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SYNTHETIC STRATEGIES FOR BENZIMIDAZOLES: ADVANCES AND GREEN PERSPECTIVES

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ABSTRACT

Benzimidazoles represent an important class of heterocyclic compounds with broad pharmacological significance, including antimicrobial, antiviral, antitumor, anti-inflammatory, and anthelmintic activities. Their biological versatility has driven the development of diverse and efficient synthetic strategies. The current review represents a concise and systematic overview of synthetic approaches to benzimidazoles, emphasising the reaction of 1,2-benzenediamine with different amines, aldehydes, alcohols, carboxylic acids, β-ketoesters, and other nucleophilic partners. Comparative insights into catalyst-mediated, catalyst-free, and green synthetic methodologies are highlighted, including the use of inorganic acids, solid-supported catalysts, natural catalysts, and environmentally benign reaction conditions. Additionally, emerging approaches using alternative diamine precursors and modified reaction pathways are discussed. By summarising advancements in both traditional and sustainable synthetic practices, this review provides a practical reference for researchers involved in designing benzimidazole scaffolds for medicinal and chemical applications. Furthermore, this review emphasises the advantages and limitations of different methodologies, which will help researchers select the suitable synthetic routes for efficient synthesis of benzimidazoles.

Keywords: Benzimidazoles, Catalyst-Free Synthesis, Green Synthesis, Heterocyclic Compounds, Synthetic Strategies.

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INTRODUCTION

Benzimidazole is a prominent heterocyclic aromatic scaffold containing benzene and an imidazole ring fused at the 4th and 5th positions, resulting in a bicyclic, nitrogen-containing system.[1] This structural framework is well recognised for its resemblance to naturally occurring nucleotides, enabling benzimidazole derivatives to interact effectively with biomacromolecules.[2] It shows different pharmacological, medicinal, and biological activities and has also been found to be useful in agricultural fields.[3,4] The pharmacological versatility of benzimidazole derivatives has been extensively documented.[5] Structure Activity Relationship (SAR) analyses consistently reveal that substitution at the C-2 position plays a decisive role in modulating biological activity, often enhancing potency or selectivity.[6] Because of these structural advantages, it exhibits a wide range of therapeutic activity, such as antiulcer, anti-cancer, antiviral, antimicrobial, antifungal, antimalarial, anthelmintic, and antibacterial activities.[7] Additionally, several derivatives act on specific molecular targets, such as serotonergic 5-HT_3/5-HT_4 receptors, protein tyrosine phosphatase-1B, protein kinases, and JAK-1. Their documented roles as cytotoxic agents, anticonvulsants, analgesics, anti-inflammatories, antidepressants, antidiabetics, and anti-estrogenic agents further expand their clinical significance.[8-12] Benzimidazole is a bicyclic heteroaromatic system containing two nitrogen atoms within the imidazole ring, imparting amphoteric character to the molecule. This review systematically highlights recent synthetic methodologies for benzimidazole derivatives, with emphasis on catalyst-assisted, catalyst-free, and green approaches.

EXPERIMENTAL

This review was conducted through an extensive search of the scientific literature from 2012 to 2025 using various online databases, including PubMed, Google Scholar, and ScienceDirect. All collected

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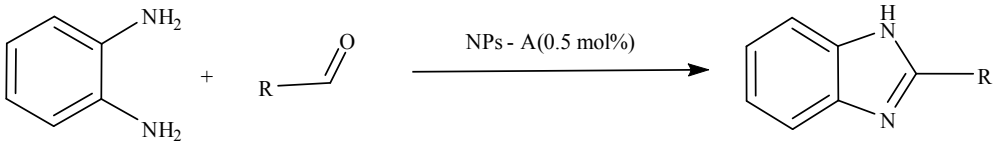
literature was critically analysed to compare reaction strategies, catalysts, substrates, and emerging green chemistry approaches. Only peer-reviewed articles focusing on synthetic methodologies were included, while purely biological studies were excluded.

Synthesis Strategies for Benzimidazole Derivatives

Synthesis of Benzimidazole Derivatives via Condensation of Aldehydes with 1,2-Benzenediamine

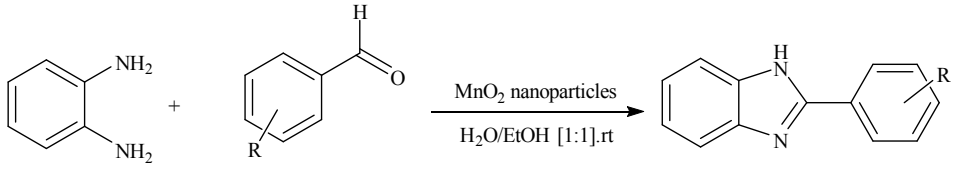
Synthesis of benzimidazole derivatives using inorganic catalysts

Sharma *et al.* successfully synthesised benzimidazole by reacting 1,2-benzenediamine with several aldehydes, employing ZnO-NP as a catalyst. This method offers several benefits, such as easy purification of the final product, high efficiency, solvent-free conditions, and scalability. [13]



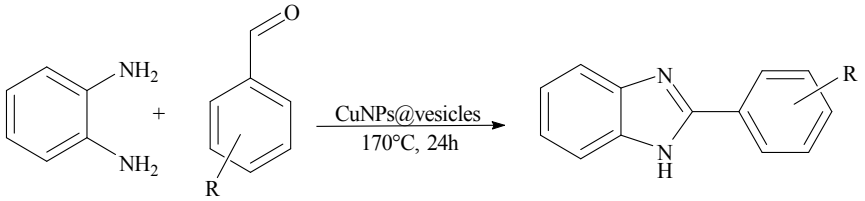
Scheme-1: Synthesis of benzimidazole derivatives catalysed by ZnO-NP.

Naeimi *et al.* utilised MnO_2 nanoparticles as a catalyst under ultrasound-assisted conditions for the synthesis of 2-substituted benzimidazoles. In this reaction, the aldehydes react with *o*-phenylenediamine in an ethanol–water mixture (1:1), where MnO_2 nanoparticles act as catalysts in the oxidative cyclocondensation that forms the benzimidazole ring.[14]



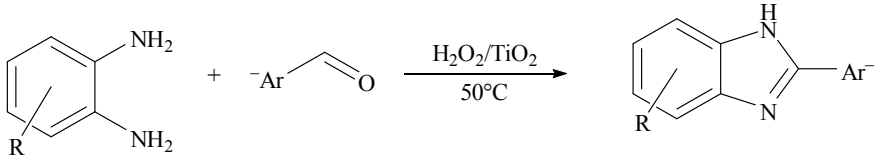
Scheme-2: Synthesis of benzimidazole derivatives catalysed by MnO_2

Shukla *et al.* synthesised benzimidazole using Cu nanoparticle–loaded polymer vesicles as nanoreactors to convert 2-nitroaniline into benzimidazoles through a cascade process. Inside the vesicles, the Cu nanoparticles first reduce the nitro group to *o*-phenylenediamine, which then immediately reacts with an aldehyde to form a Schiff base, followed by cyclization and oxidation to yield the benzimidazole.[15]



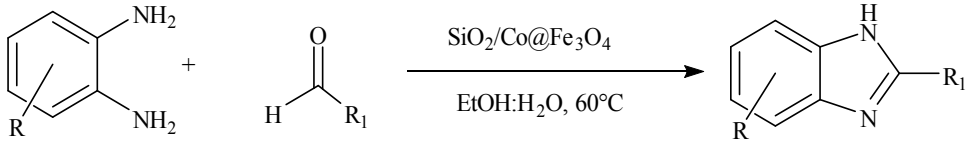
Scheme-3: Synthesis of benzimidazole derivatives catalyzed by CuNPs

Kiumars Bahrami *et al.* reported a new catalyst system that is H_2O_2/TiO_2 nanoparticle for the synthesis of benzimidazoles. The catalyst was found to enhance the reactivity due to its better surface area and mixed-phase anatase–rutile composition. The catalyst also showed good recyclability and a highly efficient route for heterocyclic scaffold construction.[16]



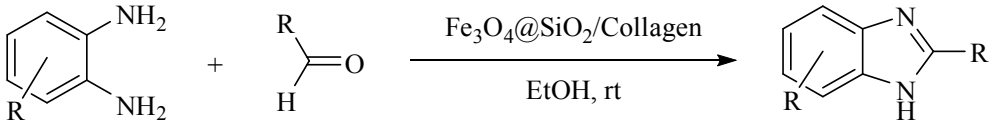
Scheme-4: Synthesis of benzimidazole derivatives catalyzed H_2O_2 and TiO_2

Kumara *et al.* synthesised 2 aryl benzimidazole by the condensation reaction of *o*-phenylenediamine (13) and aldehydes (14) using $CO@Fe_2O_4$ and $SiO_2/Co@Fe_2O_4$ as catalysts.[17]



Scheme-5: Synthesis of benzimidazole derivatives catalyzed by $CO@Fe_2O_4$ and $SiO_2/Co@Fe_2O_4$

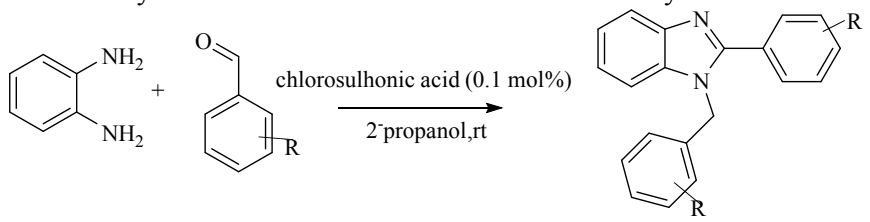
Ghafuri *et al.* synthesised $Fe_3O_4@SiO_2$ nanostructure and then combined it with collagen to make a strong $Fe_3O_4@SiO_2$/collagen hybrid catalyst. The catalyst worked very well when used to make derivatives of benzimidazole, by the condensation of *o*-phenylenediamine with aldehydes, giving high yields, fast reaction speeds. environmentally sustainable, operationally simple, and highly efficient platform for heterocyclic synthesis. [18]



Scheme-6: Synthesis of benzimidazole derivatives catalyzed by Fe_3O_4

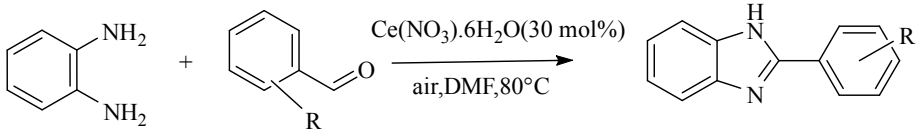
Acid-Catalyzed Synthesis of Benzimidazole Derivatives

Nana V. Sithole *et al.* synthesised benzimidazole derivatives using chlorosulfonic acid ($ClSO_3H$) as a powerful acidic catalyst at room temperature, using 2-propanol as the most solvent, providing good yields (80-90 %) within a short duration of reaction time. The reaction method employed minimal use of catalyst (0.05–0.10 mol), making the process easier and scalable, avoiding any harsh conditions and lengthy processes that are commonly associated with traditional benzimidazole syntheses.[19]



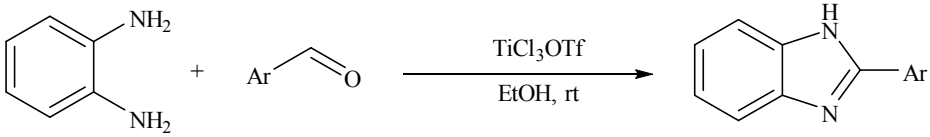
Scheme-7: Synthesis of benzimidazole derivatives catalyzed by chlorosulfonic acid

Martins *et al.* used 1,2-diaminobenzene and aldehyde for the synthesis of a series of 2-substituted benzimidazoles. This Method resulted in a higher yield of the desired product. The researchers employed air (oxidant) and $Ce(NO_3)_3.6H_2O$ as the catalyst for the reaction.[1,20]



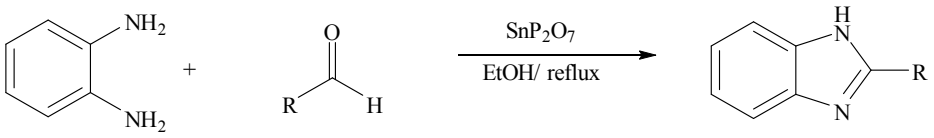
Scheme-8: Synthesis of benzimidazole derivatives catalysed by $Ce(NO_3)_3.6H_2O$

Azizian *et al.* developed and synthesised benzimidazoles using *o*-phenylenediamine and aldehyde via a condensation reaction using $TiCl_3$ OTf as a catalyst, affording the product in good yield under mild reaction conditions.[1,21]



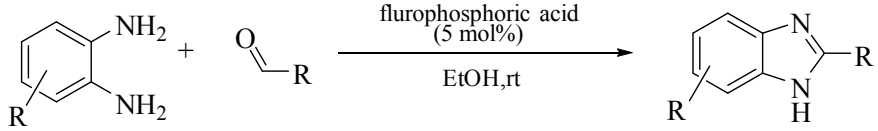
Scheme-9: Synthesis of benzimidazole derivatives catalysed by $TiCl_3$ OTf

Merroun *et al.* synthesised benzimidazoles by reacting 1,2-diaminobenzene with an aromatic aldehyde and using SnP_2O_7 as a catalyst. The reaction results in the formation of desired products with high yield and in a shorter reaction time.[22]



Scheme-10: Synthesis of benzimidazole derivatives catalysed by SnP_2O_7

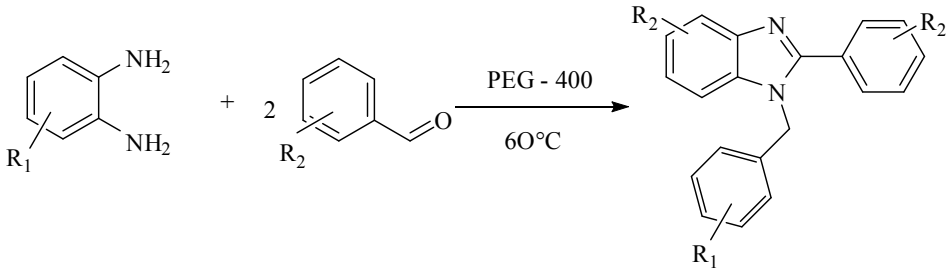
Mathapati *et al.* synthesised benzimidazoles via the cyclisation reflux of 1,2-phenylenediamine by aldehyde using fluoro-phosphoric acid. The products were obtained in good yield under mild reaction conditions.[1,23]



Scheme-11: Synthesis of benzimidazole derivatives catalysed by fluorophosphoric acid

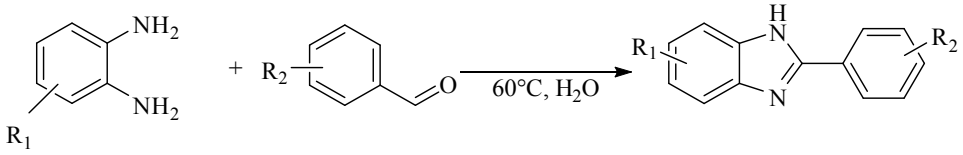
Catalyst-Free Approaches for the Synthesis of Benzimidazole Derivatives:

Mekala *et al.* conducted the condensation of 1,2-phenylene diamines and aryl aldehyde in Polyethylene glycol (PEG-400) medium, resulting in a synthesis yield of 82-85% of 1,2-disubstituted benzimidazole. This Method is a one-pot synthesis approach.[24]



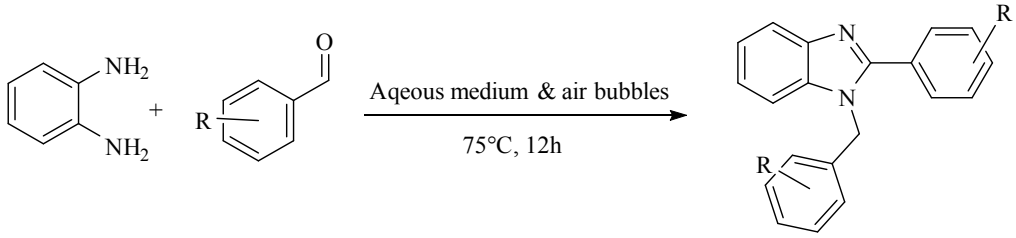
Scheme-12: Synthesis of benzimidazole derivatives catalyzed by Polyethylene glycol (PEG-400)

Bala and colleagues synthesised disubstituted benzimidazoles by heating a 1,2-phenylenediamine aryl aldehyde mixture in water at 80°C, resulting in a yield of 89-94%.[25]



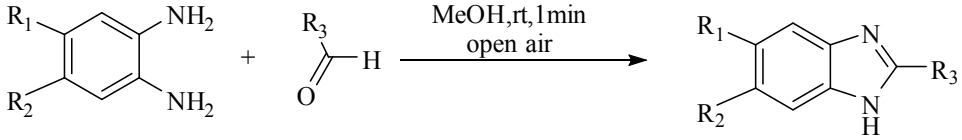
Scheme-13: Synthesis of benzimidazole derivatives catalysed by water

Mahato *et al.* utilized 2-phenylene imidamine and aryl aldehydes in the appearance of water and air to produce 23-26% yield of distributed benzimidazoles.[26]



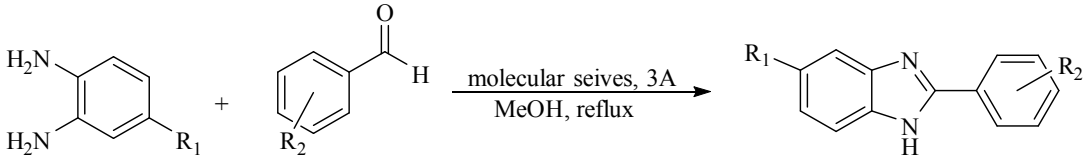
Scheme-14: Synthesis of benzimidazole derivatives catalyzed by aqueous medium and air bubbles

Elumalai *et al.* synthesised benzimidazoles using 1,2-diamines and aldehydes via condensation in the presence of air and MeOH to synthesise 2-substituted benzimidazoles with good yields ranging from 33% to 96%. This Method of synthesis has various benefits, including higher yields, shorter reaction times, and the absence of catalysts and additives.[1,27]



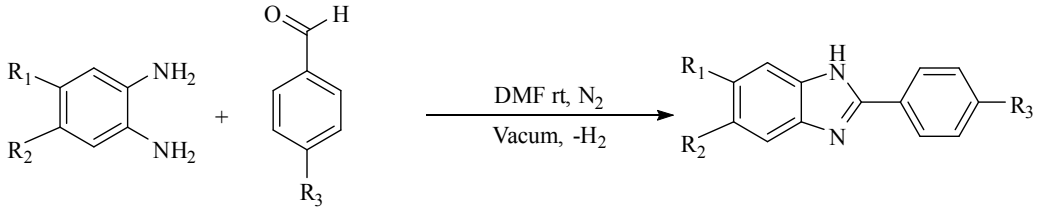
Scheme-15: Synthesis of benzimidazole derivatives catalyzed by air and MeOH

Chaturvedia employed a methyl hydroxy molecular sieve system to condense *o*-phenylenediamines and aromatic aldehydes, resulting in the formation of 2-substituted aryl benzimidazoles with good yields ranging from 30% to 89%. These synthesised products are utilised for their Anti Tubercular Activity.[28]



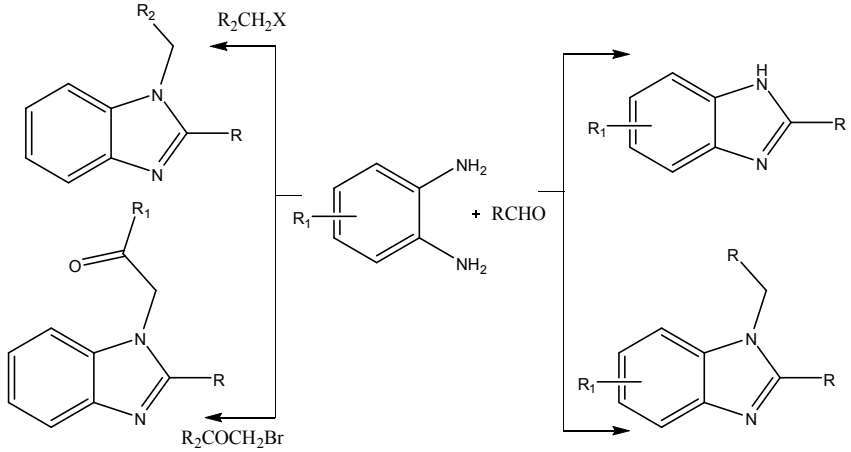
Scheme-16: Synthesis of benzimidazole derivatives catalyzed by methyl hydroxy molecular sieve system

Sutapin and colleagues synthesised benzimidazole by condensing phenylenediamine and aromatic aldehydes under severe conditions, achieving 85%–90% yield without the use of a catalyst.[29]



Scheme-17: Synthesis of benzimidazole derivatives with no catalyst

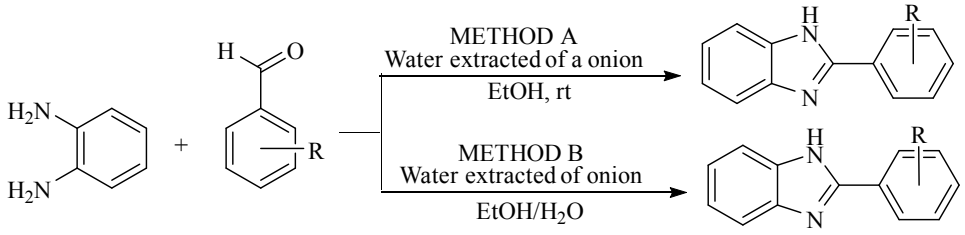
Arya *et al*. synthesized 2-substituted and 1,2-disubstituted benzimidazoles using sodium fluoride as the catalyst. The process is "solvent-controlled," using anhydrous DMF or glacial acetic acid to determine the specific chemical outcome.[30]



Scheme-18: Synthesis of benzimidazole derivatives catalyzed by sodium fluoride

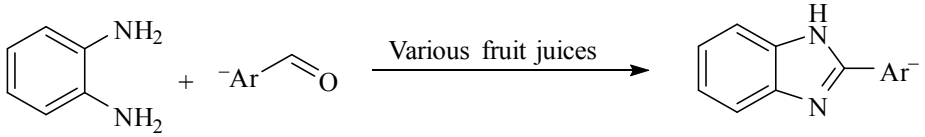
Green Synthesis of Benzimidazole Derivatives Using Natural Catalysts

Prabakaran *et al.* conducted a reaction between Phenylenediamines and an aromatic-substituted aldehyde using an aqueous onion extract, resulting in the synthesis of benzimidazoles with good yields ranging from 72% to 96%. [31,32]



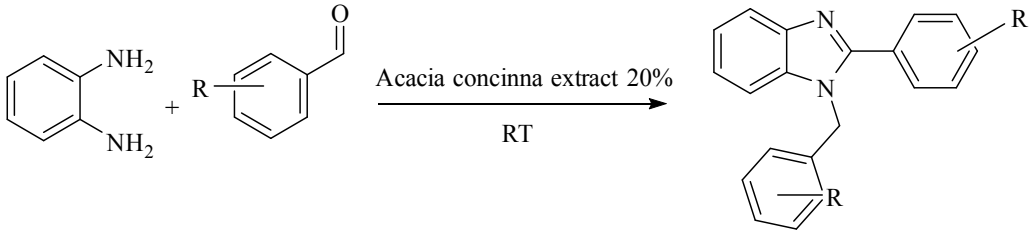
Scheme-19: Synthesis of benzimidazole derivatives catalyzed by aqueous onion extract

Gulati and colleagues conducted a study in which they reacted substituted aldehydes with *o*-phenylenediamines using various fruit juices, including citrus sinensis L. juice, CoCos nucifera L. juice, and citrus limetta juice. This reaction resulted in the synthesis of benzimidazoles with yields ranging from 78% to 93%.[1,33]



Scheme-20: Synthesis of benzimidazole derivatives catalysed by fruit juices

Kadu and colleagues utilised *o*-Phenylenediamine and substituted aldehydes with the assistance of the catalyst Acacia concinna pod extract, to produce 88-98% of the substituted benzimidazole. [34]

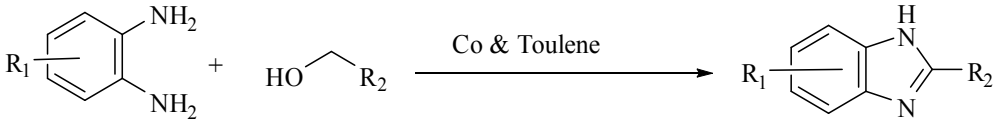


Scheme-21: Synthesis of benzimidazole derivatives catalyzed by concinna pod extract

Condensation of 1,2-Benzenediamine with Alternative Substrates

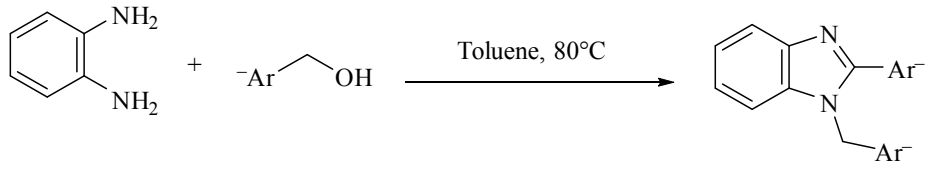
Condensation of 1,2-Benzenediamine with Primary Alcohols

Daw *et al.* synthesised benzimidazole derivatives using a cobalt complex that acts as a catalyst in the presence of toluene for direct dehydrogenative coupling. It promoted the oxidation of the alcohol to an aldehyde in situ, followed by condensation with the diamine and cyclisation to the benzimidazole, releasing H_2O and H_2 as by-products and resulting in the production of benzimidazoles with good yields ranging from 28% to 99%. [35]



Scheme-22: Synthesis of benzimidazole derivatives catalysed by cobalt in the presence of toluene

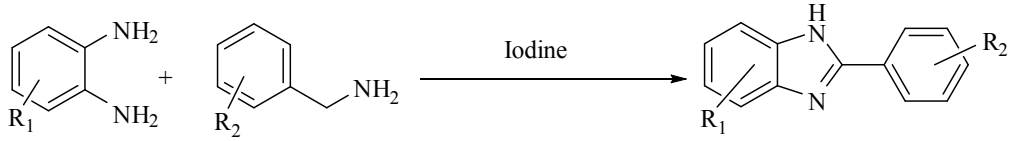
Sharma *et al.* synthesized 1,2-disubstituted benzimidazole derivatives using four complexes of toluene in yields of 82%–92%. This was achieved using condensed benzylic alcohols and *o*-phenylenediamines. [36]



Scheme-23: Synthesis of benzimidazole derivatives catalyzed by complexes of toluene

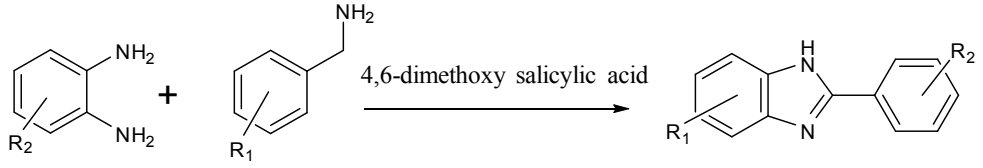
Condensation of 1,2-Benzenediamine with Primary Amines

Under aerobic and mild conditions, Naresh *et al.* successfully synthesized benzimidazole derivatives with 85%yields by treating 1,2-diaminocarbenes and benzylamine using iodine as catalyst in presence of air. [37]



Scheme-24: Synthesis of benzimidazole derivatives catalyzed by I_2 and an air

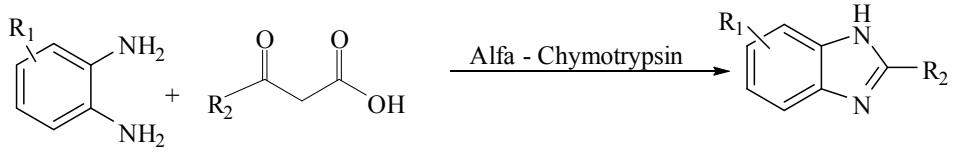
Dong *et al*. developed a multistep synthesis of benzimidazole using a metal-free oxidative coupling method that converts benzylamines to imines using organocatalysts (salicylic acid derivatives). Catalyst like 4,6-dimethoxysalicylic acid and 4,6-dihydroxysalicylic acid show strong catalytic activity, enabling benzyl amines to undergo oxidative dehydrogenation to form the corresponding imines. The resulting imines then condense in situ with *o*-phenylenediamine to form the benzimidazole ring with yields ranging from 54%–96%.[38]



Scheme-25: Synthesis of benzimidazole derivatives catalysed by 4,6-dimethoxy salicylic acid

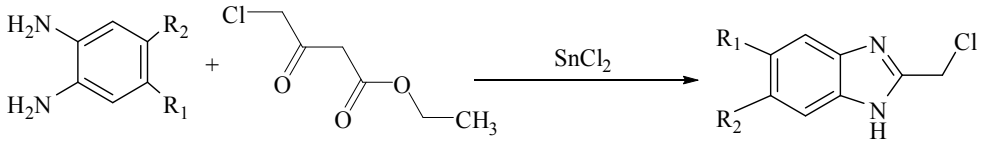
Condensation of 1,2 benzenediamine with beta-ketoesters

Liu *et al*. utilised the enzyme catalytic chymotrypsin. Chymotrypsin facilitated the condensation of *o*-phenylenediamines with beta-keto esters through a retro-Claisen reaction pathway to yield the 2-substituted benzimidazole derivatives with yields ranging from 73%–96%.[39]



Schem-26: Synthesis of benzimidazole derivatives catalysed by chymotrypsin

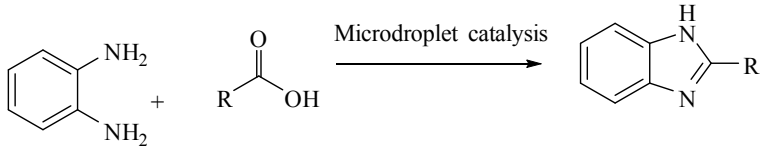
Dayakar *et al*. utilised a straightforward condensation reaction where *o*-phenylenediamines are reacted with ethyl 4-chloro-3-oxobutanoate using either no catalyst or catalysts like AcOH, p-TsOH, $AlCl_3$, CuI, $CuCl_2$, $Cu(OAc)_2$, $Sc(OTf)_3$, $SnCl_2$, $La(OTf)_3$, and $Bi(OTf)_3$. It was found that the maximum yield of benzimidazole derivatives was obtained with SnCl2. of 82%.[1,40]



Scheme-27: Synthesis of benzimidazole derivatives catalysed by $SnCl_2$

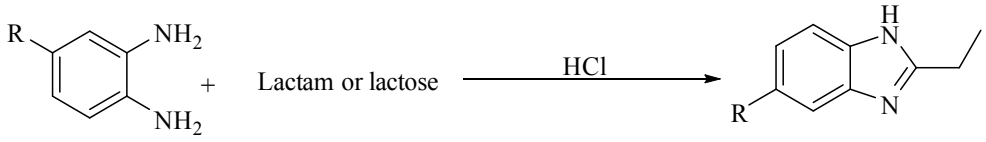
Condensation of 1,2-Benzenediamine with Carboxylic Acids and Their Derivatives

Using a nano-electroscopy ion source, Basuri *et al.* In this method, a solution containing an *o*-phenylenediamine and a protonated carboxylic acid is sprayed to generate highly charged microdroplets. Within these droplets, rapid nucleophilic addition occurs: the amine of the diamine attacks the protonated carboxylic acid, forming an amide-type intermediate. Due to the microdroplet environment, the intermediate that undergoes intramolecular cyclisation, followed by dehydration, to yield the benzimidazole ring, ranges from 5% to 93%.[41]



Scheme-28: Synthesis of benzimidazole derivatives catalyzed by nano-electroscopy ion source

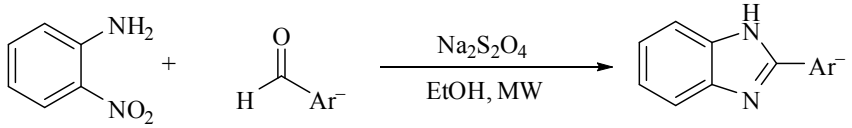
Castillo *et al.* synthesised benzimidazole, in which, instead of the typical condensation of *o*-phenylenediamine with carboxylic acids, which often leads to unwanted dialkylation, they used the ring-opening of lactones or lactams under acidic conditions (HCl, heat). This approach enabled direct formation of 1H-benzimidazoles bearing flexible alkyl or amino alkyl side chains at the 2-position in yields of 44%–90%.[1,42]



Scheme-29: Synthesis of benzimidazole derivatives catalyzed by HCl

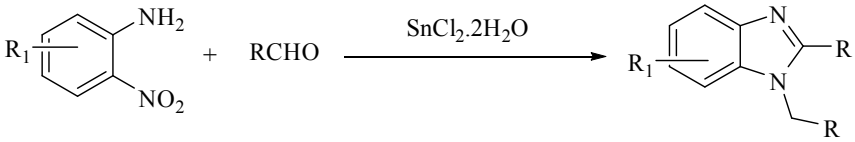
Condensation Reaction between 1,2-benzenediamine and o-nitroaniline.

Naeimi *et al.* developed the synthesis of 2-substituted benzimidazoles from o-nitroaniline and aryl aldehydes under microwave irradiation. Using sodium dithionite as a catalyst, which is a mild and inexpensive reducing agent, the nitro group of o-nitroaniline is rapidly converted into an amine, which then condenses with the aldehyde and undergoes intramolecular cyclisation to form the benzimidazole ring. Microwave heating dramatically accelerates the reaction, giving excellent yields in very short times while operating under mild conditions.[43]



Scheme-30: Synthesis of benzimidazole derivatives catalyzed by $Na_2S_2O_4$.

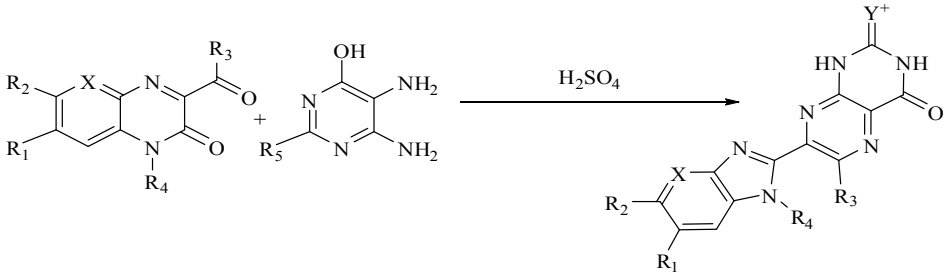
Rodriguez-Huerto *et al.* synthesised benzimidazoles using nitroarenes as starting materials. In the reaction, nitroarenes react with phenyl isocyanate (or benzyl isothiocyanate) in a tin (II) chloride dihydrate/choline chloride eutectic mixture, which acts as a reducing medium and facilitates the transformation of nitro groups into the corresponding amine intermediates. When different aldehydes are introduced, the reaction pathway diverges: o-nitroaniline or 4-methoxy-2-nitroaniline preferentially yield N-arylmethyl-2-substituted benzimidazoles through reductive cyclisation.[1,44]



Scheme-31: Synthesis of benzimidazole derivatives catalysed by Tin (II) choline eutectic mixture /Chloride dehydrate

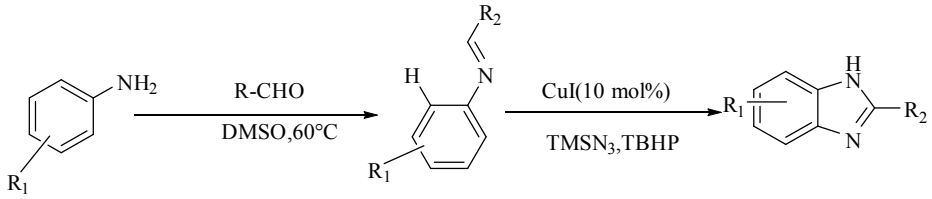
Miscellaneous Synthetic Approaches to Benzimidazole Derivatives:

Mamedove *et al.* developed a one-pot method for the synthesis of benzimidazoles using H_2SO_4 - catalyzed rearrangement of quinoxalinones in the presence of 5,6-diamino-2-mercaptopyrimidin-4-ols or 2,5,6-triaminopyrimidin-4-ols. In this transformation, both the benzimidazole and pteridine ring systems are formed in a single synthetic operation via the addition of a nucleophile, ring opening, and ring closure.[45]



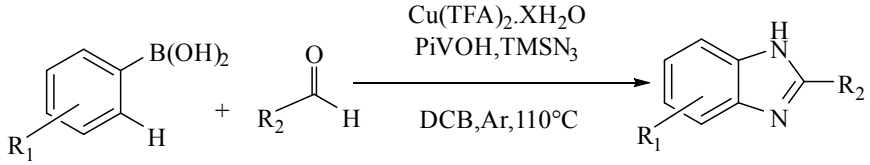
Scheme-32: Synthesis of benzimidazole derivatives catalyzed by H_2SO_4.

Mahesh *et al.* synthesised a one-pot multi-component reaction using copper(I)-catalyzed regioselective amination of N-aryl imines to synthesise substituted benzimidazoles. In this reaction, $TMSN_3$ (Trimethylsilyl azide) as the nitrogen source and TBHP (3,2 tert-Butyl Hydroperoxide) as the oxidant, the copper catalyst promotes a cascade sequence leading to benzimidazole ring formation.[46]



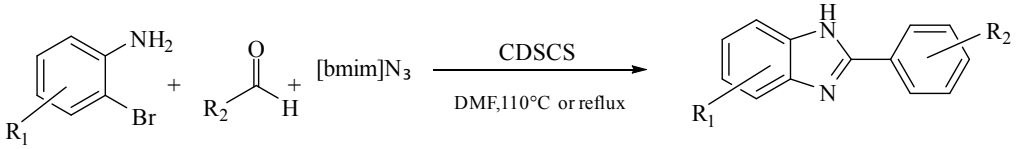
Scheme-33: Synthesis of benzimidazole derivatives catalyzed by TBHP [3,2 tert-Butyl Hydroperoxide] and $TMSN_3$[Trimethyl Azide]

Xie *et al.* developed a one-pot three-component reaction in which arylboronic acids, aldehydes, and trimethylsilyl azide react together to form 2-aryl benzimidazoles. In this process, $TMSN_3$ gives nitrogen for the benzimidazole ring, while the arylboronic acid and aldehyde introduce the R^1 and R^2 substituents, respectively. Using $Cu(TFA)_2 \cdot xH_2O$ as the catalyst in the presence of pivalic acid at 110 °C, the reaction proceeds efficiently and tolerates a wide range of substituted aldehydes and boronic acids, giving moderate to high yields.[47]



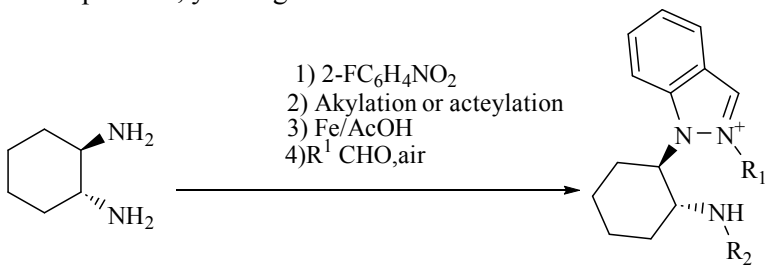
Scheme-34: Synthesis of benzimidazole derivatives catalyzed by $TMSN_3$

Somaych Behrocuz devised a highly efficient technique for synthesising 1-H-2-substituted benzimidazole derivatives. This Method involves the reaction of 2-bromoanilines, aldehyde, $[bmim]N_3$ (1-butyl-3-methylimidazolium cation) in a one-pot, three-component reaction. This reaction is catalysed by copper-doped silica copper sulphate (CDSCS), yielding products ranging from good to excellent. [48]



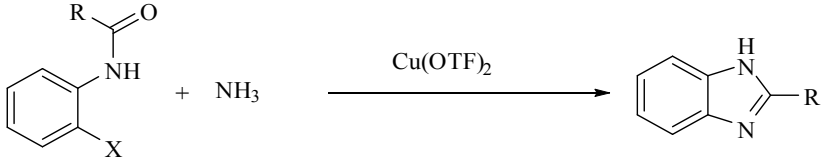
Scheme-35: Synthesis of benzimidazole derivatives catalysed by copper-doped silica copper sulfate

Boratynski *et al.* synthesised a benzimidazole derivative using a multistep reaction starting from the reaction of trans-1,2-diaminocyclohexane with 2-$O_2NC_6H_4F$, which introduced a nitro-fluorophenyl moiety that aided in benzimidazole ring formation. In the next step, the amine group was alkylated or acylated, allowing structural diversification and controlling the subsequent cyclisation pathway. Treatment with Fe/AcOH then reduced the nitro group and caused intramolecular cyclisation to form a benzimidazole framework. Finally, reaction with an aldehyde (R^1CHO) followed by air oxidation installs the R^1 substituent at the 2-position, yielding the final chiral benzimidazole derivatives.[49]



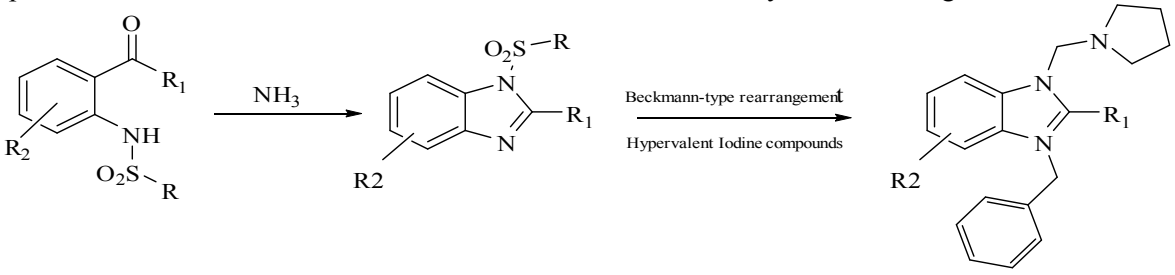
Scheme-36: Synthesis of benzimidazole derivatives catalyzed by $FC_6H_4NO_2$

Li *et al.* developed a procedure for the synthesis of 2-substituted benzimidazole using an NNP-type pincer ligand to assist the condensation reaction between O-halo benzanilides and ammonia. As a result, the desired product was obtained with significantly improved yields.[1,50]



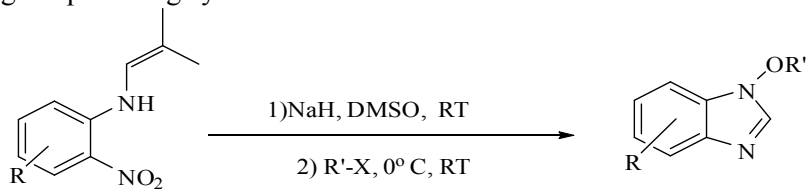
Scheme-37: Synthesis of benzimidazole derivatives catalyzed by NNP-type pincer ligand

Zhang *et al.* reported the synthesis of N-Ts benzimidazole by reacting O-aminoaryl N-H ketamine in a Backmann reaction. Ammonia is condensed with ketones to achieve this rearrangement, with (Diacetoxyiodo) benzene acting as an oxidising agent. The researchers successfully applied this method to prepare chlormidazole and lemizola, both of which are commercially available drugs.[1,51]



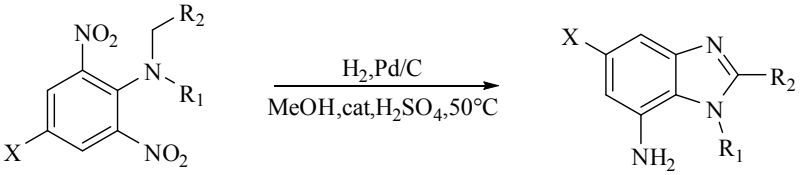
Scheme-38: Synthesis of benzimidazole derivatives catalyzed by ammonia

Ansari *et al.* synthesised benzimidazole derivatives using a simple, two-step reaction starting from 2-nitro-N-(propen-1-yl) benzenamines (enamines). They used Potassium tert-butoxide, a strong base, as a catalyst to promote intramolecular cyclisation/rearrangement. After that reaction with various electrophiles such as alkyl halides, allylic/propargylic bromides, and acyl chlorides produced benzimidazole in good percentage yield.[1,52]



Scheme-39: Synthesis of benzimidazole derivatives catalyzed by potassium tert-butoxide

Joardar *et al*. reported a one-pot synthesis of diverse substituted benzimidazoles using a robust catalyst, Palladium on Carbon, in the presence of methanol, to promote a tandem sequence involving nitro reduction followed by cyclisation products in the moderate to excellent yield range.[1,53]



Scheme-40: Synthesis of benzimidazole derivatives catalyzed by MeOH

Table-1: Comparative Overview of Synthetic Methods for Benzimidazole Derivatives

Method	Catalyst Used	Reaction Conditions	Yield Range	Advantages	Limitations
Inorganic-catalyzed	ZnO-NP, MnO_2, CuNPs, Fe_3O_4	Solvent-free, ultrasound, reflux	70-98%	High efficiency, reusable catalysts	Requires catalyst preparation
Acid-catalyzed	Chlorosulfonic acid, $Ce(NO_3)_3 \cdot 6H_2O$, $TiCl_3OTf$	Mild to strong acidic conditions	60-95%	Fast reactions, wide substrate scope	Corrosive reagents, work-up issues
Catalyst-free synthesis	Water, PEG-400, air, MeOH	Heating, microwave, solvent-assisted	30-96%	Eco-friendly, cost-effective	Sometimes, longer reaction times
Green catalysts	Onion extract, fruit juices, *Acacia concinna*	Aqueous conditions	72-98%	Highly sustainable, low cost	Scale-up challenges
Primary alcohol route	Co complexes	Toluene reflux	28 - 99%	Suitable for N-alkyl derivatives	Requires strict conditions
Primary amine route	I_2 –air, salicylic acid	Mild aerobic	54 - 96%	Good yields, mild conditions	Limited substrate variety
β-Ketoesters route	Chymotrypsin, $SnCl_2$	Enzymatic / Lewis's acid	73 -96%	Novel biological applications	Enzyme cost, optimisation needed
Carboxylic acid route	Nano-electrospray, HCl	Microdroplet reactions	5–93%	Innovative, fast	Low yields for some substrates
Using o-nitroaniline	$Na_2S_2O_4$, Sn(II) choline chloride	Microwave or reflux	70–96%	High efficiency	Specialized equipment

CONCLUSION

Benzimidazole continues to be a crucial heterocyclic pharmacophore due to its structural flexibility and wide-ranging biological activities. The synthetic methodologies developed over the years demonstrate that benzimidazole scaffolds can be accessed through numerous efficient and versatile strategies. The synthesis of benzimidazole derivatives has been explored through numerous pathways, each offering unique advantages in terms of efficiency, yield, and environmental impact. The use of inorganic, acidic, and natural catalysts and catalyst-free and novel Methods provides a broad spectrum of benzimidazole synthesis options. This review highlights the versatility of benzimidazole synthesis, emphasizing the importance of selecting appropriate conditions to achieve desired outcomes. The continuous development of new synthetic routes reflects the ongoing interest in optimising the production of valuable compounds for various therapeutic applications. The objective focuses on the synthesis of the benzimidazole derivatives, highlighting the importance of comparing different methods to optimise future drug development for improved human health and well-being. This study successfully highlighted the most effective synthetic strategies that influence the efficacy of the compounds, with the ultimate goal of guiding the development of more potent and selective benzimidazole-based compounds. Furthermore,

exploring catalyst-free and solvent-less methods and microwave-assisted approaches could significantly reduce reaction times and environmental impact. Future studies should emphasise scalable, sustainable, and atom-economic approaches for benzimidazole synthesis.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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