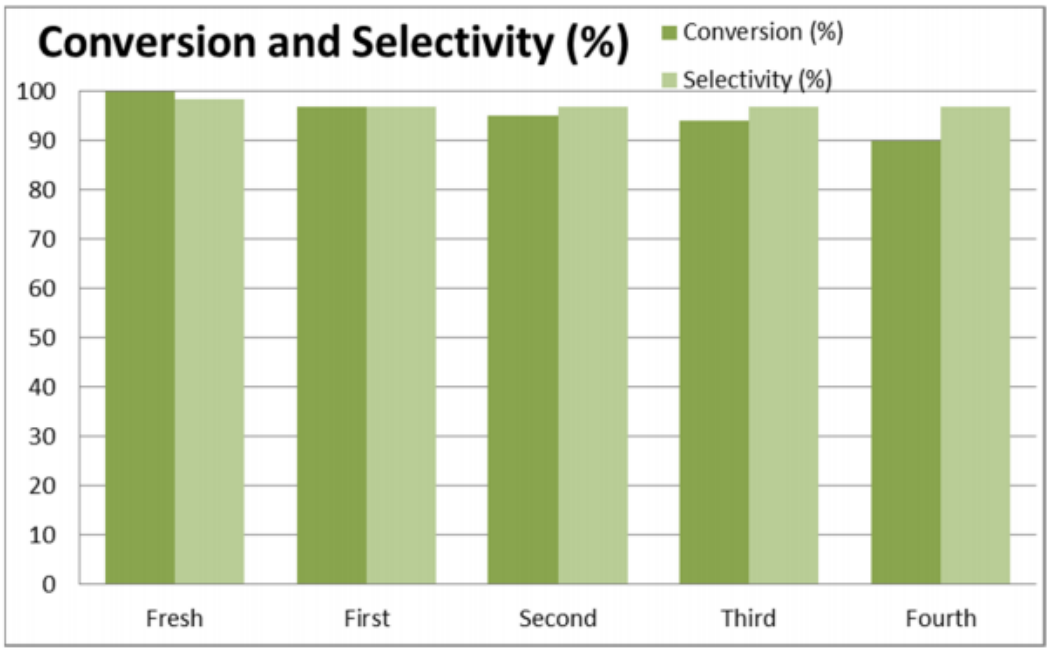


Figure 1. Cycling performing of MK10 in synthesis of 1-benzyl-2-phenyl-benzimidazole using the optimal reaction conditions.

Synthesis of Privileged Benzimidazole Scaffolds Using Green Solvent

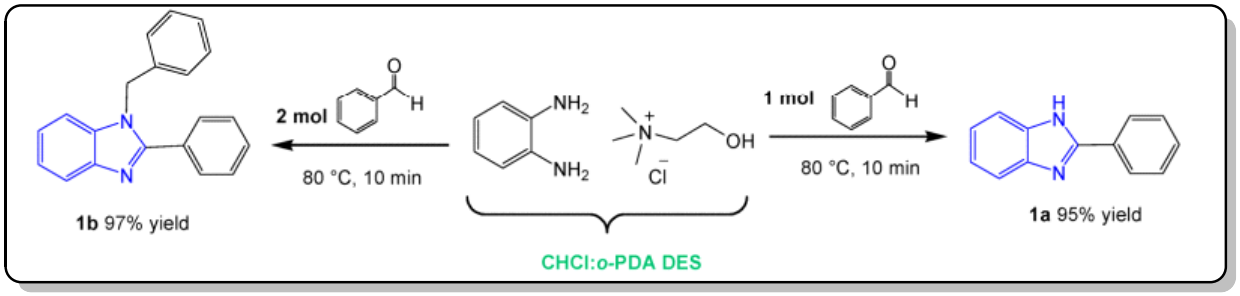
In the last years, the most essential pharmaceutical industries have been inspired by green chemistry principles. The use of biomass derivatives, reduction of toxic solvents, reductions in waste production, and eco-friendly organic synthetic methods [24] have been introduced. In this regard, given the large amount of hazardous conventional solvents used by the pharmaceutical industry, most of the studies are currently converging on the use of more eco-friendly alternatives. The use of water or ionic liquids (ILs) as green media and/or the use of organometallic catalysts have been developed.

The synthesis of 2-substituted benzimidazole derivatives with equimolar amounts of aromatic aldehydes and *o*-phenylenediamine under microwave irradiation is investigated using [BMIM]HSO_4 as ionic liquid. The same method was also reported for the synthesis of 1,2-disubstituted benzimidazole derivatives by using 2-molar amounts of aromatic aldehydes in high yield [25].One of the salient features of this method is that electron withdrawing as well as electron donating groups substitute aromatic aldehydes, giving excellent yields and purity. It must be considered that ILs are toxic and dangerous to the environment [26]. Furthermore, their organic synthesis and purification are often costly and time-consuming [27]. Deep eutectic solvents (DES) are new green solvents with massive applicability in all areas of the chemical industry [28].

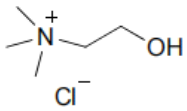
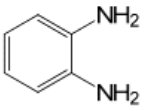
DESs are like ionic liquids from physical point of view, but quite different regarding the chemical character. Ionic liquids are composed by cations and anions, while DES are generally a combination of two or more components, with at least one hydrogen bond acceptor (HBA) and one hydrogen bond donor (HBD). These components (two or more natural compounds) interact between themselves by hydrogen bonding, behaving as one single entity. Because the production of these important solvents relies exclusively on the physical mixture of natural compounds, their

production has practically no effect on the environment. These green solvents are also low-cost alternatives to most common solvents [29].

In the last years, particular interest has been shown in the synthesis of DESs, in which one of the components of DES itself is the reactant to be converted into the reaction product. A new synthetic route to benzimidazole derivatives has recently been presented. The novelty of the proposed method is that in the first phase a DES is formed from *o*-phenylenediamine (*o*-PDA) and choline chloride (ChCl) as components [30].



A differential scanning calorimetry (DSC) analysis of the obtained DES and of the individual components was performed. The analysis showed the formation of the DES. ChCl and *o*-phenylenediamine showed melting points at 302 °C and 102 °C, respectively, while the obtained mixture showed a eutectic that melts at 32 °C. This result (a melting point significantly lower than that of its single components) demonstrated the successful formation of a eutectic mixture.

ChCl	HBD	Molar Ratio	T_f (°C)	T_m HBD (°C)	Δ (°C)	Appearance
		1:1	32	102	70	Light yellow liquid that tends to become greenish.

The obtained eutectic mixture was tested as solvent and, at the same time, reactant in the pilot reaction to obtain benzimidazole derivatives. To the DES synthetized, 1 mol of benzaldehyde (respect component *o*-PDA) was added and magnetically stirred for 10 min at 80 °C. The reaction obtained the compound mono substituted (95% yield) and compound disubstituted as the only product (97% yield) using 2 mol benzaldehyde.

Using DES solvent as starting material with different molar ratio of the aldehyde, various 2- substituted or 1,2-disubstituted benzimidazoles can be obtained in good selectivity and yields. An essential benefit of this solvent system is that the use of the DES enables an easy work-up without using any purification methods, thanks to the selectivity method[31].

Conclusion:

The biological uses of benzoimidazoles are widely recognised, making them heterocyclic compounds. These scaffolds are used in a variety of medicinal contexts, including antihistamine and antidiabetic antibacterial betic, etc.These powerful and biologically effective compounds have several applications in several industries, including as agrochemicals and medicine. Naturally, they are the substances that, while providing numerous benefits to human existence, also has several synthesis routes as well. This review aims to investigate and gather the several documented synthesis routes involving benzomidazoles. This investigation and compilation action of several benzomidazole synthesis routes will effectively help researchers to get information about various benzimidazole production techniques and would also help for the creation of a new protocol that can be used in large-scale manufacturing.

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