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Samuthirarajan Senthilkumar, Mayilvasagam Kumarraja

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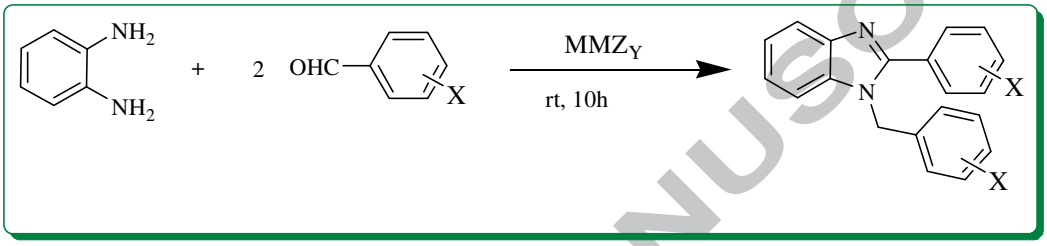
Samuthirarajan Senthilkumar & Mayilvasagam Kumarraja*

Centre for Research and Post-graduate Studies in Chemistry,

Ayya Nadar Janaki Ammal College (Autonomous), Sivakasi – 626 124, Tamilnadu, India.

GRAPHICAL ABSTRACT



Where, X= H, *o*-OH, *p*-Cl, *p*-F, *p*-NO_2, *p*-CH_3, *p*-OCH_3, *p*-^{i}Pr and furyl.

Abstract - A highly ordered nanoporous aluminosilicate (MMZ_Y) is prepared and employed as a catalyst for the synthesis of benzimidazoles from 1,2-diaminobenzene and aromatic aldehydes. In all the cases, the reactions are highly chemoselective and afford 1,2-disubstituted benzimidazoles in excellent yield. The catalyst was characterized by electron microscopy and X-ray methods and its other advantages like functional tolerance, mildness of the reaction conditions, easy separation and reusability are also highlighted.

Keywords: Nanoporous zeolite; chemoselectivity; 1,2-disubstituted benzimidazole; solid acid; bisimine; o-phenylenediamine; aromatic aldehyde.

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In medicinal chemistry, the benzimidazole scaffold acts as an important class of heterocyclic compounds that shows a wide range of biological properties[1] such as anesthetic, antipyretic, antiulcer, antihypertensive, anticancer and antiviral activities,[2] including non-nucleoside inhibitors of HIV-1 reverse transcriptase and NS5B polymerase of the hepatitis C virus(HCV).[3] Recently it is reported that benzimidazole derivatives are also used for the treatment of diseases like hypertension and obesity.[4] Though many reports are available for the syntheses of 2-substituted benzimidazoles,[5] only very few reports are available for the selective synthesis of 1,2-disubstituted benzimidazoles. The classical methods for the synthesis of 1,2-disubstituted benzimidazoles normally involve (i) N-alkylation/arylation of benzimidazole in the presence of a strong base/transition metal ions[6] (ii) cyclocondensation of N- substituted *o*-aminoanilides[7] (iii) Suzuki coupling of 2-halo-1-arylbenzimidazole with arylboronic acids.[8] However, the straightforward synthesis of 1,2-disubstituted benzimidazole from *o*-phenylenediamine with an aldehyde is still in demand due to its easy approach and can be applied to a variety of substituents in the benzimidazole scaffold. Synthesis of disubstituted benzimidazole include the use of catalysts such as TFE/ HFIP,[6] montmorillonite K-10,[9] CuI/L-proline,[10] TMSCl,[11] amberlite IR–120,[12] $SiO_2/ZnCl_2$,[13] Dowex- 50W,[14] SDS micelles,[15]

*Corresponding author: Phone: +91-9443570835; Fax: +91-4562 254970

E-mail address: dr.kumarraja@gmail.com

AcOH/O_2,[16] $SbCl_3/Al_2O_3$,[17] silica sulfuric acid,[18] $FePO_4$,[19] CAN,[20] $Cu(NO_3)_2.3H_2O$[21] and $FeCl_3/Al_2O_3$.[22] But in many cases, the reaction shows poor selectivity in terms of N-1 substitution, which results in the formation of a mixture of 1,2-disubstituted and 2-substituted benzimidazoles. In addition, most of the described procedures suffer from the disadvantages such as use of expensive catalysts, hazardous solvents, tedious work-up, longer reaction time and functional intolerance. As a consequence, search for new methods or catalysts to overcome these limitations are still an important experimental challenge to synthetic organic chemists.

In recent years, hierarchical nanoporous materials[23] have been receiving a great attention due to its multidisciplinary field of study,[24] drug delivery,[25] gas separation and hydrocarbon cracking,[26] *etc.;* However, the catalytic applications of nanoporous materials in fine chemical synthesis are very few in number. We have already successfully explored the catalytic efficiency of zeolite as a mesoporous material,[27] microporous material for shape selectivity,[28] solid acid catalyst[29] and source of metal ions[30] for various organic transformations. In continuation of our interest in studying the catalytic applications of zeolites, herein we investigate the use of zeolite as a hierarchical nanoporous material for the synthesis of benzimidazoles by the condensation of 1,2-phenylenediamine with aromatic aldehydes in a simple experimental procedure and the results are discussed below.

In order to study the feasibility of cyclocondensation reaction in zeolite framework, *o*-phenylenediamine**(1)** and benzaldehyde**(2)** were added to three different kinds of Y-type faujasite zeolites namely NaY, HY and MMZ_Y for the synthesis of 1,2-disubstituted benzimidazoles. These three zeolites differ mainly in their acidity and pore size. Generally NaY of high purity contains no detectable acidity. Upon removal of ammonia by calcination of ammonium ion-exchanged Y-zeolite, HY is obtained generating Bronsted acidic sites.[31] In the

preparation of MMZ_Y from HY under basic conditions, the initially formed nanounits are assembled into highly ordered hierarchically nanoporous architecture. It is noteworthy that the preparation of nanoporous zeolite and its characterization have been well demonstrated in previous reports.[32, 33]

The catalytic activities of these three different zeolites are studied and the observed results are presented in Table 1. In the absence of zeolite, the reaction afforded only 1-*H*-2-substituted benzimidazole(**4**) in less than 5% yield, even after a very long time of stirring the solution. However in presence of NaY, the reaction between 1,2-phenylenediamine and benzaldehyde yielded a mixture of **(3)** and **(4)** benzimidazoles (entry 2).

In contrast to NaY, the reaction is sensitive to Bronsted acidity as evident from that HY catalyzed reaction produces the 1,2-disubstituted benzimidazole (**3**) but also with the significant amount of 1-*H*-2-arylbenzimidazole(**4**) (entry 3). When the same reaction is carried out in presence of MMZ_Y zeolite, we have obtained chemoselectively, an excellent amount of 1,2-disubstituted benzimidazole at the expense of **4**. We have also examined the recycling of the catalyst to see its efficiency which afforded the same yield even after two times usage.

To check the functional tolerance of MMZ_Y zeolite, we have employed substituted benzaldehydes to synthesize 1,2-disubstituted benzimidazole derivatives **3a- i** (Table 2). The reaction proceeds faster and also there is not much difference in yield with substituted benzaldehydes containing electron releasing as well as electron withdrawing groups as evident from the entries 1-8, Table 2. However, the reaction involving salicylaldehyde (entry 9) led to the unexpected formation of Schiff base product (bisimine) under the present experimental conditions. Bisimine was isolated and confirmed by NMR. The unexpected formation of

bisimine may be due to the presence of intramolecular hydrogen bonding which prevents the further cyclization of bisimine intermediate to yield the final product.[11] However, when heating the same reaction at 80 °C, it produced the expected product by breaking the energy barrier. This reaction also supports the proposed mechanistic pathway[6,11] which involves the presence of acidic sites in MMZ_Y facilitating (i) the formation of bisimine followed by cyclization and (ii) 1,3-hydride shift followed by deprotonation leading to the selective formation of the 1,2-disubstituted benzimidazole. The chemoselectivity of MMZ_Y may be 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. Moreover the presence of increased surface area and acidic sites[33] promotes the catalytic conversion of *o*-phenylenediamine and aldehydes selectively into 1,2-disubstituted benzimidazoles in excellent yield. The morphology of the as prepared hierarchical MMZ_Y zeolite was characterized by Powder XRD, SEM and TEM methods, which clearly demonstrate the uniform formation of pore structure and particles about 1μm (See Fig. 1 & 2 in supporting data).

Thus the present study offers a simple procedure for the selective synthesis of 1,2-disubstituted benzimidazoles promoted by an inexpensive, reusable, non-toxic and environmentally benign solid acid MMZ_Y zeolite. The other advantages of this procedure are high chemoselectivity, shorter reaction time and functional groups tolerance. Further works are now in progress to explore the scope of the catalyst for other organic synthesis.

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Supporting Data

Supplementary data associated with this article can be found in the online version.

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34. *General procedure for the synthesis of 1,2-disubstituted benzimidazole derivatives using Nanoporous zeolite:*100mg of nanoporous material from zeolite HY (designated as MMZ_Y) was taken in a silica crucible and activated in a muffle furnace at 450 ^oC for 6 hours. A mixture of *o*-phenylenediamine(1mmol) and aldehyde(2mmol) were added to the reaction tube which contains acetonitrile (3ml) and 100mg of freshly activated MMZ_Y. The reaction mixture was stirred for 10h at room temperature. The proceeding

of the reactions was constantly monitored by TLC carried out on silica plates with iodine and UV light for visualization. Column chromatography was performed on silica gel 60-120 mesh with a mixture of petether and ethylacetate (80:20) solvent as eluent.

The products were isolated and characterized by the IR Spectra recorded on a Shimadzu 8004S model FT-IR using KBr pellets and the ^{1}H NMR and ^{13}C NMR, were obtained on Bruker NMR(300MHz) instrument in $CDCl_3$ and DMSO. The melting point of solid products were determined and also compared with the literature report.

1-Benzyl-2-phenyl-1*H*-1,3-benzimidazole (3a): mp = 130 °C (lit.[6] 130 – 132 °C); IR (KBr) γ_{max} = 3031, 2923, 1602, 1581, 1490, 1278, 1155, 1114, 1027cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 1H) ; 7.53 – 7.49 (m, 2H) ; 7.47 – 7.42(m, 3H); 7.29 – 7.21 (m, 6H); 7.0 (dd, 2H); 5.58 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 155.01, 142.9, 136.25, 135.9, 129.91, 129.81, 129.15, 128.93, 128.63, 127.98, 127.65, 125.84, 122.94, 122.59, 119.85, 110.43, 48.23.

Bisimine from salicylaldehyde:

2,2'-(1,2-phenylenebis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)diphenol:

mp:161 °C (lit.[11] mp 160 – 162 °C); IR (KBr) γ_{max} = 3317, 2923, 1614, 1479, 1336, 1276, 1191; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.15 (s, OH); 8.63 (s, NH); 7.38 (s, 2H); 7.35 (s,2H); 7.33-7.31 (m, 2H); 7.25-7.20 (m, 2H); 7.05 (s, 1H); 7.03 (s, 1H); 6.94-6.88 (m, 2H); ^{13}C NMR ($CDCl_3$) 163.74, 161.35, 142.55, 133.30, 132.26, 127.57, 119.76, 119.21, 118.88, 117.50.

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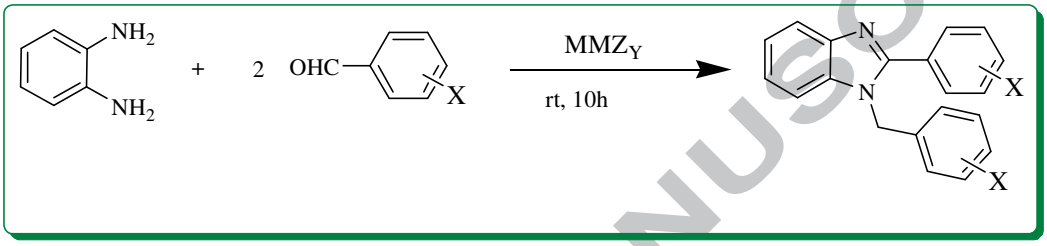

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