Synthesis of Bis-4-hydroxycoumarins via a Multi Component Reaction Using Silica Boron-sulfuric Acid Nanoparticles (SBSANs) as an Efficient Heterogeneous Solid Acid Catalyst

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The silica boron sulfuric acid nanoparticles (SBSANs) as an efficient heterogeneous solid acid catalyst with both Brønsted and Lewis acidic sites catalyzed the preparation of bis-4-hydroxycoumarin derivatives using reaction of aldehydes and 4-hydroxycoumarin under mild and solvent-free condition at room temperature. This new and efficient methodology has advantages in comparison with currently used methods such as: easy work-up, simple separation of catalyst from the reaction mixture, reusability and lower catalyst loading, relatively short reaction time, eco-friendly with environment, excellent yields, simple purification of products and mild reaction condition. Using this method a range of biologically active bis-4-hydroxycoumarin derivatives were synthesized in good to excellent yield. The catalyst system was reusable at least for 5 times in this reaction without significant decreasing in its catalytic activity.

Keywords: Silica boron-sulfuric acid nanoparticles (SBSANs), Solid acid, Lewis-protic acid, Biscoumarin

INTRODUCTION

Solid acids as an important class of heterogeneous catalysts are one of the best catalytic systems in organic transformations, because they have several advantageous including, simple operation, decreased reactor and plant corrosion problems, while they are environmentally friendly and easily available. These catalysts can also provide efficient and green conditions for excellent implement of acid catalyzed processes with maximum yield of products and minimum waste as major principles of green chemistry [1-7]. Silica is the most popular substrate for synthesis of solid acid catalysts in most industrial and academic research due to its more stability, easier functionalization and abundant availability. In the case that the silica support is selected in the nanometer scale, the catalyst will even be dispersible in solution as pseudo-homogenous catalyst [8-10]. Consequently, the reaction rate is enhanced dramatically because the diffusion rate of reactants to the surface of catalyst is increased [11].

In a solid acid catalyst, when the Lewis acidic sites exist near the protic acidic sites, they can increase the strength of each other; called Brønsted/Lewis acid synergy (BLAS) [12-14]. Recently, our research group has reported a dual solid acid catalyst in the nanometer scale based on silica support as silica boron sulfuric acid nanoparticles (SBSANs) catalyst. This solid acid catalyst has two acidic sites, one of them is Lewis (boron atoms) and the other one is Brønsted (SO\textsubscript{3}H groups). There seems to be a BLAS effect between the boron atoms as Lewis acid and the SO\textsubscript{3}H groups as Brønsted acid in this solid acid catalyst (SBSANs) that causes the high activity in this catalyst. The catalytic performance of the SBSANs catalyst was examined in organic reactions such as the Ritter and Strecker reactions as acid catalyzed processes, and very excellent results were achieved under mild condition [15]. The excellent results obtained in the previously works persuaded us to perform the current study. In the present study, another important application of SBSANs catalyst for the synthesis of bis-4-hydroxycoumarin derivatives under mild condition is
Coumarins are an important class of organic heterocyclic compounds that have received greater attention because of their wide range of biological and industrial applications [16]. Among coumarin derivatives, 4-hydroxycoumarin is of paramount importance because of its enormous biological activity, including anticoagulant [17], antibacterial [18], anti-HIV [19], anticancer [20], analgesic [21], anti-inflammatory [22], anti- pyretic [23], antioxidant and spasmolytic activities [24]. A series of 4-hydroxyl Coumarins with their pharmaceutical and biological properties are shown in Fig. 1.

Bis-4-hydroxycoumarins can be prepared from the reaction of 4-hydroxylcoumarin with a variety of aldehydes in the presence of different catalysts or reagents in various conditions [25-31]. However, several strategies have been reported for the synthesis of biscoumarin derivatives in literature that some of them has disadvantageous such as, tedious work-up, expensive reagents or catalysts [25,27], long reaction time, harsh condition and low yield of desired products [29]. There are also reports on improving the yields and reaction times by the use of cheap, easily available and reusable catalysts such as silica and nano silica, however under traditional condition or in organic solvent [30,31]. Herein, a simple and efficient procedure for preparation of a wide range of bis-4-hydroxycoumarins in the presence of SBSANs as an efficient heterogeneous and reusable catalyst under mild and solvent-free condition is reported (Scheme 1).

Fig. 1. The chemical structures of 4- hydroxyl coumarin derivatives with pharmaceutical and biological activities.

Scheme 1. Preparation of biscoumarin derivatives
EXPERIMENTAL

Chemicals were purchased from Fluka and Aldrich Chemical Companies and used without further purification. 1H and 13C NMR spectra were recorded on a Bruker Avance 250 MHz spectrometer in DMSO or CDCl3 solution with TMS as an internal standard. FTIR spectroscopy (Shimadzu FT-IR 8300 spectrophotometer) was employed to characterize the compounds. Melting points were determined in open capillary tubes in a Barnstead Electro thermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on the silica gel PolyGram SILG/UV254 plates. The desired products were identified by their physical and spectral data in comparison with the euthenics sample reported in the literature.

Preparation of SBSANs Catalyst

For preparation of SBSANs, at first, the silica boric acid nanoparticles (SBANs) were prepared based on the chemical vapor deposition (CVD) process. To this end, a brief mixture of Ar and O2 gases and the aerosols of the aqueous solution of boric acid (~2.0 g ml−1) was injected to the solid silica supports positioned inside a quartz tube located in a tubing furnace at temperatures of about 600 °C. After that, a 100 ml suction flask was equipped with a dropping funnel containing chlorosulfonic acid (7.64 g, 0.066 mol, 4.5 ml) and a gas inlet tube for conducting HCl gas over an adsorbing solution (10% NaOH). Then, 10 g of SBANs were charged into the flask and chlorosulfonic acid gas was dropped into the mixture of 4-hydroxycoumarin (2 mmol, 0.324 g), aromatic aldehyde (1 mmol) and SBSANs catalyst (0.1 g) and then, the reaction mixture was stirred at room temperature for an appropriate time for each compound. After completion of reaction, as indicated by TLC (n-hexane:EtOAc, 3:1), the reaction mixture was dissolved in CHCl3 or hot ethanol and catalyst was separated by simple filtration and washed with solvent. The filtrate was evaporated under reduced pressure until the crude product was solidified. The pure product was obtained by recrystallization in hot ethanol.

Spectral and Physical Data for Synthesized Compounds

Compound 3a. Yield: 92%; white solid, m.p.: 230-232 °C (Lit: 228-230 [32]). 1H NMR (CDCl3/TMS, 250 MHz) δ (ppm): 6.10 (s, 1H), 7.21-7.43 (m, 9H), 7.59-7.67 (m, 2H), 7.99-8.08 (m, 2H), 11.30 (s, 1H). 13C NMR (CDCl3/TMS, 62.5 MHz) δ (ppm): 35.9, 104, 115.8, 117.9, 123.6, 123.8, 125.4, 126.6, 128, 131.8, 139.9, 152.1, 164.7, 165.3.

Compound 3b. Yield: 94%; white solid, m.p.: 259-261 °C (Lit: 258-259 [35]). 1H NMR (CDCl3/TMS, 250 MHz) δ (ppm): 6.03 (s, 1H), 7.15 (d, 2H, J = 8.5 Hz), 7.28 (d, 2H, J = 8.7 Hz), 7.4 (d, 4H, J = 8.2 Hz), 7.60-7.67 (m, 2H), 7.99 (d, 1H, J = 7.7 Hz), 8.06 (d, 1H, J = 7.7 Hz), 11.31 (s, 1H), 11.54 (s, 1H). 13C NMR (CDCl3/TMS, 62.5 MHz) δ (ppm): 35.6, 103.7, 115.8, 118, 123.6, 123.8, 127.8, 128.6, 130, 131.8, 139.3, 152.2, 164.6, 165.5.

Compound 3c. Yield: 90%; white solid, m.p.: 247-250 °C (Lit: 249-250 [35]). 1H NMR (CDCl3/TMS, 250 MHz) δ (ppm): 3.79 (s, 3H), 6.05 (s, 1H), 6.85 (d, 2H, J = 8.7 Hz), 7.12 (d, 2H, J = 8.7 Hz), 7.40 (d, 4H, J = 8.5 Hz), 7.59-7.66 (m, 2H), 8.03 (br, 1H), 11.29 (br, 1H), 11.50 (br, 1H).

Compound 3d. Yield: 89%; white solid, m.p.: 220-223 °C (Lit: 222-225 [33]). 1H NMR (DMSO-d6/TMS, 250 MHz) δ (ppm): 5.72 (s, 1H), 6.21 (s, 1H), 6.59 (d, 2H, J = 8.5 Hz), 6.90 (d, 2H, J = 8.7 Hz), 7.26-7.34 (m, 4H), 7.52-7.59 (m, 2H), 7.86 (d, 2H, J = 8 Hz).

Compound 3e. Yield: 94%; white solid, m.p.: 270-272 °C (Lit: 269-270 [35]). 1H NMR (CDCl3/TMS, 250 MHz) δ (ppm): 2.53 (s, 3H), 6.06 (s, 1H), 7.07-7.15 (m, 4H), 7.40 (d, 4H, J = 8.2 Hz), 7.59-7.66 (m, 2H), 8.02-8.04 (m, 2H), 11.30 (br, 1H), 11.52 (br, 1H). 13C NMR (CDCl3/TMS, 62.5 MHz) δ (ppm): 20.4, 35.5, 104.1, 115.8, 117.8, 123.6, 123.8, 126.5, 128.6, 131.8, 134.3, 136.6, 152.1, 164.7, 165.1.

Compound 3f. Yield: 90%; green solid, m.p.: 216 °C (dec) (Lit: 213 (dec) [33]). 1H NMR (CDCl3/TMS, 250
MH) δ (ppm): 6.20 (s, 1H), 6.84-6.87 (m, 1H), 6.93-6.97 (m, 1H), 7.22 (d, 1H, J = 5 Hz), 7.41 (d, 4H, J = 8.2 Hz), 7.60-7.67 (m, 2H), 8.04 (br, 2H), 11.28 (br, 1H), 11.79 (br, 1H).

**Compound 3g.** Yield: 96%; white solid, 256-259 °C (Lit: 252-254 °C [33]). ¹H NMR (DMSO-d₆/TMS, 250 MHz) δ (ppm): 6.44 (s, 1H), 7.20-7.30 (m, 4H), 7.49-7.56 (m, 2H), 7.79 (d, 4H, J = 6.2 Hz), 8.65 (d, 2H, J = 6.2 Hz). ¹³C NMR (DMSO-d₆/TMS, 62.5 MHz) δ (ppm): 37.7, 101.3, 115.7, 119.2, 123.1, 124.1, 125.1, 131.5, 140.8, 152.6, 164, 164.8, 168.

**Compound 3h.** Yield: 91%; white solid, m.p.: 212-215 °C (Lit: 212-215 [34]). ¹H NMR (CDCl₃/TMS, 250 MHz) δ (ppm): 6.5 (s, 1H), 7.12-8.34 (m, 12H), 11.35 (s, 1H), 11.63 (s, 1H).

**Compound 3i.** Yield: 97%; white solid, m.p.: 236-238 °C (Lit: 232-234 [32]). ¹H NMR (CDCl₃/TMS, 250 MHz) δ (ppm): 6.11 (s, 1H), 7.39-7.45 (m, 6H), 7.63-7.70 (m, 2H), 8.00 (d, 1H, J = 7.2 Hz), 8.08 (d, 1H, J = 7.2 Hz), 8.18 (d, 2H, J = 8.7 Hz), 11.37 (s, 1H), 11.56 (s, 1H).

**Compound 3j.** Yield: 92%; white solid, m.p.: 201-204 °C (Lit: 200-202 [34]). ¹H NMR (CDCl₃/TMS, 250 MHz) δ (ppm): 6.58 (s, 1H), 7.12-8.06 (m, 12H), 11.29 (s, 1H), 11.64 (s, 1H).

**Compound 3k.** Yield: 90%; cream solid, m.p.: 224-226 °C (Lit: 222-224 [34]). ¹H NMR (CDCl₃/TMS, 250 MHz) δ (ppm): 6.07 (s, 1H), 7.22-8.18 (m, 12H), 11.33 (s, 1H), 11.59 (s, 1H).

**Compound 3l.** Yield: 88%; orange solid, m.p.: 243-245 °C (Lit: 240-244 [32]). ¹H NMR (DMSO-d₆/TMS, 250 MHz) δ (ppm): 5.85 (s, 1H), 6.76 (s, 1H), 7.15-8.93 (m, 12H), 12.64 (s, 1H).

**RESULT AND DISCUSSION**

**Catalyst Characterization**

Some different microscopic and spectroscopic techniques have been used to characterize the SBSANs catalyst such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), patterned X-ray diffraction (XRD), FT-IR spectroscopy and FT-Raman spectrometry. A thermo gravimetric (TG) analyzer was also used for investigation of the thermal behavior of the SBSANs. In this study, the average diameter of the synthesized SBSANs based on the proposed procedure is evaluated to be ~38 nm [15]. TEM image of the SBSANs catalyst (Fig. 2) shows the SBSANs with near spherical morphology generated by the CVD process. According to the SEM image (Fig. 3), it is clear that the silica nanoparticles are regular in shape and arranged in an approximately good orderly manner. The SEM image also confirms this point that the SBSANs are produced with near spherical morphology.

The histogram revealing the size distributions of the SBSANs is shown in Fig. 4. The histogram was proposed according to the results obtained from the TEM and SEM images. To further explore the chemically modification of the silica support with boron-sulfuric acid nanoparticles, the morphology of the catalyst was studied using XRD spectrometry. The XRD patterns of both silica and the SBSANs are shown in Fig. 5. Comparison between the XRD pattern of SBSANs and pure silica reveals significant peaks positioned at 2θ = 25.6 and 28.1° for SBSANs. These two peaks are related to the presence of Si-O and B-O bonds in the crystalline structure of the SBSANs, respectively [39].

According to the obtained data from the TEM, SEM and XRD we can surely say that this catalyst has a nanostructure nature, however these techniques do not provide much information about the catalyst’s chemical bonds and functional groups. Thus, for further identification of the catalyst and characterization of the chemical bonds, we need other techniques such as FT-IR spectroscopy and Raman spectrometry. The FT-IR spectra of both pure silica and SBSANs are shown in Fig. 6. In agreement with the FT-IR spectra, the peaks positioned at ~609 and ~1632 cm⁻¹ are related to the B-O-B and B-O bonds formation, respectively [40]. The band at 1122 cm⁻¹ was attributed to the Si-O-Si stretching vibrations in the SBSANs catalyst [41]. The stretching vibrations of B-OH bonds were observed at ~1450 and 1350 cm⁻¹. The bond at ~710 cm⁻¹ is probably related to the B-O-Si bond [41]. The asymmetric and symmetric stretching of the O=S=O fragment was observed at 1320 and 1198 cm⁻¹, respectively. The FT-IR spectrum gives a good indication of the successful preparation of the SBSANs.

The formation of B-O as well as B-O-B bonds was also approved using Raman spectrometry. According to the
Raman spectrum (Fig. 7), sharp peaks positioned at ~480 cm$^{-1}$ and ~590 cm$^{-1}$ belong to the formation of B-O and B-O-B bonds, respectively [39]. This reveals that the proposed procedure is considered as a good method for modification of the silica support for doping different functional groups such as boron sulfuric acid. As obviously seen, the FT-IR and Raman techniques demonstrate the chemical bonds and functional groups as well, in the structure of the SBSANs catalyst.

**Catalytic Activity**

First, the SBSANs catalyst was prepared in a two-step
reaction according to our previous procedure [15]. In this way, silica boric acid nanoparticles (SBANs) were formed during the modification of silica by boric acid \([\text{B(OH)}_3]\) employing the chemical vapor deposition (CVD) process. Then, the SBANs were treated with chlorosulfonic acid (\(\text{ClSO}_3\text{H}\)) under solvent-free condition at room temperature to achieve the SBSANs catalyst (Scheme 2).

Our investigations upon SBSANs catalyst have shown that boron atoms play a key role in the reactivity of the catalyst. Considering to the suggested structure for the SBSANs catalyst, it seems that only tri-coordinated boron atoms have a Lewis acidic character in the structure of this catalyst. As mentioned previously, there are also Brønsted acidic sites (\(\text{OSO}_3\text{H}\) groups connected to the boron atoms.)

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**Fig. 4.** Histogram representing the size distribution of the SBSANs catalyst.

**Fig. 5.** XRD patterns of A) pure silica and B) SBSANs.

Fig. 6. Comparison between FT-IR spectra of pure silica and the SBSANs.

Fig. 7. The Raman spectra of A) pure silica and B) SBSANs catalyst.
and sulfonated hydroxyl groups on silica) on the SBSANs catalyst. It is noteworthy that, the SO₃H groups as strongly electron withdrawing groups on the boron atoms increase the Lewis acidity of the boron atoms in the structure of SBSANs catalyst. The SBSANs catalyst efficiently catalyzes the chemical process because there is a BLAS effect between the Lewis and protic acidic sites in the catalyst. To achieve the optimization reaction parameters in this study, the reaction of 4-hydroxycoumarin (2 mmol) and benzaldehyde (1 mmol) was selected as a simple model reaction for the synthesis of bis-4-hydroxycoumarins. The optimization results are depicted in Table 1. As seen in Table 1, the reaction of 4-hydroxycoumarin and benzaldehyde was carried out in the presence of 0.100 g of SBSANs catalyst under solvent-free condition at room temperature and the desired product was achieved after 12 minutes by 92% isolated yield (Table 1, entry 5). This reaction was also performed in the same condition at 80 °C with 95% isolated yield after 12 min (Table 1 entry 4). Considering these results, increasing temperature to 80 °C did not have significant effect on the reaction progress, so the room temperature was selected as optimum. The solvent effects were also examined on the model reaction, as the results are shown in Table 1. As obviously seen in Table 1, when the reaction is accomplished in refluxing ethanol or refluxing acetonitrile (CH₃CN) the yield of the desired product is decreased to some extent, because they are donor solvent and can coordinate with Lewis sites of catalyst and therefore decrease its activity (Table 1, entries 2, 3). However, by the use of dichloromethane (CH₂Cl₂) as solvent better results were obtained (Table 1, entry 1) because it is not a donor solvent. Consequently, the solvent-free condition was chosen as the best condition for this purpose. It is noteworthy that, in the absence of any catalyst in the same reaction condition, the reaction does not progress even after long reaction time (Table 1, entry 10). Employing the SBAN as a catalyst in the same reaction condition gave the product 3a with 42% isolated yield after 4 h (Table 1, entry 15). Considerable progress was not observed (Table 1, entries 11, 12) when the reaction was carried out in presence of silica or boric acid [B(OH)₃] alone. A mixture of silica and boric acid [B(OH)₃] also did not have special effect on the yield and reaction time of 3a (Table 1, entry 13). These experiments obviously showed that the structure of SBAN is different from silica and boric acid. Also, SSA was used as a catalyst in the reaction (Table 1, entry 14) to show that the catalytic performance of SBSANs catalyst does not only result from sulfonic groups (SO₃H) in the catalyst and this test confirms it. As a result, boron atoms have had a key role in the catalytic activity of SBSANs and so there has been a BLAS effect on this catalyst between Lewis acidic sites and Brønsted acidic sites. Various Lewis acids as catalyst were also used in the reaction and the obtained results were not comparable with the SBSANs catalyst (Table 1, entries 16-18). To optimize the catalytic loading of SBSANs catalyst on the model reaction, different amounts of it were used and the results were shown in Table 1. When the reaction was performed in the presence of 0.025 g of the SBSANs catalyst, 64% isolated yield of corresponding product was obtained in 1h (Table 1, entry 6). With an increase in the amount of catalyst loading to 0.050 g and 0.075 g the yield of 3a increased to 71% and 83% after 45 min and 30 min, respectively (Table 1, entries 7, 8), while increasing amount of SBSANs catalyst to 0.150 g did not have significant effect on the reaction yield and time (Table 1, entry 9). Thus optimum

Scheme 2. The chemical process for the synthesis of SBSANs catalyst
condition for this reaction is entry 5 of Table 1. In order to evaluate the generality and versatility of this method, a range of bis-4-hydroxycoumarin derivatives were prepared under optimized reaction conditions from the multi-component reaction of various aromatic and heteroaromatic aldehydes with 4-hydroxycoumarin in the presence of 0.100 g SBSANs catalyst. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-

**Table 1. Optimization of the Reaction Parameters for the Synthesis of Bis-4-hydroxycoumarins**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalys&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent&lt;sup&gt;b&lt;/sup&gt;</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SBSANs</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Reflux</td>
<td>0.50</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>SBSANs</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>Reflux</td>
<td>0.75</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>SBSANs</td>
<td>EtOH</td>
<td>Reflux</td>
<td>0.75</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>SBSANs</td>
<td>None</td>
<td>80</td>
<td>0.20</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>SBSANs</td>
<td>None</td>
<td>r.t.</td>
<td>0.20</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>SBSANs</td>
<td>None</td>
<td>r.t.</td>
<td>1.00</td>
<td>64&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>SBSANs</td>
<td>None</td>
<td>r.t.</td>
<td>0.75</td>
<td>71&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>SBSANs</td>
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<td>r.t.</td>
<td>0.50</td>
<td>83&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>SBSANs</td>
<td>None</td>
<td>r.t.</td>
<td>0.20</td>
<td>94&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>None</td>
<td>r.t.</td>
<td>12</td>
<td>N.R&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Silica</td>
<td>None</td>
<td>r.t.</td>
<td>5</td>
<td>Trace</td>
</tr>
<tr>
<td>12</td>
<td>B(OH)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>None</td>
<td>r.t.</td>
<td>5</td>
<td>26</td>
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<tr>
<td>13</td>
<td>Silica/B(OH)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>None</td>
<td>r.t.</td>
<td>4</td>
<td>35&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td>SSA</td>
<td>None</td>
<td>r.t.</td>
<td>2</td>
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<tr>
<td>15</td>
<td>SBAN</td>
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<td>r.t.</td>
<td>4</td>
<td>42</td>
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<td>16</td>
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<td>r.t.</td>
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<td>17</td>
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<td>r.t.</td>
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<td>27</td>
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<tr>
<td>18</td>
<td>ZnCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>None</td>
<td>r.t.</td>
<td>8</td>
<td>Trace</td>
</tr>
</tbody>
</table>

Amount of materials in all reactions: 4-hydroxyl coumarin (2 mmol), benzaldehyde (1 mmol).<sup>a</sup>0.100 g of catalysts were used. <sup>b</sup>5 ml of solvent was used. <sup>c</sup>Isolated yield. <sup>d</sup>0.025 g of SBSANs was used. <sup>e</sup>0.050 g of SBSANs was used. <sup>f</sup>0.075 g of SBSANs was used. <sup>g</sup>0.150 g of SBSANs was used. <sup>h</sup>No reaction. <sup>i</sup>0.100 g from the mixture with 1:1 ratio to silica and B(OH)<sub>3</sub> was used.
Table 2. Synthesis of Bis-4-hydroxycoumarin Derivatives in the Presence of Catalytic Amount of SBSANs Catalyst

\[
\begin{array}{ccccccc}
\text{Entry} & \text{Aldehyde} & \text{Product} & \text{Time (min)} & \text{Yield} & \text{m. p. (°C)} & \text{Ref.} \\
1 & \text{Benzaldehyde} & 3a & 12 & 92 & 230-232 & 228-230 \ [30] \\
2 & \text{4-Chlorobenzaldehyde} & 3b & 12 & 94 & 259-261 & 258-259 \ [33] \\
3 & \text{4-Methoxybenzaldehyde} & 3c & 15 & 90 & 247-250 & 249-250 \ [33] \\
4 & \text{4-Hydroxybenzaldehyde} & 3d & 14 & 89 & 224-226 & 222-225 \ [31] \\
5 & \text{4-Methylbenzaldehyde} & 3e & 15 & 94 & 270-272 & 269-270 \ [33] \\
6 & \text{Thiophen-2-carbaldehyde} & 3f & 14 & 90 & 216 (dec) & 213 (dec) \ [31] \\
7 & \text{Pyridine-4-carbaldehyde} & 3g & 12 & 96 & 256-259 & 252-254 \ [31] \\
8 & \text{3-Nitrobenzaldehyde} & 3h & 13 & 91 & 212-215 & 212-215 \ [32] \\
9 & \text{4-Nitrobenzaldehyde} & 3i & 11 & 97 & 236-238 & 232-234 \ [30] \\
10 & \text{2-Nitrobenzaldehyde} & 3j & 12 & 92 & 201-204 & 200-202 \ [32] \\
11 & \text{3-Chlorobenzaldehyde} & 3k & 12.5 & 90 & 224-226 & 222-224 \ [32] \\
12 & \text{Indol-3-carbaldehyde} & 3l & 16 & 88 & 243-245 & 240-244 \ [30] \\
\end{array}
\]

*Reaction conditions: aldehyde (1 mmol), 4-hydroxycoumarin (2 mmol) and SBSANs (0.100 g). bIsolated yield.

Table 3. Reusability Study of SBSANs Catalyst

<table>
<thead>
<tr>
<th>Run</th>
<th>Yield of product (%)</th>
<th>Recovery of SBSANs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh</td>
<td>92</td>
<td>&gt;99</td>
</tr>
<tr>
<td>1</td>
<td>92</td>
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<td>98</td>
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<td>3</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>97</td>
</tr>
</tbody>
</table>

*Reaction conditions: benzaldehyde (1 mmol), 4-hydroxycoumarin (2 mmol) and SBSANs catalyst (0.100 g). Reaction time is 20 min.

withdrawing groups reacted successfully and gave the expected products in excellent yields and short reaction times. The type of aromatic aldehyde had no significant effect on the reaction (Table 2). It should be noted that, the acid sensitive aldehydes such as thiophen-2-carbaldehyde converted to the desired product in an excellent yield and short reaction time (Table 2, entry 6).

To examine the recycling possibility of the catalyst, the reaction between 4-hydroxycoumarin (2 mmol) and benzaldehyde (1 mmol) was performed under optimized conditions. After completion of reaction, the reaction mixture was dissolved in chloroform and then catalyst was separated by simple filtration and washed with hot ethanol. The recycled catalyst was dried in an oven for 2 h at 100 ºC and stored for the next operation. It adopted the same procedure for all the recycling studies. Considering the results of Table 3, the catalyst exhibited good catalytic activity up to five runs without appreciable loss of its catalytic activity and no marginal difference in the yield of the product. After five runs of reusability we checked the catalytic activity of SBSANs by measuring the sulfur content on catalyst with elemental analysis instrument, and the results showed that only 0.8% of sulfur was lost during the reactions. These results are in good agreement with catalytic performance of SBSANs catalyst after each run and no appreciable loss of catalytic activity of SBSANs was observed.

Also, to evaluate the efficiency of our catalyst with the reported catalysts for the synthesis of bis-4-hydroxycoumarins, we have tabulated the obtained results from these catalysts for the synthesis of compound 3a in Table 4. As depicted in Table 4, our catalyst is superior to some of the previously reported catalysts in terms of reaction condition, reaction time, and yield.

Also, we propose a plausible mechanism for the synthesis of bis-4-hydroxycoumarins by using the SBSANs catalyst to show the effect of catalyst in the reaction progress (Scheme 3). As can be seen in Scheme 3, the promoted aldehyde 2 by protonation reacts with 4-hydroxycoumarin 1 activated by boron atoms (as a Lewis acid) and produces the Knoevenagal intermediate 4. Afterward, the intermediate 4 reacts with another activated

Table 4. Comparison of the Results from the Synthesis of Compound 3a by Use of SBSANs Catalyst with the other Catalytic Systems

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time/Yield (%)&lt;sup&gt;a&lt;/sup&gt;Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHSO&lt;sub&gt;4&lt;/sub&gt;, SiO&lt;sub&gt;2&lt;/sub&gt;/toluene/100 ºC</td>
<td>30 min/89&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>I&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;2&lt;/sub&gt;O/100 ºC</td>
<td>25 min/97&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Zn(Prolinc)&lt;sub&gt;2&lt;/sub&gt;/H&lt;sub&gt;2&lt;/sub&gt;O/reflux</td>
<td>5 min/92&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>[MIM(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;SO&lt;sub&gt;3&lt;/sub&gt;H][HSO&lt;sub&gt;4&lt;/sub&gt;]/solvent-free/80 ºC</td>
<td>30 min/92&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Silica-supported Preyssler nanoparticles/EtOH/r.t.</td>
<td>30 min/92&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Catslyst-free/microwave irradiation/H&lt;sub&gt;2&lt;/sub&gt;O/150 W, 150 ºC</td>
<td>9 min/85&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Catslyst-free/ultrasound irradiation/H&lt;sub&gt;2&lt;/sub&gt;O/100 W</td>
<td>5 min/98&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Catslyst-free/H&lt;sub&gt;2&lt;/sub&gt;O/95 ºC</td>
<td>5 h/93&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>SiO&lt;sub&gt;2&lt;/sub&gt;/H&lt;sub&gt;2&lt;/sub&gt;O/reflux</td>
<td>60 min/95&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Nano SiO&lt;sub&gt;2&lt;/sub&gt;/Cl/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;/40 ºC</td>
<td>2.5 h/85&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>SBSANs/solvens-free/ r.t.</td>
<td>12 min/92&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>This work.
4-hydroxycoumarin 1 via Michael addition and creates the corresponding product 3. It seems that the Lewis and Bronsted acidic sites of SBSANs catalyst are effective completely in the progress of reaction.

**CONCLUSIONS**

In summary, a simple, rapid and efficient approach for the synthesis of a wide range of bis-4-hydroxycoumarins via three-component condensation reaction between 4-hydroxycoumarin and aromatic & hetero aromatic aldehydes employing SBSANs as a dual Lewis-protic solid acid catalyst under mild and solvent-free condition at room temperature was reported. This class of Coumarins has a wide range of biological activity and thus our methodology may have clinical significant. Reusability, easy work-up and purification procedure, short reaction time, high yield of products and environmentally benign are advantages of this method.

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REFERENCES


