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## NaHSO<sub>4</sub>-SiO<sub>2</sub> promoted synthesis of Benzimidazole derivatives

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### ABSTRACT

*a library of benzimidazole derivatives have been prepared through the reaction of o-phenylenediamine and aldehydes in the presence of catalytic amount of silica supported sodium hydrogen sulphate (NaHSO<sub>4</sub>-SiO<sub>2</sub>) under refluxing in ethanol solvent to obtained excellent yields. This method is simple, convenient, environmental friendly, reusable, efficient and practical.*

**Key words:** NaHSO<sub>4</sub>-SiO<sub>2</sub>, o-phenylenediamine, benzimidazole derivatives, aldehydes, reusable catalyst.

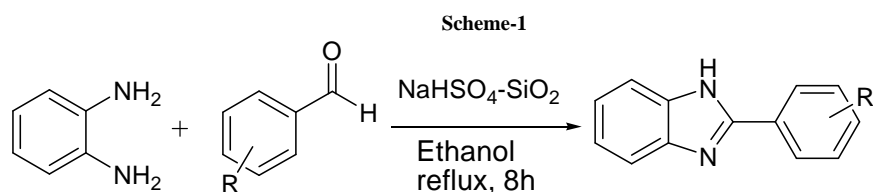
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### INTRODUCTION

Benzimidazole structures are classified under several classes of drugs [1], based on the possible substitution at different positions of the benzimidazole nucleus. Introduction of a small substituent into the 2- and 5- position is characteristic for benzimidazole anti-helmentics; alternatively, bulky 2-substituents characterizing drugs used in the treatment of peptic ulcer and are sometimes referred as proton pump inhibitors; bulky 1-and 2-substituents are found in H1-anti-histaminics. All these compounds contain the benzimidazole skeleton and hence it has been assumed that this skeleton is necessary for the therapeutic effect.

Methods of benzimidazole synthesis include the condensation of o-aryldiamines and aldehyde in refluxing nitrobenzene [2,3], the condensation of o-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid [4] or mineral acids [5] and the thermal or acid promoted cyclization of N-(N-arylbenzimidoyl)-1,4-benzoquinoneimine [6]. Direct condensation of o-aryldiamines and aldehydes is not a good synthetic reaction, as it is well known to yield a complex mixture, being 1,2-disubstituted benzimidazoles, the bis anil and dihydrobenzimidazoles as the main side products [7]. In this case, however, the addition of transition metal, namely copper (II) acetate [8], mercury oxide [9] or lead tetraacetate [10] allow a partial selective synthesis of benzimidazoles. In recent Years Solvent-free synthesis of benzimidazoles under microwave irradiation using Yb(OTf)<sub>3</sub> [11], KSF clay [12], PPA [13], metal halide supported alumina [14], and solid support [15,16], BF<sub>3</sub>.OEt<sub>2</sub> promoted solvent free condition [17], Iodine mediated aqueous condition [18], Indion 190 resin [19], have been reported. Unfortunately, many of these processes suffer some limitations, such as drastic reaction conditions, low yields, tedious work-up procedures and co-occurrence of several side reactions.

Silica supported sodium hydrogen sulphate ( $\text{NaHSO}_4\text{-SiO}_2$ ) is a heterogeneous catalyst used in a wide variety of applications, such as THP protection of alcohols and phenols [20], deprotection of THP ethers [21], trityl ethers [22], TBDMS ethers [23], mom ethers [24] and also used in the synthesis of benzoxazoles [25]. In our present work we are preparing the substituted benzimidazoles through the reaction of aldehydes and *o*-phenylenediamine under reflux in ethanol solvent with this  $\text{NaHSO}_4\text{-SiO}_2$  as a catalyst. The catalyst  $\text{NaHSO}_4\text{-SiO}_2$  can easily be prepared (26) from the readily available  $\text{NaHSO}_4$  and silica gel (230-400 mesh) and these are inexpensive and nontoxic as the reaction is heterogeneous in nature the catalyst can easily be removed by simple filtration.



## MATERIALS AND METHODS

### Experimental section

All  $^1\text{H}$  NMR spectra were recorded on 400 MHz Varian FT-NMR spectrometers. All chemical shifts are given as  $\delta$  value with reference to Tetra methyl silane (TMS) as an internal standard. Melting points were taken in open capillaries. The IR spectra were recorded on a PerkinElmer 257 spectrometer using KBr discs. Products were purified by flash chromatography on 100-200 mesh silica gel. The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem and they were used without purification prior to use.

### General experimental procedure

A mixture of *o*-phenylenediamine (1 mmol), aldehyde (1 mmol) and  $\text{NaHSO}_4\text{-SiO}_2$  (25%/wt) in Ethanol (5ml) were placed in 50 ml round bottom flask and stirred at reflux for 8h. The progress of the reaction was monitored by TLC Hexane: EtOAc (4:1) after completion of the reaction, the reaction mixture was cooled and treated by dilution with EtOAc and the catalyst was removed by filtration. Obtained filtrate was evaporated under reduced pressure to get the crude product was purified by column chromatography to give 2- substituted benzimidazole derivatives.

#### 2-phenyl-1H-benzo[d]imidazole<sup>27</sup>

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  13.02 (br s, 1H), 8.20 (d,  $J=7.6$  Hz, 2H), 7.67-7.65 (m, 1H), 7.56-7.49 (m, 4H), 7.22-7.18 (m, 2H); (LC-MS)  $m/z$ : 195.08  $[\text{M}+\text{H}]^+$ ; IR (KBr,  $\text{cm}^{-1}$ ): 3420, 2920, 2627, 1623, 1410, 1276, 1119, 970, 738. Anal. Calcd. For  $\text{C}_{13}\text{H}_{10}\text{N}_2$ : C, 80.39; H, 5.19; N, 14.42. Found: C, 80.11; H, 5.01; N, 14.38.

#### 2-*o*-tolyl-1H-benzo[d]imidazole<sup>27</sup>

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  7.82-7.79 (m, 3H), 7.60-7.58 (m, 1H), 7.56-7.45 (m, 4H), 2.58 (s, 3H); (LC-MS)  $m/z$ : 209.10  $[\text{M}+\text{H}]^+$

#### 2-*p*-tolyl-1H-benzo[d]imidazole<sup>27</sup>

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  12.81 (br s, 1H), 8.06 (d,  $J=8$  Hz, 2H), 7.56 (m, 2H), 7.36 (d,  $J=8$  Hz, 2H), 7.19 (m, 2H), 2.38 (s, 3H); (LC-MS)  $m/z$ : 209.10  $[\text{M}+\text{H}]^+$

#### 2-(2-methoxyphenyl)-1H-benzo[d]imidazole<sup>28</sup>

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  13.5 (br s, 1H), 8.29 (d,  $J=7.2$  Hz, 1H), 7.76-7.74 (m, 2H), 7.63-7.59 (m, 1H), 7.39-7.32 (m, 3H), 7.22-7.18 (m, 1H), 4.06 (s, 3H); (LC-MS)  $m/z$ : 225.07  $[\text{M}+\text{H}]^+$

#### 2-(4-methoxyphenyl)-1H-benzo[d]imidazole<sup>27</sup>

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  8.21 (d,  $J=8.4$  Hz, 2H), 7.70-7.68 (m, 2H), 7.38-7.36 (m, 2H), 7.21 (d,  $J=8.8$  Hz, 2H), 3.88 (s, 3H); (LC-MS)  $m/z$ : 225.07  $[\text{M}+\text{H}]^+$

#### 2-(2-chlorophenyl)-1H-benzo[d]imidazole<sup>29</sup>

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  12.80 (br s, 1H), 7.91-.89 (m, 1H), 7.67-7.62 (m, 3H), 7.57-7.52 (m, 2H), 7.25-7.23 (m, 2H); (LC-MS)  $m/z$ : 229.04  $[\text{M}+\text{H}]^+$

**2-(3-chlorophenyl)-1H-benzo[d]imidazole**<sup>29</sup>

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ8.40 (s, 1H), 8.27 (d, J= 6.8 Hz, 1H), 7.81-7.72 (m, 4H), 7.49-7.47 (m, 2H); (LC-MS) m/z: 229.04 [M+H]<sup>+</sup>

**2-benzyl-1H-benzo[d]imidazole**<sup>27</sup>

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ13.0 (br s, 1H), 7.52-7.50 (m, 2H), 7.34-7.16 (m, 7H), 4.21 (s, 2H); (LC-MS) m/z: 209.10 [M+H]<sup>+</sup>

**RESULTS AND DISCUSSION**

In our preliminary investigation on the model reaction of *o*-phenylenediamine and benzaldehyde, it was found that the reaction could be finished under very simple reaction conditions in the presence of catalytic amount of NaHSO<sub>4</sub>-SiO<sub>2</sub> in reflux of ethanol solvent, which gives the desired 2-phenyl benzimidazole product in good yield. The effect of solvent, reaction temperature and time on the reaction was systematically investigated and the results were summarized in Table-1. As can be seen from Table-1, the solvent play an important role in the model reaction. It was found that Ethanol is the best solvent for this condensation reaction, because the reaction was completed in 8h under reflux condition and gave 95% yield. While 1,4-Dioxane solvent also gave best results, but reaction was completed in 12h at 100°C. Use of Toluene, THF and solvent-free conditions are long time reactions and gave fewer yields compared to Ethanol. The optimized reaction conditions for the reaction were found to be NaHSO<sub>4</sub>-SiO<sub>2</sub> under reflux in Ethanol solvent for 8h.

**Table-1 Preparation of 2-phenyl benzimidazole using various solvents and temperature<sup>s</sup>**

Entry	Solvent	Time/ Temp(°C)	Yield (%) <sup>b</sup>
1	Ethanol	8hr/80	95
2	Dioxane	12hr/100	90
3	Toluene	12hr/100	74
4	THF	12hr/70	72
5	Solvent-free	12hr/100	76

<sup>a</sup>Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), NaHSO<sub>4</sub>-SiO<sub>2</sub> (25%/wt) were stirred in solvent (5ml), the temperature and time indicated in Table-1, <sup>b</sup> isolated yields

Herein, we wish to disclose a novel protocol for the rapid synthesis of a variety of biologically significant benzimidazoles using a catalytic amount of NaHSO<sub>4</sub>-SiO<sub>2</sub> under optimized reaction conditions. As shown in Table-2, different aldehydes and *o*-phenylenediamine react without any significant difference to give the corresponding benzimidazoles in good yield. When the mole ratio of *o*-phenylenediamine and aldehyde are taken in 1:1 ratio the product 2-substituted benzimidazoles were obtained as selectively. It indicated that silica supported sodium hydrogen sulphate catalyzed reaction has a favorable selectivity for the synthesis of 2-substituted benzimidazoles. Later we tried a reaction with 2 equivalent of aldehyde was used, in this case we observed of 1,2-disubstituted benzimidazole was also formed as a major along with 2-substituted benzimidazole.

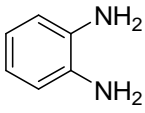
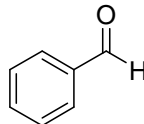
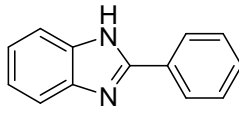
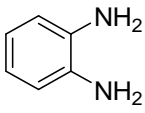
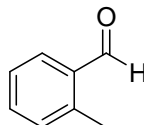
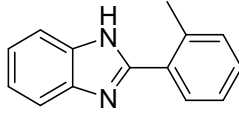
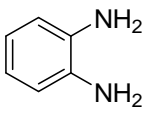
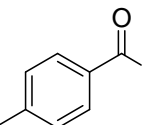
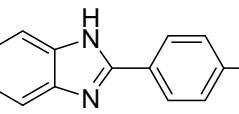
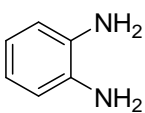
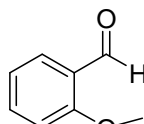
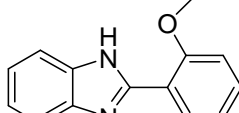
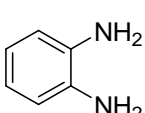
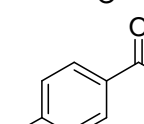
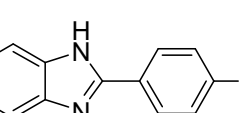
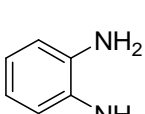
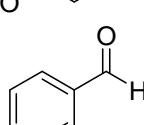
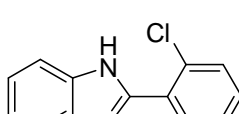
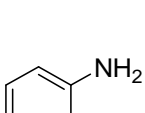
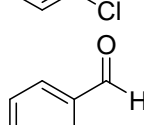
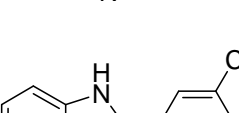
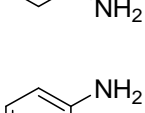
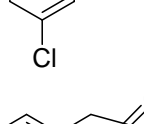
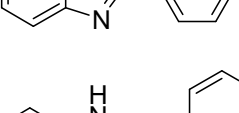
The reusability of the catalyst is an important factor from economical and environmental point of view and has attracted much attention in recent years. Therefore, the reusability of silica supported sodium hydrogen sulphate was examined in the reaction of simple benzaldehyde with *o*-phenylenediamine under optimized reaction conditions. As NaHSO<sub>4</sub>-SiO<sub>2</sub> is a heterogeneous catalyst, it was separated by simple filtration after dilution of reaction mixture with EtOAc. The filtered catalyst was dried at 100°C and reused. In first time we used fresh catalyst to give 95% yield, after second time reuse we got 88% yield and also we tried for third time reuse to get 71% yield under optimized condition. The results showed that the catalyst can be used 3 times without loss of its activity.

**CONCLUSION**

In conclusion we have developed a simple and efficient method for synthesis of 2-substituted benzimidazole derivatives by using this NaHSO<sub>4</sub>-SiO<sub>2</sub> catalyst. The method offers several advantages like simple reaction

conditions, short reaction time, high yields of products and simple experimental operation, which leads to a useful and attractive process for synthesis of benzimidazole derivatives.

Table-2 Synthesis of 2-Substituted Benzimidazole derivatives<sup>a</sup>

Diamine	Aldehyde	Product	Yield (%) <sup>b</sup>	M.P (°C) Reported	M.P (°C) Found <sup>c</sup>
			95	285-287	289-291
			87	222-223	220-222
			93	266-268	265-267
			89	175-176	173-175
			96	220-221	218-221
			87	230-232	231-233
			91	236-238	234-236
			94	179-180	177-179

<sup>a</sup>Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), NaHSO<sub>4</sub>-SiO<sub>2</sub> (25%/wt) were stirred for 8h under reflux in Ethanol, <sup>b</sup> isolated yields, <sup>c</sup> All products are solids.

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