Polymer supported sulphanilic acid – A novel green heterogeneous catalyst for synthesis of benzimidazole derivatives

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Abstract Polymer supported sulphanilic acid was synthesized and used as green, reusable and heterogeneous catalyst and duly characterized using chemical methods like determination of free hydroxyl content, epoxy equivalent weight and free sulphonic acid content as well as infrared spectroscopy and thermogravimetric analysis. The prepared catalyst was applied for one-pot synthesis of 2-substituted benzimidazoles from α-phenylenediamine and various aromatic aldehydes in absolute ethanol under thermal condition. Catalyst was separated from the product by simple filtration and could be reused for at least five times with almost retention in its efficiency. Due to three dimensional network structures, it shows high thermal stability and can be reused without any further purification.

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1. Introduction

Epoxies are important thermosetting polymers. They are currently used in advanced composites (Guo et al., 2008), nanocomposites, coatings (Lin et al., 2007), structural adhesives (Wang et al., 2008), matrices for fiber composite and microelectronics (Liu et al., 2008), due to their high stability, high strength, good chemical resistance and dimensional stability (Zhang et al., 2002). The primary requirement for high-temperature performance necessitates the selection of polyfunctional epoxy resins and curing agents which are capable of creating high crosslink densities. Thus, novolac epoxy resin, can produce a more firmly crosslinked three-dimensional network compared to epoxy diglycidyl ether of bisphenol A and hence can give enhanced adhesive strength retention at elevated temperatures (Gouri et al., 2000). Epoxy resins are extensively investigated and widely used in the electronic/electrical instruments because of their great versatility, good chemical and electrical properties and excellent adherence to many substrates (Kinjo et al., 1989). As alternatives to halogen-containing epoxy resin, phosphorus-containing epoxy resins (Cheng et al., 2002a,b) have been investigated. Although they exhibit high flame retardance, its industrialization is difficult for its complex synthesis and high cost, as well as debating environmental problems (Shieh and Wang, 2002).

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containing epoxy resins have excellent thermal stability and good flame retardance and are suitable materials for high-quality electronic/electrical instruments. Herein, we have synthesized epoxy novolac phenol formaldehyde resin (ENPFR) with reactive epoxy groups. This was modified by sulphanilic acid to develop network polymeric structure having free –SO₃H group and it was applied as a solid heterogeneous catalyst for the synthesis of benzimidazole and its derivatives.

Benzimidazole and its derivatives have been the area of much research interest due to their importance in various applications and its widespread biochemical significance (Alexander et al., 1996). Benzimidazole structure is found in several classes of drugs based on the substituents present at different positions (Velik et al., 2004). Benzimidazole derivatives find many applications in several therapeutic area such as antimicrobial agents (Fonseca et al., 2001), antiviral agent against several viruses such as HIV (Roth et al., 1997), influenza (Migawa et al., 1998), and herpes (HSV-1) (Migawa et al., 1998), and as antiprotozoal agents (Valdez-Padilla et al., 2009). The amidure derivatives of imidazo [1,2-a] benzimidazoles are potent adrenoblockers, spasmolytics, antiarrhythmogens, and antimicrobial agents (Anisimova et al., 2002). Benzimidazoles are also important intermediates in organic synthesis (Bai et al., 2001; Hasegawa et al., 1999). A number of methods have been adopted for the synthesis of benzimidazoles from different reactants and reaction conditions such as reaction between o-phenylenediamine and aldehyde under oxidative conditions (Lombardy et al., 1996; Middleton and Wibberley, 1980; Pätzold et al., 1992; Stephens and Bower, 1949), o-phenylenediamine and carboxylic acid (Geratz et al., 1979; Middleton and Wibberley, 1980; Wright, 1951) in the presence of catalyst such as H₂O₂/HCl (Bahrani et al., 2007), Sc(OTf)₃ (Itoh et al., 2004; Nagata et al., 2003), Cu(OTf)₂ (Chari et al., 2010), KHSO₄ (Ma et al., 2006), ionic liquids (Ma et al., 2007), p-TsOH (Han et al., 2007), and solid support (Ben-Alloum et al., 1998) and under microwave irradiation using Poly phosphoric acid as catalyst (Lu et al., 2002). However many of these methodologies suffer one or more disadvantages like low yields, lack of easy availability of the starting materials, prolonged reaction time, high temperature, excess requirement of catalysts, special apparatus, harsh reaction conditions, extraction of product, formation of byproduct etc. Thus there is a need of simple and efficient protocol for the synthesis of benzimidazole derivatives. Herein, we report a method for the synthesis of benzimidazole derivatives by using polymer supported recyclable heterogeneous catalyst to obtain product with high yield in moderate reaction time and easy extraction of catalyst for reuse with high efficiency (Scheme 1).

The heterogeneity of catalyst has avoided number of reported disadvantages for the synthesis of benzimidazole by different reagents and reaction conditions (Hein et al., 1957).

2. Experimental

2.1. Chemicals and reagents

All chemicals used were of laboratory reagent grade and used without further purification. Phenol, formaldehyde and epichlorohydrin were obtained from Sd. Fine Chem. Pvt. Ltd., Mumbai, India. o-phenylenediamine, sodiumhydroxide and sulphanilic acid were obtained from Samir Tech Chem. Pvt. Ltd., Vadodara, India. Various aldehydes, ethyl acetate and n-hexane were used as received from Merck, Mumbai, India. 1,4-Dioxane was supplied by Sisco Chem. Pvt. Ltd., Mumbai, India.

2.2. Analytical methods

Melting points were determined by open capillary method and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ¹H NMR, and 100 MHz for ¹³C NMR, as solutions in DMSO-d₆. Chemical shifts (δ) are expressed in parts per million (ppm) and referenced to the residual protic solvent. FT-IR spectra were recorded on Shimadzu FT-IR 8401 spectrometer using pressed KBr disc, and are expressed in wavenumbers (cm⁻¹). The mass spectra (ESI-MS) were recorded on Shimadzu LCMS-2010 spectrometer. Thermogravimetric analysis (TGA) data were recorded on a TGA/DTA (TA instrument Model 5000/2960 thermogravimetric analyser, USA) and Carbon, Hydrogen and Nitrogen were estimated on a PerkinElmer 2400 Series II CHNS/O Elemental Analyzer. All the reactions were monitored by thin-layer chromatography (TLC) performed on Silica Gel 60 F₂₅₄ precoated plates (Merck).

2.3. General procedure for the synthesis of catalyst ENPFSA

2.3.1. Preparation of novolac phenol formaldehyde resin (NPFR)

NPFR was prepared by condensation reaction between phenol and formaldehyde under acidic condition by following a reported method (Scheme 2) (Motawie et al., 2008).

The IR spectrum of the prepared NPFR exhibited absorption bands of –OH at 3134 cm⁻¹, C=C aromatic at 1600 cm⁻¹ and CH₂ at 1405 cm⁻¹.

2.3.2. Epoxidation of NPFR

ENPFSA was prepared by condensation reaction between above prepared NPFR and epichlorohydrin in the presence of sodium hydroxide (Scheme 3) as per the procedures described elsewhere (Motawie and Sadek, 1998).

Scheme 1  General synthetic pathway for the synthesis of benzimidazole derivatives.
Scheme 2 General synthetic pathway for the synthesis of NPFR.

Scheme 3 General synthetic pathway for the synthesis of ENPFSA.

Scheme 4 General synthetic pathway for the synthesis of ENPFSA.

The FT-IR spectrum of prepared ENPFSA exhibited absorption bands for C–H alkane at 2925 cm⁻¹, C=C aromatic at 1510 cm⁻¹, CH₃ at 1460 cm⁻¹, C–O at 1170 cm⁻¹ and epoxy group at 910 cm⁻¹.

2.3.3. Modification of ENPFSA by sulphanilic acid

Mixture of ENPFSA and sulphanilic acid (equiv. mole) was refluxed in dioxane in the presence of catalytic amount of pyridine in a three neck RB flask equipped with a mechanical stirrer for 3–4 h. Mixture was cooled to room temperature. Formulation of epoxydized novolac phenol formaldehyde resin modified using sulphanilic acid (ENPFSA) was indicated by pH change from 8 to 4. The prepared catalyst was cured with resole phenol formaldehyde resin and washed with hot water followed by ethanol, diethyl ether and finally dried (Scheme 4).

The IR spectrum of ENPFSA exhibited absorption bands for C–H alkane at 2927 cm⁻¹, C–C aromatic at 1520 cm⁻¹, CH₃ at 1470 cm⁻¹, S–O at 1200 cm⁻¹, C–O at 1175 cm⁻¹.

2.4. General experimental procedure for the synthesis of benzimidazoles 3a–p

To a refluxing solution of aldehyde (1 mmol) and o-phenylenediamine (1.05 mmol) in ethanol (10 mL) in a 250 mL RB flask, sulphonic acid functionalized polymer supported catalyst ENPFSA (20% w/w with respect to o-phenylenediamine) was added. The progress of the reaction was monitored by TLC. After completion of reaction, the catalyst was recovered by filtration and filtrate was extracted with ethyl acetate. The extract was dried over anhydrous Na₂SO₄, residue of product was obtained in excellent yield with high purity by adding n-hexane to the extracted filtrate. The recovered catalyst was washed with ethanol, chloroform, diethyl ether and subsequently dried at 80 °C for recycling.

2.5. Spectral data analysis of selected compounds

2.5.1. 2-(4-chlorophenyl)-1H-benzo[d]imidazole 3a

IR (KBr): 3044 (w), 1455, 1404, 1270, 749 cm⁻¹; ¹H NMR (DMSO-d₆, δ ppm): 12.98 (s, 1H, NH), 8.21 (d, 2H, J = 8.4 Hz, Ar–H), 7.22–7.73 (m, 6H, Ar–H); ¹³C NMR (DMSO-d₆, δ ppm): 150.63 (C-2), 135.50 (C-8, C-9), 134.95 (C-4'), 129.52 (C-1'), 129.39 (C-3', C-5'), 128.61 (C-2', C-6'), 123.23 (C-5, C-6), 119.44 (C-4, C-7); ESI-MS: m/z 229.53 (M + H)⁺; Anal. Calcd. for C₁3H₁0N₂: C, 80.39; H, 5.19; N, 12.25; Found: C, 68.58; H, 4.01; N, 12.31.

2.5.2. 2-phenyl-1H-benzo[d]imidazole 3b

IR (KBr): 3036 (w), 1455, 1404, 1270, 749 cm⁻¹; ¹H NMR (DMSO-d₆, δ ppm): 12.94 (s, 1H, NH), 8.21 (d, 2H, J = 7.6 Hz, Ar–H), 7.62–7.21 (m, 7H, Ar–H); ¹³C NMR (DMSO-d₆, δ ppm): 151.72 (C-2), 140.1 (C-8, C-9), 130.68 (C-4'), 130.28 (C-1'), 129.40 (C-3', C-5'), 126.92 (C-2', C-6'), 122.57 (C-5, C-6), 116.4 (C-4), 116.4 (C-7); ESI-MS: m/z 195.10 (M + H)⁺; Anal. Calcd. for C₁₂H₁₀N₂: C, 80.89; H, 5.19; N, 14.42; Found: C, 80.69; H, 5.16; N, 14.46.

2.5.3. 5-methyl-2-(3-nitrophenyl)-1H-benzo[d]imidazole 3k

IR (KBr): 3044 (w), 1455, 1404, 1270, 749 cm⁻¹; ¹H NMR (DMSO-d₆, δ ppm): 13.13 (s, 1H, NH), 8.99–7.07 (m, 7H, Ar–H), 2.45 (s, 3H, CH₃); ¹³C NMR (DMSO-d₆, δ ppm): 154.53 (C-2), 148.84 (C-3'), 136.12 (C-6'), 134.48 (C-8), 132.84 (C-6), 132.37 (C-9), 131.12 (C-1'), 130.20 (C-5), 124.47 (C-5), 122.77 (C-7'), 121.14 (C-2'), 119.53 (C-7'), 117.44 (C-4), 21.84 (CH₃); Mass spectrum (ESI-MS): m/z 254.15 (M + H)⁺; Anal. Calcd. for C₁₄H₁₁N₃O₂: C, 66.40; H, 4.38; N, 16.59; Found: C, 66.35; H, 4.34; N, 16.57.

3. Results and discussion

3.1. Characterization of ENPFSA

ENPFSA was characterized by determining epoxy equivalent weight by the reported method (Guo et al., 2008) and determination of free hydroxyl group in NPFR and in ENPFSA (Ahluwalia and Aggarwal, 2000). It was observed that free –OH content in NPFR and in ENPFR was characterized by determination of free sulphonic acid –OH groups were converted into epoxy groups. ENPFSA was characterized by determination of free sulphonlic acid group and free –OH content (Ahluwalia and Aggarwal, 2000). An increase in –OH content was observed upon modification of ENPF with sulphonlic acid. The % –OH content and moles of –SO₃H groups per gram for ENPFSA were found to be 34 and 20, respectively. It was observed that epoxy equivalent weight was found to decrease compared to ENPF.
with increasing hydroxyl content as equimol to free –SO₃H group. This indicates that epoxy ring gets opened up by sulphanilic acid leaving free –OH group equivalent to opening of each epoxy ring. Formation of ENPFR was characterized by IR spectroscopy, appearance of characteristic band at 910 cm⁻¹ due to epoxy group. The formation of ENPFSA was characterized by appearance of characteristic band at 3400 cm⁻¹ due to N–H along with disappearance of band at 910 cm⁻¹ for epoxy group. Formation of catalyst could also be confirmed by comparing thermogram of ENPFR and ENPFSA. It was found that % of weight loss in ENPFR at temperature 200°C showed 9.90% whereas at same temperature the ENPFSA showed 3.13% of weight loss due to the removal of sulphanilic acid (Table 1).

### 3.2. Optimization of the reaction condition

Reaction was optimized by varying the amount of catalyst. We chose the reaction between o-phenylenediamine 1a and benzaldehyde 2c as the model reaction. First we carried out model reaction in the absence of catalyst (Table 2, entry 1), and found that the reaction did not proceed. Next, the amount of catalyst was varied with respect to 1a (Table 2, entries 2–5). It was found that only 70% and 75% yields were obtained by taking 10% and 25% amounts of catalyst ENPFSA (Table 2, entry 2 & 5) respectively. The best result (88% yield of product 3c) was obtained by using 20% amount of catalyst (Table 2, entry 4). By using this optimized conditions, various benzimidazole derivatives 3a-p were synthesized in shorter time as well as in high yields using ENPFSA as the catalyst.

It was observed that the aromatic aldehyde bearing an electron withdrawing substituent underwent the conversion smoothly as compared to that bearing an electron donating substituent (Table 3). We have synthesized compounds 3e-g bearing an electron withdrawing substituent (–NO₂) in 3 h with high yields where as compounds 3b & 3i bearing an electron donating substituent (–OH & –OCH₃, respectively) in 4 h.

All prepared products were well characterized by ¹H NMR, ¹³C NMR and IR spectroscopy. In ¹H NMR spectra of compounds 3a-p, the N–H proton of benzimidazole moiety reso-

### Table 1 % Weight loss as a function of temperature for NPFR, ENPFR and ENPFSA from thermogravimetric study.

<table>
<thead>
<tr>
<th>Resin</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>350</th>
<th>400</th>
<th>450</th>
<th>500</th>
<th>550</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENPFR</td>
<td>1.46</td>
<td>5.87</td>
<td>9.90</td>
<td>19.64</td>
<td>28.54</td>
<td>38.58</td>
<td>50.41</td>
<td>55.25</td>
<td>58.13</td>
<td>60.57</td>
<td>62.61</td>
</tr>
<tr>
<td>ENPFSA</td>
<td>2.23</td>
<td>2.48</td>
<td>3.13</td>
<td>8.93</td>
<td>22.66</td>
<td>31.74</td>
<td>42.73</td>
<td>48.93</td>
<td>52.72</td>
<td>55.76</td>
<td>58.04</td>
</tr>
</tbody>
</table>

### Table 2 Model reaction of o-phenylenediamine (1.0 mmol) with benzaldehyde (1.05 mmol) by using different amounts of catalyst ENPFSA in absolute ethanol under reflux.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount of catalyst (%)</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>4.5</td>
<td>75</td>
</tr>
</tbody>
</table>

- Reaction was monitored by TLC.
- Isolated yields.

### Table 3 Synthesis of benzimidazole 3a-p by using polymer supported sulphanilic acid as heterogeneous catalyst.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R₁</th>
<th>R₂</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>4-Chlorophenyl</td>
<td>3</td>
<td>80</td>
<td>290</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>4-Hydroxy-3-methoxphenyl</td>
<td>4</td>
<td>70</td>
<td>224</td>
</tr>
<tr>
<td>3c</td>
<td>H</td>
<td>Phenyl</td>
<td>3</td>
<td>88</td>
<td>290</td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td>4-Hydroxy phenyl</td>
<td>3.5</td>
<td>78</td>
<td>253</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>4-Nitro phenyl</td>
<td>3</td>
<td>90</td>
<td>312</td>
</tr>
<tr>
<td>3f</td>
<td>H</td>
<td>2-Nitro phenyl</td>
<td>3</td>
<td>84</td>
<td>211</td>
</tr>
<tr>
<td>3g</td>
<td>H</td>
<td>3-Nitro phenyl</td>
<td>3</td>
<td>90</td>
<td>200</td>
</tr>
<tr>
<td>3h</td>
<td>H</td>
<td>Furfuryl</td>
<td>3</td>
<td>85</td>
<td>284</td>
</tr>
<tr>
<td>3i</td>
<td>H</td>
<td>4-Methoxy phenyl</td>
<td>4</td>
<td>78</td>
<td>225</td>
</tr>
<tr>
<td>3j</td>
<td>H</td>
<td>2-Hydroxy phenyl</td>
<td>3.5</td>
<td>78</td>
<td>241</td>
</tr>
<tr>
<td>3k</td>
<td>CH₃</td>
<td>3-Nitro phenyl</td>
<td>3</td>
<td>80</td>
<td>212</td>
</tr>
<tr>
<td>3l</td>
<td>CH₃</td>
<td>4-Hydroxy phenyl</td>
<td>3.5</td>
<td>77</td>
<td>300</td>
</tr>
<tr>
<td>3m</td>
<td>CH₃</td>
<td>2-Nitro phenyl</td>
<td>3.5</td>
<td>81</td>
<td>213</td>
</tr>
<tr>
<td>3n</td>
<td>CH₃</td>
<td>Phenyl</td>
<td>3.5</td>
<td>85</td>
<td>246</td>
</tr>
<tr>
<td>3o</td>
<td>CH₃</td>
<td>4-Hydroxy-3-methoxphenyl</td>
<td>4</td>
<td>76</td>
<td>225</td>
</tr>
<tr>
<td>3p</td>
<td>CH₃</td>
<td>2-Hydroxy phenyl</td>
<td>3.5</td>
<td>78</td>
<td>240</td>
</tr>
</tbody>
</table>

- Reaction was monitored by TLC.
- Isolated yields.

NPFR showed 9.62% of weight loss at 200°C whereas ENPFSA showed 8.93% of weight loss due to the removal of sulphanilic acid (Table 1).
nates in more down field region i.e. around $\delta$ 13 ppm. The plausible mechanism for the formation of benzimidazole derivative is suggested in Scheme 5.

The first step may involve H-bond formation between the catalyst and aldehyde followed by intramolecular oxidative cyclization via imine to produce benzimidazole. Advantages of this method are its simplicity, and easy isolation of the product from the reaction mixture with high yields. The catalyst could be recovered easily by simple filtration because of its heterogeneity. It has high thermal stability as evident from the thermogravimetric analysis (Table 1). It could be recycled and reused five times with almost comparable efficiency without loss in amount as shown in Fig. 1. The reaction of o-phenylenediamine 1a with benzaldehyde 2c was repeated five times using the same portion of catalyst recovered from the previous batch.

4. Conclusion

Herein we report a high-yielding, one-pot synthesis of 2-substituted benzimidazole derivatives from readily available o-phenylenediamines and aromatic aldehydes, under simple and convenient conditions. The conditions are mild, and a wide range of functional groups can be tolerated. ENPFSA as catalyst offers advantages including simplicity of operation, easy workup procedure, product obtained in high yields with excellent purity, less time consuming and the recyclability of the catalyst.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jscs.2012.07.014.

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