

Synthetic of Benzimidazole analogs based on the O-phenylenediamine: A mini review

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CHRONICLE

Article history:

Received August 3, 2024

Received in revised form

September 16, 2024

Accepted November 5, 2024

Available online

November 5, 2024

Keywords:

Benzimidazole

Condensation

Metal-catalysed

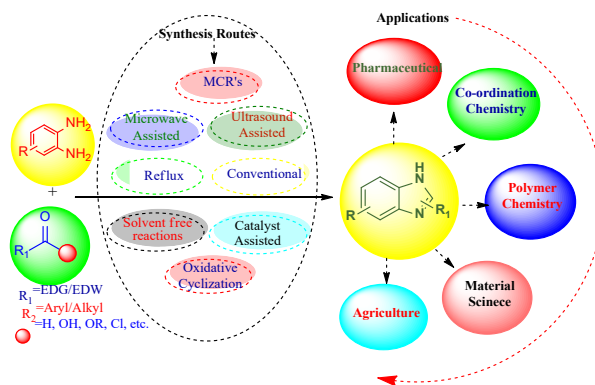
Nano-catalyst

o-phenyldiamine

ABSTRACT

Heterocyclic molecules are found in many parts of living things, so they are being used more and more in medicinal chemistry. Benzimidazoles, which are naturally occurring compounds, exhibit a diverse array of pharmaceutical properties that have been extensively documented. Benzimidazole derivatives serve as valuable intermediates or subunits in the synthesis of pharmaceutical or biologically significant compounds. Substituted benzimidazole derivatives have been utilized in various therapeutic domains, encompassing but not limited to antiulcer, anticancer agents, and anthelmintic species. This study provides a systematic and comprehensive overview of the latest advancements in benzimidazole-based compounds within the field of synthetic organic chemistry.

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Graphical Abstract

1. Introduction

Benzimidazole **1** has an imidazole ring fused with a phenyl ring. It is a chemical compound, which is commonly known by various nomenclatures such as 3-azaindole, azindole, benzimidazole, benzoglyoxaline, 3-benzothiazole, and 1,3-diazaindene. It appears in two identical tautomeric forms. When hydrogen is present, the nitrogen atom at position 1 displays acidic characteristics, while the nitrogen atom at position 3 displays basic characteristics. In the field of heterocyclic organic

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molecules, substituted benzimidazole derivatives¹⁻⁴ are among the most interesting structures. These compounds are synthesized using nucleophilic substitution reactions and condensation reactions between o-phenylenediamine and carbonyl compounds. According to studies that have been conducted, benzimidazoles are found in nature in a wide range of forms and have a wide range of medicinal properties. As scaffolds, these molecules can bind to different receptor sites, making them ideal for discovering new drug targets. The benzimidazole nucleus is a noteworthy nitrogen-containing heterocycle that finds diverse applications in the realm of bioactive molecules (**Fig. 1**). Nitrogen-containing five-membered heterocycles are integral components of bioactive compounds due to their diverse biological functions, ability to form essential interactions with biological systems, and potential for modification in drug design.^{5, 6} The number of nitrogen atom containing five membered heterocycles are available commercially due to their huge applications^{7, 8} in the various fields are as follows:

The bioactivity of this substance encompasses antiviral **2**, antifungal **3**, antiprotozoal **4**, anti-inflammatory **5**, anthelmintic **6**, antimalarial **7,8** anticancer **9**, etc., and diverse pharmaceutical activities (Figure 2).⁹ The synthesis of heterocyclic cores holds significant prominence within the realm of organic synthesis, owing to its extensive array of pharmacological properties. Numerous methodologies for synthesis have been employed.¹⁰

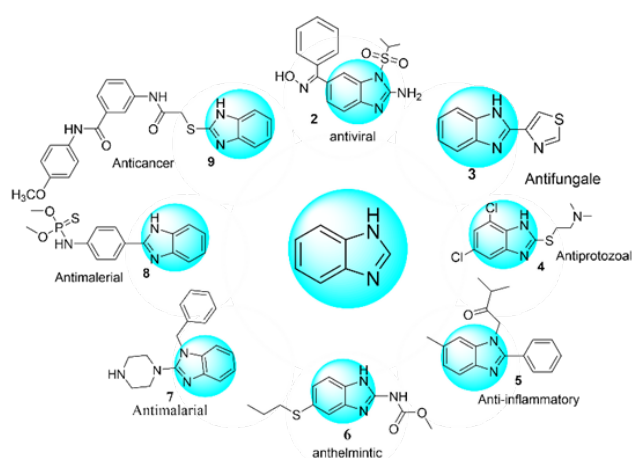
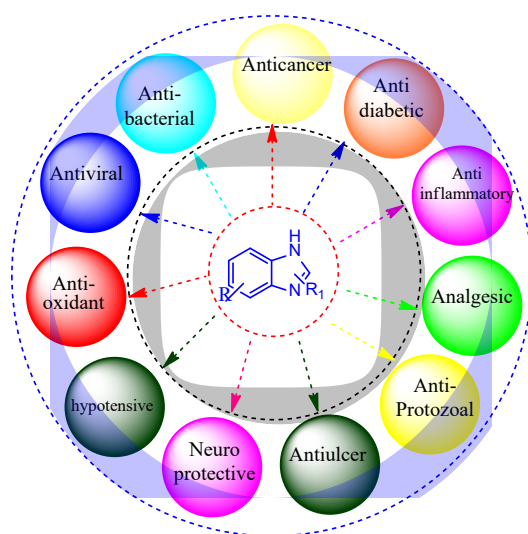
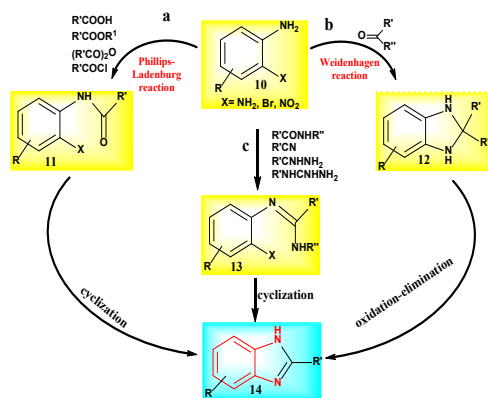


Fig. 1. Benzimidazole has diverse applications in the realm of bioactive molecules

Fig. 2. Bioactive molecules containing benzimidazole moiety.

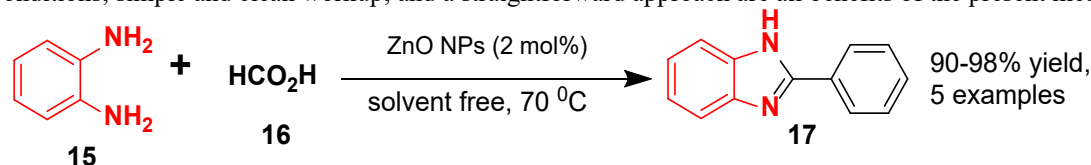
2. Synthesis of benzimidazoles

The process of generating novel benzimidazole derivatives entails the oxidative coupling of o-phenylenediamines with diverse reagents at elevated temperatures. Substituted benzimidazoles **14** can be synthesised through conventional techniques such as the Phillips-Ladenburg reaction, which couples 1,2-diaminobenzenes **10** with carboxylic acids and their derivatives (Scheme 1, rout a), and the Weidenhagen reaction, which couples 1,2-diaminobenzenes **10** with aldehydes/ketones via benzimidazoline **12** (Scheme 1, route b).



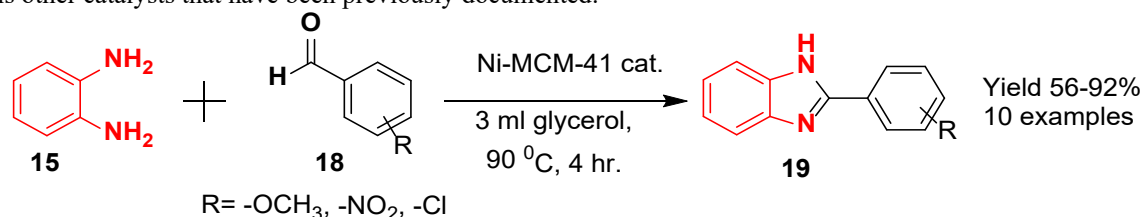
Scheme 1. benzimidazole synthesis using conventional methods

Benzimidazoles can be obtained via cyclization of amide **11** with acid substitutes such as esters, acid anhydrides, acid chlorides, and lactones. The cyclization amidine **13** uses the Phillips-Ladenburg reaction, which involves the use of amides, nitriles etc. to obtain benzimidazole **14**. These conventional techniques exhibit restricted applicability and diminished productivity. Scholars are currently engaged in the pursuit of devising solvent-free methodologies and more environmentally friendly approaches, including but not limited to ionic liquids, water-based media, and microwave irradiation. In recent years, researchers have explored various novel methods for benzimidazole synthesis that offer advantages in terms of efficiency, selectivity, and sustainability. Here are some examples of novel methods for benzimidazole synthesis. Alinezhad H et al.¹¹ reported the synthesis of benzimidazole derivative **17** catalysed by NAP-ZnO with formic acid in high yields (scheme 1). It is cost-effective and non-toxic because it does not require the use of any solvents in the reaction. All derivatives were carried out in between 30 to 150 minutes and yields of products 90 to 98 percents, at 70 °C. Easy NAP-ZnO production; reusable, non-toxic, and economical heterogeneous nanocatalyst; mild reaction conditions; simple and clean workup; and a straightforward approach are all benefits of the present method.



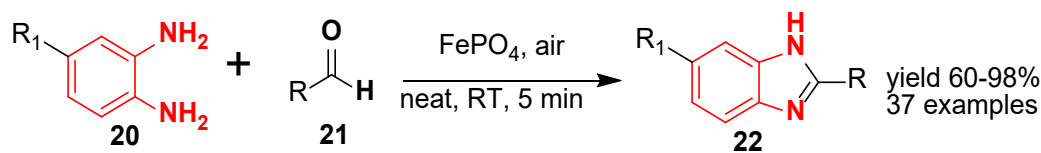
Scheme 2. NAP-ZnO catalysed the synthesis of benzimidazole derivatives.

The potential of glycerol as a solvent is highly regarded in academic circles owing to its environmentally sustainable properties. In addition, the Ni-MCM-41 compound that has been synthesised recently has been recognised as a remarkably efficient catalyst for the process of oxidative condensation involving o-phenylenediamine **15** and aromatic aldehyde **18** (scheme 3). The results suggest that the product's **19** yields were considered satisfactory.¹² All the yields of products were observed 56 to 92 percent within 4 hours at 90°C. The observation of sustained yield after four cycles of recovery and reuse of catalyst and solvent is significant. The comparative assessment of the catalytic efficacy of the catalyst was conducted vis-à-vis other catalysts that have been previously documented.



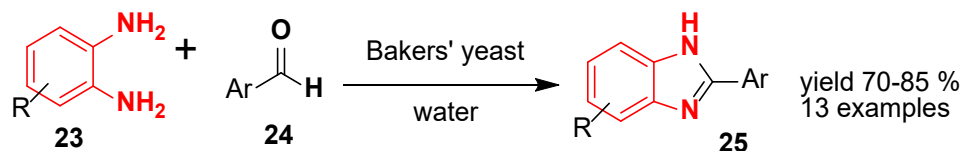
Scheme 3. Synthesis of benzimidazole derivatives using Ni-MCM-41 catalyst.

An innovative catalytic protocol that is environmentally friendly for the production of 2-substituted benzimidazole derivatives **22** which involves a rapid and uncomplicated approach for the production of 2-substituted benzimidazoles utilizing anhydrous FePO₄ under ambient conditions was reported.¹³ The reactions were carried out within 5 minute and product of derivatives are 60 to 98 % At Room Temperature. To ascertain the optimal parameters for this conversion process, several quantities of FePO₄ were examined as a catalyst for the model reaction between o-phenylenediamine **20** and benzaldehyde **21** conducted in the absence of a solvent. The investigation also evaluated the catalyst's capacity for reuse. The regenerated catalyst exhibits the potential to undergo an additional cycle of reaction.



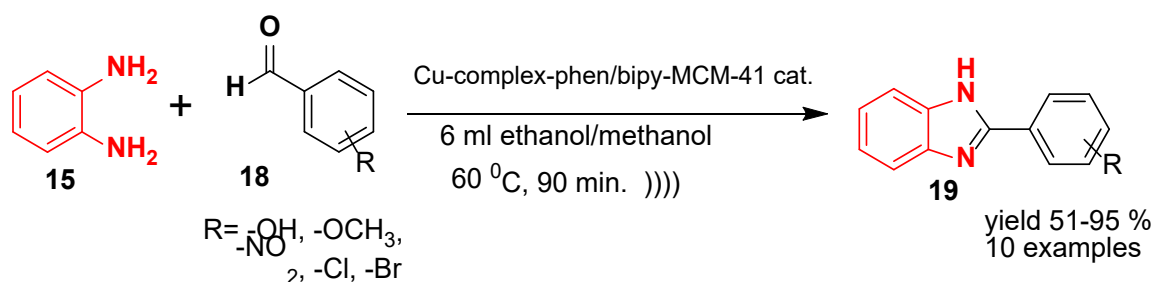
Scheme 4. Synthesis of 2-substituted benzimidazoles utilizing anhydrous FePO₄.

Beheshtiha et al. have reported a sustainable methodology for the synthesis of benzimidazole derivatives **25** and quinoxaline derivatives.¹⁴ The yields of products founded 70 to 85 %. The present methodology entails the chemical reaction between 1,2-diaminoarene **23** derivatives and aldehydes **24**, under the catalytic influence of bakers' yeast, in an aqueous medium at ambient temperature (scheme 5). The procedure exhibits efficacy and eco-friendliness. The protocol eliminates the requirement for expensive and perilous catalysts. The efficient reactions of aromatic aldehydes, which are substituted with either electron-donating or electron-withdrawing groups, have led to the production of corresponding products with good yields. The anticipated outcomes were not obtained upon examination of aliphatic aldehydes under optimised reaction conditions.



Scheme 5. Bakers' yeast catalysed synthesis of benzimidazole derivatives.

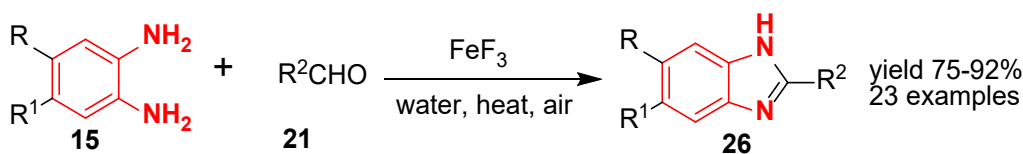
The significance of N, N-bidentate ligands, vanillin, and Schiff base moiety has led to the development and analysis of two heterogeneous catalysts, namely Cu-complex-phen/bipy-MCM-41, were utilized for the synthesis of benzimidazole derivatives **19** through a green pathway, employing methanol/ethanol as a solvent, along with ultrasonic irradiation.¹⁵ The all derivatives showed 51 to 95 % yield of products in 90 minutes time and 60°C. The influence of the steric factor on the yield of the catalytic product has been examined, taking into account the position of the substituent in the substrates. The results have been determined to be favourable, with yields varying from good to excellent, and the recovery procedure being uncomplicated (**Scheme 6**).



Cu-complex-phen-MCM-41	10 examples, yield 51-95%
Cu-complex-biphen-MCM-41	10 examples, yield 59-93%

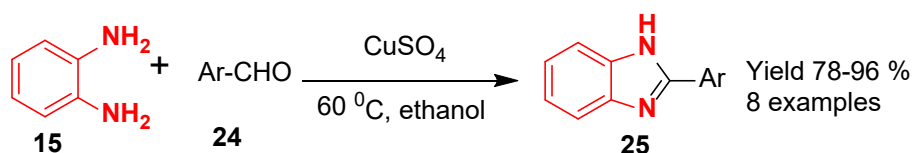
Scheme 6. Synthesis of benzimidazole derivatives

A highly efficient and environmentally friendly protocol for the synthesis of 1,2- disubstituted benzimidazole derivatives **26** reported by Bhaskar et al.¹⁶ The products of yields were founded 75 to 92 % using specific time and temperature. The synthesis was achieved through a one-pot condensation of 1,2-phenylenediamine **15** with 2.0 equivalent of alkyl/aryl aldehyde **21** catalysed by FeF₃ in open air (**Scheme 7**). The catalyst was conveniently retrieved and subjected to recycling, while the products were segregated through the process of filtration. This approach offers several advantages, including cost-effectiveness, enhanced safety, and minimized environmental impact. Furthermore, it is characterized by user-friendliness, high product yields, and favourable chemoselectivity.



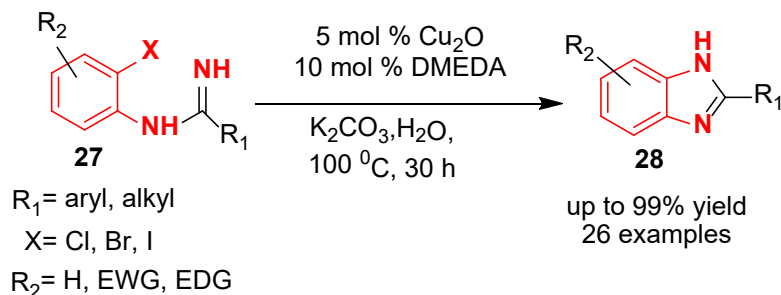
Scheme 7. FeF₃ catalysed synthesis of 1,2- disubstituted benzimidazole derivatives.

In brief, a copper-catalyzed approach has been effectively devised for synthesizing 2-substituted benzimidazoles **25** in high yield using o-phenylenediamine **15** and diverse aryl aldehydes **24**.¹⁷ All products of yields founded between 76 to 96 % by applying 60°C. This method is characterized by its simplicity, efficiency, and enhanced sustainability. One of the benefits of this approach is the utilization of ambient air as the oxidizing agent. The experimental procedure did not employ any hazardous substances or resultant waste materials. Furthermore, the cost-effectiveness, eco-friendliness, accessibility, and notable chemo selectivity of this approach render it a valuable addition to the current procedures in the realm of benzimidazole derivative synthesis.



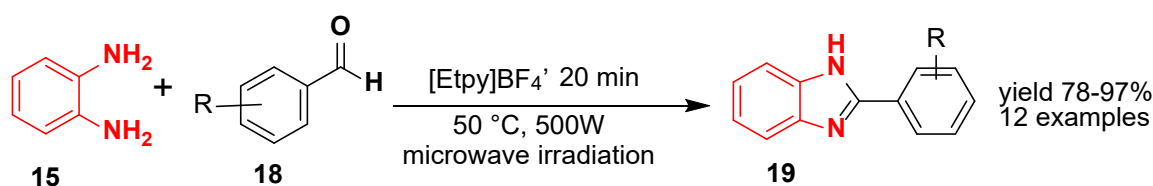
Scheme 8. Copper catalysed synthesis of 1,2- disubstituted benzimidazole derivatives.

The formation of the 2-substituted benzimidazole **28** ring system has been achieved through a newly developed method that employs copper catalysis for intramolecular N-arylation.¹⁸ This approach is characterized by its simplicity and resource efficiency. The current investigation utilized Cu₂O as the catalyst, with a concentration of 5 mol %, DMEDA as the ligand, with a concentration of 10 mol %, and K₂CO₃ as the base to implement the procedure for producing a restricted range of benzimidazoles (scheme 9). The yield of products founded up to 99 % in 30 hours and 100°C. Additionally, the utilization of water as the solvent confers economic and environmental benefits, thereby enhancing the practicality of this approach for industrial purposes.



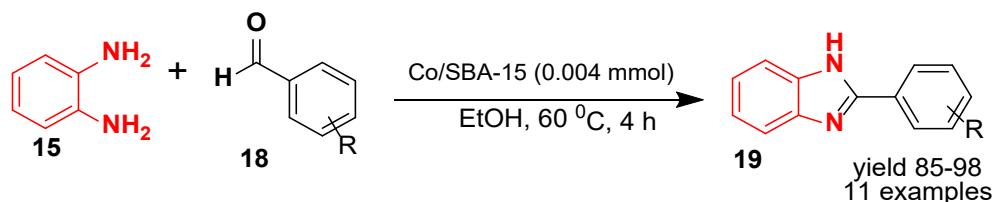
Scheme 9. Copper catalysis for intramolecular N-arylation.

An efficient protocol for the synthesis of 2-substituted benzimidazole **19** derivatives assisted by microwave irradiation was reported (Scheme 10). The reactions between o-phenylenediamine **15** and various aryl aldehydes **18** were carried out using ionic liquid [EtPy]BF₄ as a catalyst.¹⁹ The product yields founded between 78 to 97 % within 20 minutes and 50°C temperature. Additionally, this approach is not restricted solely to aryl and heteroaryl aldehydes but can be expanded to encompass aliphatic aldehydes as well. However, it is important to acknowledge that the production of straight-chain aldehydes is relatively less efficient when compared to that of aromatic aldehydes. The chemical reaction exhibits the ability to attain an augmented production of benzimidazole derivatives, regardless of the existence of an electron-withdrawing or electron-donating moiety in the aromatic aldehydes. The method of synthesis demonstrates a broad scope of applicability in the context of scaling up the production of benzimidazole.



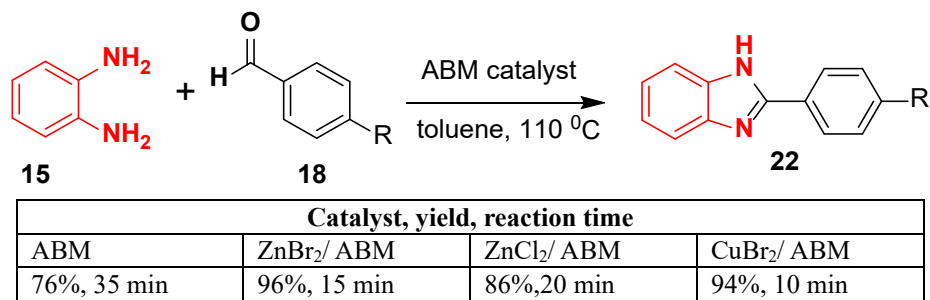
Scheme 10. Benzimidazole synthesis using ionic liquid [EtPy]BF₄ as a catalyst.

Rajabi et al.²⁰ reported a one-pot reaction between o-phenylenediamine **15** and various aromatic aldehydes **18**, catalyzed by low-loaded Co-containing SBA-15 to yield 2-aryl benzimidazole **19** derivatives (Scheme 11). The product yields founded between 85 to 98 % within 4 hours and 60°C temperature. The absence of metal leaching was noted in the course of the reaction, indicating the catalyst's potential for use in more environmentally friendly organic reactions when compared to the majority of heterogeneously catalyzed protocols that have been reported thus far. Aldehydes possessing electron-withdrawing groups exhibited comparatively superior yields in contrast to aldehydes containing electron-donating groups, which is a widely observed trend in coupling-type reactions.



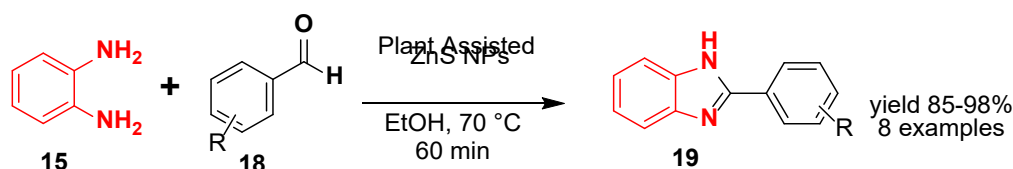
Scheme 11. Heterogeneous catalysed synthesis of benzimidazole.

The MX₂ Lewis acid-doped ABMs are a promising and cost-effective type of solid support that can enhance catalytic processes and address environmental concerns. The benefits encompass improved energy efficiency, utilisation of waste materials as sustainable and reusable catalysts, non-toxicity of the catalyst, and decreased solvent consumption. The heterocycle construction reaction proceeded smoothly using ABM with a high level of efficacy and selectivity in the synthesis of benzimidazoles **22**.²¹ The product yields founded between 76 to 96 % in between 10 to 35 minutes and 110°C temperature. This method involves the utilisation of o-phenylenediamine **15** in combination with aromatic aldehydes **18**, under refluxing toluene conditions (Scheme 12). The presence of an electron-donating group on aldehyde **2** resulted in a reduction in the efficiency of the heterocyclic building process.



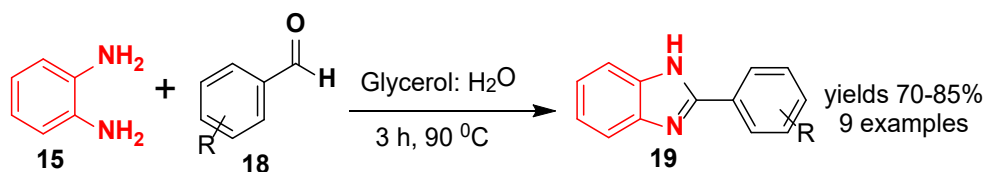
Scheme 12. ABM catalysed synthesis of benzimidazole derivative

Currently, ZnS holds significant importance due to its extensive research and investigation. The remarkable properties of ZnS nanoparticles,²² including their low cost, ease of synthesis, high stability, and small size, have garnered significant attention.²³ In light of the significance of benzimidazoles and the catalytic prowess exhibited by ZnS nanoparticles in organic reactions, a straightforward and effective approach for synthesising benzimidazole derivatives involving condensation of *o*-phenylenediamine with the aromatic aldehyde in an ethanol solvent at a temperature of 70°C. *Trigonella foenum-graecum* plant stems were used to make the catalyst (**Scheme 13**). The product yields founded between 85 to 98 % within 60 minutes and 70°C temperature. Additionally, the catalyst utilised in this process shows the ability to be recycled, making a significant contribution to a more sustainable and environmentally conscious methodology.



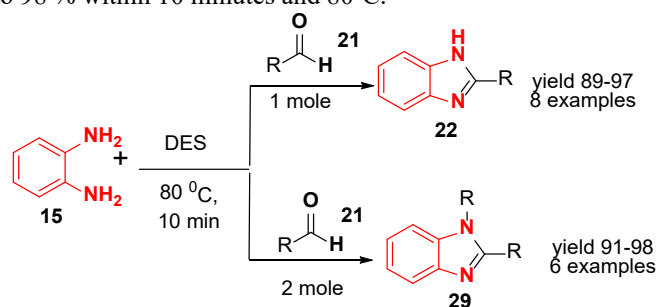
Scheme 13. Organic transformation using plant assisted nanoparticles.

Benzimidazoles have been synthesised using a wide variety of synthetic approaches and starting materials. To investigate the extent and constraints of glycerol as a potential environmentally friendly reaction medium, a methodology with high efficiency has been described for the synthesis of benzimidazole derivatives.²⁴ The product yields founded between 70 to 85 % within 3 hours and 90°C. The methods employed in this study involved the condensation of *o*-phenylenediamine **15** with various substituted aldehydes **18** (**Scheme 14**). Typically, aromatic aldehydes possessing substituents that donate electrons exhibit heightened reactivity and yield more favourable outcomes compared to aromatic aldehydes with substituents that withdraw electrons.



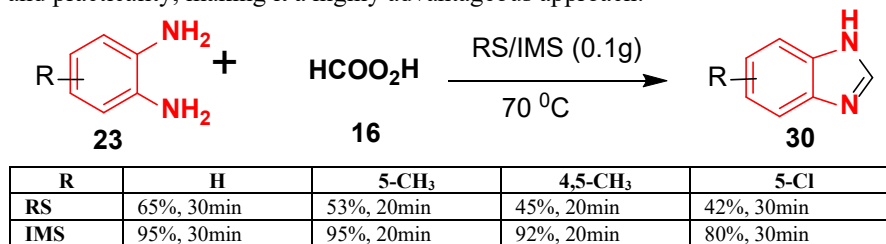
Scheme 14. Preparation of 2-arylbenzimidazole

In the contemporary era, the advent of deep eutectic solvents (DES) has bestowed upon us a remarkable class of environmentally friendly solvents, owing to their remarkable versatility across a diverse array of chemical industrial domains. Di Gioia et al. reported the utilisation of ChCl as a quaternary ammonium salt, coupled with the employment of *o*-phenylenediamine **15** (*o*-PDA) as a hydrogen bond donor (HBD), has facilitated the development of a pioneering type III deep eutectic solvent (DES).²⁵ The ChCl *o*-PDA DES was employed as both a reaction medium and a reagent in the synthesis of benzimidazole derivatives **22** and **29** (**Scheme 15**). The product yields of method A founded between 89 to 97 % and method B founded 91 to 98 % within 10 minutes and 80°C.



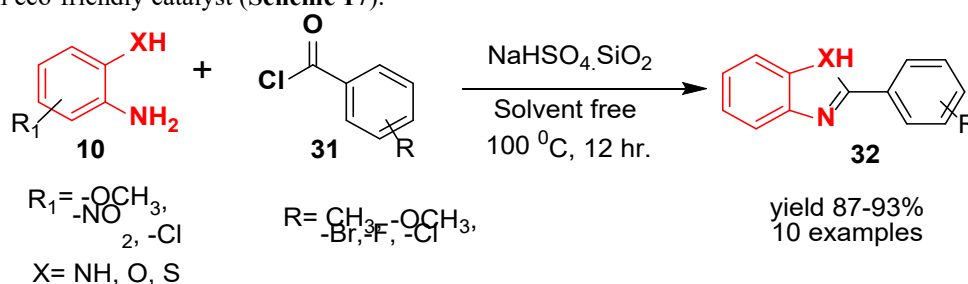
Scheme 15. Synthesis of substituted benzimidazole.

In order to develop a reliable and cost-effective method, B Eren and Erdogan G.²⁶ reported a utilisation of iron oxide-modified sepiolite (IMS) for the condensation reaction between *o*-phenylenediamines **23** and formic acid **16** at a temperature of 70°C (Scheme 16). The application of mixture design in the context of a condensation process is distinguished by its inherent simplicity and practicality, making it a highly advantageous approach.



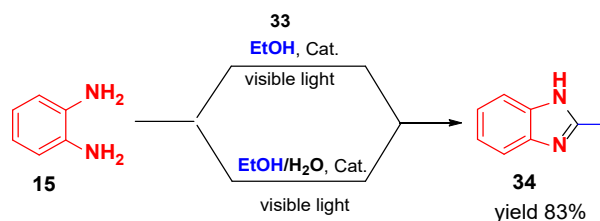
Scheme 16. condensation of formic acid with *o*-phenylenediamines using IMS

A remarkably efficacious methodology has been formulated for the synthesis of a wide range of benzimidazole derivatives. This pertains to the chemical process wherein acyl chlorides undergo a reaction with *o*-substituted aminoaromatic compounds, employing a catalytic amount of NaHSO₄ supported by silica in the absence solvent.²⁷ The product yields founded between 87 to 93 % within 12 hours and 100°C. The present protocol demonstrates noteworthy attributes, including a simple workup methodology, a substantial output, convenient availability, reusability, and the utilisation of an eco-friendly catalyst (**Scheme 17**).



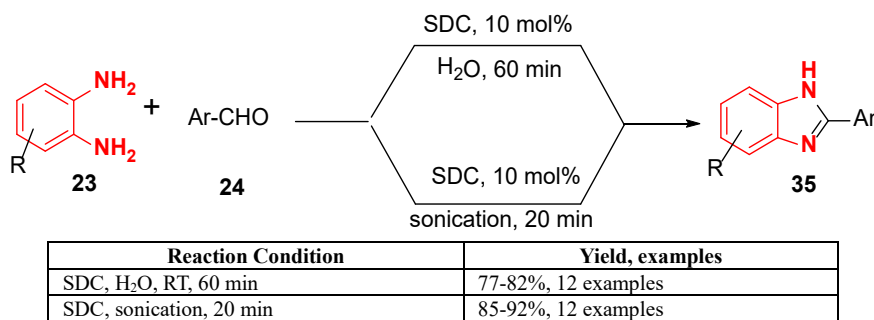
Scheme 17. synthesis of benzimidazole derivatives.

Li Z et al. effectively underscores the remarkable photocatalytic efficacy exhibited by C-TiO₂/1(600) in the context of benzimidazole synthesis.²⁸ An exploration was conducted on the photoinduced synthesis of 2-(methyl)-1H-benzo[d]imidazole **34** utilising C-TiO₂/1(600) in a one-pot reaction involving 1,2-phenylenediamine **15** and ethanol (EtOH) **33** under the influence of visible light irradiation (wavelength greater than 420 nm). The product yields founded between 70 to 85 %



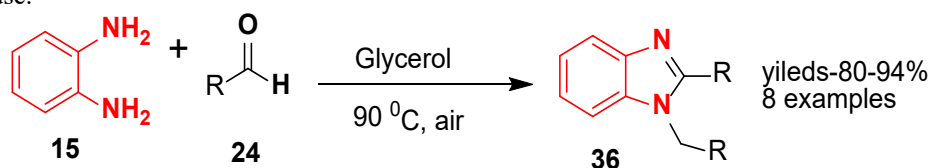
Scheme 18. Synthesis of 2-(methyl)-1H-benzo[d]imidazole.

A novel and highly efficient methodology have been developed for the synthesis of 2-Aryl benzimidazole **35**.²⁹ The study involves investigating the interaction between *o*-phenylenediamine **23** and aromatic aldehydes **24** in an aqueous solution at ambient temperature, with the addition of a 10 mol% concentration of sodium dodecyl sulphate (**Scheme 19**). The aforementioned methodology offers a plethora of benefits, encompassing the employment of a reliable and economically viable catalyst, a straightforward procedural approach, mild reaction conditions, and a significant output of products, all accomplished without the need for any oxidising agents.



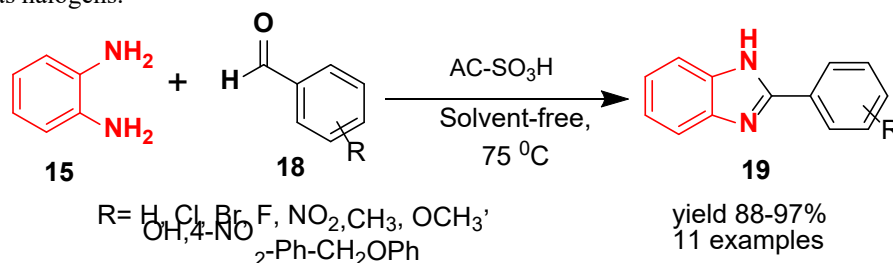
Scheme 19. Synthesis of 2-Aryl benzimidazoles

The distinctive characteristics of glycerol, such as its inherent polarity, low toxicity, biodegradability, and ample supply from renewable sources, have prompted our investigation into its potential as an environmentally friendly solvent for organic synthesis.³⁰ This study explores the application of glycerol as an eco-friendly and sustainable solvent in the synthesis of benzimidazole derivatives **36**, eliminating the requirement for a catalyst (**Scheme 20**). The product yields founded between 80 to 94 % using 90°C temperature. The synthesis process entails the condensation of *o*-phenylenediamine **15** with a range of ketones and aldehydes **24**. The efficiency of glycerol remained consistently high even after undergoing four cycles of reuse.



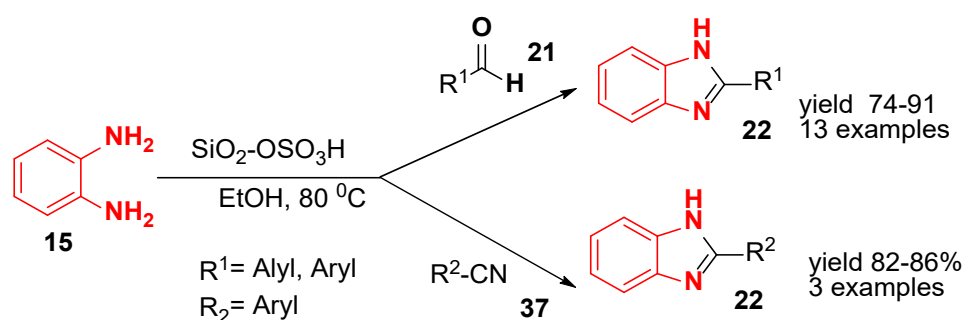
Scheme 20. Eco-friendly and sustainable solvent free synthesis of benzimidazole derivatives

The benzimidazole derivative **19** was synthesised using the catalyst AC-SO₃H under mild reaction conditions via condensation between 1,2-phenyldiamine **15** with arylaldehyde **18**, resulting in high product yields.³¹ Notably, the absence of a solvent was found to be sufficient for the successful synthesis (**Scheme 21**). The product yields founded between 88 to 97 % using 75°C. The catalyst displayed several advantageous attributes, including remarkable efficacy, environmental compatibility, cost efficiency, absence of metallic constituents, and potential for reusability. The research investigated the reaction of aldehydes containing different substituents, including both groups that donate electrons and groups that withdraw electrons, as well as halogens.



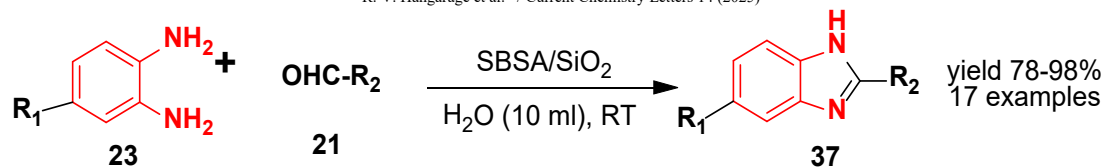
Scheme 21. Activated carbon sulfonic acid (AC-SO₃H) catalysed synthesis of benzimidazoles.

Sadeghi et al. proposed a novel and highly efficient method for synthesising 2-substituted benzimidazole derivatives **22**, utilising silica sulfuric acid as a catalyst.³² The product yields of method A founded between 74 to 91 % and method B founded 82 to 86 % at 80°C temperature. The catalyst exhibits characteristics of reusability, environmental friendliness, water stability, suitability for large-scale operations, and ease of handling. The catalyst responsible for initiating the process exhibits heterogeneity. Some additional advantages of this approach include high yields, relatively rapid reaction times, user friendliness, and a straightforward work-up procedure (**Scheme 22**).



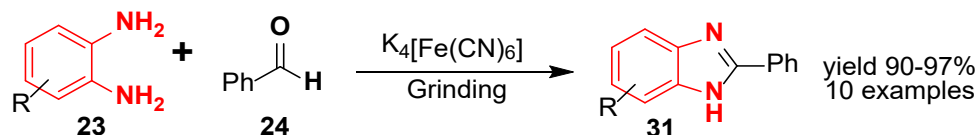
Scheme 22. Acid-catalysed synthesis of 2-aryl benzimidazoles.

A novel and efficient methodology has been developed for the synthesis of 2-arylsubstituted benzimidazoles **37** via the condensation reaction involving *o*-phenylenediamine **23** and arylaldehyde **21**, facilitated by the utilization of SBSA as a catalyst.³³ It was observed that a wide variety of aromatic compounds and α , β -unsaturated aldehydes, characterized by the presence of both electron-donating and electron-withdrawing groups, undergo a chemical transformation in the presence of substituted *o*-phenylenediamine (**Scheme 23**). The product yields founded between 78 to 98 % using rt. The aforementioned reaction leads to the synthesis of benzimidazole derivatives with a notably high level of efficiency.



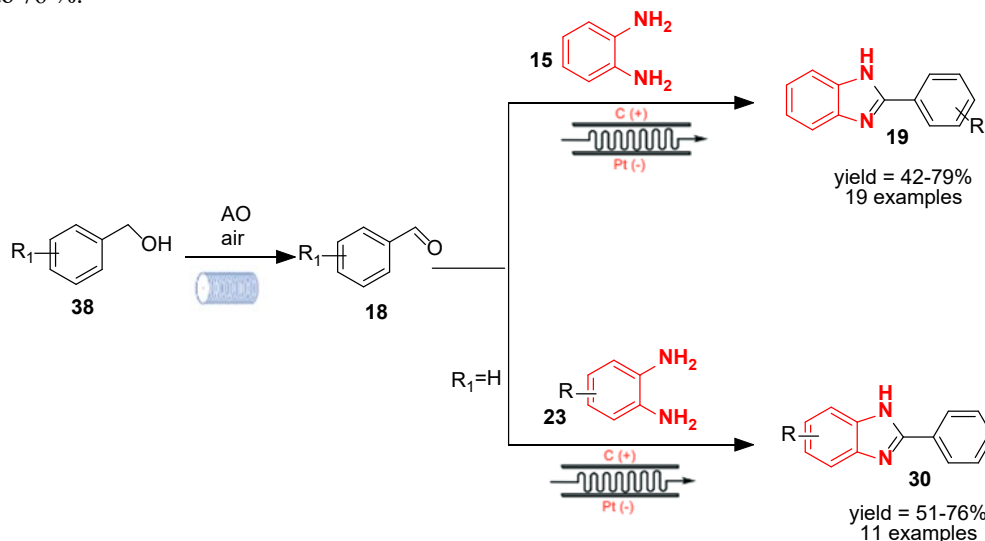
Scheme 23. Synthesis of 2-arylsubstituted benzimidazoles.

Shaikh et al. have demonstrated the application of the metal co-ordinate complex $\text{K}_4[\text{Fe}(\text{CN})_6]$ as a sustainable catalyst in the efficient synthesis of benzimidazole derivatives.³⁴ This was achieved by subjecting 1,2-diamine **23** to different various aldehydes **24** under solvent-free conditions (**Scheme 24**). The product yields founded between 90 to 97 %. The present methodology facilitates the synthesis of derivatives of biologically active benzimidazole **31** compounds through a process distinguished by its straightforwardness, efficacy, environmental friendliness, energy efficiency, and substantial product yield.



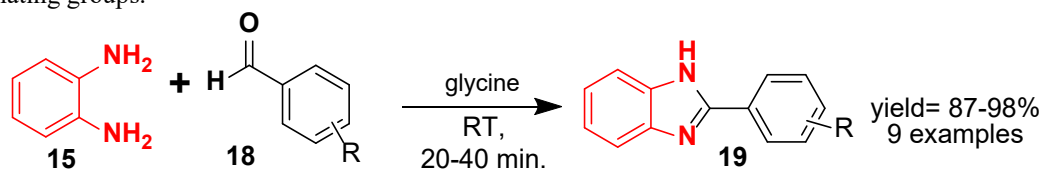
Scheme 24. $\text{K}_4[\text{Fe}(\text{CN})_6]$ Catalysed synthesis of benzimidazoles.

A novel and environmentally sustainable approach has been developed for the synthesis of substituted benzimidazoles, utilising a two-step continuous flow system.³⁵ This study reports the results of enzymatic electrochemical cascade reactions that involve the combination of aromatic alcohols and o-phenylenediamines. The experiment was conducted under mild reaction conditions, using air as an environmentally friendly oxidant and oxidase as the biocatalyst. The separate processes of alcohol oxidation and substituted benzimidazole formation were successfully integrated into a unified operation. The successful completion of a scale-up experiment in a continuous flow system showcases the practicality, efficiency, and industrial applicability of this approach (**Scheme 25**). The product yields of route A founded between 42 to 79 % and route B founded 51 to 76 %.



Scheme 25. Synthesis of substituted benzimidazoles using a two-step continuous flow system.

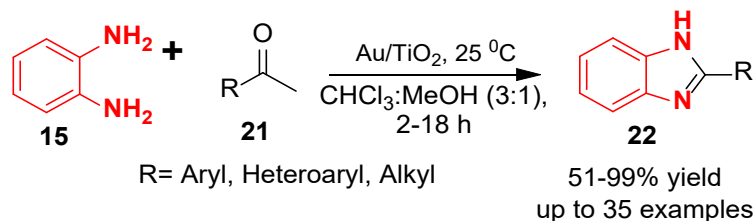
Sonawale (year) demonstrated a method of utmost simplicity for synthesising benzimidazole **19** derivatives through condensing 1,2-phenyldiamine **15** and various aldehydes **18**, employing glycine as a catalyst.³⁶ Notably, this process was executed utilising the esteemed apparatus of a pestle and mortar. The aforementioned reaction exhibits a remarkable level of both productivity and integrity (**Scheme 26**). The product yields founded between 87 to 98 % in between 20 to 40 minutes at rt. Aldehydes bearing electron-withdrawing groups exhibit a higher rate of reaction compared to aldehydes possessing electron-donating groups.



Scheme 26. Condensation of 1,2-phenyldiamine with aryl aldehyde.

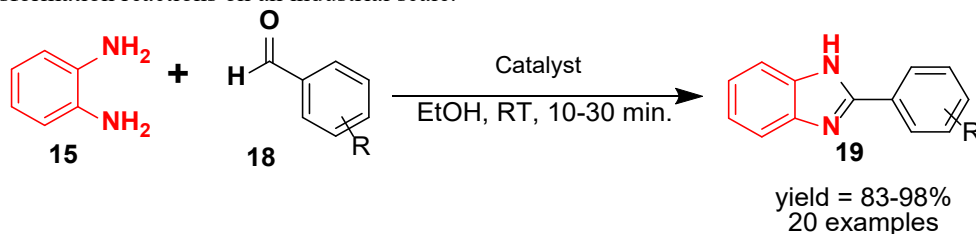
The utilisation of commercially accessible Au/TiO₂ catalysts, which encompass gold nanoparticles varying in size from 2 to 3 nm, has exhibited noteworthy effectiveness in promoting the discriminative formation of 2-aryl and 2-alkyl substituted

benzimidazoles.³⁷ The current heterogeneous catalytic process involves a unipolar reaction between the respective aldehyde **21** and *o*-phenylenediamine **15**, carried out at ambient temperature and in a blend of chloroform and methanol (in a proportion of 3:1). The product yields founded between 51 to 99 % within 2 to 81 hours using 25°C temperature. The a forementioned reaction showcases a wide range of substrates and introduces a novel methodological strategy for the efficient formation of C-N bonds under mild reaction conditions, obviating the need for supplementary additives or oxidising agents (**Scheme 27**).



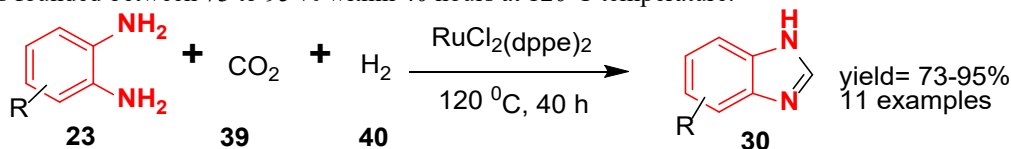
Scheme 27. Synthesis of 2-aryl and 2-alkyl substituted benzimidazoles

A novel nanocatalyst, namely sulfonated magnetic cobalt ferrite (CFNP@SO₃H), has been successfully engineered to facilitate the synthesis of biologically relevant 2-substituted benzimidazoles **19**.³⁸ The present study encompassed the condensation reaction between *o*-phenylenediamine **15** and a variety of aromatic, aliphatic, and heterocyclic aldehydes **18** (**Scheme 28**). The product yields founded between 83 to 98 % within 1- to 30 minutes using rt. The aforementioned protocol exhibits commendable efficiency, cost-effectiveness, and environmental conscientiousness, characterised by a notably brief reaction period and a commendably high product yield. The nanocatalyst exhibits a remarkable attribute of facile retrieval and recyclability, allowing for a commendable span of up to seven consecutive cycles. The inherent adaptability and capacity to effectively immobilise a wide range of chemical entities render it a highly promising alternative for a multitude of organic transformation reactions on an industrial scale.



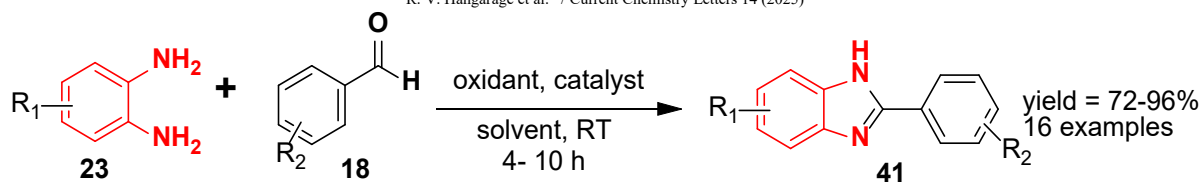
Scheme 28. Synthesis of biologically relevant 2-substituted benzimidazoles.

The synthesis of benzimidazoles **30** was achieved via the cyclization process of *o*-phenylenediamines **23**, wherein carbon dioxide (CO₂) **39** was employed as a reactant alongside the coexistence of hydrogen gas (H₂) **40** (**Scheme 29**). The utilisation of the catalyst RuCl₂(dppe)₂ demonstrates remarkable efficacy and discernment in the production of various benzimidazole derivatives, thereby yielding exceptional outcomes.³⁹ Moreover, it is worth noting that the reactions can be effectively carried out in the absence of any solvents. This aspect adds significant value to the approach of synthesising benzimidazoles from carbon dioxide, as it offers distinct advantages in terms of environmental sustainability and economic viability. The present synthetic pathway for benzimidazoles, derived from carbon dioxide (CO₂), offers a groundbreaking alternative to traditional routes. This particular approach also presents a novel opportunity for the utilisation of carbon dioxide. The product yields founded between 73 to 95 % within 40 hours at 120°C temperature.



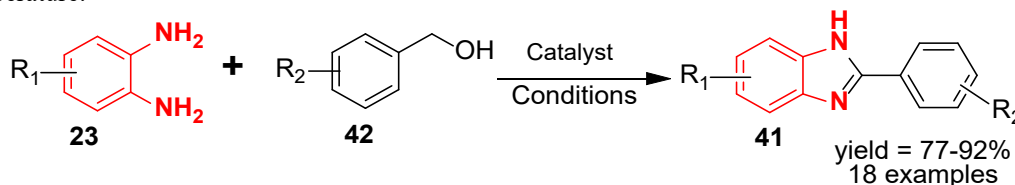
Scheme 29. Synthesis of benzimidazoles via the cyclization process of *o*-phenylenediamines with CO₂ and H₂

An innovative inorganic iodine-catalysed oxidative system has been developed to facilitate the proficient synthesis of benzimidazole derivative **41** employing hydrogen peroxide under ambient conditions.⁴⁰ The current investigation entailed the condensation reaction involving *o*-phenylenediamine **23** and a variety of alkyl or aryl aldehydes **18**. It offers mild reaction conditions, simplicity, and easy management of reaction conditions and reagents (**Scheme 30**). The product yields founded between 72 to 96 % within 4 to 10 hours at rt temperature. The non-transition metal catalytic system is expected to be widely used in organic synthesis and industrial sectors.



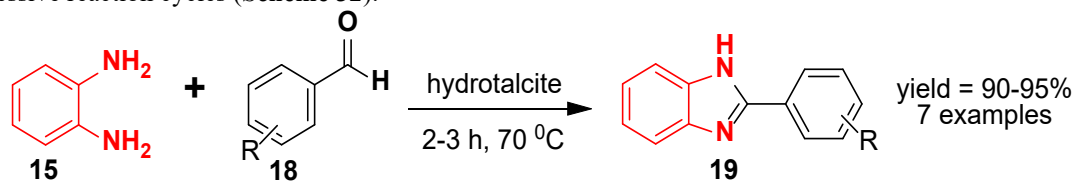
Scheme 30. Iodine-catalyzed oxidative synthesis of benzimidazoles.

The successful synthesis of a novel catalyst, TPTZn@MS, exhibiting heterogeneous characteristics, has demonstrated remarkable efficacy in facilitating the synthesis of 2-aryl-1H-benzo[d]imidazole derivatives through the reaction of 1,2-phenyldiamines **23** with various benzyl alcohols **42** (Scheme 31).⁴¹ The product yields founded between 77 to 92 % using specific temperature.



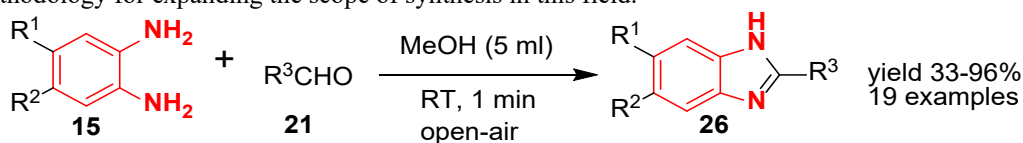
Scheme 31. Synthesis of 2-aryl-1H-benzo[d]imidazole derivatives.

A novel and sustainable methodology has been formulated to facilitate the production of hydrotalcite. This innovative approach adopts a green paradigm by eliminating the requirement for solvents, thereby ensuring an environmentally conscious synthesis of substituted benzimidazoles **19**.⁴² The product yields founded between 90 to 95 % within 2-3 hours at 70°C temperature. The interdependence between the catalytic efficacy and fundamental attributes of calcined hydrotalcite is evident. This research endeavour signifies the preliminary attempt to synthesize substituted benzimidazoles through the utilization of hydrotalcite as a reusable heterogeneous catalyst, exhibiting the capacity to be employed for a maximum of eight successive reaction cycles (Scheme 32).



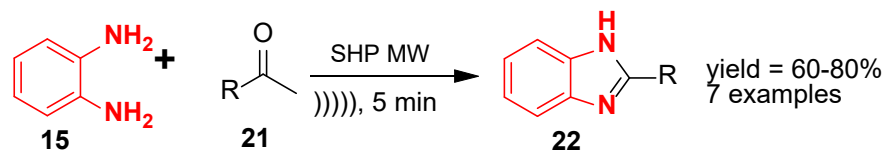
Scheme 32. Benzimidazole synthesis using hydrotalcite as a reusable heterogeneous catalyst.

Elumalai and Hansen provide a comprehensive analysis of an innovative methodology for the production of 2-substituted benzimidazoles **26**, using methanol as the solvent.⁴³ The conventional hetero cyclization process utilised for the production of benzimidazoles involves the use of *o*-phenylenediamines **15** in conjunction with a variety of aromatic aldehydes **21** (scheme 33). The product yields founded between 33 to 96 % within 1 minutes at rt temperature. The rediscovery of this reaction has occurred in recent times. In addition, it demonstrates a notable degree of tolerance and an impressively swift response time, requiring only a duration of one minute. The protocol described in this study demonstrates a high level of efficiency, allowing for the synthesis of heterocyclic systems on a larger scale. As a result, it has become the preferred methodology for expanding the scope of synthesis in this field.



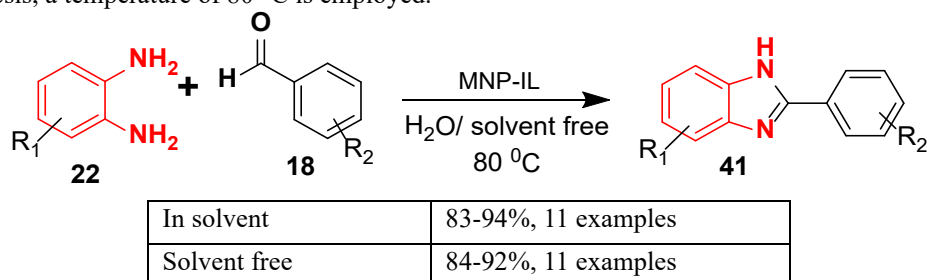
Scheme 33. Synthesis of substituted benzimidazoles.

Tayade and Pawar investigated the synthesis of benzimidazole derivatives that are substituted at the 2-position which involves the utilization of aldehyde **21**, 1,2-phenylenediamine **15**, and sodium hypophosphite as a catalyst, with the reaction being facilitated by microwave irradiation.⁴⁴ The product yields founded between 60 to 80 % within 5 minutes. The effective use of sodium hypophosphite enables the attainment of a synthesis process that is both highly efficient and environmentally sustainable, leading to a substantial yield within a relatively brief reaction time frame. This particular pathway presents notable advantages, such as a substantial level of product output, minimal presence of impurities, a straightforward purification process, readily available catalyst, and a favourable yield of the desired product. The utilization of microwave irradiation presents numerous benefits in comparison to the traditional approach (Scheme 34).



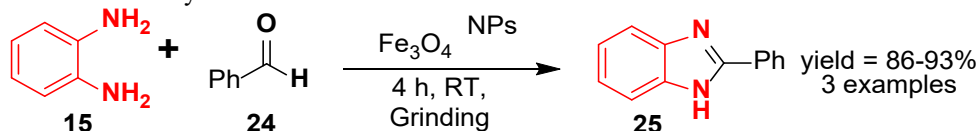
Scheme 34. Sodium hypophosphite catalyzed synthesis of benzimidazole derivatives.

To effectively catalyze the synthesis of benzimidazole derivatives **41**, Fe_3O_4 nanoparticles and supported ionic liquid ($\text{Fe}_3\text{O}_4\text{-IL}$) were synthesized and utilized as highly efficient magnetic catalysts, both in the presence and absence of solvents.⁴⁵ The results of product yields mentioned in given table. In the absence of a solvent, the reactants underwent a complete transformation. Through the utilization of a straightforward magnetic decantation technique, it was observed that the catalyst exhibited the ability to undergo recycling without experiencing any discernible loss in its initial effectiveness. Even after undergoing seven cycles, the catalyst's activity may remain unaffected by the process of magnetic separation. A study investigates the utilization of magnetic nanoparticles as carriers for ionic liquids, with the aim of exploring their potential application as heterogeneous catalysts in the production of benzimidazole derivatives. In both solvent-free and solvent-containing synthesis, a temperature of 80 °C is employed.



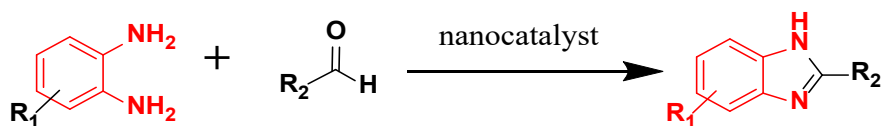
Scheme 35. Fe_3O_4 nanoparticles and supported ionic liquid ($\text{Fe}_3\text{O}_4\text{-IL}$) catalysed synthesis of benzimidazole.

A highly effective method for synthesising benzimidazole derivatives **25** via the condensation reaction between 1,2-phenylenediamine **15** and aromatic aldehydes **24** reported by Cahyana et. al.⁴⁶ The utilisation of Fe_3O_4 NPs as a catalyst in this process provides several benefits in terms of cost-effectiveness and environmental sustainability (scheme 36). The product yields founded between 86 to 93 % within 4 hours at rt. The successful achievement of efficiently and rapidly separating Fe_3O_4 nanoparticles from the reaction mixture was accomplished. The magnetic catalyst exhibits a notable level of durability, enabling multiple recycling processes without substantial degradation. As a result, the catalytic efficiency of Fe_3O_4 nanoparticles is effectively maintained.



Scheme 36. Fe_3O_4 nanoparticles catalysed Condensation reaction between 1,2-phenylenediamine and aromatic aldehydes.

The utilization of heterogeneous transition metal (TM) catalysts is currently being investigated due to their efficacy, affordability, and convenient reusability. Nanocatalysts represent a noteworthy advancement in eco-friendly chemical procedures, owing to their amorphous surface distribution, which renders them readily accessible to reactants. The catalysts exhibit selective functionality towards hydroperoxides, thereby reducing the formation of deleterious by-products. The necessity for environmentally sustainable procedures is emphasized by the latest advancements in the TM-catalyzed production of benzimidazoles utilizing o-phenylenediamine (Table 1).



Scheme 37. Cu/Fe/Ti/Co/Ni based noncatalyzed synthesis of benzimidazole derivatives.

Table 1. Transition metal catalysed synthesis of benzimidazole derivatives

Sr. No.	Catalyst	Reaction Condition	R ₁	Substituents R ₂	Yield (%)	Ref.
1	CuI	CH ₃ CN; rt; 1–4h	H	-C ₆ H ₅ , C ₅ H ₁₁ , C ₃ H ₇ , cinnamyl, 2-C ₆ H ₄ , 4-C ₆ H ₄ , 2-CH ₃ C ₆ H ₄ , 4-CH ₃ C ₆ H ₄ , 2,6-diC ₆ H ₃ , 2,6-diCH ₃ C ₆ H ₃ , 4-OCH ₃ C ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 2-NO ₂ C ₆ H ₄ , cyclohexyl	55–97	47
2	CuFe ₂ O ₄	C ₆ H ₅ CH ₃ , 110°, 24 h	H, 4-Br	4-C ₆ H ₄ , 4-BrC ₆ H ₄ , 4-CH ₃ C ₆ H ₄ , 4-FC ₆ H ₄	53–94	48
3	Fe ₃ O ₄	PEG/H ₂	H, 4-NO ₂	C ₆ H ₅ , 3-NO ₂ C ₆ H ₄ , 4-OHC ₆ H ₄ , 4-BrC ₆ H ₄ , 4-N(CH ₃) ₂ C ₆ H ₄ , 2-C ₆ H ₄ , 4-C ₆ H ₄ , 2,4-diC ₆ H ₃	74–96	49
4	Fe (III)-Schiff base SBA-15 complex	H ₂ O, Refluxed, 3 h	H	-C ₆ H ₅ , 4-NO ₂ C ₆ H ₄ , 3-C ₆ H ₄ , 4-C ₆ H ₄ , 3,4,5-triOCH ₃ C ₆ H ₂ , 2-C ₆ H ₄	79–92	50
5	Fe ₃ O ₄ -SiO ₂ -polyionene/Br ₃	Neat, 110°C, 12–90 min	H	-C ₆ H ₅ , 4-OCH ₃ C ₆ H ₄ , 4-OHC ₆ H ₄ , 4-CH ₃ C ₆ H ₄ , 4-C ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 3-phenylpropyl	67–98	51
6	NiFe ₂ -xEuO ₄	H ₂ O, ultrasonic, 45–60 min	H	-C ₆ H ₅ , 4-C ₆ H ₄ , 4-NO ₂ C ₆ H ₄ , 4-CH ₃ C ₆ H ₄ , 3-CH ₃ C ₆ H ₄ , 4-OCH ₃ C ₆ H ₄	90–97	52
7	Co/Ce-ZrO ₂	Neat, Rt, 10–45 mi	H, 4-CH ₃ , 4-NO ₂	4-C ₆ H ₄ , 2-C ₆ H ₄ , 3-NO ₂ C ₆ H ₄ , 4-OCH ₃ C ₆ H ₄ , 3,4-di-OCH ₃ C ₆ H ₃ , hexanal, trans-styryl	73–98	53
8	TiO ₂ P25	ambient-light, 50°C, 4–27 min	H, CH ₃ , NO ₂ , COC ₆ H ₅	4-FC ₆ H ₄ , 4-OHC ₆ H ₄ , 4-N(CH ₃) ₂ C ₆ H ₄ , 4-CH ₃ C ₆ H ₄ , 4-CHOC ₆ H ₄ , 2-furyl, 2-pyridinyl	90–96	54

3. Conclusion

The present review provides an overview of the current state of knowledge regarding the synthesis of benzimidazole compounds and their interactions with various functional groups. Synthetic methodologies encompass the process of combining o-phenylenediamine with aromatic and aliphatic aldehydes through the utilisation of metal catalysts, acids, polyacids, and bases. The arylaldehydes as well as the O-phenylenediamine are full available commercially. Other potential methodologies encompass the utilisation of nitroaniline and acid. Nevertheless, the majority of techniques exhibit environmental drawbacks as a result of the utilisation of solvents and metal catalysts. Benzimidazole derivatives play a pivotal role in the pharmaceutical domain due to their capacity to stabilise and interact with specific sites, facilitating the identification of a wide range of ligands and the exploration of structurally unique medications. This review provides a brief overview of modern synthesized benzimidazole derivatives and their reactions with various moieties. The review highlights different synthetic methods reported in literature, which include the condensation of o-phenylenediamine with various aromatic and aliphatic aldehydes and acids in the presence of metal catalysts, acids, polyacids, hypervalent iodine, solvents, bases, and other conditions. Nucleophilic substitution reactions and other methods are also employed for the synthesis of benzimidazole derivatives.

Conflict of Interest

The Authors declare no conflict to interest.

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