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# Eco-friendly synthesis of benzimidazole derivatives using solid acid scolecite catalyst

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## Abstract

A series of benzimidazole derivatives were synthesized expeditiously in good yields by condensation of 1,2-diaminobenzene and aromatic aldehydes in the presence of modified scolecite catalyst. The world wide availability, easy handling and reusability of catalyst, higher yields and shorter reaction times are the advantages of the present method.

*Keywords:* Benzimidazole; Ethanol; Natural zeolite–scolecite

Benzimidazole and their derivatives display a wide range of biological properties, and they have commercial applications in various realms of therapy, including ulcerative, anti-hypertensive, antiviral, antibacterial, anti-tumor, antihistaminic and antihelminthic agents in veterinary medicine [1]. Benzimidazole derivatives exhibit significant activity against several viruses such as HIV [2,3], influenza [4] and human cytomegalovirus (HCMV) [2], it also act as topoisomerase inhibitors [5], selective neuropeptide YY1 receptor antagonists [6], angiotensin II inhibitors [7], smooth muscle cell proliferation inhibitors [8] and have much more importance in organic synthesis.

As a result of their importance from industrial, pharmacological and synthetic point of view, several synthetic routes of benzimidazoles have been reported, which includes the condensation of 1,2-diaminobenzene and aldehydes [9,10], the condensation of 1,2-diaminobenzene and carboxylic acids or their derivatives in the presence of acids such as polyphosphoric acid [11] or mineral acids [12], boric acid [13], p-toluene sulphonic acid [14], cerric ammonium nitrate [15] as a catalyst.

Few recent protocols reported for the synthesis of benzimidazole derivatives include solvent-free synthesis of benzimidazoles under microwave-irradiation using Yb(OTf)$_3$ [16], KSF clay [17], PPA [18] $Na_2SO_4$ [19], metal halide supported alumina [20] and solid support [21]. As many of these processes have limitations, such as use of some toxic acids as a catalyst, drastic reaction conditions, low yields, high temperature, tedious workup procedures, there is need to develop new route for the synthesis of benzimidazole derivatives to overcome these limitations.

In the recent years, the use of heterogeneous catalysts has received considerable interest in various disciplines including organic synthesis. Synthetic organic routes followed by using heterogeneous catalysts have advantages over their counterparts in which, used-catalyst can be easily recycled.

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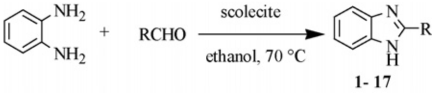

Scheme 1.

Since last decade, there has been increased improvement in the synthetic methodology due to the use of solid acid catalysts, such as clays and zeolites [22–24]. Zeolite catalyst has a Bronsted and Lewis acidic sites, which are responsible for their reactivity. An extensive application of heterogeneous catalysts in synthetic organic chemistry can make the synthetic process more efficient from both environmental and economic point of view [25].

We have previously reported the use of scolecite as a solid acid catalyst for the synthesis of 3,4-dihydropyrimidones, 2,4,5-triarylimidazoles and polyhydroquinoline [26]. Herein, we report the synthesis of benzimidazole derivatives by the condensation of 1,2-diaminobenzene and substituted aldehydes in ethanol using modified scolecite as a catalyst (Scheme 1).

## 1. Experimental

All the reagents and aromatic aldehydes were obtained from S.D. Fine-Chem. Ltd. (Mumbai) and were used as such. Melting points were determined in open capillaries apparatus and are uncorrected. The reactions were monitored by TLC and visualized with UV light. IR spectra were recorded on a matrix of KBr with FTIR-4100 (Jasco, Japan) spectrometer. $^1$H NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus (200 MHz) and the chemical shifts are given in ppm relative to TMS as an internal standard.

The naturally occurring scolecite zeolite is a calcium zeolite with NAT topology and an ordered (Si:Al) distribution. The chemical compositions of natural scolecite (atom %) were Si, Al, Fe, Na, Ca and O in the ratio 16.03, 10.34, 0.03, 0.20, 7.05, 66.34 respectively. It was collected from the Ellora valley, Aurangabad (MS), Deccan traps of India. It was subsequently washed with distilled water and acetone for several times, dried and crushed into fine powder which was further washed with distilled water 3–4 times and dried at 110 °C in an oven. The resulting sample was heated at 500 °C in high temperature muffle furnace for 1 h at rate 3 °C per minute. The sample was naturally cooled and used in organic synthesis. The surface area, pore volume, pore diameter of the catalyst was determined by the nitrogen adsorption on Quantachrome Autosorb Instrument and Acidity of the sample measured by temperature programmed desorption (TPD) of ammonia on Quantachrome TPR.

Aldehydes (0.5 mmol) and 1,2-diaminobenzene (0.5 mmol) were thoroughly mixed in ethanol (5 mL) then scolecite (3 wt% with respective initial concentration of reactants) was added, and the solution was refluxed for appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the resulting solid was collected by filtration and dissolved in 20 mL ethyl acetate. The catalyst was recovered by filtration and the solution was washed with NaOH (5%, w/w). After evaporation of the solvent, the resulting solid product was recrystallized from ethanol to obtain pure product.

*Spectral data of typical compounds*

2-(3-*Chlorophenyl*)*benzimidazole* (**5**): $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.18–7.22 (m, 2H), 7.52–7.59 (m, 4H), 8.11 (dd, 1H), 8.20 (s, 1H), 13.01 (s, 1H): IR (KBr, cm$^{-1}$): 1618 (C=N), 3458 (NH). *m/z* 229 (M+H)$^+$.

2-(4-*Methylphenyl*)*benzimidazole* (**11**): $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 2.37 (s, 3H), 7.19 (d, 2H), 7.34–7.39 (m, 2H), 7.45–7.50 (m, 1H), 7.60–7.63 (m, 1H), 8.06 (d, 2H), 12.80 (s, 1H): IR (KBr, cm$^{-1}$): 1622 (C=N), 3432 (NH). *m/z* 209 (M+H)$^+$.

## 2. Results and discussion

The cumulative desorption surface area of catalyst from adsorption–desorption isotherm of nitrogen ($S_{\mathrm{BJH}} = 26.39$ m$^2$/g), pore volume at $p/p_o = 0.993$ ($P_V = 0.0344$ cm$^3$/g) and pore diameter ($P_d = 11.08$ Å) was determined by BJH method. Temperature programmed desorption (TPD) method was used to determine the acidic properties of solid catalyst. This provides information about the total concentration and strength of acidic sites (Bronsted and Lewis). It was found that the total ammonia desorbed is 0.376 mmol/g of the catalyst.

In order to find the optimum reaction conditions for eco-friendly synthesis of benzimidazole derivatives, we have selected model reaction by refluxing 1:1 molar ratio of 1,2-diaminobenzene and 4-chlorobenzaldehyde in presence of

Table 1
Effect of catalyst quantity in the synthesis of 2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole.

| Weight of catalyst (%) | Time (min) | Yield (%)[a] |
|---|---|---|
| No catalyst | 60 | 29 |
| 1 | 60 | 71 |
| 2 | 60 | 82 |
| 3 | 60 | 94 |
| 4 | 60 | 94 |

[a] Yield refer to isolated products.

Table 2
Scolecite catalyzed synthesis of benzimidazole derivatives.

| Entry | R | Time (min) | Yield (%)[a,b] | M.P. (°C) Found | reported |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | 55 | 89 | 292–293 | 290–293 [27] |
| 2 | $2\text{-}NO_2C_6H_4$ | 60 | 92 | 261–263 | 264–265 [27] |
| 3 | $2\text{-}ClC_6H_4$ | 55 | 93 | 234–235 | 234 [28] |
| 4 | $4\text{-}ClC_6H_4$ | 60 | 94 | 291–292 | 288–291 [14] |
| 5 | $3\text{-}ClC_6H_4$ | 65 | 85 | 236–238 | 238 [28] |
| 6 | $2\text{-}OCH_3C_6H_4$ | 55 | 90 | 179–180 | 179–180 [29] |
| 7 | $3\text{-}OCH_3C_6H_4$ | 70 | 87 | 205–206 | 205 [29] |
| 8 | $4\text{-}NO_2C_6H_4$ | 45 | 91 | >300 | 322–323 [27] |
| 9 | $3\text{-}NO_2C_6H_4$ | 75 | 79 | 204–205 | 204–206 [30] |
| 10 | $2\text{-}BrC_6H_4$ | 50 | 86 | 247–248 | 246 [28] |
| 11 | $4\text{-}CH_3C_6H_4$ | 65 | 87 | 263–265 | 264–265 [27] |
| 12 | $C_6H_5CH{=}CH$ | 60 | 84 | 200–201 | 199–201 [14] |
| 13 | $2\text{-}OHC_6H_4$ | 75 | 81 | 239–240 | 242 [10] |
| 14 | $4\text{-}OCH_3C_6H_4$ | 60 | 82 | 224–225 | 223–226 [15] |
| 15 | $C_4H_3O$(2-furyl) | 60 | 78 | 284–285 | 284–286 [31] |
| 16 | $C_4H_3S$(2-thiophene) | 65 | 75 | >300 | 330 [15] |
| 17 | $C_6H_5N$(2-pyridine) | 65 | 85 | 214–216 | 216–219 [15] |

[a] Yield refers to isolated products.
[b] All compounds are known and their physical and spectroscopic data consistent with those of authentic samples.

various amount of modified scolecite in ethanol medium and the results are summarized in Table 1. It was observed that the reaction completed in 60 min giving maximum yield (94%) of the product when 3 wt% catalyst was used. This synthetic route is found to be inspiring. In a similar fashion, a variety of benzimidazole derivatives were synthesized using different reactants and in each case it is observed that the time period for condensation was reduced considerably and the yield of the products changed to excellent yields (Table 2). Aldehyde compounds which have electron donating or electron withdrawing groups were used and as expected it gives good yield of products, only meta substituted compound require comparatively more time. This indicates that the present catalyst efficiently makes the condensation reaction much faster with increased yields.

In this reaction the catalyst can be recovered by filtration and washing with n-hexane and subjected to further reaction after heating it at 110 °C in oven for an hour. The reusability of recovered catalyst was tested by performing condensation reactions using the same amount of catalyst again and again and observed that the percentage yield remains almost same as depicted in Table 3. This indicates that the catalyst could be recycled without much loss of catalytic activity.

Table 3
Recovery and reusability studies of modified scolecite catalyst for the synthesis of 2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole in ethanol solvent.

| Entry | Cycle | Yield (%)[a] |
|---|---|---|
| 1 | Fresh | 94 |
| 2 | First | 93 |
| 3 | Second | 93 |
| 4 | Third | 92 |

[a] Yield refers to isolated product.

## 3. Conclusion

The present synthetic protocol for the synthesis of benzimidazole derivatives is advantageous over the earlier reported methods as (i) the reaction could be performed with an environmentally benign zeolite catalyst, (ii) it provides a good yield of product (iii) the reaction occurs more rapidly, (iv) the catalyst was easily separated from the reaction mixture and (v) efficiency of catalyst remains almost same in recycling process.

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