## **REVIEW ARTICLE**

# Various approaches for the synthesis of benzimidazole derivatives and their catalytic application for organic transformation

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### ABSTRACT

Imidazole and phenyl rings are fused at positions 4 and 5 to form the benzimidazole structure. The benzimidazole mono- and disubstituted derivatives are extremely intriguing heterocyclic chemical compounds. They can be synthesized using a straightforward condensation method between o-phenylenediamine and a carbonyl compound under various conditions as well as a nucleophilic substitution reaction. The catalytical effects of benzimidazole derivatives, which include oxidation of olefins, oxidation of alcohol, etc, play a significant role in the catalysis. This review describes various synthetic routes for synthesizing functionalized benzimidazole derivatives and catalytic application of benzimidazole Schiff base metal complexes and benzimidazole amide.

*Keywords:* benzimidazole derivatives; oxidation; reduction; synthesis methods; catalytic application; organic transformation

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### **1. Introduction**

Imidazole and benzene combine to produce a bicyclic compound which is called benzimidazole<sup>[1]</sup>. It is a desirable structure in pharmaceutical chemistry and an important pharmacophore<sup>[2]</sup>. The most frequent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B12<sup>[3]</sup>.

Benzimidazole has been used for several years. Fluorine, propylene, tetrahydro quinoline, and cyclized molecules were substituted for diverse benzimidazole derivatives in 1990, creating compounds with improved bioavailability, stability, and considerable biological activity<sup>[4–6]</sup>. Additionally, it was demonstrated that adding an electron-donating group to pyridine boosts activity. In 1991, it was possible to create benzimidazole derivatives by derivatizing benzimidazole at the N-H position with an electron-donating group and substituting big chains of propyl, acetamido, thio, thiazole-amino, and tetramethyl piperidine on pyridine, which had strong antiulcer activity<sup>[7,8]</sup>.

Several attempts have been made in the past to establish an efficient and low-cost process for the synthesis of benzimidazole derivatives. There are three main techniques for synthesising 2-substituted benzimidazoles. The first is the Phillips-Ladenburg reaction, which is based on the relationship of diaminobenzenes with

carboxylic acids and their derivatives<sup>[9–13]</sup>, and the second is the Weidenhagen reaction, which is based on the interaction of ortho-phenylenediamine with aldehydes and ketones<sup>[14]</sup>. The extreme temperature conditions, often reaching 250 °C to 300 °C, and low yields limit the utilisation of these processes in their traditional form. In fact, all of the currently accessible benzimidazole synthesis techniques are variations on the Phillips-Ladenburg and Weidenhagen processes. The third one is the Mamedov hetrocycle rearrangement, which is an acid-catalyzed transformation of quinoxalinone derivatives into 2-heteroaryl-substituted benzimidazoles<sup>[15–18]</sup>. **Figure 1** shows the molecule structure of benzimidazole.



Figure 1. Benzimidazole molecule structure.

### 2. Synthesis of benzimidazole

The condensation of 1,2-diaminobenzene derivatives with carboxylic acids in the presence of a dilute mineral acid yields benzimidazole derivatives and this reaction is called Phillips-Ladenburg reaction<sup>[18]</sup> (Scheme 1).



Another traditional technique for producing benzimidazoles is the Weidenhagen reaction, which involves reacting 1,2-diaminobenzene with aldehydes and ketones in water or alcohol in the presence of oxidising agents such as copper acetate or a comparable bivalent copper salt<sup>[18]</sup> (Scheme 2).



Hoebrecker created the benzimidazole by reducing and dehydrating 2-nitro-4-methylacetanilide<sup>[19]</sup> (**Scheme 3**).



Scheme 3. Preparation of benzimidazole from 2-nitro-4-methylacetanilide.

### 2.1. From O-phenylenediamines (o-phenylenediamine)

### 2.1.1. Phillips-Ladenburg reaction in benzimidazole synthesis

According to various studies, o-phenylenediamine and carboxylic acids can be used to create a variety of benzimidazole derivatives. Condensation of o-phenylenediamine and aromatic acid (salicylic acid, benzoic acid, cinnamic acid, etc.) at 80 °C–90 °C with the use of ammonium chloride (NH<sub>4</sub>Cl) as a catalyst in EtOH gives 72%–90% yield of Benzimidazole derivatives<sup>[20]</sup> (**Scheme 4**).



Scheme 4. Benzimidazole preparation from carboxylic acids.

Alam et al. discovered that by refluxing a 1:1 molar ratio of o-phenylenediamine and 4-aminobenzoic acid in dimethylbenzene and polyphosphoric acid for just six hours, 2-(4-aminophenyl)-1H-benzimidazole were produced with 51% yield<sup>[21]</sup> (Scheme 5).



Scheme 5. Benzimidazole preparation from an aromatic carboxylic acid.

Nguyen et al. discovered an efficient Fe/S catalytic redox condensation technique for generating large amounts of benzimidazole derivatives from phenylacetic acid and 2-nitroaniline with no organic by-products<sup>[22]</sup> (Scheme 6).



Scheme 6. Benzimidazole preparation from Fe/S catalytic redox condensation method.

The condensation of o-phenylenediamine with 4-aminobenzoic acid in *o*-phosphoric acid at 200 °C for two hours gives a 70% yield of 4-(1*H*-benzimidazol-2-yl)benzenamine<sup>[23]</sup> (**Scheme 7**).



Scheme 7. Preparation of benzimidazole from 4-aminobenzoic acid.

According to the study when 4-methyl-1,2-phenylenediamine is reacted with formic acid in the presence of nanoparticle of ZnO at 70 °C produce a 94% yield of 5-Methyl-1H-benzimidazole<sup>[24]</sup> (**Scheme 8**).



Scheme 8. Preparation of benzimidazole from formic acid.

When 4-methoxy-1,2-phenylenediamine is reacted with formic acid in the presence of a nanoparticle of ZnO at 70 °C produces a 98% yield of 5-Methoxy-1H-benzimidazole<sup>[24]</sup> (**Scheme 9**).



Scheme 9. Preparation of benzimidazole from formic acid.

Benzimidazole derivatives were synthesized by coupling o-phenylenediamine with organic acids in solvent-free conditions at 140 °C<sup>[25]</sup> (Scheme 10).



 $R = H (95\%); CH_3 (90\%); C_6H_5 (83\%); 4-ClC_6H_4 (92\%); 4-OHC_6H_4 (85\%); 4-NO_2C_6H_4 (95\%); 4-OCH_3 C_6H_4 (80\%); 2-ClC_6H_4 (88\%); 4-CH_3C_6H_4 (80\%); 2-ClC_6H_4 (85\%); 4-OHC_6H_4 (85\%)$ 

Scheme 10. Preparation of benzimidazole from aldehyde.

According to several studies, o-phenylenediamine heat with 4 4-dimethoxy 3-oxobutanoate in the presence of 5 mol% of 1-butyl imidazolium trifluoroacetate (HBIm.TFA) for 4-12 hours at 80 °C gives 95% yield of benzimidazole 2-carboxldehyde dimethyl acetal<sup>[26]</sup> (Scheme 11).



Scheme 11. Preparation of benzimidazole from 4 4-dimethoxy 3-oxobutanoate with mechanism.

The Reaction of o-phenylenediamine, aryl isothiocyanate, and methyl acetylenecarboxylate in CH<sub>2</sub>Cl<sub>2</sub>-toluene under reflux conditions for ten-hour produce benzimidazole derivatives with 65%–70% yield<sup>[27]</sup> (Scheme 12).



Scheme 12. Preparation of benzimidazole from aryl isothiocyanate, and methyl acetylenecarboxylate with mechanism.

#### 2.1.2. Weidenhagen reaction in benzimidazole synthesis

A good yield of the benzimidazole derivatives obtained from the condensation of o-phenylenediamine with an aldehyde at ambient temperature in methanol conditions by using  $Cu(OH)_2$  as a catalyst for 6 hours in an open oxygen environment<sup>[28]</sup> (Scheme 13).



 $\begin{array}{l} R = Ph \ (98\%); \ 4-ClC_6H_4 \ (99\%); \ 4-OCH_3C_6H_4 \ (90\%); \ 4-OHC_6H_4 \ (95\%); \ Fur-2-yl \ (86\%); \ Napth-2-yl \ (84\%); \ 4-NO_2C_6H_4 \ (88\%); \ 3,4-2(OCH_3)C_6H_3 \ (88\%); \ 2,4-2(OH)C_6H_3 \ (88\%); \ 3-OHC_6H_4 \ (88\%); \ 3-OHC_6H_4 \ (88\%); \ 3,4-2(OCH_3)C_6H_3 \ (88\%); \ 3,4-2(OCH_3)C_$ 

Scheme 13. Preparation of benzimidazole from aldehydes.

Venkateswarlu et al.<sup>[29]</sup> defined the one-pot synthesis of benzimidazole derivatives from 3,4,5trimethoxybenzaldehyd and o-phenylenediamine utilizing lanthanum chloride catalysis in acetonitrile (**Scheme 14**). The reactions were performed in 2 to 4 hours and yields ranged from 85% to 95%.



 $R = 2,3,4-3(OMe)C_{6}H_{2} (95\%); 4-Me_{2}NC_{6}H_{4} (88\%); Fur-2-yl (90\%); 4-FC_{6}H_{4} (85\%); 4-MeC_{6}H_{4} (92\%); Ph (88\%); 4-OHC_{6}H_{4} (86\%); 3-ClC_{6}H_{4} (91\%); Napth-2-yl (87\%); 2-chloro-6-methylquinolin-3-yl (90\%)$ Scheme 14. One-pot preparation of benzimidazole derivatives by LaCl<sub>3</sub> catalysis.

The reactions of o-phenylenediamine with aryl aldehydes in aqueous micellar media, using aqueous extract of Acacia concinna pods at 25 °C give 1,2-disubstituted benzimidazole. The yield of the product

depends on the concentration of the aqueous extract of Acacia concinna pods when concentration increases like (10, 20, 30, 40) the mol% yield of the product is also affected (89, 97, 95, 95)% respectively<sup>[30]</sup> (**Scheme 15**). **Table 1** shows the variation in yield concerning changes in the concentration of catalyst.

Table 1. Optimization of catalyst concentration.					
S.no.	Catalyst concentration %(W/V)	Time	Yield %		
1.	10	270	89		
2.	20	180	97		
3.	30	130	95		
4.	40	130	95		
5.	50	80	91		

Table 1. Optimization of catalyst concentration.



 $Ar = Ph (94\%); 4-ClC_6H_4 (90\%); 2-ClC_6H_4 (88\%); 4-OCH_3C_6H_4 (94\%); 4-OHC_6H_4 (98\%); 3-NO_2C_6H_4 (92\%); 3,4-2(OCH_3)C_6H_3 (94\%); 4-BrC_6H_4 (93\%); 3-OHC_6H_4 (88\%); 4-hydroxy-3OCH_3C_6H_3 (94\%))$ 

Scheme 15. Preparation of benzimidazole derivatives with a surfactant catalyst (aqueous extract of Acacia concinna pods).

The condensation of o-phenylenediamine with 4-chlorobenzaldehyde for half an hour in the presence of tert-butyl nitrite in tetrahydrofuran at 25 °C gives an 80% yield of 2-(4-chlorophenyl) benzimidazole<sup>[31]</sup> (Scheme 16).



Scheme 16. Preparation of benzimidazole from 4-chlorobenzaldehyde.

Benzimidazole derivatives were synthesized by coupling o-phenylenediamine with an aldehyde in solvent-free conditions at 140 °C<sup>[25]</sup> (Scheme 17).



 $R = Ph (88\%); 4 - ClC_6H_4 (75\%); 4 - CH_3C_6H_4 (72\%); 4 - C_2H_5C_6H_4 (65\%); Fur-2-yl (55\%); Napth-2-yl (61\%); 4 - NO_2C_6H_4 (92\%); 4 - OCH_3C_6H_4 (78\%); 2 - ClC_6H_4 (70\%); C_5H_{11} (65\%)$ 

Scheme 17. Preparation of benzimidazole from aldehyde.

When 3,4-Toluenediamine heated with methyl phenyl ketone for a while at 180 °C to produce 2-phenyl-5(or 6)-methyl benzimidazole in this manner. In this instance, the methyl group is removed, resulting in benzimidazole<sup>[32]</sup> (Scheme 18).



Scheme 18. Preparation of benzimidazole using acetophenone.

Dhanalakshmi et al. produced high-quality yields of benzimidazole derivatives from  $\alpha,\beta$ -unsaturated ketones using either thermal or microwave irradiation<sup>[33]</sup> (Scheme 19).



Ar = C<sub>6</sub>H<sub>5</sub> (95%); 2-naphthyl (92%); 1-naphthyl (93%); 4-ClC<sub>6</sub>H<sub>4</sub> (88%); Ferrocenyl (88%); 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (87%); Pyrenyl (90%); 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> (89%); 3-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (88%); 2-FC<sub>6</sub>H<sub>4</sub> (82%); 4-BrC<sub>6</sub>H<sub>4</sub> (90%); 3-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>(84%) Scheme 19. Preparation of benzimidazole from  $\alpha$ , β-unsaturated ketones.

### 2.2. From rearrangement of quinoxalinones

#### Mamedov hetrocycle rearrangement in benzimidazole synthesis

When equimolar amount of alkanoyl(aroyl)quinoxalin-2(1H)-ones and 4,5-diamino-6- hydroxy-2mercaptopyrimidine is reflux for 6 hours in n-butanol (n-BuOH) in the presence of  $H_2SO_4$  gives benzimidazole derivatives<sup>[34]</sup> (**Scheme 20**). **Table 2** shows the variation in yield concerning changing the R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub>.



Scheme 20. Synthesis of benzimidazole derivatives from alkanoyl(aroyl)quinoxalin-2(1H)-ones.

S.no	<b>R</b> <sub>1</sub>	<b>R</b> <sub>2</sub>	<b>R</b> <sub>3</sub>	<b>R</b> <sub>4</sub>	Yield%
1.	Н	Н	Ph	Н	88
2.	Н	Н	4-FC <sub>6</sub> H <sub>4</sub>	Н	77
3.	Н	Н	2-FC <sub>6</sub> H <sub>4</sub>	Н	75
4.	Н	Н	4-ClC <sub>6</sub> H <sub>4</sub>	Н	89
5.	Н	Н	4-BrC <sub>6</sub> H4	Н	78
6.	Н	Н	4-O2NC6H4	Н	89
7.	Н	Н	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Н	71
8.	Cl	Cl	Ph	Н	88
9.	Cl	Cl	$4-ClC_6H_4$	Н	77
10.	Cl	Cl	2-FC <sub>6</sub> H <sub>4</sub>	Н	83

Table 2. Variation in yield concerning changing R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub>.

When 2-cyano-1-hydroxybenzimidazole is generated after the thermolysis of 2-azidoquinoxaline 1-oxide, another example of ring contraction has been documented<sup>[16]</sup> (**Scheme 21**).



Scheme 21. Thermolysis of 2-azidoquinoxaline 1-oxide.

The reaction of quinoxalin-2-one with 1,2-diaminobenzene in boiling acetic acid gives 91% yield of the product 2-benzimidazolylquinoxaline<sup>[35]</sup> (**Scheme 22**).



Scheme 22. Synthesis of 2-benzimidazolylquinoxaline.

The reaction of 3-(2-aminophenyl)quinoxalin2(1)-one with acetone in acetic acid with varied reagent ratios for 2 hours gives good yields 85% of 2-Methyl-4-(benzimidazol-2-yl)quinoline and 2-Methyl-4-(benzimidazol-2-yl)-6-fluoroquinoline<sup>[36]</sup> (Scheme 23).





Scheme 23. Synthesis of 2-Methyl-4-(benzimidazol-2-yl)quinoline and 2-Methyl-4-(benzimidazol-2-yl)-6-fluoroquinoline.

When 3-Cyanoquinoxalin2(1H)-one refluxed with benzo[c]furazane4,5-diamine and quinoxaline-5,6-diamine in AcOH gives 78% and 57% yield of benzimidazole derivative respectivily<sup>[37]</sup> (**Schemes 24** and **25**).



Scheme 24. Synthesis of benzimidazole derivative from benzo[c]furazane4,5-diamine.



Scheme 25. Synthesis of benzimidazole derivative from quinoxaline-5,6-diamine.

When 3-benzoylquinoxalin-2(1H)-one reacted with malononitrile in the presence of sodium acetate in boiling MeOH gives benzimidazole derivatives<sup>[38]</sup> (Scheme 26).



 $R = CH_3 (55\%); C_2H_5 (47\%):C_4H_9 (56\%); C_7H_{15} (20\%)$ Scheme 26. Synthesis of benzimidazole derivative from malononitrile.

### 2.3. Reaction with urea

The reaction of o-phenylenediamine with urea in the medium of hydrochloric acid at 130 °C for 2 hours gives 2 (3H)-benzimidazolone with 95% yield<sup>[32]</sup> (**Scheme 27**).



Scheme 27. Preparation of benzimidazole from urea.

### 3. Catalytic properties of benzimidazole derivatives

### 3.1. Oxidation of alcohol

Copper complexes of 3,3-disulfanediyl-bis(N-((1H-benzo[d]imidazol-2-yl)methyl)propanamide (Compound 1) are used to oxidize 3-Pyridyl carbinol to nicotinaldehyde, 1,2,3,4-Tetrahydronaphthol to 3,4-tetrahydronaphthalenal-(2H)-one, 4-Methoxybenzyl alcohol to 4-methoxy benzaldehyde and 4-Nitrobenzyl alcohol to 4-nitrobenzaldehyde<sup>[39]</sup>.





### 3.2. Oxidation of 1-phenyl propyne

Cu(II) complexes of a benzimidazole Schiff base ligand (Compound 2) catalyze the oxidation of 1-phenyl propyne efficiently. When 1-phenyl propyne is broken down, three different compounds are formed that are diketone, aldehyde, and acid. Diketone formation shows the entire oxidation of the triple bond, whereas benzoic acid formation denotes alkyn cleavage. In this series, the nitrate-bound complex has the highest overall conversion (60%) to the three products<sup>[40]</sup>.

In the oxidation of 1-phenyl propyne under basic conditions using the catalyst, the yield of the aldehyde is much higher than that of the diketone, increasing the total yield to 81%, whereas the same reaction under acidic conditions produces higher yields for the diketone and the overall yields are only 69%. In acidic conditions, the fact that around 40% of the complex dissolves during catalysis is a disadvantage. As a result, the reaction is not entirely heterogeneous.



### 3.3. Oxidation of 1,10-phenanthroline

Copper complexes of the Schiff base ligand N-methyl benzo-imidazol-2-yl ethylimino methyl naphanal-2-ol (Compound 3) catalyse the aerobic oxidation of 1,10-phenanthroline utilising molecular oxygen.



This catalysis occurs at room temperature and does not require a strong oxidizing agent. The catalyst is 5.0 times more efficient under aerobic conditions, based on the relative velocity of the oxidation reaction. Although the relative velocity of the in-situ produced catalyst is 3.8 times lower than that of the original catalyst, it still exclusively catalyzes in aerobic circumstances<sup>[41]</sup>.

### 3.4. Oxidation of olefins

The iron complexes of benzimidazole derivatives (Compound 4) N N'-bis(1-butyl-Bnzd.-2-yl-methyl)hexane-1,6-dicarboxamide and (Compound 5) N N'-bis(Bnzd.-2-yl-methyl)-benzene-1,4-dicarboxamide is used in the oxidation of olefins. The oxidation of styrene gives benzoic acid and benzaldehyde, the oxidation of 1,5-cycloctadiene gives cyclooct-4-enone and cyclooctanepoxide, oxidation of cyclohexene gives cyclohex-2-enone<sup>[42]</sup>.



#### 3.5. Oxidation of 2-aminophenol

The copper complex of 1-(4-methoxybenzyl)-2-(4-methoxyphenyl)benzimidazole(Compound 6) is used in the oxidation of 2-aminophenol. The oxidation of 2-aminophenol gives 2-amino-3H-phenoxazine-3-one<sup>[43]</sup>.



### 3.6. Oxidation of ethyl benzene

The Cobalt nanocomposites of poly(benzimidazole-amide) (Compound 7) which is synthesized from (2, 6-Bis (5-Amino-1H-Benzimidazol-2-YI)Pyridine) is used in the oxidation of ethyl benzene. The oxidation of ethyl benzene which occurs with the help of cobalt nanocomposites of poly(benzimidazole-amide) as a catalyst gives a 55% yield of acetophenone<sup>[44]</sup>.



Compound 7

### 3.7. Oxidation of dopamine

Copper complexes of benzimidazolyl 2-[2-(1H-benzo[d]-imidazol-2-yl)ethylimino)methyl]phenol (Compound 8) is used into the oxidation of dopamine. Oxidation of dopamine with the help of copper complex of benzimidazolyl 2-[2-(1H-benzo[d]-imidazol-2-yl)ethylimino)methyl]phenol gives aminochrome<sup>[45]</sup>.





### 4. Reduction of olefins, nitroarenes, and Schiff base

The palladium complex of [2-(2'-pyridyl)benzimidazole] is used in the reduction of olefins, nitroarenes, and Schiff base. Compared to closed-chain olefins, open-chain olefin hydrogenation was typically quicker. Due to their tendency to assemble into complexes with the catalyst, the type of double bond structure and the type of ligand on the olefins both affect the rate of hydrogenation. Schiff base p-nitrobenzylideneaniline hydrolyzed to 4-nitrobenzylaniline, demonstrating specific hydrogenation of C=N in the presence of a NO<sub>2</sub> group<sup>[46]</sup>. **Table 3** shows the conversion rate of the substrest into product with respect to time.

S.No	Substrate	Product	Time (min)	Conversion %
1	1-Hexene	n-Hexane	40	96
2	Cyclohexene	Cyclohexane	58	88
3	Styrene	Elhylbenzene	54	84
4	Cinnamaldehyde	Phenylpropanal	140	94

Table 3. Some substrates are following in the table with the conversion rate.

Table 3. (Continued).

S.No	Substrate	Product	Time (min)	Conversion %
5	Cinnamonitrile	Phenylpropionitrile	130	96
6	p-Chlorobcnzylideneaniline	N-(4-Chlorobenzyl)aniline	90	75
7	p-nitrobenzylideneaniline	4-nitrobenzylaniline	97	72
8	p-Chlorobenzylideneaniline	N-(4-Chlorobenzyl)aniline	90	75
9	p-Nitrophenol	p-Aminophenol	80	86
10	p-Nitrotoluene	p-Toluidine	92	70

### **5.** Conclusion

Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic substance is created when imidazole and benzene combine. A prominent position is held by heterocyclic compounds among the many classes of aromatic organic compounds. Benzimidazole derivatives show catalytical properties like as the oxidation of alcohol, oxidation of 1-phenyl propyne, oxidation of 1,10-phenanthroline, oxidation of olefins oxidation of 2-aminophenol and oxidation of ethyl benzene. Benzimidazole metal complexes are also used in the reduction of olefins, nitroarenes, and Schiff bases.

## **Conflict of interest**

The authors declare no conflict of interest.

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