Application of SBA-Pr-SO$_3$H in the synthesis of benzoxazole derivatives

Ghodsi Mohammadi Ziarani a,*, Alireza Badiei b, Monireh Shakiba Nahad a and Malihe Hassanzadeh a

a Department of Chemistry, Alzahra University, Vanak Square, Tehran, 199389-1176, Iran
b School of Chemistry, College of Science, University of Tehran, Tehran, 14155-6655, Iran

*Corresponding author at: Department of Chemistry, Alzahra University, Vanak Square, Tehran, 199389-1176, Iran.
Tel.: +98.21.88041344; Fax: +98.21.88044134. E-mail address: gzmziarani@hotmail.com (G.M. Ziarani).

ARTICLE INFORMATION
Received: 19 August 2012
Received in revised form: 23 September 2012
Accepted: 23 September 2012
Online: 31 December 2012

KEYWORDS
Benzoazole
Nanoreactor
SBA-Pr-SO$_3$H
2-Aminophenol
Benzyl chlorides
Hydroxybenzaldehyde

1. Introduction

Benzoxazoles and other heterocycles are found in very important classes of bioactive compounds such as antibiotic, antibacterial, antiinflammatory, antistress, antiulcer, and anticancer agents [1-7]. They have recently received considerable attention for their pharmaceutical activities. Flunoxaprofen, benoxaprofen and boxazomycine B are three example of this class of compounds (Figure 1).

![Figure 1. Structure of some benzoxazole drugs.](image)

General methods for the synthesis of benzoxazoles involve two approaches. The first approach is the copper-catalyzed intramolecular ortho-arylation of $o$-haloanilides or the intermolecular annulations of $o$-arylhalides with acylamides. The second approach is the condensation of 2-aminophenol with carboxylic acid derivatives in the presence of strong acid/high temperature conditions, or aldehydes with subsequent oxidation using strong oxidants such as PhI(OAc)$_2$, pyridiniumchlorochromate (PCC) [8]. In this reaction, different catalysts such as ThClO$_4$ [9], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and BaMnO$_4$ [10], In(OTf)$_3$ [11], I$_2$ [12], N,N'-dibenzyl-1,1'binaphthyl-2,2'-diamine-copper(II) complex [13], p-TsOH.H$_2$O [14], 4-methoxy-2,2,6,6-tetramethyl-1-piperidinyloxy(4-methoxy-TEMPO) [10], Cu(OTf)$_2$ [15], CuI/1,10-phenanthroline [15], Cu(OTf)$_2$ [16-17], FeCl$_3$/2,2,6,6-tetra-methyl-3,5-heptanediol (TMHD) [18], Zn(OAc)$_2$/2H$_2$O [19], SiO$_2$/FeCl$_3$ [20] and CuO nano particles [21] were also used. However many of these methodologies have difficulties in recovery and reusability of the catalysts.

Therefore, in this article we used SBA-Pr-SO$_3$H as heterogeneous nanocatalyst in the one pot synthesis of benzoxazoles. The heterogeneous catalysts can conveniently be removed from the reaction mixture, making the experimental procedure simple and eco-friendly [22]. SBA-Pr-SO$_3$H has mesoporous silica structure with pore size of 6 nm which can act as reactive nano-reactor in organic synthesis [23].

2. Experimental

2.1. Instrumentation

Electronic ionization GC-MS spectra were recorded on a 5973 network mass selective detector, GC 6890 Agilent spectrometer. IR spectra were obtained with a FT-IR Bruker 500 scientific spectrometer as KBr pellets. The $^1$H NMR was run on a Bruker DPX, 250 MHz, in CDCl$_3$. Chemical shifts are reported in $\delta$ from TMS. Melting points were measured by the capillary tube method with a 9200-Barnstead electro thermal apparatus. SEM analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV while TEM was carried out on a Tecnai G$^+$F30 at 300 kV.
2.2. Synthesis

2.2.1 Preparation of catalyst

The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report and the modified SBA-15-Pr-SO₃H was used as nanoporous solid acid catalyst in the following reaction [24-26]. For the preparation of the catalyst, calcinated SBA-15 (2 g) and (3-mercaptopropyl) trimethoxysilane (10 mL) in dry toluene (20 mL) were refluxed for 24 h. The product was filtered and extracted for 6 h in CH₂Cl₂ using a soxhlet apparatus, then dried under vacuum. Then, the solid product was oxidized with H₂O₂ (excess) and one drop of H₂SO₄ in methanol (20 mL) for 24 h at room temperature. Then the mixture was filtered and washed with H₂O, and acetone. The modified SBA-15-Pr-SO₃H was dried and used as nanoporous solid acid catalyst in the following reaction.

2.2.2. General procedure for the synthesis of hydroxybenzazidene derivatives (3)

SBA-Pr-SO₃H (0.02 g) was placed in a flask and activated at 100 °C under vacuum condition for 20 min. Then the catalyst was allowed to cool to room temperature. The reaction mixture of substituted benzoyl chloride (2a-i) (3 mmol) and 2-aminophenol (1) (3 mmol, 0.33 g) was stirred at 70 °C (Scheme 1, Table 1). The solid benzoyl chlorides (3-nitro, 4-nitro- and 3,5-dinitro-benzoyl chloride) were kept in 90 °C. After completion of the reaction which was monitored by TLC (n-hexane:EtOAC, 1:1), convenient crystallization solvent was added to the reaction mixture for recrystallization of crude product and catalyst was separated by simple filtration.

2.2.3. General procedure for the synthesis of benzoxazoles (4)

Substituted benzoyl chloride (2a-i) (3 mmol), 2-aminophenol (1) (3 mmol, 0.33 g) and acetic acid (3 mL) was added to activate catalyst (SBA-Pr-SO₃H (0.02 g)) (Scheme 2, Table 2). The mixture was stirred for 8 h under reflux conditions. After completion of the reaction which was monitored by TLC (n-hexane:EtOAC, 3:1), the crude product was dissolved in acetic acid, and catalyst was removed by simple filtration of reaction mixture. The gradual evaporation of acetic acid, gave the pure crystals of product.

2-Phenyl benzoxazole (4a): FT-IR (KBr, cm⁻¹): 3043 v(C-H) (aromatic), 1693 v(C=N) (imine), 1579 v(C=C) (aromatic), 1247 v(C-O) (ether). 1H NMR (250 MHz, DMSO-d₆, δ, ppm): 7.28-7.37 (m, 2H, Ar-H), 7.47-7.58 (m, 4H, Ar-H), 8.22-8.25 (m, 1H, Ar-H). MS (m/z (%)): 240 (100), 194 (44), 139 (16), 63 (13).

2-(4-Dichlorophenyl)benzoxazole (4e): FT-IR (KBr, cm⁻¹): 3073 v(C-H) (aromatic), 1700 v(C=N) (imine), 1647 v(C=C) (aromatic), 1282 v(C-O) (ether). 1H NMR (250 MHz, DMSO-d₆, δ, ppm): 7.26 (m, 4H, Ar-H), 7.34 (s, 1H, Ar-H), 7.36 (d, 2H, Ar-H). MS (m/z, %): 263 (100, 63 (60).

2-(3-Nitrophenyl)benzoxazole (4f): FT-IR (KBr, cm⁻¹): 2979 v(C-H) (aromatic), 1611 v(C=N) (imine), 1513 v(C=C) (aromatic), 1260 v(N=O). 1H NMR (250 MHz, DMSO-d₆, δ, ppm): 9.1 (d, 1H, Ar-H), 8.37-8.61 (m, 3H, Ar-H), 7.26-7.85 (m, 4H, Ar-H). MS (m/z (%)): 240 (100), 194 (44), 139 (16), 63 (13).

2-(5-Dinitrophenyl)benzoxazole (4h): FT-IR (KBr, cm⁻¹): 3181 v(C-H) (aromatic), 1657 v(C=N) (imine), 1535 v(N=O). 1H NMR (250 MHz, DMSO-d₆, δ, ppm): 6.88-7.15 (m, 4H, Ar-H), 7.73 (s, 1H, Ar-H), 9.15 (s, 1H, Ar-H), 9.31 (s, 1H, Ar-H).

3. Results and discussion

In this investigation the synthesis of 2-hydroxy-benzazidene derivatives (3) (Scheme 1) and 2-aryl benzoxazoles (4) (Scheme 2) from the condensation of 2-aminophenol (1) and benzoyl chlorides (2a-i) in the presence of SBA-Pr-SO₃H as heterogeneous and reusable nanocatalyst were studied.
Table 1. Synthesis of hydroxyl-benzanilide derivatives (3a-i) catalyzed by SBA-Pr-SO3H in solvent free conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>X</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
<th>M.p. (°C)</th>
<th>M.p. (Lit.)</th>
<th>Crystallization solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>2-Cl</td>
<td>70</td>
<td>1 h</td>
<td>71</td>
<td>190-191</td>
<td>192-193</td>
<td>EtOH</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>3-Cl</td>
<td>70</td>
<td>1.30 h</td>
<td>52</td>
<td>173-175</td>
<td>171-172</td>
<td>Acetone</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>2,4-di-Cl</td>
<td>70</td>
<td>1.30 h</td>
<td>46</td>
<td>173-174</td>
<td>173-174</td>
<td>Acetone</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>3-N02</td>
<td>90</td>
<td>2 h</td>
<td>93</td>
<td>205-207</td>
<td>206[30]</td>
<td>EtOH</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>4-N02</td>
<td>90</td>
<td>50 min</td>
<td>72</td>
<td>209-210</td>
<td>206-207[28]</td>
<td>Acetone</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>3,5-di-N02</td>
<td>90</td>
<td>40 min</td>
<td>98</td>
<td>255-260</td>
<td>-</td>
<td>EtOH</td>
</tr>
</tbody>
</table>

Table 2. Synthesis of benzoxazole derivatives (4a-1) catalyzed by SBA-Pr-SO3H.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>M.p. (°C)</th>
<th>M.p. (Lit.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>H</td>
<td>8</td>
<td>91</td>
<td>102-103</td>
<td>105-104[31]</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>2-Cl</td>
<td>8</td>
<td>83</td>
<td>72-74</td>
<td>70-72[11]</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>3-Cl</td>
<td>8</td>
<td>85</td>
<td>123-125</td>
<td>124-125[32]</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-Cl</td>
<td>8</td>
<td>78</td>
<td>140-142</td>
<td>140-142[13]</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>2,4-di-Cl</td>
<td>8</td>
<td>82</td>
<td>119-120</td>
<td>118-118[13]</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>3-N02</td>
<td>8</td>
<td>81</td>
<td>205-207</td>
<td>207[33]</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>4-N02</td>
<td>8</td>
<td>75</td>
<td>258-260</td>
<td>257-263[34]</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>3,5-di-N02</td>
<td>8</td>
<td>87</td>
<td>205-207</td>
<td>205-207[35]</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>2-Me</td>
<td>8</td>
<td>85</td>
<td>66-70</td>
<td>68-69[10]</td>
</tr>
</tbody>
</table>

A plausible mechanism was shown in Scheme 3. At first, SBA-Pr-SO3H as a Bronsted nano-catalyst protonates the carbonyl group of benzoyl chloride. Then, the reaction was followed by nucleophilic attack of amino group of 2-amino phenol to carbonyl group of benzoyl chloride. The nucleophilic attack of OH to carbonyl group of compound (3), gave the cyclization product (5) which converted to benzoxazole derivatives by dehydration.

The acid catalyst can be reactivated by simple washing subsequently with diluted acid solution, water and acetone, and then reused without noticeable loss of reactivity. The new products were characterized by IR and NMR spectroscopy data. Melting points are compared with reported values in the literature as shown in Table 2.

For the preparation of the catalyst, at first, the surface of SBA-15 was functionalized and grafted with (3-mercaptopropyl)trimethoxysilane (MPTS), the thiol groups have been incorporated to surface of SBA-15 under reflux condition in dry toluene. Then the thiol groups were oxidized into sulfonic acid groups by hydrogen peroxide (Figure 2) [36,37].

The SEM and TEM images of SBA-Pr-SO3H illustrated in Figure 4. Figure 4a shows SEM image of SBA-Pr-SO3H that indicates uniform particles about 1 µm. The TEM image (Figure 4b) represents the parallel channels that were not collapsed during two step reactions. In general, organic functionalization did not alter the long-range mesoporous arrangement [25,26].

Figure 2. Preparation of SBA-Pr-SO3H.

Nanopore size about 6 nm of SBA-Pr-SO3H could act as nano-reactor and catalyzed synthesis of benzoxazole derivatives. A schematic illustration for this activity was shown in Figure 3.
4. Conclusion

In summary, we have described the use of nano acid solid catalyst of SBA-Pr-SO3H in the synthesis of benzoxazole derivatives and 2-hydroxy-benzanilide. Furthermore, operational and experimental simplicity, readily availability, easy work-up procedure and good yields make it, a facile method for the synthesis of these compounds.

Acknowledgements

We gratefully acknowledge for financial support from the Research Council of Alzahra University and University of Tehran.

References