Selective Synthesis of 1,2-Disubstituted Benzimidazoles from the Condensation of *o*-Phenylenediamines with Aldehydes: A review

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Abstract: *1,2-Disubstituted benzimidazole moiety showed promising application in biological and clinical studies. Attention has been focused toward the synthesis of the 1,2-disubstituted benzimidazoles dueto their special biological properties. Herein several methods to selective synthesis of 1,2-disubstituted benzimidazoles from the condensation of o-phenylenediamines with aldehydes are reviewed.*
Keywords: *Chemoselective; 1,2-Disubstitutedbenzimidazoles; o-Phenylenediamine;Selective synthesis.*
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I.   Introduction

The *N*-heterocyclic compounds played an important role in drug discovery because the majority of therapeutic drugs contain an *N*-heterocyclic unit. The benzimidazole is a well-known bioactive *N*-heterocyclic system found in a large number of natural and synthetic medicinal compounds. The 1,2-disubstituted benzimidazoles and their derivatives represent an important branch of benzimidazoles family and played an important role in several areas and particularly as drug discovery targets [1-10](**Scheme 1**).
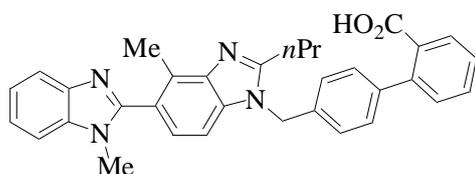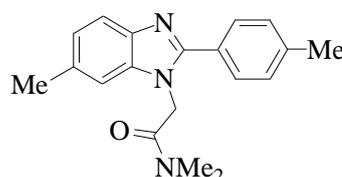
Telmisartan   **GABA_A Agonist**
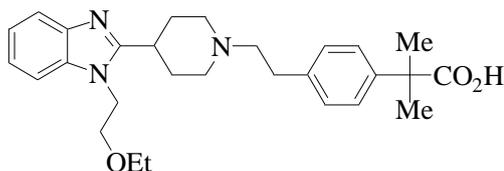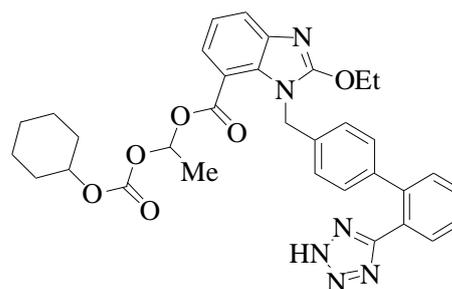
Bilastain   **Candesartan**
Scheme 1: Selected examples of 1,2-disubstituted benzimidazole containing drugs.

Owing to their special biological properties, attention has been focused toward the synthesis of the 1,2-disubstituted benzimidazoles. Many synthetic strategies reported **(Scheme 2)** for the construction of 1,2-disubstituted benzimidazole scaffold include intermolecular coupling of *o*-iodo-*N*-alkylaniline with amide [11] **(Scheme 2, route A)** or *o*-iodo/bromoanilides with alkyl/aryl amines[12,13]**(Scheme 2, route B)**, intramolecular coupling of Z-*N*′-(*o*-halophenyl)-*N*-alkyl/phenyl)amidines [14,15]**(Scheme2, route C)**, and the reductive cyclisation of in situ formed *o*-nitroanilides from *o*-nitrochlorobenzenes by palladium-catalyzed amidation**(Scheme 2, route D)**[16].
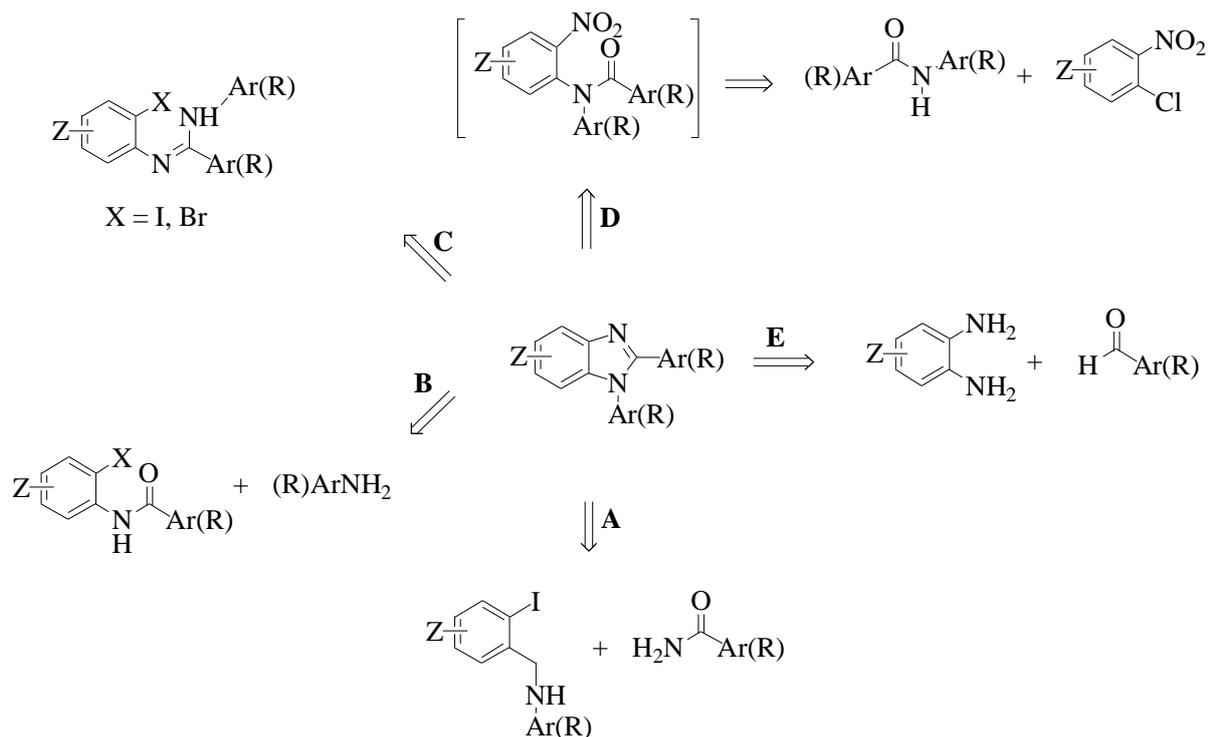
Scheme 2: Reported synthetic strategies for construction of 1,2-disubstituted benzimidazoles.

The direct condensation of *o*-phenylenediamines with aldehydes under oxidative conditions **(Scheme 2, route E)** appears to be a straightforward approach and it has been extensively used, because the availability of a variety of substituted aldehydes. In addition various oxidative and catalytic reagents have been also tested.However, the cyclocondensation between *o*-phenylenediamine and aldehyde **(Scheme2 rote E)** has a potential selectivity problem due to the possibility of competitive formation of the 1,2-disubstituted and the 2-substituted benzimidazoles **(Scheme 3)**.
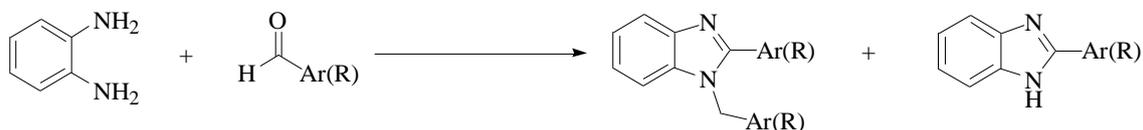
Scheme 3: Competitive formation of 1,2-disubstituted and 2-substituted benzimidazoles during the direct cyclocondensation between *o*-phenylenediamine and an aldehyde.

Therefore, search for new methods or catalysts to overcome the issue of selectivity during the condensation of *o*-phenylenediamines with aldehydes are still an important experimental challenge to attract the attention of researchers. While methods to prepare 2-substituted benzimidazoles have highly increased during the last years [17-30],the synthesis of 1,2-disubstituted benzimidazoles remains a challenging task.
This article aims to review the work reported on the selective synthesis of 1,2-disubstituted benzimidazoles from the condensation of *o*-phenylenediamines with aldehydes during the last few years.

Selective Synthesis of 1,2-Disubstituted Benzimidazoles from the Condensation of o-Phenylenediamines with Aldehydes:
Chakraborti*et al.*[31] reported that the fluorous alcoholstrifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP) efficiently promote the cyclocondensation of *o*-phenylenediamine with aldehydes to afford selectively the 1,2-disubstituted benzimidazoles at room temperature in short times **(Scheme 4)**.
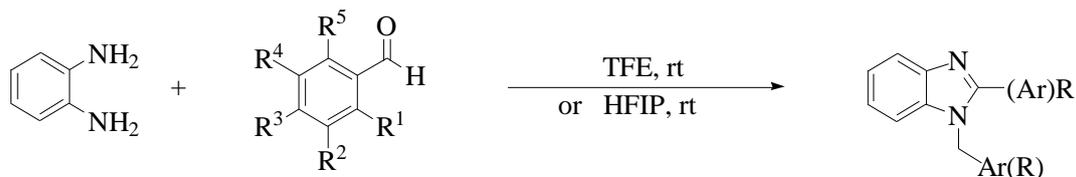
$$R^1 = R^2 = R^3 = R^4 = R^5 = H$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = CH_3$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = OCH_3$$
$$R^2 = R^3 = R^4 = R^5 = H, R^1 = OCH_3$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = N(CH_3)_2$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = Cl$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = Br$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = OH$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = CF_3$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = CN$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = NO_2$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = OCH_2Ph$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = OCOPh$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = OCOBut$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = OBoc$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = OTBDMS$$
$$R^1 = R^2 = R^4 = R^5 = H, R^3 = CH_3$$
$$R^1 = R^3 = R^5 = H, R^2 = R^4 = OCH_3$$
$$R^1 = R^4 = R^5 = H, R^2 = OEt, R^3 = OH$$
2-pyridyl
2-furyl
2-thiopyl
2-naphtyl
cinnamyl
cyclohexyl

Scheme 4: Fluorous alcohols (TFE/HFIP) promoted selective synthesis of 1,2-disubstituted benzimidazole.

Mechanistic investigation by NMR, mass spectrometry, and chemical studied to rationalize theselectivity. The ability of the fluorous alcohol in promoting the reaction and controlling the selectivity can be investigated from their better hydrogen bond donor (HBD) abilities compared to that of the other organic solvents as well as of water. Due to the better HBD values, the fluorous alcohols efficiently promote the initial bisimine formation by electrophilic activation of the aldehyde carbonyl. Subsequently the hydrogen-bond-mediated activation of the in situ-formed bisimine triggers the rearrangement via 1,3-hydride shift to form the 1,2-disubstituted benzimidazoles **(Scheme 5)**.
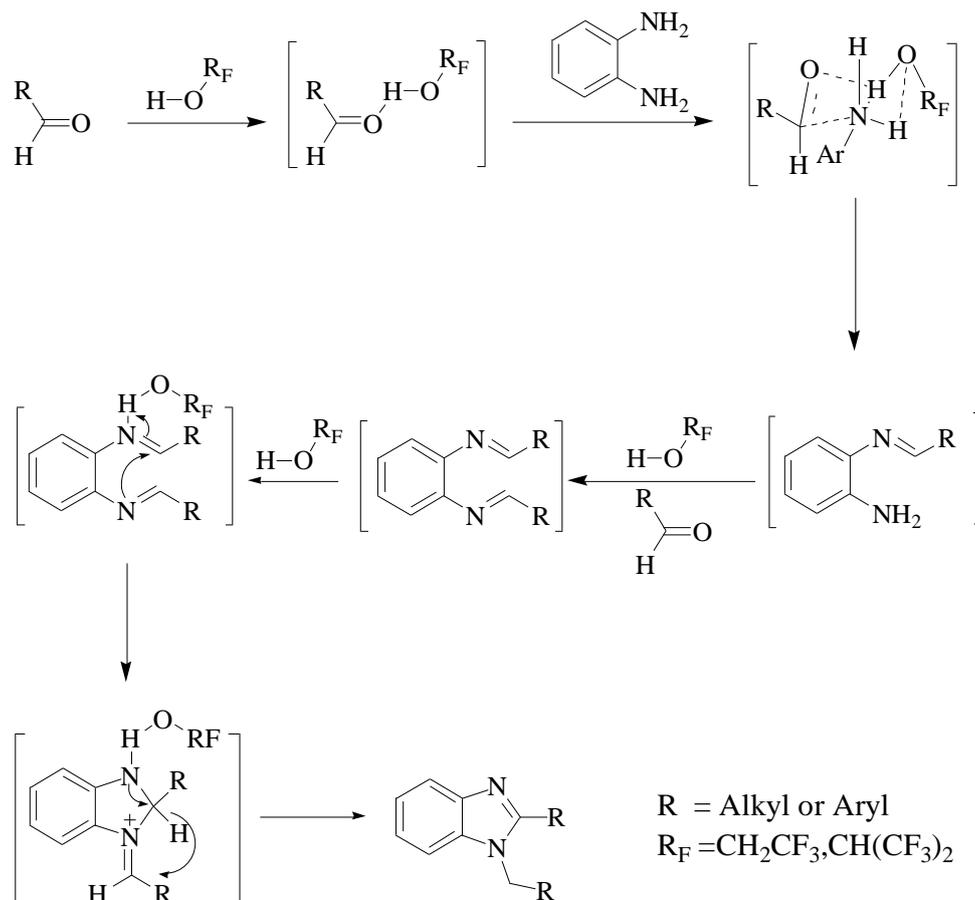
Scheme 5: Mechanism for formation of 1,2-disubstituted benzimidazole using fluorous alcohols.

Song *et al.*[32] used Lactic acid as a biocompatible medium for the chemoselective synthesis of the 1,2-disubstituted benzimidazole scaffold *via* a direct one-pot cyclocondensation of *o*-phenylenediamine with aldehydes**(Scheme 6)**.The procedure was found to be practical for scale-up synthesis affording 1,2-disubstituted benzimidazoles in multi-gram scale reaction.

$R = R^1 = H$

$R = CH_3, R^1 = H$

$R = CH_3, R^1 = CH_3$

$R = Cl, R^1 = H$

$R = Cl, R^1 = H$

$R = Cl, R^1 = Cl$

$R_2 = C_6H_5$

4-ClC$_6$H$_4$

4-MeC$_6$H$_4$

4-HO,3-MeOC$_6$H$_4$

4-NO$_2$C$_6$H$_4$

3-BrC$_6$H$_4$

4-FC$_6$H$_4$

4-MeOC$_6$H$_4$

4-N(CH$_3$)$_2$

2-naphtyl

2-furyl

2-pyridyl
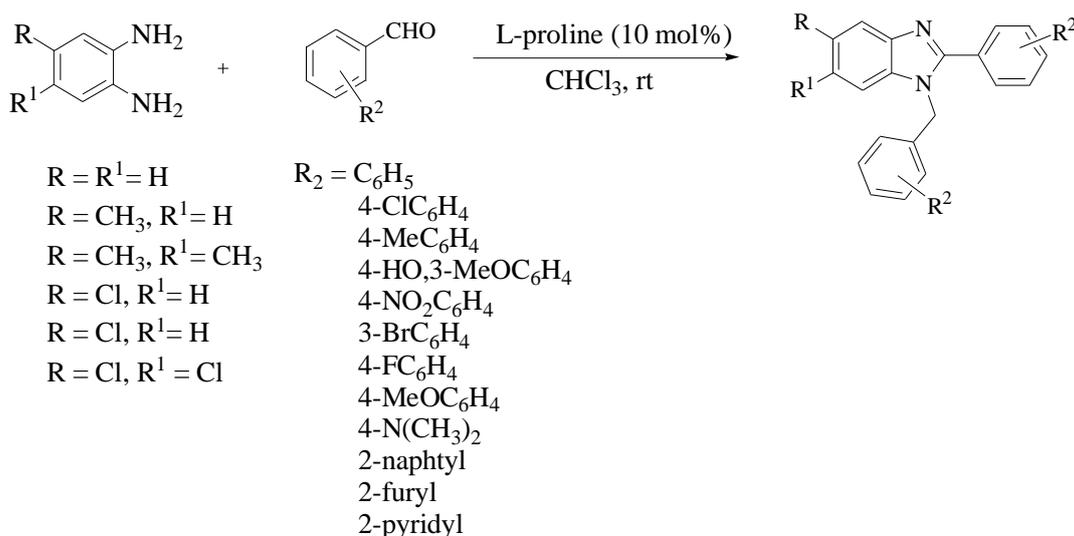
Scheme6: Chemoselective synthesis of the 1,2- disubstituted benzimidazoles in lactic acid.

They proposed a plausible reaction mechanism for the selective formation of 1,2-disubstituted benzimidazoles in lactic acid **(Scheme 7)**. First, Schiff base bisimine E-1 is formed in lactic acid. Subsequently, lactic acid promotes the formation of immonium E-2 by the intramolecular cyclisation of E-1. Finally, lactic acid mediated the rearrangement of imminium E-2 to afford 1,2-disubstituted benzimidazole derivatives.

E-1　　　　　　E-2
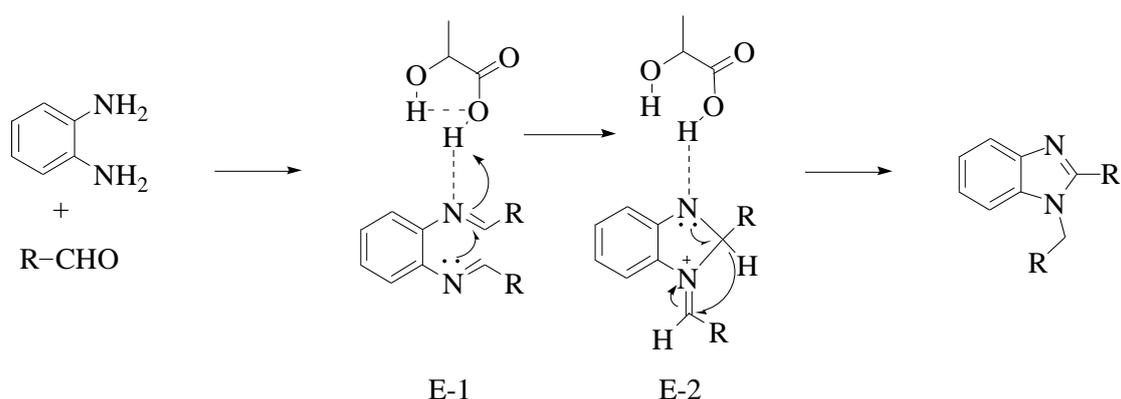
Scheme7: Plausible reaction mechanism for the selective formation of 1,2-disubstituted benzimidazoles in lactic acid.

Adapa*et al.*[33] used the commercially available, inexpensive *L*-proline as an organocatalysis for the selective synthesis of 1,2-disubstituted benzimidazoles by the reaction of *o*-phenylenediamines with aldehydes under mild conditions using chloroform as a solvent at ambient temperature**(Scheme 8)**.

R = R^1= H
R = CH$_3$, R^1= H
R = CH$_3$, R^1= CH$_3$
R = Cl, R^1= H
R = Cl, R^1= H
R = Cl, R^1 = Cl

R$_2$ = C$_6$H$_5$
4-ClC$_6$H$_4$
4-MeC$_6$H$_4$
4-HO,3-MeOC$_6$H$_4$
4-NO$_2$C$_6$H$_4$
3-BrC$_6$H$_4$
4-FC$_6$H$_4$
4-MeOC$_6$H$_4$
4-N(CH$_3$)$_2$
2-naphtyl
2-furyl
2-pyridyl
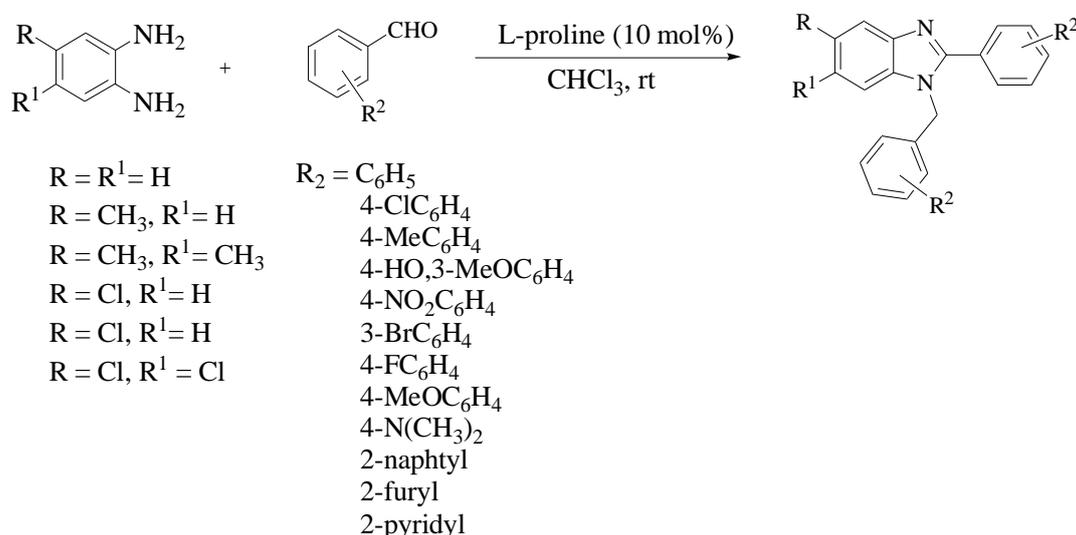
Scheme8: L-proline catalyzed selective synthesis of 1,2-disubstituted benzimidazoles.

The proposed mechanism for the L-proline-catalyzed synthesis of 1,2-disubstituted benzimidazoles was suggested to occur via a tandem sequence of reactions as described in **(Scheme 9)** involving Path I (i) formation of dibenzylidene-*o*-phenylenediamine via iminium catalysis, (ii) protonation of the dibenzylidene-*o*-phenylenediamineand ring closure leading to a five-membered ring either in a sequential or concerted manner, (iii) 1,3-hydride transfer and (iv) deprotonation or via Path II involving the activation of the aldehydic carbonyl oxygen by the acid part of L-proline through intermolecular hydrogen bonding, and subsequent condensation with *o*-phenylenediamineto form dibenzylidene-*o*-phenylenediamine, followed by steps (ii)-(iv) to form 1,2-disubstituted benzimidazoles.

Scheme9: Proposed mechanism for the L-proline-catalyzed 1,2-disubstituted benzimidazole synthesis.

Adapa*et al.*[34]reported an efficient procedure for the selective synthesis of 1,2-disubstituted benzimidazole derivatives from various electronically divergent aromatic aldehydes and *o*-phenylenediaminesusing Zn-(proline)$_2$ (5 mol%) as a novel water-soluble and recyclable Lewis acid catalyst(**Scheme10**).

R = R^1 = H   R^2 = C$_6$H$_5$
R = CH$_3$, R^1 = CH$_3$ *p*-CH$_3$-C$_6$H$_4$
R = Cl, R^1 = Cl   *p*-CH$_3$O-C$_6$H$_4$
                              1,2,3⁻ Tri(OCH$_3$)C$_6$H$_2$
                              p-CNC$_6$H$_4$
                              p-NMe$_2$C$_6$H$_4$
                              o-Cl
                              p-Cl
                              m-Br
                              p-Br
                              o-F
                              p-F
                              o-OH
                              o-NO$_2$
                              p-NO$_2$
                              1-naphtyl
                              2-pyridyl
                              2-furyl

Scheme10: Zn-proline-catalyzed selective synthesis of 1,2-disubstituted benzimidazoles in water**.**

The proposed mechanism for the zinc proline-catalyzed synthesis of 1,2-disubstituted benzimidazoles depicted in (**Scheme 11**). Initially, coordination of the carbonyl oxygen to the acidic metal center and subsequent formation of imine with proline; followed by nucleophilic attack of *o*-phenylenediamine to the imine, forming dibenzylidene-*o*-phenylenediamine, which then following the usual steps (i) protonation of the dibenzylidene-*o*-phenylenediamine by acidic proton and ring closure leading to a five membered ring either a sequential or concerted manner, (ii) 1,3-hydride transfer and (iii) deprotonation, to form the desired 1,2-disubstituted benzimidazoles.
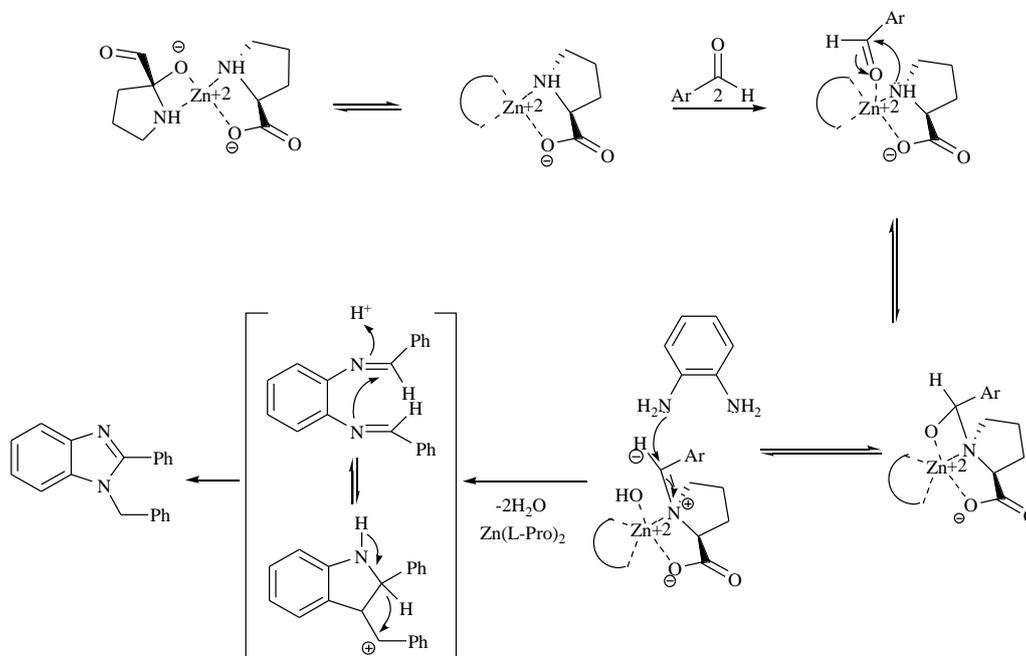
Scheme 11: Proposed mechanism for Zn(*L*-Proline)$_2$catalyzed synthesis of 1,2-disubstituted benzimidazoles.

Chakraborti*et al.*[35] described a convenient and highly selective synthesis of 1,2-disubstituted benzimidazoles from the reaction of *o*-phenylenediamine with aldehydes using HClO$_4$–SiO$_2$ as solid supported protic acid catalysis in ethanol at room temperature(**Scheme 12**).
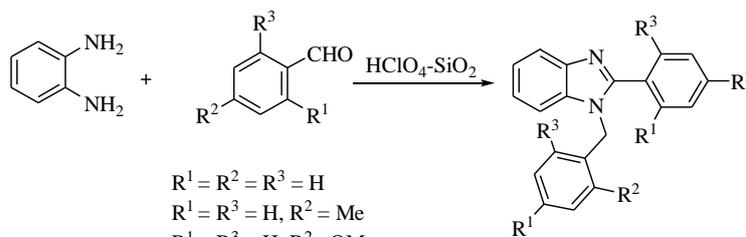
$R^1 = R^2 = R^3 = H$
$R^1 = R^3 = H, R^2 = Me$
$R^1 = R^3 = H, R^2 = OMe$
$R^1 = R^3 = H, R^2 = NMe_2$
$R^1 = R^3 = H, R^2 = Cl$
$R^1 = R^3 = H, R^2 = Br$
$R^1 = R^3 = H, R^2 = CF_3$
$R^1 = R^3 = H, R^2 = OCH_2Ph$
$R^1 = R^2 = H, R^3 = Me$
$R^1 = R^3 = H, R^2 = NO_2$
2-furyl
cyclohexyl
isopropyl
isopentyl
tert-butyl
4-pyridyl
2-thiopyl
2-naphtyl

Scheme 12: Selective synthesis of 1,2-disubstituted benzimidazoles using HClO$_4$-SiO$_2$.

A mechanistic outline for theHClO$_4$–SiO$_2$catalyzed formation of the 1,2-disubstituted benzimidazoles was derived, followed bis-imine formation, rearrangement, and a 1,3-hydride shift pathway**(Scheme 13)**. The origin of selectivity was suggested on furthering or suppressing the bis-imine formation using a judicial choice of the supported protic acid catalyst as well as an appropriate reaction medium. It was observed the electronic and steric factors of the aldehyde and the electronic factor of the *o*-phenylenediamine were also significant contributory factors in dictating the selectivity.
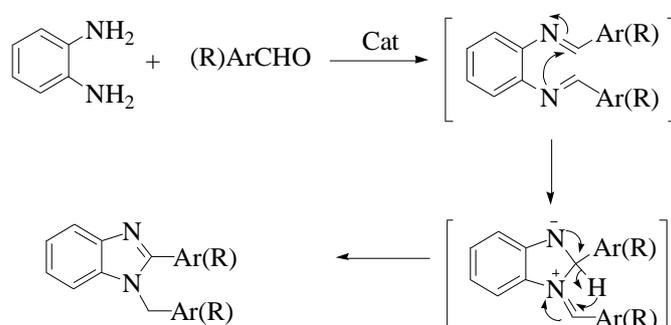
Scheme 13: Pathways of 1,2-disubstituted benzimidazole formation during the HClO$_4$–SiO$_2$catalyzed reaction of *o*-phenylenediamine with aldehyde.

Fan*et al.*[36]reported the Sc(OTf)$_3$catalyzed condensation of *o*-phenylenediamine with aldehydes in ethanol, furnishing a practicable approaches for the formation of 1,2-disubstituted benzimidazoles with high chemoselectivity and excellent yields**(Scheme14)**.

$R^1 = H$	$R^2 = C_6H_5$
H	$4\text{-}ClC_6H_4$
H	$4\text{-}MeOC_6H_4$
H	$4\text{-}MeC_6H_4$
H	$4\text{-}FC_6H_4$
NO$_2$	C_6H_5
NO$_2$	$4\text{-}ClC_6H_4$
NO$_2$	$4\text{-}MeOC_6H_4$
NO$_2$	$4\text{-}FC_6H_4$
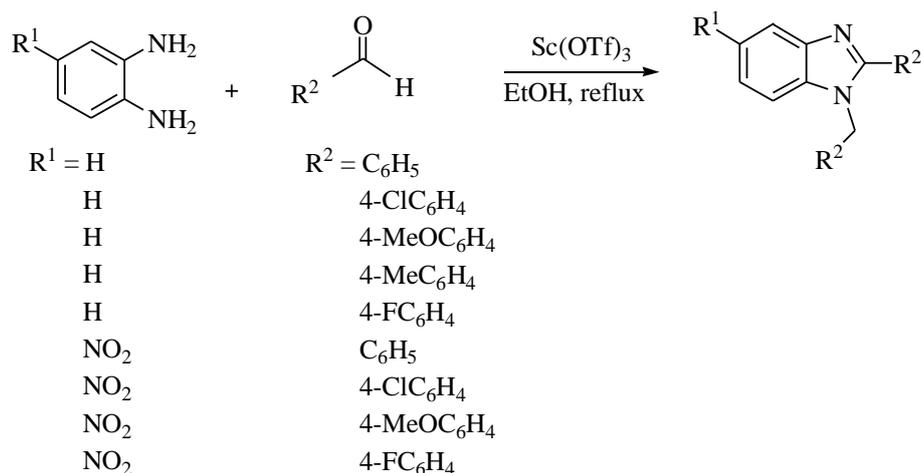
Scheme 14:Chemoselective synthesis of 1,2-disubstituted benzimidazoles in Sc(OTf)$_3$ catalyzed system.

It was suggested a reasonable mechanism for the condensation reaction of *o*-phenylenediamine and aldehydescatalyzed by Sc(OTf)$_3$ as shown in **(Scheme 15)**.
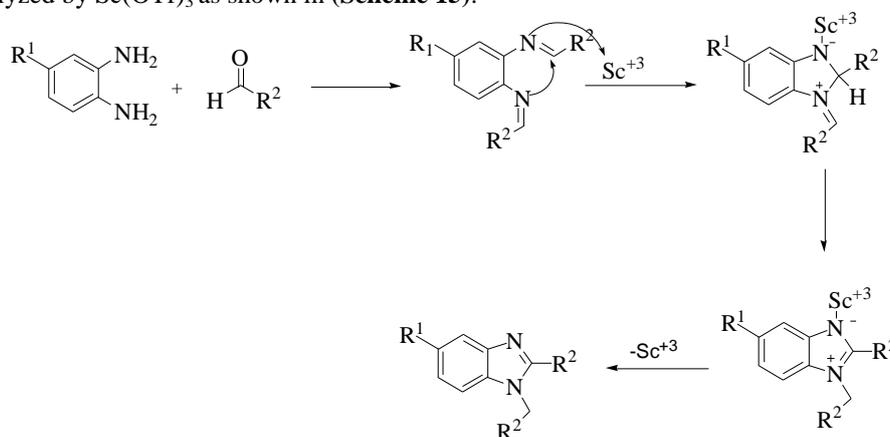
Scheme 15:Proposed mechanism for the condensation reaction of *o*-phenylenediamine and aldehydes catalyzed by Sc(OTf)$_3$.

Santra*et al.* [37]synthesized different 1,2-disubstituted benzimidazoles in very good yield under mild condition in aqueous media from *o*-phenylenediamine and aldehydesin the presence of nanoIn$_2$O$_3$ as catalyst **(Scheme 16)**. The method is applicable to aryl, aliphatic andheteroaryl aldehydes. In addition, In$_2$O$_3$ nanoparticles were recyclable without the loss of significant catalytic activity.
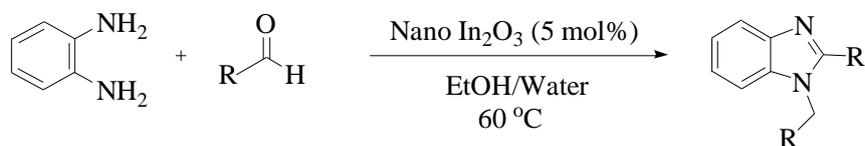
R = C$_6$H$_5$
4-H$_3$COC$_6$H$_4$
4-CH$_3$C$_6$H$_4$
4-OHC$_6$H$_4$
3-OCH$_3$, 4-OHC$_6$H$_3$
4-ClC$_6$H$_4$
4-BrC$_6$H$_5$
phCH=CH$_2$
propyl
isopropyl
butyl
2-furyl
2-pyridyl

Scheme 16: Selectivesynthesis of 1,2-disubstituted benzimidazoles using nanoIn$_2$O$_3$ as catalyst.

Santiago *et al.*[38]descried a practical and environmentally friendly one-pot method for the simple and selective synthesis of 1,2-disubstituted benzimidazoles from the reaction of *o*-phenylenediamine with aromatic or aliphatic aldehydes using Er(OTf)$_3$ as commercially available and easily recyclable catalyst **(Scheme 17)**.
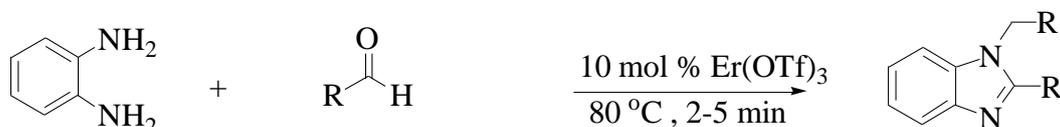
R = C$_6$H$_5$
4-H$_3$COC$_6$H$_4$
4-CH$_3$C$_6$H$_4$
CH$_3$CH$_2$
CH$_3$
C$_6$H$_5$-CH$_2$
4-ClC$_6$H$_4$
4-NO$_2$C$_6$H$_5$
4-CNC$_6$H$_5$

Scheme 17: Selective synthesis of 1,2-disubstituted benzimidazoles using Er(OTf)$_3$as catalyst.

To explain the essential role of Er(OTf)$_3$ on the selectivity observed in reaction, the reaction pathway was proposed as shown in **(Scheme 18)**. In the pathway, when the aldehyde approaches Er(OTf)$_3$, the carbonyl carbon of the aldehyde becomes highly reactive toward the nucleophilic attack of *o*-phenylenediamine, generating dibenzylidenediamine. Consequently, the 1,2-disubstituted benzimidazole will be formed through bisimine, under catalytic action of the Lewis acid Er(OTf)$_3$. Thus, the catalyst acts as an effective electrophilic activating agent for the formation of the bisimine and promotes the subsequent steps (intramolecular nucleophilic attack and the following 1,3-hydride shift), finally affording the 1,2-disubstitutedbenzimidazoles.
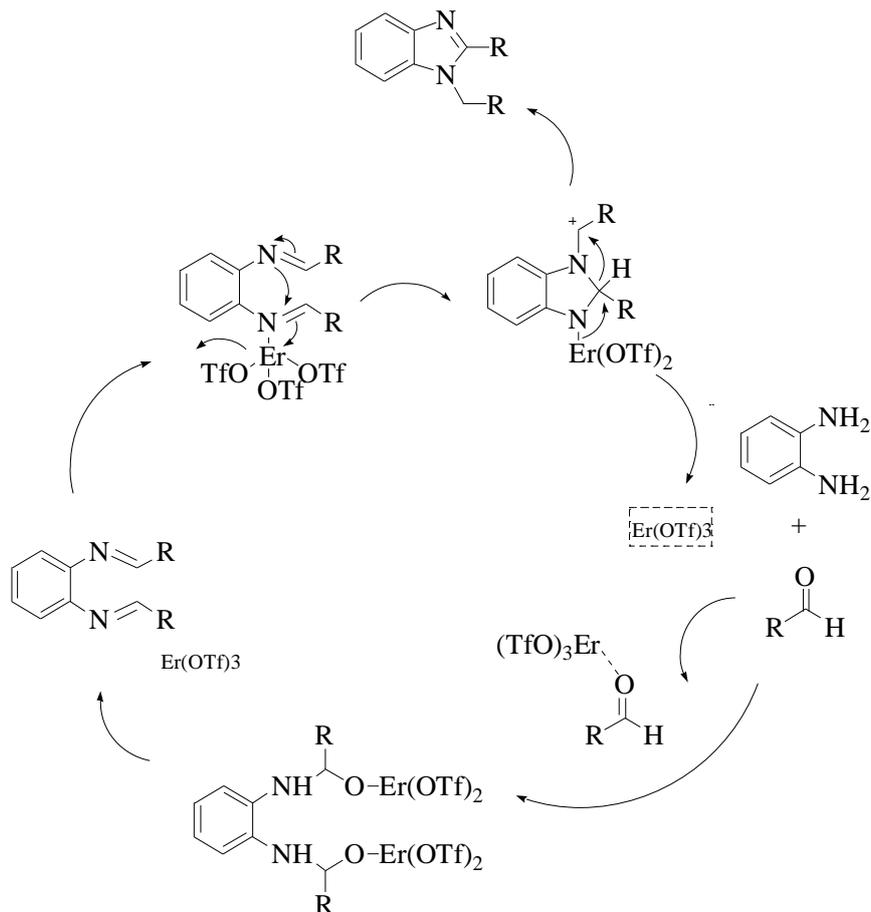
Scheme 18: Proposed mechanism for Er(OTf)$_3$catalyzed synthesis of 1,2-disubstituted benzimidazoles.

Azarifa*et al.* [39]reported an efficient and simple procedure for the green synthesis of 1,2-disubstituted benzimidazoles in high yields by acetic acid-promoted condensation of *o*-phenylenediamine with aromatic aldehydes both under microwave irradiation and conventional thermal heating **(Scheme 19)**.

R = C$_6$H$_5$
  4-MeC$_6$H$_4$
  4-MeOC$_6$H$_4$
  2-MeOC$_6$H$_4$
  4-HOC$_6$H$_4$
  2-HOC$_6$H$_4$
  4-ClC$_6$H$_4$
  2-ClC$_6$H$_4$
  4-MeNC$_6$H$_4$
  2-Furyl
  4-CNC$_6$H$_4$
  4-NO$_2$C$_6$H$_4$
  2-NO$_2$C$_6$H$_4$
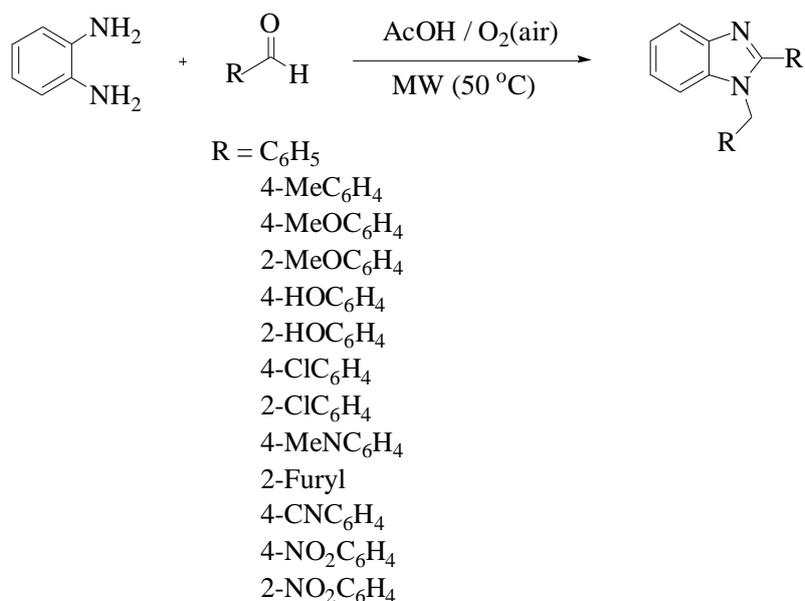
Scheme 19: Acetic acid-promoted synthesis of 1,2-disubstituted benzimidazoles under microwave irradiation.

A possible mechanism was proposed for the reaction is depicted in **(Scheme20)**. The mechanism probably involves an initial acetic acid-promoted condensation of *o*-phenylenediamine with aldehydes to yield a di-imine intermediate followed by cyclization to the 1,2-disubstituted benzimidazoles through the intermediate.
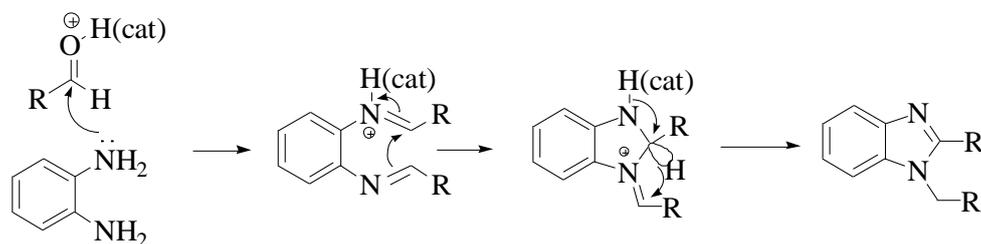
Scheme20: Suggested mechanism for the formation of the 1,2-disubstituted benzimidazoles using acetic acid.

Aniket*et al.*[40] reported that Iodine was introduced as effective catalyst for selective synthesis of 1,2-disubstituted benzimidazoles via condensation reaction of *o*-phenylenediamine and aldehydes in aqueous media at 80–90 $^{\circ}$C **(Scheme 21)**.

R = C$_6$H$_5$
    4-ClC$_6$H$_4$
    3-NO$_2$C$_6$H$_4$
    4-MeC$_6$H$_4$
    4-FC$_6$H$_5$
    4-CNC$_6$H$_4$
    2-furyl
    4-MeOC$_6$H$_4$
    4-Me$_2$NC$_6$H$_4$
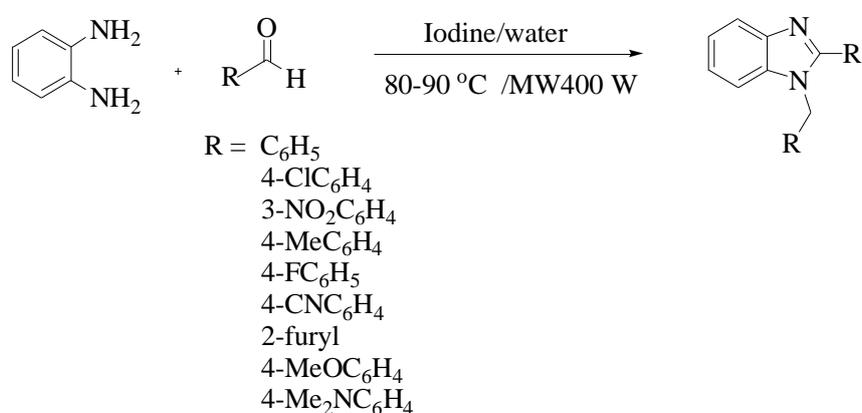
Scheme 21: Selective synthesis of 1,2-disubstituted benzimidazoles using iodine as catalysis.

The reaction was suggested to proceed via the mechanism shown in **(Scheme 22)**, which involve the iminium catalyzed formation of an *N,N*-dibenzylidene-*o*-phenylenediamine and ring closure to give a five membered ring.
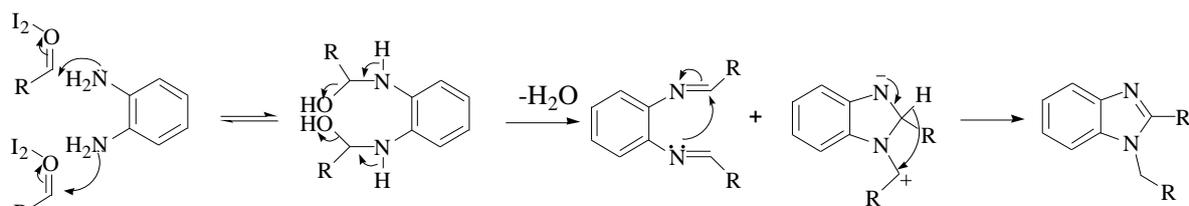
Scheme 22: Proposed mechanism for the formation of 1,2-disubstituted benzimidazoles catalyzed by iodine in aqueous media.

Bahrami*et al.*[41] synthesized differently 1,2-disubstituted benzimidazoles from the reaction of *o*-phenylenediamine with aryl aldehydes in aqueous micellar media in the presence of sodium dodecylsulfate(SDS) as a catalyst **(Scheme 23)**. This catalyst could enhance reaction rate as well as work as a surfactant in solubilizing the organic substrates.

$$R = C_6H_5$$
$$4\text{-}MeOC_6H_4$$
$$4\text{-}HOC_6H_4$$
$$4\text{-}MeC_6H_4$$
$$4\text{-}(Me_2N)C_6H_4$$
$$2\text{-}ClC_6H_4$$
$$4\text{-}ClC_6H_5$$
$$4\text{-}NO_2\text{-}C_6H_5$$
$$2\text{-}Pyridyl$$
$$2\text{-}Furyl$$
$$CH_3(CH_2)_2$$
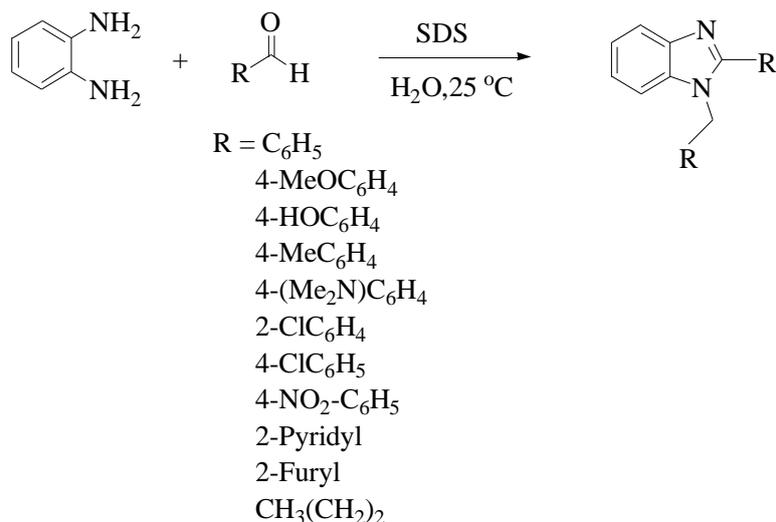
Scheme 23: Selective synthesis of 1,2-disubstituted benzimidazoles in SDS micelles.

It was suggested a possible mechanism for the reaction consists of a two-step sequence involving the micelle-promoted formation of the *N,N*-dibenzylidene-1,2-phenylenediamine derivative followed by ring closure. Aromatization then takes place by a deprotonation-reprotonation process. The catalytic effect of micellar sodium dodecyl sulfate in this reaction was explained as follows. In the micellar solution, 1,2-phenylenediamine and aryl aldehyde, which are both hydrophobic, are forced inside the hydrophobic core of the micelles, thus allowing the reaction to take place more easily (**Figure 1**).
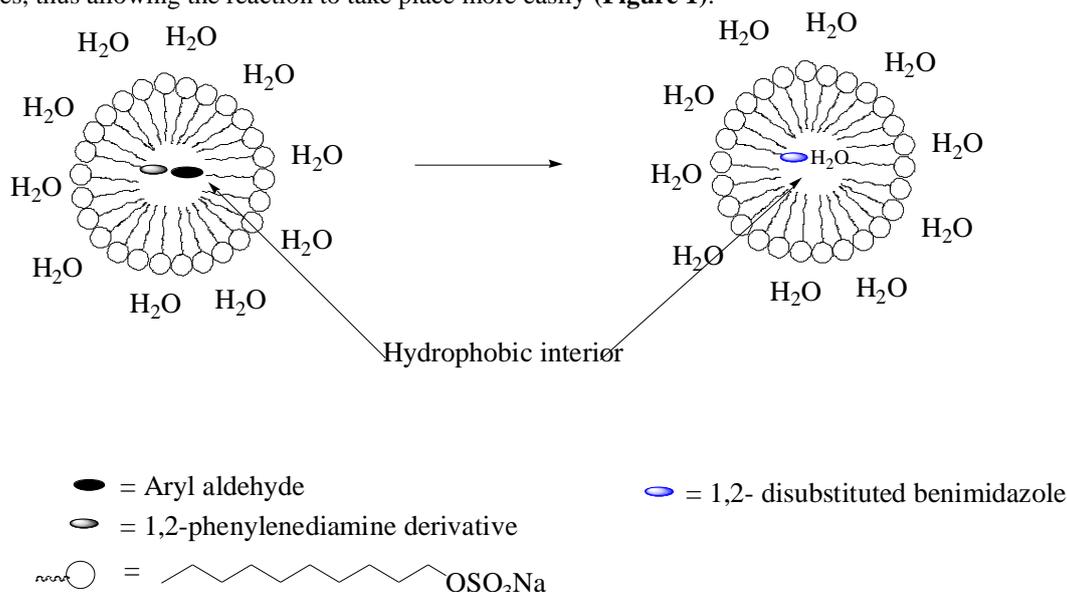
Figure 1: Proposed model for the synthesis of 1,2-disubstituted benzimidazolein water in the presence of SDS.

Ghosh *et al.*[42] also used sodium dodecyl sulfate as a catalyst for the selective synthesis of 1,2-disubstituted benzimidazoles by a one-pot reaction of *o*-phenylenediamine with both aromatic and aliphatic aldehydes in water at room temperature in open air without any organic solvent (**Scheme 24**).

$R^1 =$	H	$R^2 =$	C_2H_5
	H		$4\text{-}CH_3OC_6H_4$
	H		$4\text{-}FC_6H_4$
	H		$4\text{-}ClC_6H_4$
	H		$4\text{-}NO_2C_6H_4$
	H		$4\text{-}NMe_2C_6H_4$
	H		$4\text{-Isopropyl } C_6H_4$
	H		$3\text{-}NO_2C_6H_4$
	H		$3\text{-}OHC_6H_4$
	H		$3\text{-}OPhC_6H_4$
	H		$2\text{-}OHC_6H_4$
	H		Furan-2-yl
	H		5-Bromo-thiophene-2-yl
	H		$PhCH= CH_2$
	H		1-Naphthyl
	H		$4\text{-Isopropyl } C_6H_4$
	$3\text{-}CH_3$		$3\text{-}OPhC_6H_4$
	$3\text{-}CH_3$		5-Bromo-thiophene-2-yl
	$3\text{-}CH_3$		$2\text{-}ClC_6H_4$
	$3\text{-}CH_3$		$4\text{-}ClCH_4$
	3-benzoyl		C_6H_5
	3-benzoyl		Pyridine 4-carboxyaldehyde
	H		H
	H		Valeraldehyde
	H		Cyclohexayl
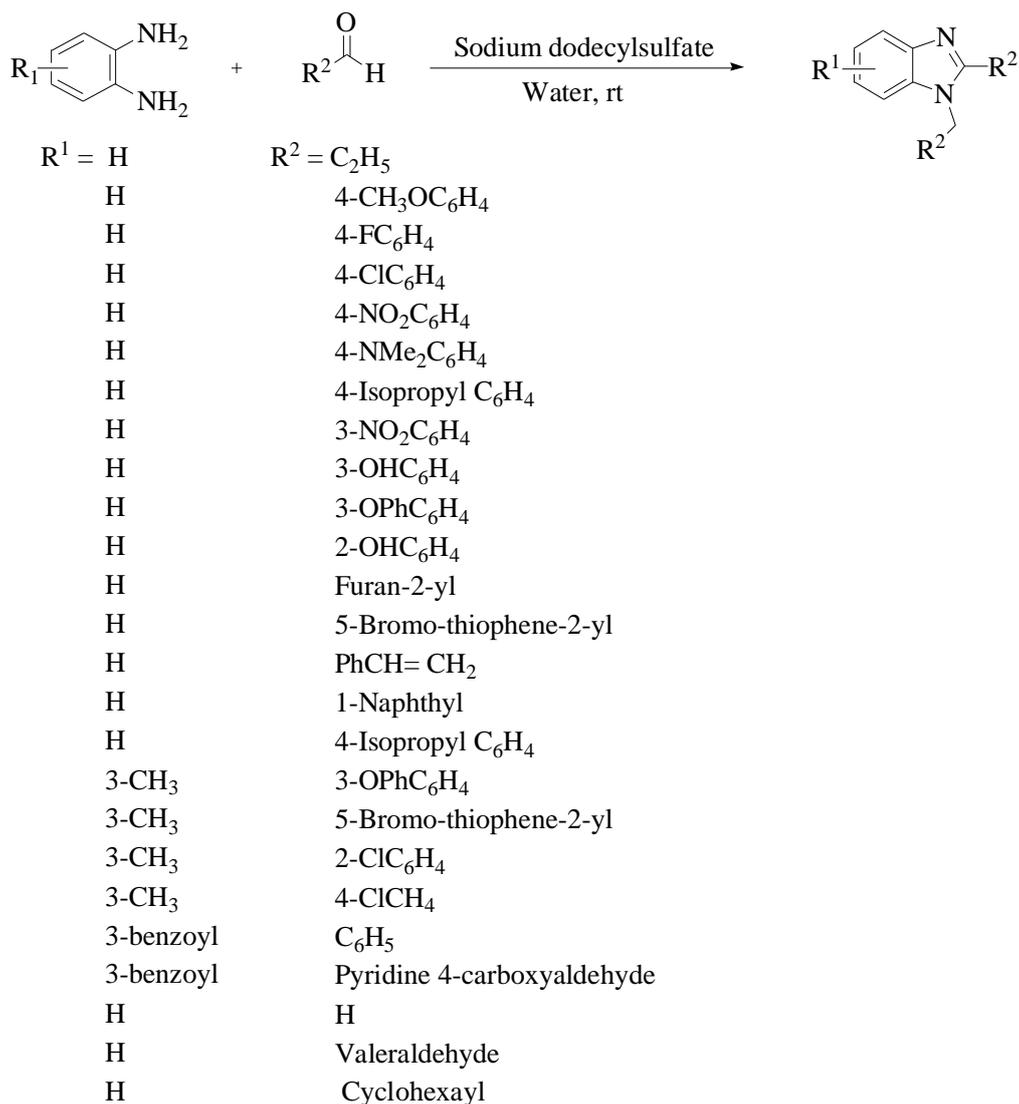
Scheme 24: Sodium dodecyl sulfate catalyzed selective synthesis of 1,2-disubstituted benzimidazoles in water**.**

A plausible mechanism (**Scheme 25**) of the reaction was proposed on the basis of formation of a Schiff base as intermediate which isolated and characterized by NMR spectroscopy. Further, it also observed that the prepared Schiff basewhen subjected to undergo the same reaction under identical condition i.e. at room temperature in presence of SDS in water also yielded the same product in excellent yield. It is then followed by the nucleophilic attack of the catalyst on one of the electrophilic imino carbon. Subsequent cyclisation and 1,3-hydride shift leads to the formation of 1,2- disubstituted benzimidazoles.
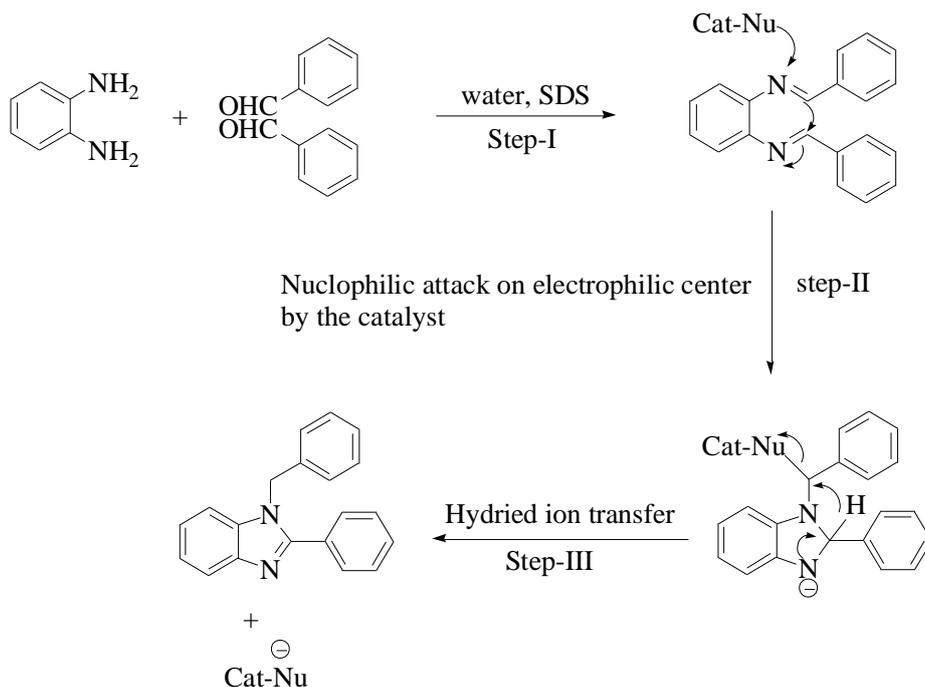
Scheme 25: Plausible mechanism of 1,2-disubstituted benzimidazole formation in water-SDS.

Wan *et al.* [43] reported one-pot reaction involving catalytic procedure for the chemoselective synthesis of 1,2-disubstituted benzimidazoles. The reaction of the substituted aldehydes with *o*-phenylenediamines in water at room temperature by using trimethylsilyl chloride furnished the desired products in excellent selectivity and yields **(Scheme 26)**.

$R_1 = H$	$R_2 = C_2H_5$
H	$4\text{-}CH_3C_6H_4$
H	$4\text{-}CH_3OC_6H_4$
H	$4\text{-}OHC_6H_4$
H	$4\text{-}FC_6H_4$
H	$4\text{-}ClC_6H_4$
H	$4\text{-}BrC_6H_4$
H	$4\text{-}NO_2C_6H_4$
H	$3\text{-}OHC_6H_4$
H	$3\text{-}OHC_6H_4$
H	$2\text{-}OHC_6H_4$
H	$2\text{-}CH_3OC_6H_4$
H	$2\text{-}BrC_6H_4$
H	$2\text{-}ClC_6H_4$
H	furan-2-yl
H	thiophene-2-yl
H	$phCH=CH_2$
$3\text{-}CH_3O$	$4\text{-}CH_3OC_6H_4$
3-benzoyl	H
3-benzoyl	$4\text{-}CH_3OC_6H_4$
3-benzoyl	$4\text{-}ClC_6H_4$
3-benzoyl	furan-2-yl
H	C_2H_5CHO
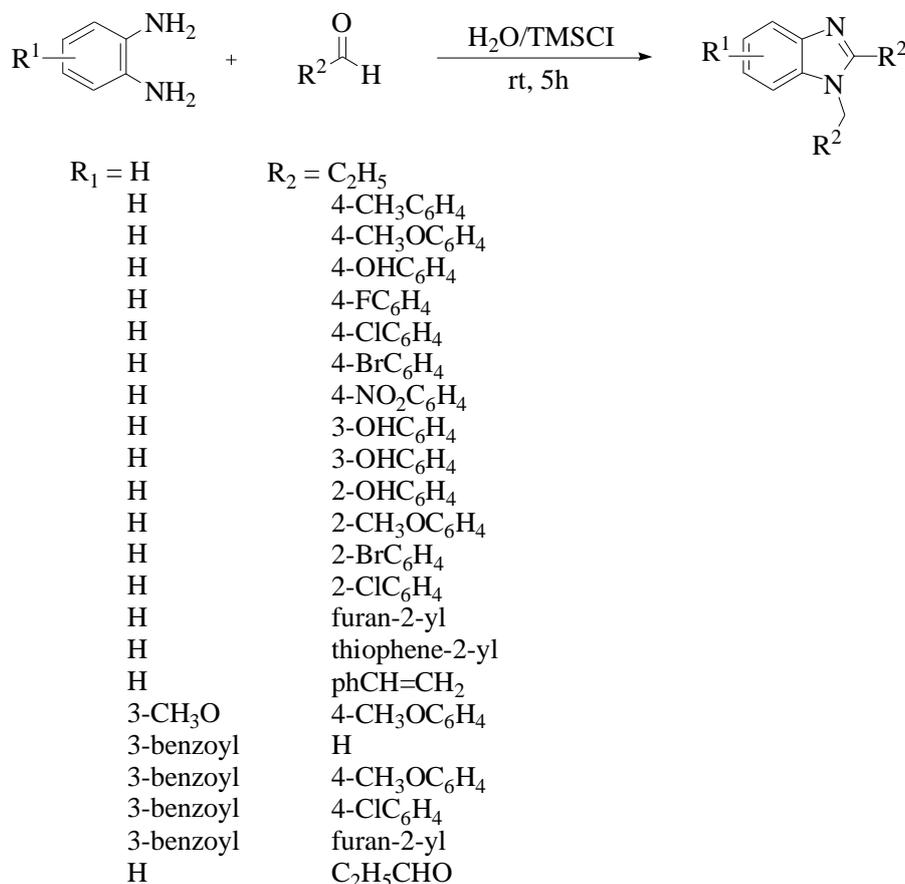
Scheme 26: Water mediated synthesis of 1,2-disubstituted benzimidazoles using trimethylsilyl chloride

To probe the possible mechanism of the reaction forming, the isotope labeling experiment was employed in the reaction of benzaldehyde-d_1 with *o*-phenylenediamine, which demonstrated the 1,3-hydride migration process during the formation of 1,2-disubstituted benzimidazoles **(Scheme 27)**.
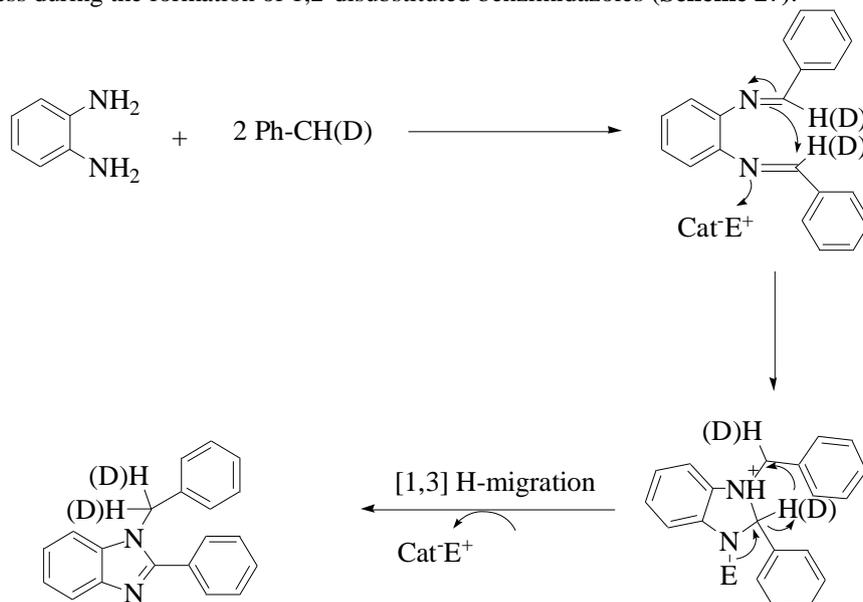
Scheme 27: Plausible mechanism of the reaction furnishing 1,2-disubstituted benzimidazoles.

Ziarani*et al.*[44]described a protocol for a simple and convenient synthesis of 1,2-disubstituted benzimidazoles *via* condensation of 1,2-phenylenediamine and aromatic aldehydes using SBA-Pr-SO$_3$H as a nanoporous solid acid catalyst**(Scheme 28)**.

R = C$_6$H$_5$
4-ClC$_6$H$_4$
4-OCH$_3$C$_6$H$_4$
4-CH$_3$C$_6$H$_4$
4-NO$_2$C$_6$H$_4$
4-N(Me)$_2$C$_6$H$_4$
4-OHC$_6$H$_5$
2-OCH$_3$
3,4-(OCH$_3$)$_2$
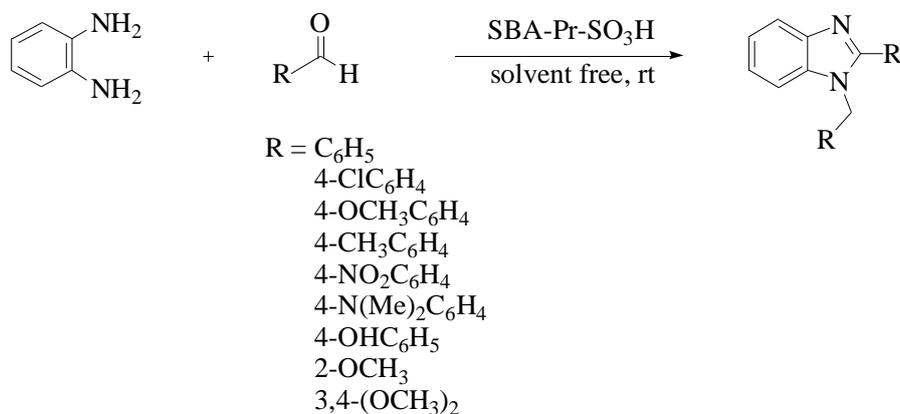
Scheme 28: Synthesis of 1,2-disubstituted benzimidazoles in the presence of SBA-Pr-SO$_3$H.

The suggested mechanism for the SBAPr-SO$_3$H catalyzed formation of 1,2-disubstituted benzimidazolesshown in **(Scheme 29)**. At first, the solid acid catalyst protonates the carbonyl group of aromatic aldehyde which then condense with 1,2-phenylendiamine to produce dibenzylidene-1,2-phenylenediamine. In the presence of catalyst, ring closure produces five membered ring which produced 1,2-disubstituted benzimidazolesby deprotonation and 1,3-hydrid shift.
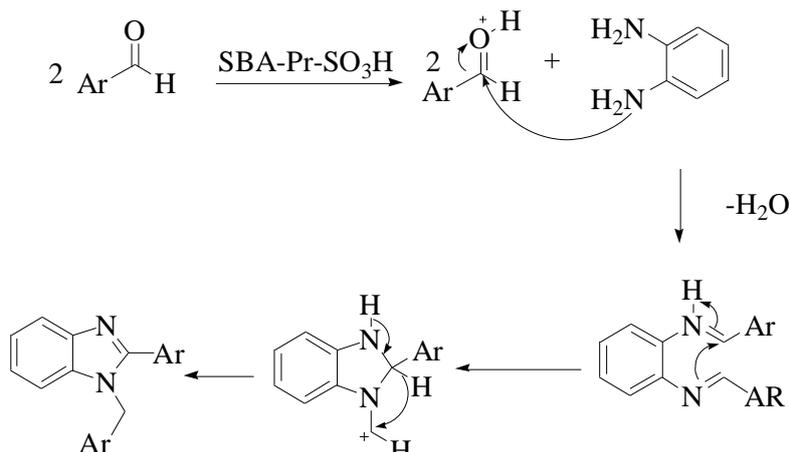
Scheme 29: Proposed mechanism for the synthesis of 1,2-disubstituted benzimidazoles using SBA-Pr-SO$_3$H as a nanoporous solid acid catalyst

The efficiency of SBA-Pr-SO$_3$H was attributed to the nanoporous structure of this solid acid catalyst, which could act as nano-reactor (**Figure 2**).
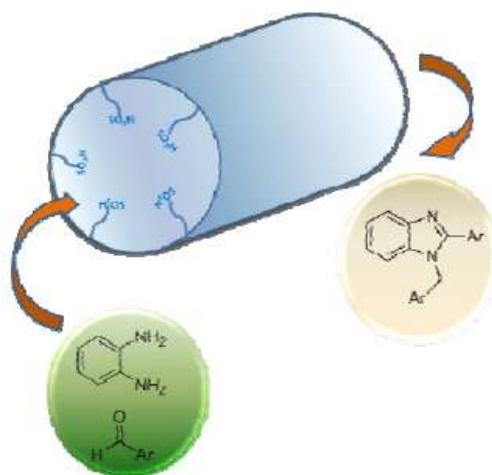
Figure 2:SBA-Pr-SO$_3$H acts as a nano-reactor

Jacob *et al.*[45]described an easy method for the synthesis of several 1,2-disubstituted benzimidazoles using SiO$_2$/ZnCl$_2$ and solvent-free conditions. The method furnished selectively and in good yields the corresponding 1,2-disubstituted benzimidazoles starting from *o*-phenylenediamine and aromatic or aliphatic aldehydes and the reaction could be accelerate using microwaves(**Scheme 30**).

R = C$_6$H$_5$
C$_3$H$_7$
C$_4$H$_9$
3-CH$_3$C$_6$H$_5$
4-CH$_3$OC$_6$H$_5$
2-CH$_3$OC$_6$H$_5$
(E)-C$_6$H$_5$CH=CH
2-Furyl
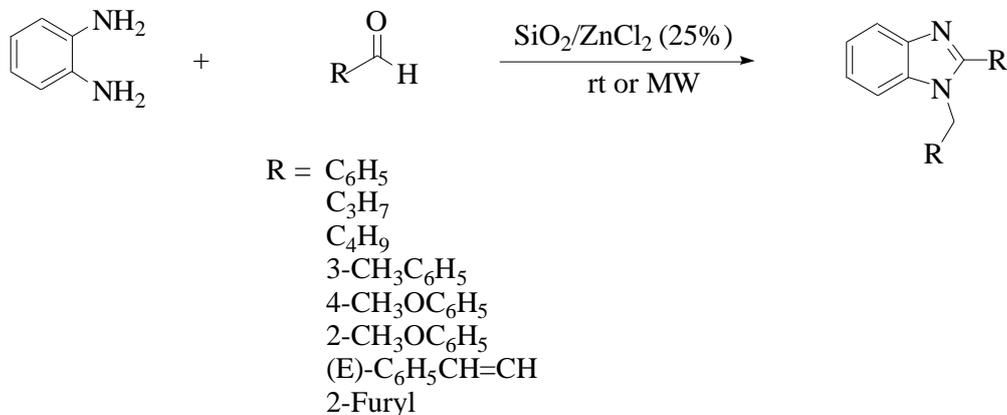
Scheme30: Synthesis of 1,2-disubstituted benzimidazoles using SiO$_2$/ZnCl$_2$

A possible mechanism explained the formation of 1,2-disubstituted benzimidazoles depicted in **(Scheme 31)**. They proved when the reaction in the presence of deuterated solvents such as D_2O and CH_3OD was performed; any amount deuterated benzimidazole was detected.
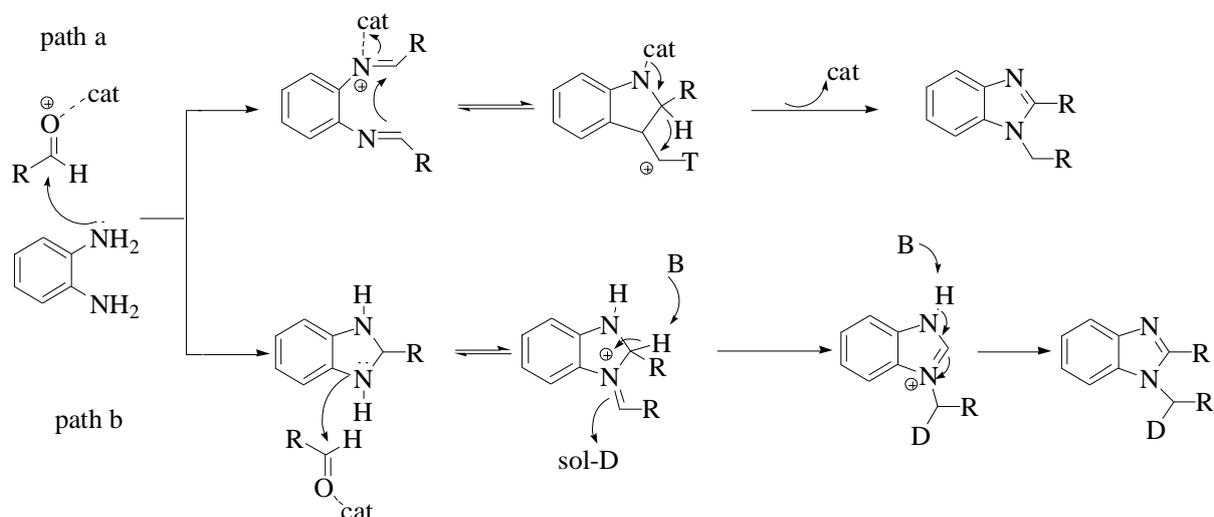
Scheme 31: A possible mechanism explained the formation of 1,2-disubstituted benzimidazoles using $SiO_2/ZnCl_2$.

Behbahani*et al.* [46]reported 1,2-disubstituted benzimidazoles are selectively synthesized in high yields under extremely mild conditions via the condensation of *o*-phenylenediamine derivatives with aldehyde derivatives using catalytic amount of iron(III) phosphate under solvent-free conditions **(Scheme 32)**.

$R^1 = $ H, Me

$R^2 = C_6H_5$
3-MeC$_6$H$_4$
4-MeC$_6$H$_4$
2-MeOC$_6$H$_4$
4-MeOC$_6$H$_4$
3,4-(MeO)$_2$C$_6$H$_3$
3-HOC$_6$H$_4$
4-HOC$_6$H$_4$
2-ClC$_6$H$_4$
3-ClC$_6$H$_4$
4-ClC$_6$H$_4$
3,5-(Cl)$_2$C$_6$H$_3$
3-NO$_2$C$_6$H$_4$
4-NO$_2$C$_6$H$_4$
4-(Me)$_2$NC$_6$H$_4$
C$_6$H$_5$
2-MeOC$_6$H$_4$
4-MeOC$_6$H$_4$
3-HOC$_6$H$_4$
2-Pyridyl
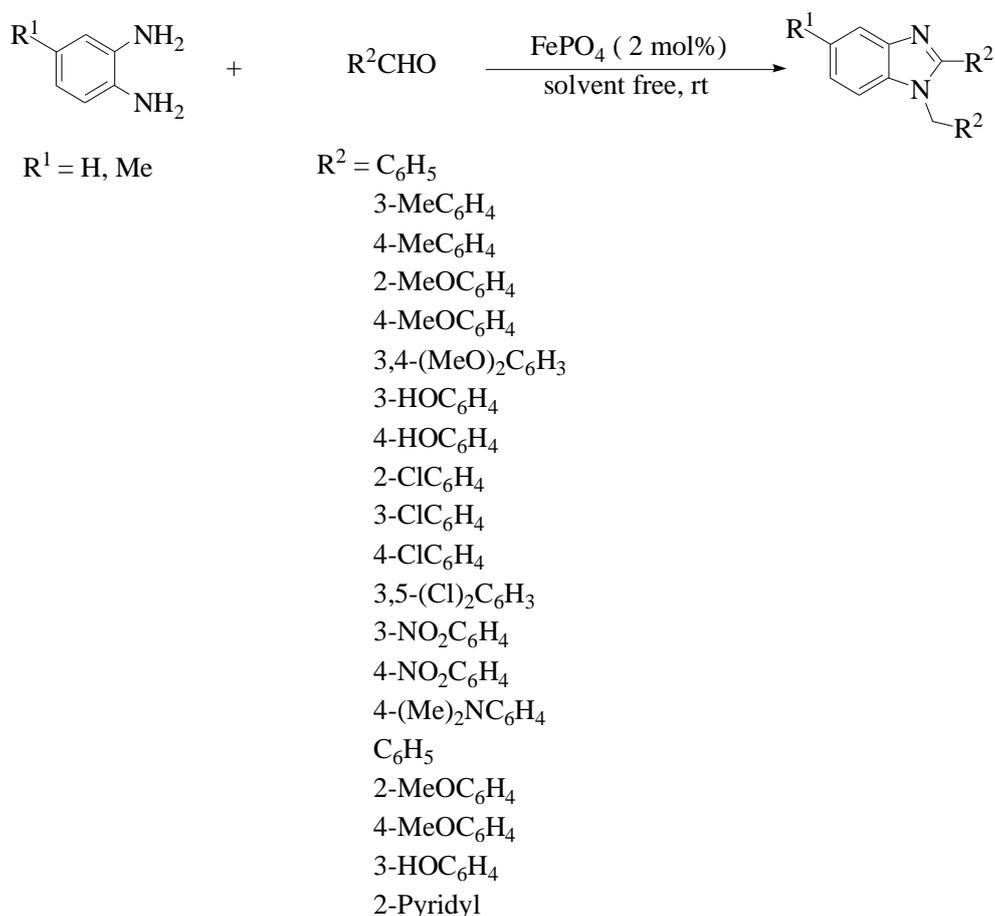
Scheme 32: Synthesis of 1,2-disubstituted benzimidazoles using $FePO_4$.

The suggested mechanism for preparation of 1,2-disubstituted benzimidazole derivatives shown in **(Scheme 33)**. $FePO_4$ activated the aldehydic carbonyl oxygen to form the dibenzylidene-*o*-phenylenediamine and ring closure leading to a five membered ring. Finally, 1,3-hydridetransfer followed to produce 1,2-disubstituted benzimidazoles.
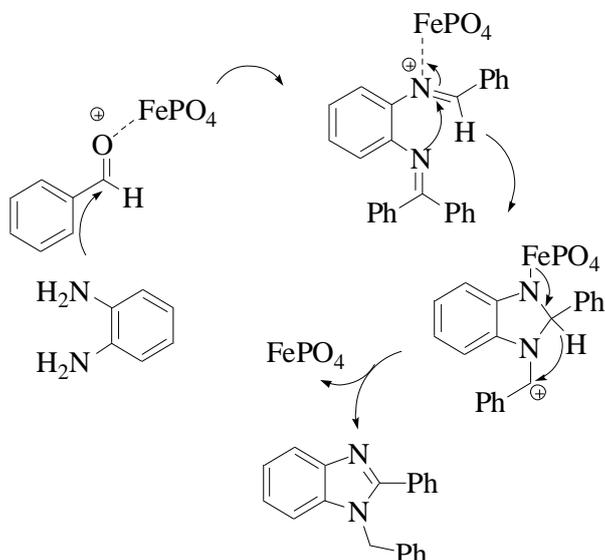
Scheme 33: Suggested mechanism for preparation of 1,2-disubstituted benzimidazoles using $FePO_4$.

Konwar*et al.*[47]described the synthetic protocol allows the formation of 1,2-disubstituted benzimidazoles exclusively under the heterogeneous catalysis of Amberlite IR-120 in aqueous media in excellent yields by the reaction of *o*-phenylenediamines and aldehydes**(Scheme 34)**.

$$Ar = C_6H_5$$
$$4\text{-}MeOC_6H_4$$
$$4\text{-}MeC_6H_4$$
$$4\text{-}ClC_6H_4$$
$$2\text{-}MeOC_6H_4$$
$$2\text{-}ClC_6H_4$$
$$2\text{-}MeOC_6H_4$$
$$3,4\text{-}(MeO)_2C_6H_4$$
$$3\text{-}OH\text{-}4\text{-}MeOC_6H_4$$
$$3\text{-}MeO\text{-}4\text{-}OHC_6H_4$$
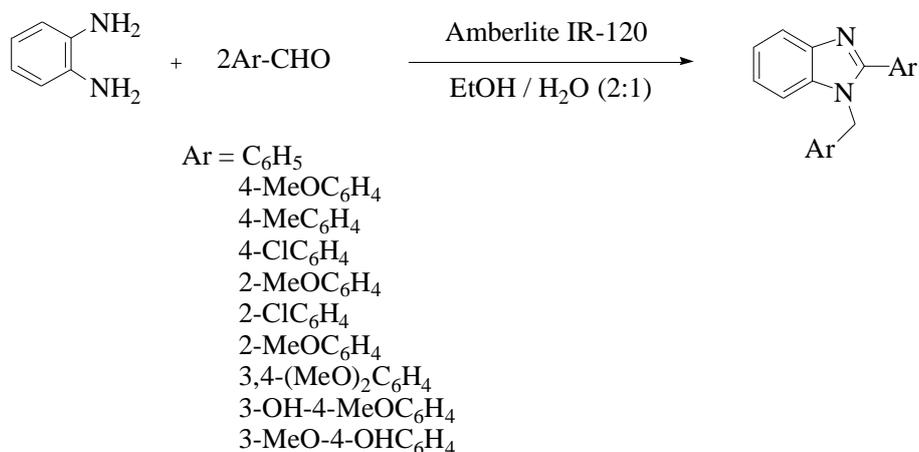
Scheme 34: Synthesis of 1,2-disubstituted benzimidazolesusing Amberlite IR-120 as a reusable heterogeneous catalyst in aqueous media.

Fihri*et al.*[48]reportedthe synthesis of 1,2-disubstituted benzimidazoles in pure water using nanostructured pyrophosphate $Na_2CaP_2O_7$. Their findings showed that this heterogeneous catalyst exhibited high catalytic activity and high selectivity in thesynthesis of 1,2-disubstituted benzimidazoles from direct cyclocondensation of aromatic aldehydes with substituted *o*-diaminoarene in pure water**(Scheme 35)**.
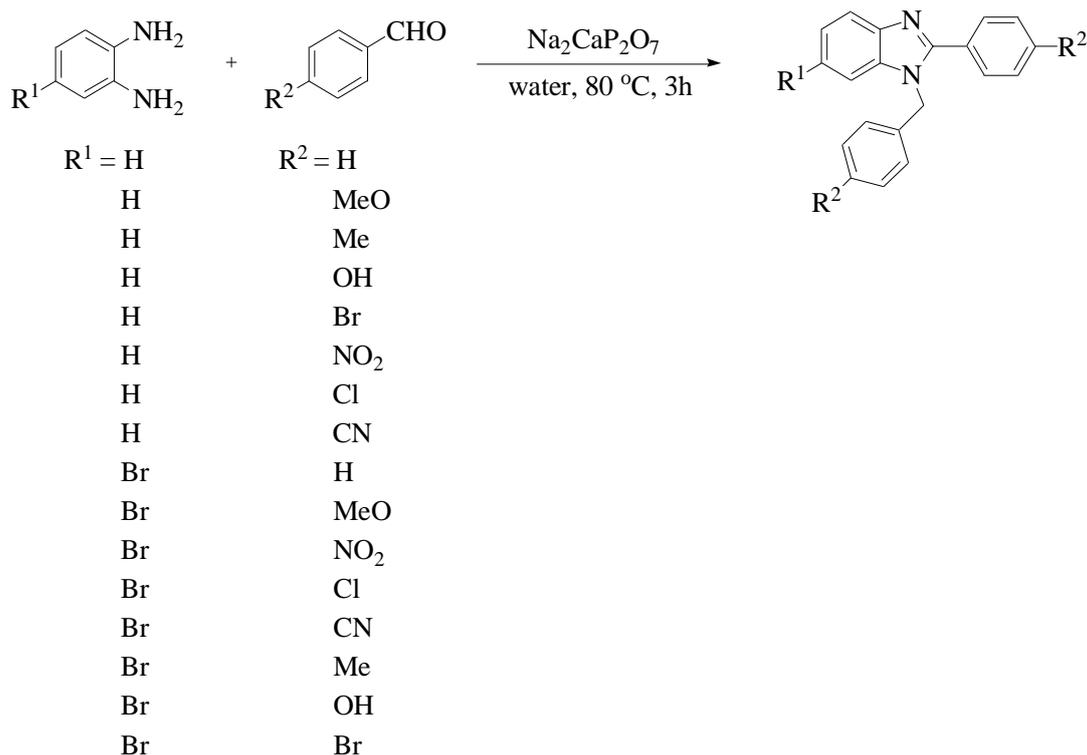
Scheme 35: Nano-structured pyrophosphate $Na_2CaP_2O_7$ as catalyst for selective synthesis of 1, 2-disubstituted benzimidazoles in pure water

The synthesis mechanism of 1,2-disubstituted benzimidazoles formation was mostly based on direct cyclocondensation process; the plausible mechanism for this reaction was proposed in **(Scheme 36)**. Initially, the acidic sites coordinate with the oxygen atom of the aldehyde and facilitate the nucleophilic attack the amino group of benzene-1,2-diamine. This first step produces dibenzylidene-*o*-phenylenediamine (Schiff base) as intermediate. In the presence of electrophilic catalyst, the intramolecular 1,3-hydride migration was induced to directly give the desired 1,2-disubstituted benzimidazole.
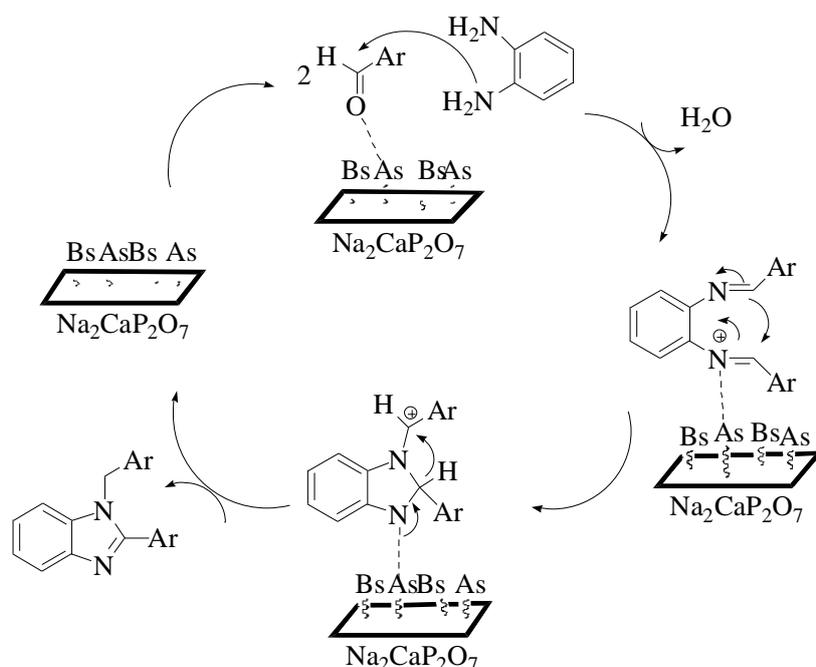
Scheme 36: A proposed pathway for the synthesis of 1,2-disubstituted benzimidazoles using nanostructured pyrophosphate $Na_2CaP_2O_7$ as a catalysis.

Dabiri*et al.*[49]described an environmentally benign method for the rapid and selective synthesis of 1,2-disubstituted benzimidazoles by the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of 1-methylimidazoliumtrifluoroacetate ([Hmim]TFA) at room temperature under aqueous conditions **(Scheme 37)**.

$$R^1 = H \qquad R_2 = C_6H_5$$

$R^1 =$ H

Me

Cl

$R_2 = C_6H_5$

2-ClC$_6$H$_4$

2-MeOC$_6$H$_4$

4-Me$_2$NC$_6$H$_4$

4-ClC$_6$H$_4$

4-MeC$_6$H$_4$

4-MeOC$_6$H$_4$

4-*i*PrC$_6$H$_4$

2-Pyridyl

2-Furyl

4-HOC$_6$H$_4$

4-ClC$_6$H$_4$

4-MeC$_6$H$_4$

4-HOC$_6$H$_4$
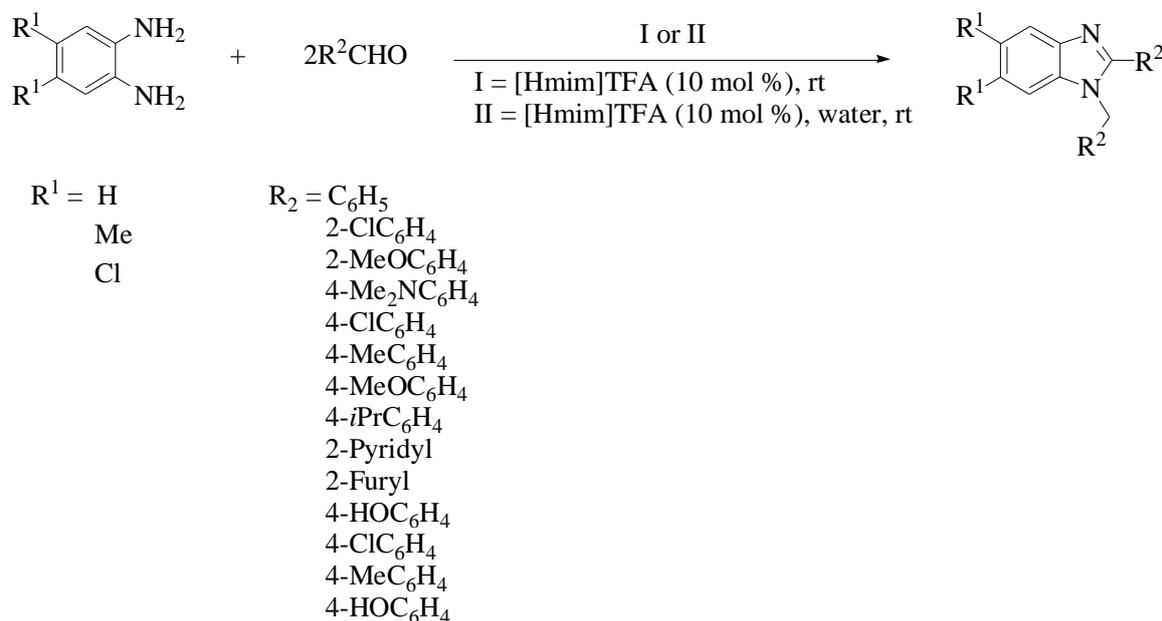
Scheme 37: Water-accelerated selective synthesis of 1,2-disubstituted benzimidazoles at room temperature catalyzed by bronstedacidic ionic liquid.

Basu*et al.*[50]developed an efficient and highly selective procedure for the synthesis of 1,2-disubstituted benzimidazoles via one-step condensation-aromatization reaction of *o*-phenylenediamines with electronically divergent aldehydes under mild conditions promoted over the surface of iron(III)sulfate-silica**(Scheme 38)**.

$R^1 =$	$R^2 =$
H	Ph
H	4-H$_3$OC$_6$H$_4$
H	4-ClC$_6$H$_4$
H	4-Me$_2$NC$_6$H$_4$
H	4-Isopopyl C$_6$H$_4$
H	3-NO$_2$C$_6$H$_4$
H	3-OHC$_6$H$_4$
H	3-OPhC$_6$H$_4$
H	1-Naphthyl
H	Furan^{-2}-yl
H	5-Bromo-thiophene-2-yl
H	2-OHC$_6$H$_4$
3-CH$_3$	5-Br-thiophene-2-yl
3-CH$_3$	2-ClC$_6$H$_4$
3-COPh	Ph
H	Cyclohexyl
H	2-Methylpropyl
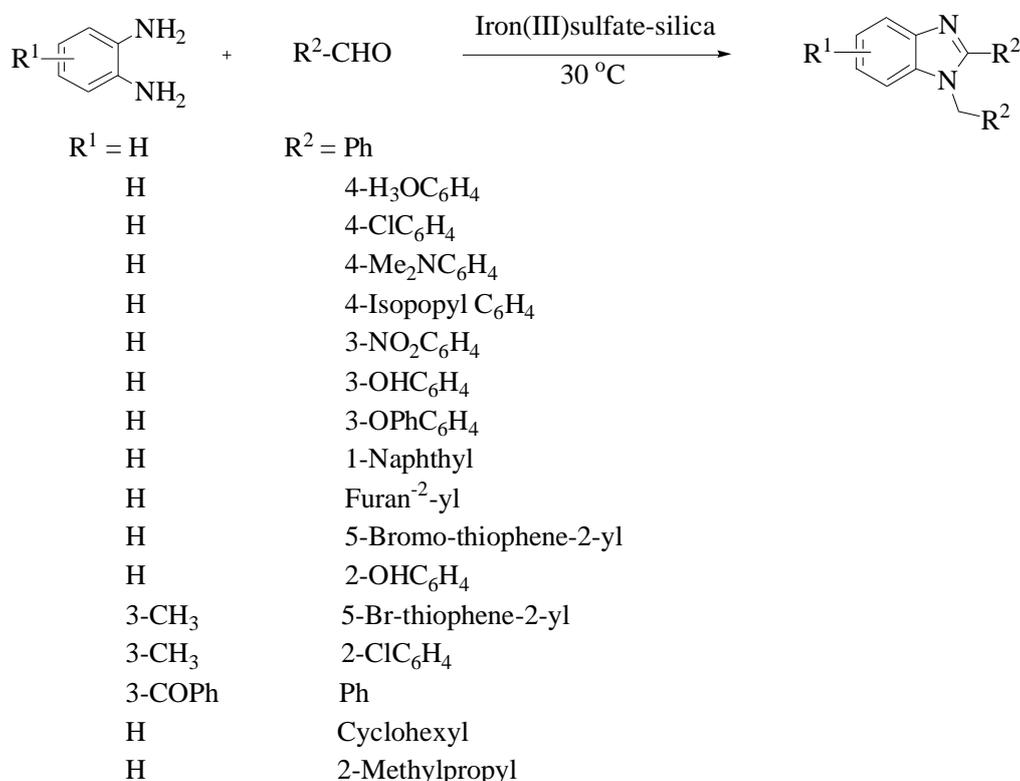
Scheme 38: Selective synthesis of 1,2-disubstituted benzimidazoles using silica gel soaked with ferric sulfate.

Although the exact mechanism was not clear, the Lewis acid-mediated mechanism is expected to play **(Scheme 39)**. Adsorption of iron(III)sulfate on the surface of silica is believed to make bond with the silanol groups in a manner analogous to the formation of OH-bridges in the polynuclear iron(III)hydroxyl complexes. Silica being a water adsorbent could facilitate formation of the bis-Schiff base, which has been reported and indeed was isolated when the reaction was stopped after 20 min. The Schiff base may undergo cyclization followed by 1,3-hydride shift, induced by electrophilic catalyst, resulting in the formation of the 1,2-disubstituted benzimidazole.
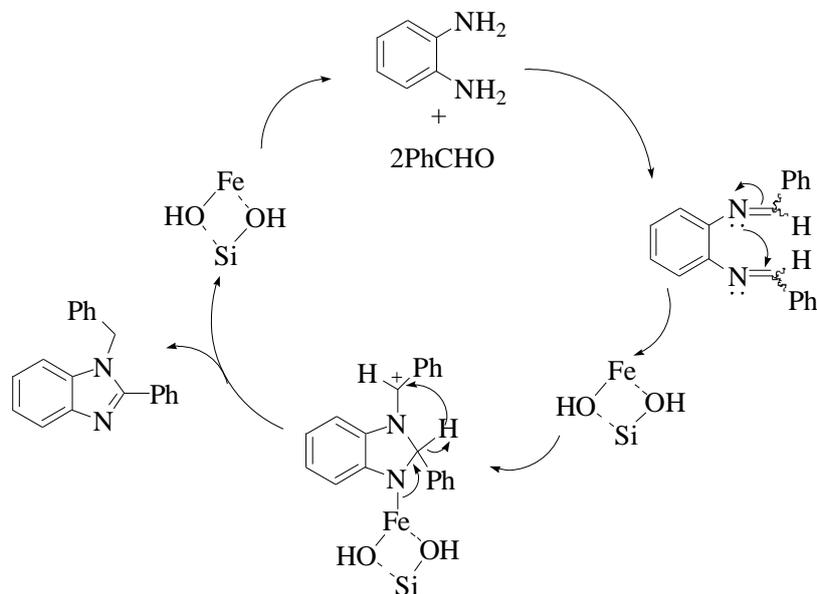
Scheme 39: Plausible mechanism of the reaction furnishing 1,2-disubstituted benzimidazole by using silica gel soaked with ferric sulfate.

Wang *et al.*[51]reported the reactions of *o*-phenylenediamine with aromatic aldehydes gave 1,2-disubstituted benzimidazoles in good to excellent yields under mild reaction conditions by using water as the reaction medium in the presence of 20 mol% $FeCl_3$ **(Scheme 40)**.

R = H
4-Me
4-F
4-Cl
4-Br
4-NO$_2$
4-OMe
2-OMe
3-NO$_2$
2-OH
2-Cl
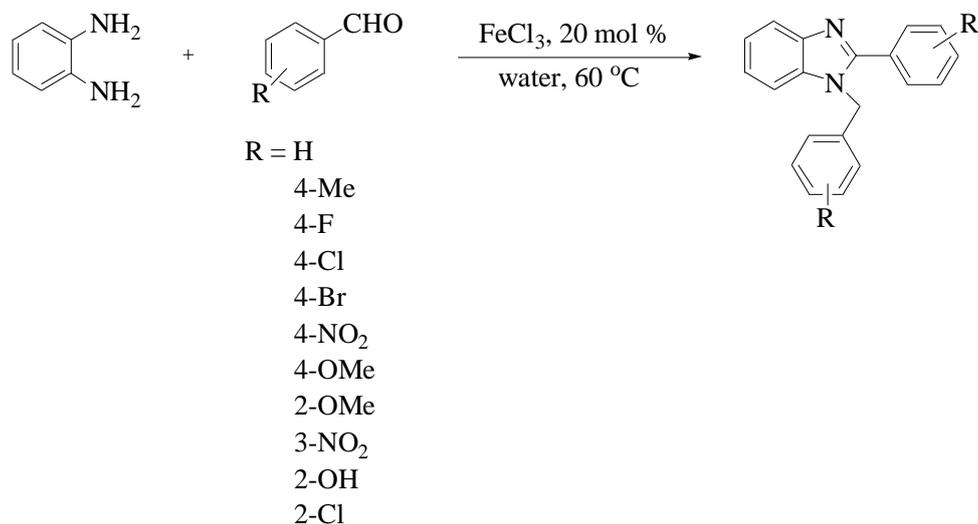
Scheme40: $FeCl_3$catalyzed selective synthesis of 1,2-disubstituted benzimidazoles in water.

Kumar *et al.*[52]reported the one-pot synthesis of 1,2-disubstituted benzimidazoles from *o*-phenylenediamine and aromatic aldehydes in the presence of silica gel supported trichloroacetic acid (SiTCA) and sonicationin aqueous media are environmentally benign, selective and easy to manipulate**(Scheme 41)**.
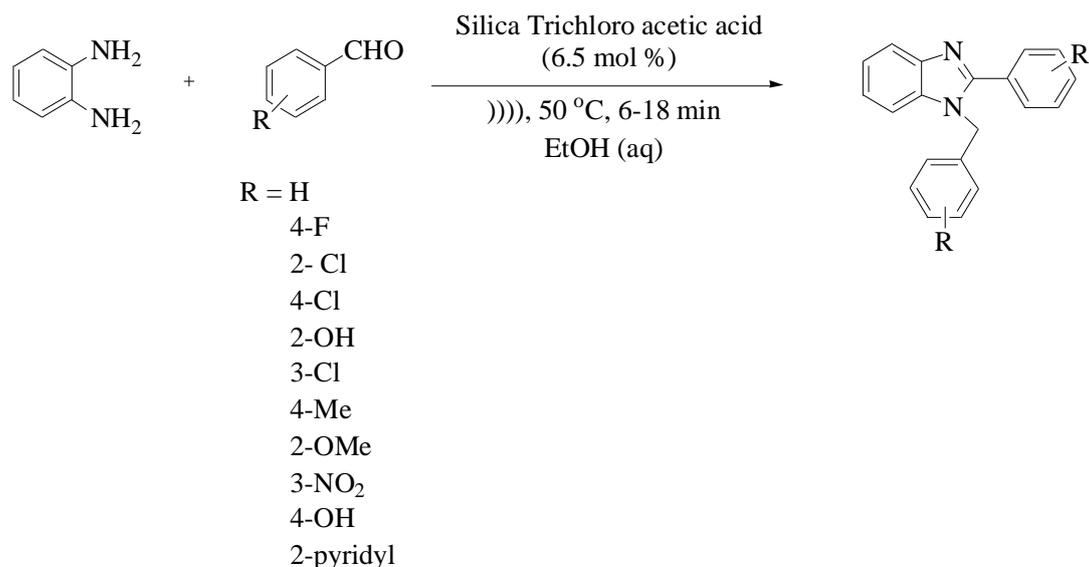
Scheme41: Synthesis of 1,2-disubstituted benzimidazoles using SiTCA and sonication in aqueous media.

The proposed mechanism for SiTCA catalyzed synthesis of 1,2-disubstituted benzimidazoles showed in **(Scheme 42)**. It has suggested, when *o*-phenylenediamine and aromatic aldehydes reacted in the presence of SiTCA, the bis-imine product was obtained. The aldehyde was partially converted to 1,2-disubstituted benzimidazoles with SiTCA within a limited period of time without any formation of monosubstitutedbenzimidazole. When the reaction was sonicated in the presence of SiTCA, the aldehyde was completely consumed and 1,2-disubstituted benzimidazoles was formed exclusively.
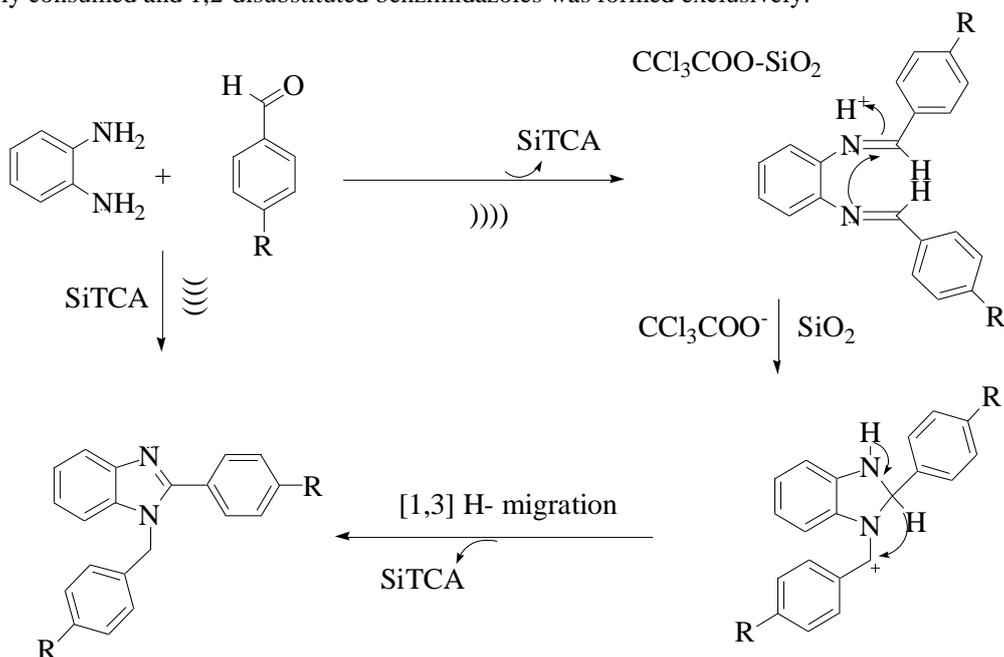
Scheme 42: The proposed mechanism for SiTCA catalyzed 1,2-disubstituted benzimidazole synthesis.

Salehi*et al.*[53]reported a highly selective synthesis of 1,2-disubstituted benzimidazoles from the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of silica sulfuric acid in ethanol or water**(Scheme 43)**.

R^1 ⟨NH$_2$, NH$_2$⟩ + R^2-CHO $\xrightarrow[\text{Solvent, rt}]{\text{Silica sulfuric acid}}$ R^1 ⟨N, N-R^2, R^2⟩

R_1 = H	R_2 = C_6H_5
H	4-MeOC_6H_4
H	4-MeC_6H_4
H	4-ClC_6H_4
H	2-MeOC_6H_4
H	2-ClC_6H_4
H	2-Furyl
H	$4\text{-Me}_2NC_6H_4$
H	4-iPrC_6H_4
H	2-Pyridyl
CH_3	4-ClC_6H_4
CH_3	4-MeC_6H_4
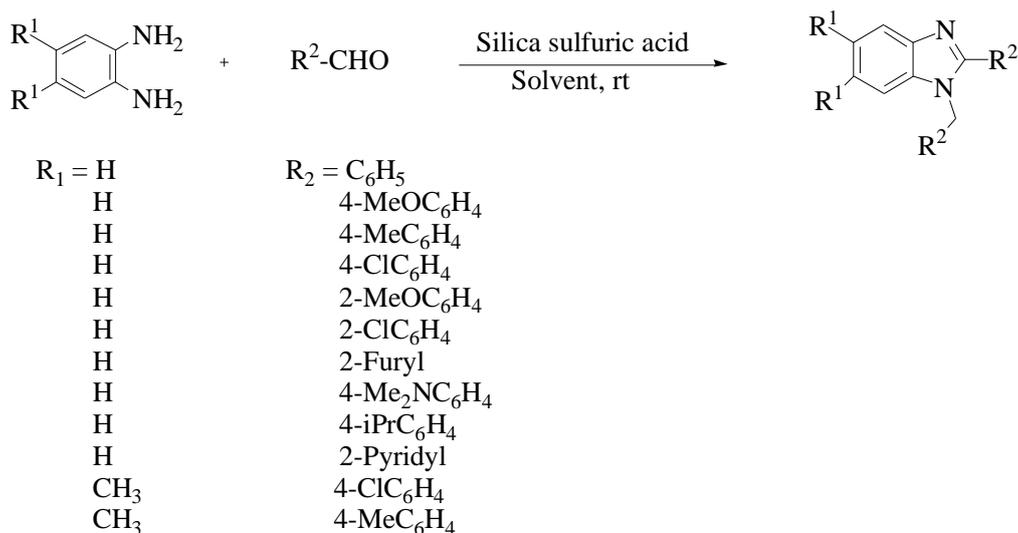
Scheme 43: Selective synthesis of 1,2-disubstituted benzimidazoles in the presence of silica sulfuric acid.

It was described, 1,2-disubstituted benzimidazolesmay be produced through a tandem sequence of reactions starting with the formation of dibenzylidene-*o*-phenylenediamine followed by ring closure. Finally, aromatisation took place via deprotonation and 1,3-hydride transfer.

Bandyopadhyay*et al.*[54]developed a simple, efficient and environmentally benign method for the selective synthesis of 1,2-disubstituted benzimidazoles by using mesoporous mixed metal oxide nanocrystalsof Al_2O_3-Fe_2O_3, Al_2O_3-V_2O_5 and Al_2O_3-CuO having high surface area and high catalytic activity**(Scheme 44)**.In addition, the solvent-free microwave assisted synthesis of these compounds was an advantageous way which resulted in excellent yields in much lesser time in comparison to conventional heating.

⟨NH$_2$, NH$_2$⟩ + 2R-CHO $\xrightarrow[\substack{\text{Thermal heating / MW} \\ \text{solvent or solvent-free}}]{\text{Mixed metal oxide nanocatalyst}}$ ⟨N, N-R, R⟩

R = C_6H_5
4-MeC_6H_4
4-MeOC_6H_4
$4\text{-(Me)}_2NC_6H_4$
$4\text{-(Me)}_3CC_6H_4$
3-EtO-4-HOC_6H_3
4-FC_6H_4
5-Br-2-HOC_6H_3
$3\text{-NO}_2C_6H_4$
$4\text{-F}_3COC_6H_4$
$3,4\text{-Cl}_2C_6H_3$
Furyl
$C_6H_5CH=CH$
$CH_3\text{-}CH_2\text{-}CH_2$
$CH_3\text{-}(CH_2)_4\text{-}CH_2$
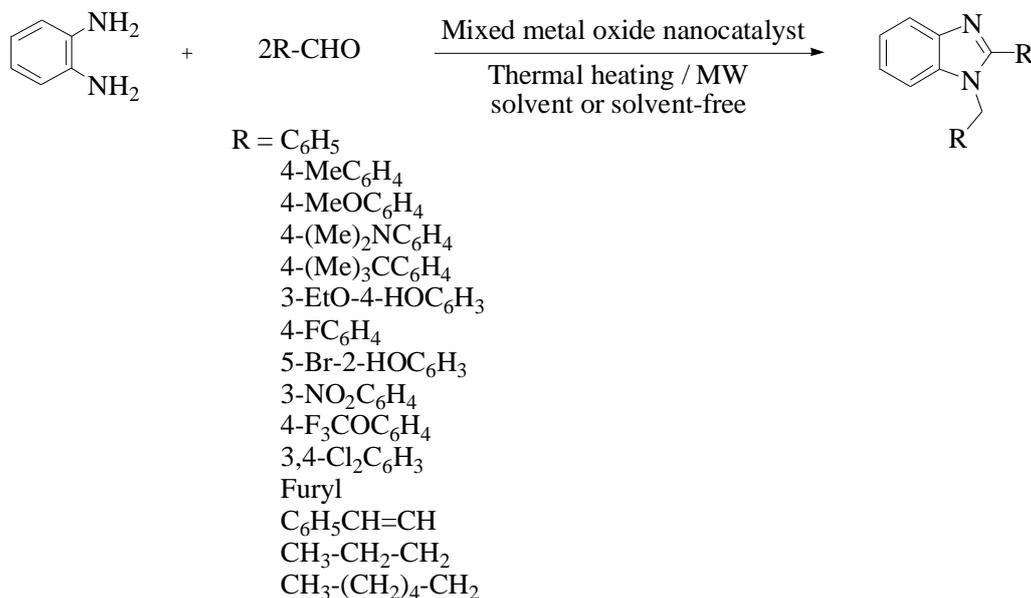
Scheme 44: Synthesis of 1,2-disubstituted benzimidazoles using mixed metal oxide nanocatalysts.

The proposed mechanistic path for the formation of 1,2-disubstituted benzimidazoles is presented in **(Scheme 45)**. The used metal oxides species contains Lewis acid sites and Bronsted acid sites in addition to basic surface sites. These acidic sites react with carbonyl oxygen of aldehyde by forming surface bound hydrogen bonded species. Surface of nanocrystallineAl_2O_3 was found to be basic in nature. Further addition of transition metal oxides would increase the number of Lewis acid sites, Bronsted acid sites and basic sites thereby increasing the reactivity of metal oxides as catalyst.
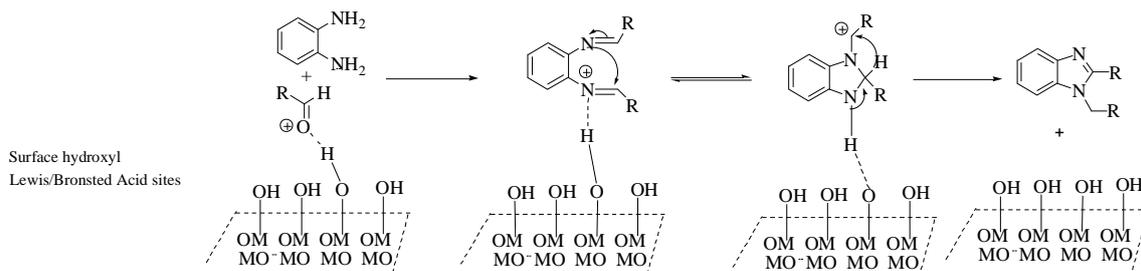
Scheme 45: Proposed mechanism for the synthesis of 1,2-disubstituted benzimidazoles using mixed metal oxide nanocatalysts.

Beheshtiha*et al.*[55]developed an efficient and green synthesis of 1,2-disubstituted benzimidazole from the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of Bronsted acid ionic liquid, 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate $[(CH_2)_4SO_3HMIM][HSO_4]$ (BAIL), in water at ambient temperature **(Scheme 46)**.

R = C_6H_5
  p-MeC_6H_4
  p-$MeOC_6H_4$
  p-$O_2NC_6H_4$
  p-ClC_6H_4
  o-$MeOC_6H_4$
  o-ClC_6H_4
  2-Furyl
  2-Pyridil
  p-$iPrC_6H_4$
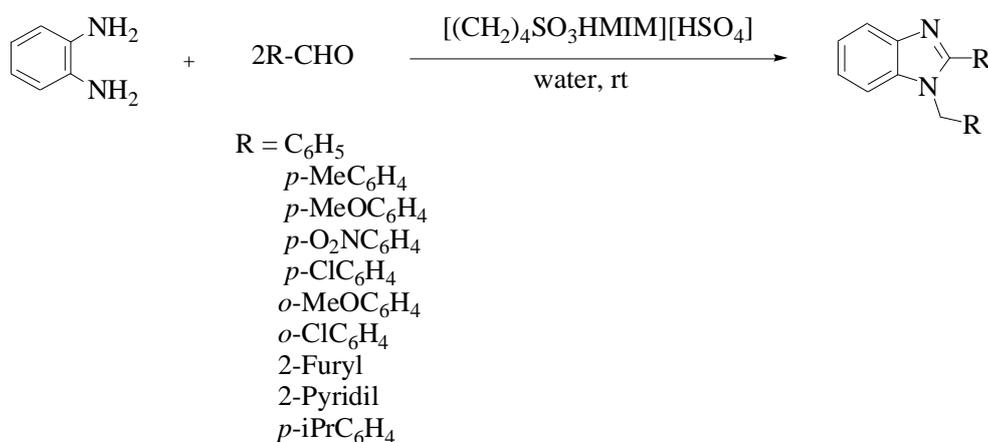
Scheme46: BAIL-catalyzed selective synthesis of 1,2-disubstituted benzimidazoles in water at room temperature.

Tahanpesar*et al.*[56]prepared and usedhighly-surface area Co_3O_4nanoparticles as a solid acid catalyst in the synthesis of 1,2-benzimidazole fromreaction of 1,2-phenylenediamine with aldehydes under solvent-free conditions at 80°C**(Scheme 47)**. The method offered the advantages of high yields and short reaction times and avoids the use of toxic organic solvents. Furthermore, the catalyst is inexpensive and can be readily recovered and reused without any significant loss of activity.

R = 4-OMe
  4-Me
  4-Cl
  4-N(Me)$_2$
  4-NO_2
  4-CN
  2-OH
  2-Cl
  naphthalene-2-yl
  H, 2-furyl
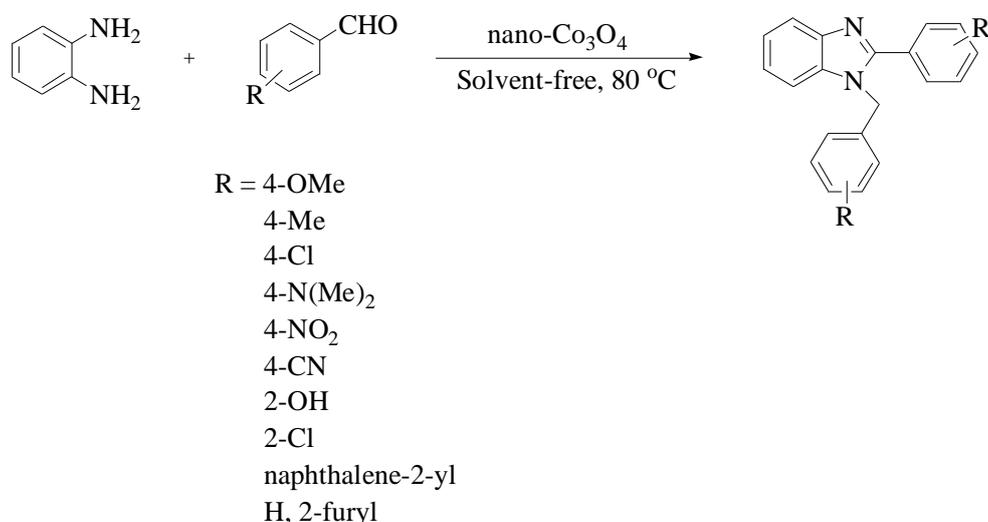
Scheme47: Synthesis of 1,2-disubstituted benzimidazoles using nano-Co_3O_4 as a solid acid catalyst under solvent-free conditions.

Scheme 48presented the proposed mechanism of formation of 1,2-disubstituted benzimidazoles. In the first step, the carbonyl group is activated due to the coordination of the Lewis acid site of nano-Co_3O_4 and then, 1,2-phenylenediamine attacks the carbonyl group of the activated aldehyde and produces a Schiff base intermediate via the elimination of H_2O. The subsequent tandem intramolecular cyclization followed by 1,3-hydride shift provides the target 1,2-disubstituted benzimidazoles.
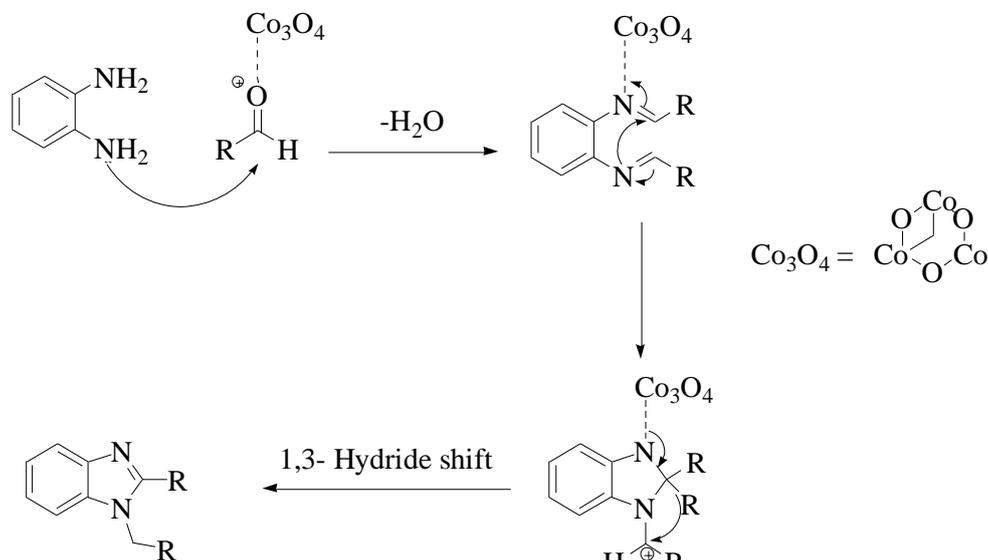
Scheme 48: Proposed mechanism of the nano-Co_3O_4-catalyzed synthesis of 1,2-disubstituted benzimidazoles.

Reddy*et al.*[57]used Montmorillonite K-10 supported lanthanum triflateLa(OTf)$_3$ as an efficient catalyst for the synthesis of 1,2-disubstituted benzimidazolesfromthe reaction of 1,2-phenylenediamine with aldehydes under conventional heating conditions **(Scheme 49)**.

$R^1 = H$	$R^2 = H$
H	2- OH
H	4- CH_3
H	4-OC_2H_5
H	3-OC_2H_5-4-OH
4-Cl	H
4-Cl	2-OH
4-Cl	4-CH_3
4-Cl	4-OC_2H_5
4-Cl	3-OC_2H_5-4-OH
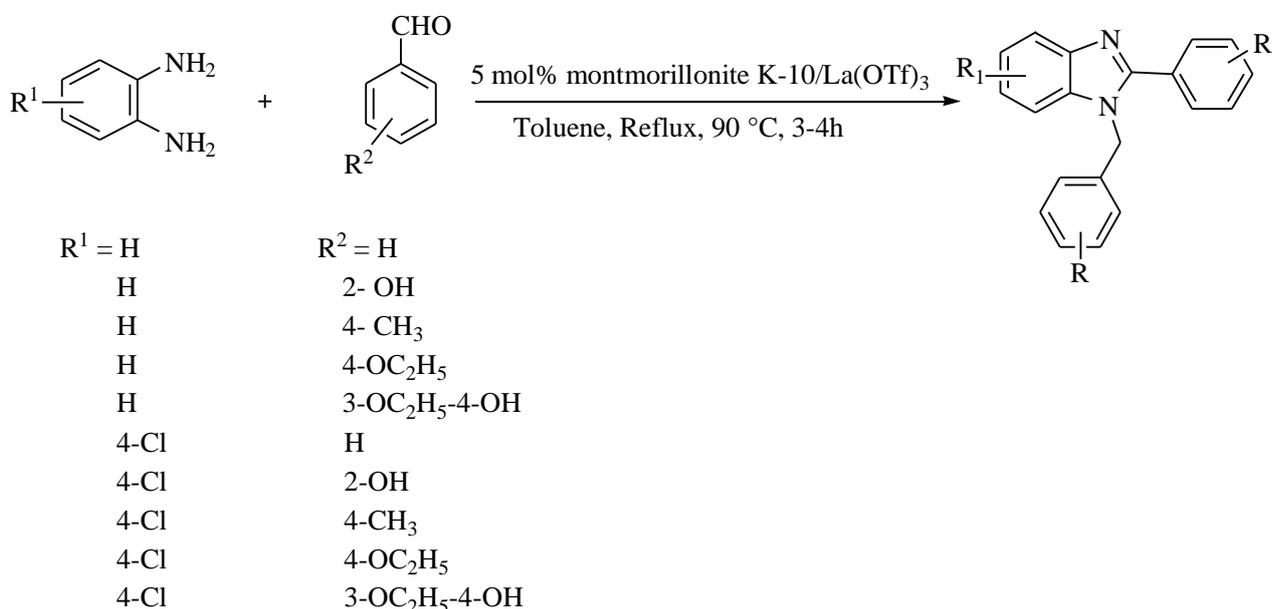
Scheme 49: Montmorillonite K-10 supported La(OTf)$_3$ catalyzed synthesis of 1,2-disubstituted benzimidazoles.

The plausible mechanism for montmorillonite K-10/La(OTf)$_3$mediated synthesis of 1,2-disubstituted benzimidazoles showed in (Scheme50), and reported the binding of $Al^{+3}$and Si^{+4}cations with triflate groups that will creates more positive charge on La^{+3} ions. Then these La^{+3} ions easily interact with aldehydes to promote the reaction with *o*-phenylenediamine *via* nucleophilic addition and cyclization steps to form the product in high yields.
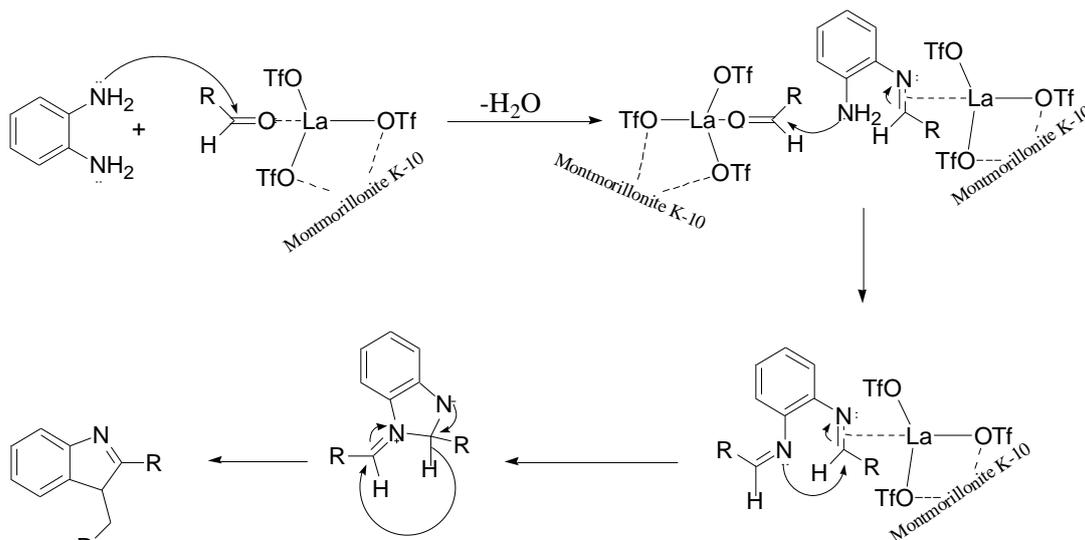
Scheme50: Plausible mechanism for montmorillonite K-10/La(OTf)$_3$ mediated synthesis of 1,2-disubstituted benzimidazoles.

Samanta*et al.*[58] reported the condensation of diamine with aldehyde in the presence of ytterbium loaded mesoporous silica nanoparticles. Catalyst was found to be solvent selective, generating 1,2- disubstituted benzimidazoles in water/ethanol medium (2:1) (**Scheme 51**).

R = C$_6$H$_5$
    4-Me
    4-MeOC$_6$H$_4$
    4-BrC$_6$H$_4$
    4-ClC$_6$H$_4$
    4-OHC$_6$H$_4$
    3-NO$_2$C$_6$H$_4$
    3-N(CH$_3$)$_2$C$_6$H$_4$
    2-OH
    2-MeO
    2-pyridyl
    3-pyridyl
    2-thiopyl
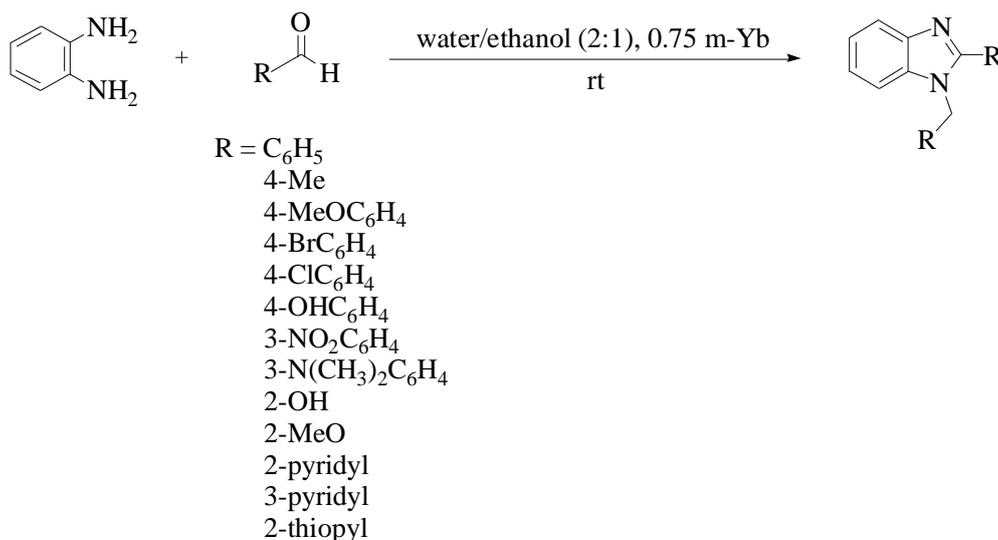
Scheme 51: Mesoporous silica supported ytterbium catalyzed synthesis of 1,2- disubstituted benzimidazoles.

In the mechanismthey suggested the higher polarity and hydrogen bonding ability ofethanol/water mixture facilitate it to act as effective electrophilic co- activating agents for bisimine formation and stabilizes bisimine through formation of hydrogen bonding. 1,2- Disubstituted benzimidazoles formed by intramolecularnucleophilic attack in bisiminefollowed by a 1,3- hydride shift(**Scheme 52**).
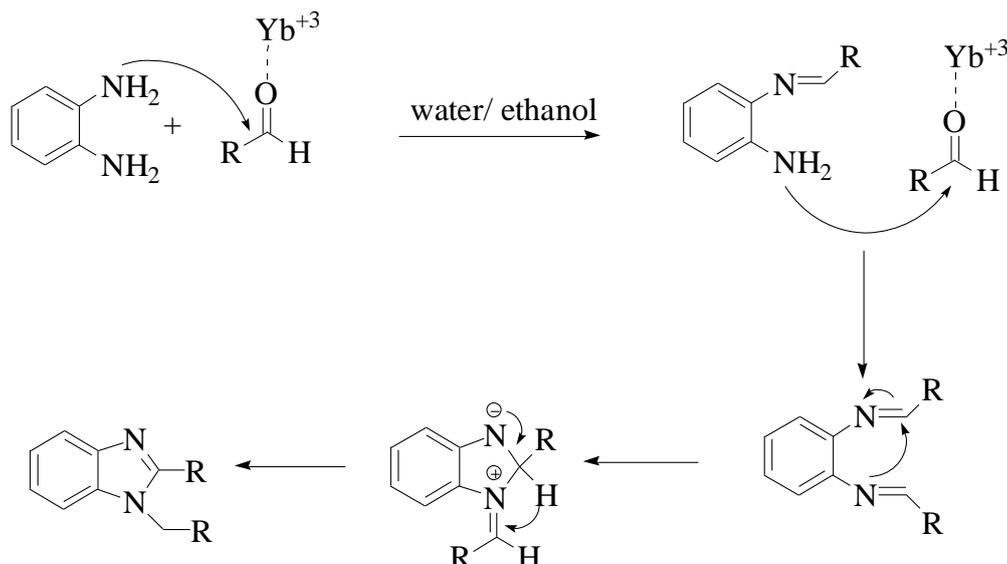
Scheme 52: Mechanism for formation of 1,2- disubstituted benzimidazole using mesoporous silica supported ytterbium as catalyst.

Kumarraja*et al.*[59]reported a simple procedure for the selective synthesis of 1,2-disubstituted benzimidazoles from 1,2-phenylenediamine and aromatic aldehydes with high chemoselectivity, shorter reaction time and functional groups tolerance. The procedure promoted by the prepared highly ordered nanoporousaluminosilicate (MMZY) zeolite **(Scheme 53)**. Moreover the solid acid MMZ_Y zeolite is an inexpensive, reusable, non-toxic and environmentally benign.

R = H
o-OH
p-Cl
p-F
p-NO$_2$
p-CH$_3$
p-O-CH$_3$
p-iPr
furyl
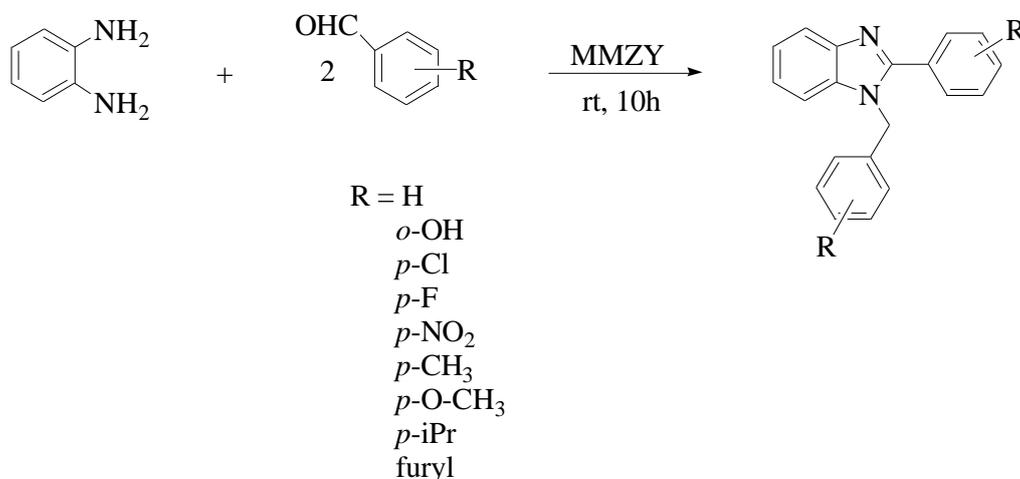
Scheme53: Chemoselective synthesis of 1,2-disubstituted benzimidazoles using nanoporousaluminosilicate (MMZY) zeolite

It has suggested the reaction supported the proposed mechanistic pathway[31,43] which involves the presence of acidic sites in MMZY facilitating the formation of bisimine followed by cyclization and 1,3-hydride shift followed by deprotonation leading to the selective formation of the 1,2- disubstituted benzimidazole. The chemoselectivity of MMZY was attributed to its nanomorphic structure within zeolite pore walls which facilitate the improved diffusion of more number of reactant molecules, leading to significant enhancement in catalytic activity.

Durgareddy*et al.*[60] reported the one pot synthesis of 1,2 disubstituted benzimidazoles by the reaction of aliphatic, aromatic and hetero aromatic aldehyde with *o*-phenylenediamine using a water soluble Cu(NO$_3$)$_2$.3H$_2$O catalyst at room/ambient temperature in excellent yield **(Scheme 54)**.

R = C_6H_5
4-MeO
4-NO_2
4-ClC_6H_4
3⁻ MeO-4-OH
4-$N(CH_3)_2$
2-OH
4-OH
propyl
2-pyridyl
2-furyl
C_2H_5
C_3H_7
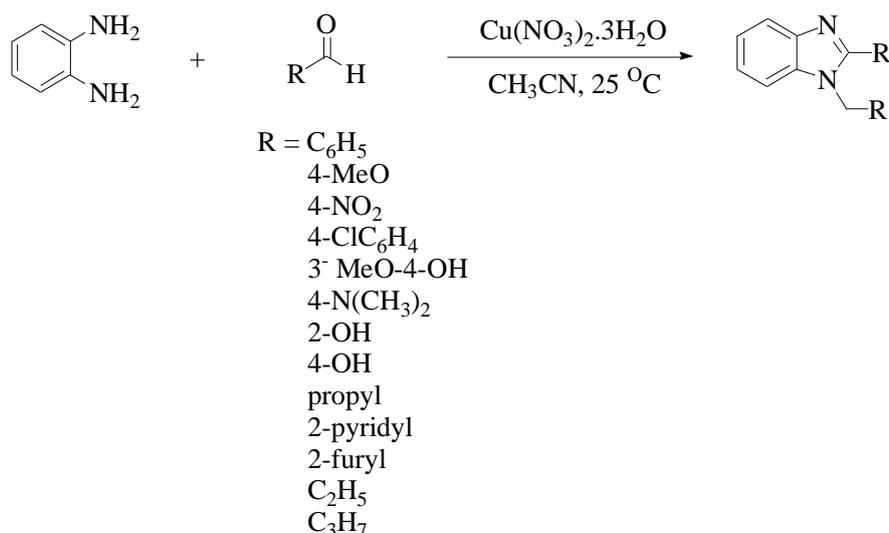
Scheme 54: Synthesis of 1,2 disubstituted benzimidazoles catalyzed by $Cu(NO_3)_2.3H_2O$ in CH_3CN at room temperature

The suggested mechanism for the condensation reaction of *o*-phenylenediamine and aldehydes catalyzed by $Cu(NO_3)_2.3H_2O$ shown in **(Scheme 55)**.
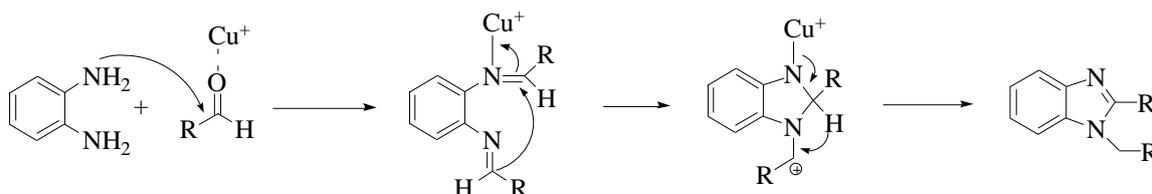
Scheme 55: Suggested mechanism for preparation of 1,2-disubstituted benzimidazoles using $Cu(NO_3)_2.3H_2O$

II. Conclusion

1,2-Disubstituted benzimidazole moiety showed promising application in biological and clinical studies. The synthesis of the 1,2-disubstituted benzimidazoles has attracted wide attention due to their useful biological and pharmacological properties. Many synthetic strategies reported for the construction of 1,2-disubstituted benzimidazole. The direct condensation of *o*-phenylenediamines with aldehydes under oxidative conditions appears to be a straightforward approach and it has been extensively used. However, the cyclocondensation between *o*-phenylenediamine and aldehyde has a potential selectivity problem due to the possibility of competitive formation of the 1,2-disubstituted and the 2-substituted benzimidazoles**.** Therefore, search for new methods or catalysts to overcome the issue of selectivity during the condensation of *o*-phenylenediamines with aldehydes are still an important experimental challenge to attract the attention of researchers. This review presented the efficient and economical methods to selective synthesis of 1,2-disubstituted benzimidazoles from the condensation of *o*-phenylenediamines with aldehyde in the presence of various conditions during the last few years.

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