Synthesis of 2,3-Dihydroquinazolin-4(IH)-ones Promoted by Polystyrene Sulfonic Acid

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In this research, we have synthesized polystyrene sulfonic acid as a new heterogeneous solid acid. A good range of 2,3-dihydroquinazolin-4(IH)-ones via condensation of 2-aminobenzamide and different aldehydes in the presence of polystyrene sulfonic acid were synthesized. The major advantages of the present methodology are good yields, ecofriendly and easy work-up.

Keywords: Synthesis of 2,3-dihydroquinazolin-4(IH)-ones, Polystyrene sulfonic acid, Heterogeneous catalyst, 2-Aminobenzamide, Solid acid

INTRODUCTION

Quinazolinones as bioactive molecules are of paramount importance in chemical and pharmaceutical industries [1]. The chemistry of quinazolinones comprehensively has been reviewed [2]. Quinazolinone and its derivatives have many biological and medicinal activities such as hypnotic/sedatives [3], antimalarial [4], antibacterial and antioxidant [5], antimicrobial [6], antitumor [7], antifungal and cytotoxic [8], antiproliferative [9], and inhibitory activities on α-glucosidase [10]. In Fig. 1, structures of quinethazone and metolazon (hypertensive) [11], febrifugine and isofebrifugine (antimalaria), and methaqualone (sedative) are shown. Quinazolinones are synthesized via condensation of 2-aminobenzamid with aldehydes in the presence of an acidic catalyst. This reaction has been catalyzed by L\textsubscript{2} [12], ZnFe\textsubscript{2}O\textsubscript{4} [13], silver triflate [14], Sc(OTf)\textsubscript{3} [15], lactic acid [16], CeCl\textsubscript{3} [17], FeCl\textsubscript{3}/egg shell [18], bismuth(III) bromide [19], Zn-2-amino-3-hydroxy-pyridine-MCM-41 [20], SOCl\textsubscript{2} [21], succinimide-N-sulfonic acid [22], ammonium chloride [23], and nano-Fe\textsubscript{2}O\textsubscript{3}/TiCl\textsubscript{4}/cellulose [24], polyethylene glycol-bonded tetraethyl ammonium hydroxide ([PEG-TEA]OH) [25], nanometasilica disulfuric acid (NMSDSA) nanometasilica monosulfuric acid sodium salt (NMSMSA) [26], silica sulfuric acid [27-30], SiO\textsubscript{2}-FeCl\textsubscript{3} [31] and ZnCl\textsubscript{2}-SiO\textsubscript{2} [32]. The use of inexpensive, ecofriendly, and heterogeneous catalysts in organic synthesis has attracted lots of attention. In this research, polystyrene sulfonic acid (acid) is prepared as a heterogeneous catalyst, and used for the synthesis of 2,3-dihydro-2-phenylquinazolin-4(IH)-ones.

EXPERIMENTAL

Materials and Methods

The chemicals were purchased from Merck and Aldrich companies and used without further purification. The products were characterized by FT-IR, and their physical properties were compared with those reported in the literature. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus. A Bruker (DRX-400 Avance) NMR was used to record the $^1$HNMR spectra.

Preparation of Polystyrene Sulfonic Acid

In a round bottom flask, 4 ml of sulfuric acid was added...
to a mixture of polystyrene (4 g) and CH₂Cl₂ (10 mL). The mixture was stirred for 4 h at room temperature. The polystyrene sulfonic acid was decanted into ice-cold water, filtered, and washed several times with distilled water and dried at room temperature.

**General Procedure for the Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones**

Polystyrene sulfonic acid (0.1 g) was added to a solution of 2-aminobenzamide (1 mmol, 0.136 g) and aldehyde (1 mmol) in EtOH (3 mL) in a 25-mL round bottom flask. The mixture was refluxed for an appropriate time. The progress of the reaction was monitored by TLC (EtOAc: n-Hexane, 1:4). After completion of the reaction, the catalyst was removed by filtration. The solid products were appeared by addition of water to filtrate, that were filtered and washed with water. The products were finally recrystallized from ethanol and water to afford the corresponding 2,3-dihydroquinazolin-4(1H)-ones in 75-96% yields.

**Physical and Spectroscopic Data for Selected Compounds**

2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 1). White solid, ¹H NMR (DMSO-d₆, 400 MHz): δ 8.45 (brs, 1H), 8.16 (m, 1H), 8.02 (m, 2H), 7.83 (m, 3H), 7.69 (brs, 1H), 7.37 (brs, 1H), 7.26 (m, 1H), 7.15 (brs, 1H), 6.27 (s, 1H). FT-IR (cm⁻¹): 3301, 3176, 3062, 1653, 1610, 1509, 1482.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 2). Yellow solid, ¹H NMR (Acetone-d₆, 400 MHz): δ 8.26 (d, J = 8 Hz, 2H), 7.87 (d, J = 8 Hz, 2H), 7.78 (m, 1H), 7.52 (brs, 1H), 7.30 (m, 1H), 6.84-6.79 (m, 2H), 6.51 (brs, 1H), 6.11 (s, 1H). FT-IR (cm⁻¹): 3352, 3291, 1658, 1609, 1513, 1484, 1346.

2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 3). Light yellow solid, ¹H NMR (Acetone-d₆, 400 MHz): δ 8.46 (brs, 1H), 8.24 (brs, 1H), 8.06 (brs, 1H), 7.77 (brs, 1H), 7.72 (brs, 1H), 7.60 (brs, 1H), 7.31 (brs, 1H), 6.86 (brs, 1H), 6.79 (brs, 1H), 6.53 (brs, 1H), 6.14 (s, 1H). FT-IR (cm⁻¹): 3281, 3186, 3074, 1649, 1605, 1520, 1483, 1349, 862, 747, 680.

2-(2-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 4). Yellow solid, ¹H NMR (Acetone-d₆, 400 MHz): δ 8.06 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.78-7.80 (m, 2H), 7.62-7.66 (m, 1H), 7.27-7.32 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.76-6.80 (m, 1H), 6.50 (s, 1H), 6.32 (brs, 1H). FT-IR (cm⁻¹): 3419, 3182, 3005, 1661, 1608, 1507, 1338, 738.

2-(4-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 5). Off white solid, ¹H NMR (DMSO-d₆, 400 MHz): δ 8.05 (brs, 1H), 7.70 - 7.52 (m, 5H), 7.25 (brs, 1H), 6.93 (brs, 1H), 6.80 (brs, 1H), 6.71 (m, 1H), 5.82 (s, 1H). FT-IR (cm⁻¹): 3307, 3186, 1651, 1603, 1476.

2-(4-Isopropylphenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 6). Pale yellow solid, ¹H NMR (Acetone-d₆, 400 MHz): δ 7.78 (brs, 1H), 7.49 (brs, 2H), 7.29 (brs, 3H), 7.11 (brs, 1H), 6.84 (m, 1H), 6.77 (m, 1H), 6.16 (brs, 1H), 5.86 (s, 1H), 2.50 (m, 1H), 1.23 (d, J = 6.4 Hz, 6H). FT-IR (cm⁻¹): 3291, 2952, 1653, 1608, 1433, 751.

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 7). White solid, ¹H NMR (Acetone-d₆, 400 MHz): δ 7.78 (m, 2H), 7.39-7.45 (m, 3H), 7.25-7.29 (m, 2H), 6.86 (brs, 1H), 6.79 (brs, 1H), 6.33 (brs, 1H), 6.24 (brs, 1H). FT-IR (cm⁻¹): 3358, 3183, 3065, 1643, 1608, 1500, 1431, 1122, 1032, 742.

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 8). White solid, ¹H NMR (Acetone-d₆, 400 MHz): δ 7.78 (brs, 1H), 7.62 (brs, 2H), 7.44 (brs, 2H), 7.29 (brs, 2H), 6.82 (2H), 6.28 (brs, 1H), 5.94 (s, 1H). FT-IR

Scheme 1

In this work, we prepared polystyrene sulfonic acid by the sulfonation of polystyrene phenyl rings by concentrated sulfuric acid in CH₂Cl₂ (Scheme 1).

For structural study of PSSA, the FT-IR (ATR) spectra of polystyrene and PSSA are compared in Fig. 2. The absorption bands at 3398, 1284, 1180, 1033 and 851 cm⁻¹ in PSSA spectrum were assigned to the stretching of the -OH, O=S=O and S-O bands in SO₃H groups.

 Thermal gravimetric analysis (TG) of PSSA was detected from 50 to 400 °C (Fig. 3). The catalyst was stable until 105 °C and only 3% of its weight was lost due to the removal of its moisture. Heating the catalyst until

**RESULTS AND DISCUSSIONS**

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**Fig. 3.** Thermal gravimetric analysis of polystyrene sulfonic acid (PSSA).

**Table 1.** Synthesis of 2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one under Various Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>PSSA (0.1)</td>
<td>r.t.</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>PSSA (0.1)</td>
<td>100 °C</td>
<td>4</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>3.25</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>H₂O,EtOH</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CN</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>4</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>4</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>3.75</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>0.8</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>EtOH</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>1.25</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>EtOH</td>
<td>PSSA (0.1)</td>
<td>Reflux</td>
<td>1.25</td>
<td>85</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>EtOH</td>
<td>PSSA (0.09)</td>
<td>Reflux</td>
<td>2</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>EtOH</td>
<td>PSSA (0.08)</td>
<td>Reflux</td>
<td>2.5</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>EtOH</td>
<td>PSSA (0.07)</td>
<td>Reflux</td>
<td>2.25</td>
<td>43</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>EtOAc</td>
<td>I₂ (0.05 equiv)</td>
<td>O₂/hv</td>
<td>15</td>
<td>88</td>
<td>[12]</td>
</tr>
<tr>
<td>15</td>
<td>H₂O</td>
<td>Lactic acid (20 mol%)</td>
<td>60 °C</td>
<td>0.33</td>
<td>88</td>
<td>[16]</td>
</tr>
<tr>
<td>16</td>
<td>Ethanol</td>
<td>Sc (OTf)₃ (5 mol%)</td>
<td>70 °C</td>
<td>0.41</td>
<td>91</td>
<td>[15]</td>
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<tr>
<td>17</td>
<td>H₂O</td>
<td>ZnFeO₄ (30 mol%)</td>
<td>M.W.</td>
<td>0.17</td>
<td>92</td>
<td>[13]</td>
</tr>
<tr>
<td>18</td>
<td>Dimethylcarbonat</td>
<td>CeCl₃ (5 mol%)</td>
<td>100 °C</td>
<td>8</td>
<td>90</td>
<td>[17]</td>
</tr>
<tr>
<td>19</td>
<td>Ethanol</td>
<td>FeCl₃/egg shell</td>
<td>r.t.</td>
<td>0.17</td>
<td>99</td>
<td>[18]</td>
</tr>
<tr>
<td>20</td>
<td>H₂O</td>
<td>Zn-2-amino-3-hydroxy-pyridine-MCM-41</td>
<td>90 °C</td>
<td>2</td>
<td>98</td>
<td>[20]</td>
</tr>
</tbody>
</table>

⁴4-Chlorobenzaldehyde (1 mmol, 0.14 g), 2-aminobenzamide (1 mmol, 0.136 g). ⁵Isolated yield.
340 °C led to the reduce of the mass by 27%. The char yield of PSSA in 340 °C was 73%.

Acidic capacity of polystyrene sulfonic acid was determined using titration method. 0.1 g of PSSA was titrated with NaOH (aq) 0.0833 M in the presence of phenolphthalein as an indicator. According to the calculations, the acidic capacity of catalyst was equal to 2.08 meq H⁺/g.

In this project, we have used PSSA in the preparation of quinazolinones via reaction of 2-aminobenzamide and aldehydes. To optimize the reaction conditions, the reaction 2-aminobenzamide and 4-chlorobenzaldehyde was investigated as a model reaction under various reaction conditions (Table 1). As shown in Table 1, entry 8, it was found that using 0.1 g of PSSA for 1 mmol of substrates under reflux condition in ethanol is the best reaction choice.

The reusability of the described catalyst is one of the most important benefits for the business applications. Therefore, the recycling of the polystyrene sulfonic acid was investigated in model reaction (Table 1, Entries 9-10). After reaction completion, the polystyrene sulfonic acid was washed with ethanol, dried and reused for other runs with a trivial decrease in its catalytic activity.

Finally, the above optimized reaction conditions were

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>M.P. Obtained</th>
<th>M.P. Reported [Ref.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1</td>
<td>65</td>
<td>208-210</td>
<td>216-218 [23]</td>
</tr>
<tr>
<td>2</td>
<td>4-NO₂</td>
<td>1</td>
<td>85</td>
<td>307-309</td>
<td>309-312 [24]</td>
</tr>
<tr>
<td>3</td>
<td>3-NO₂</td>
<td>0.75</td>
<td>85</td>
<td>190-193</td>
<td>193-195 [24]</td>
</tr>
<tr>
<td>4</td>
<td>2-NO₂</td>
<td>1</td>
<td>60</td>
<td>193-195</td>
<td>191-192 [20]</td>
</tr>
<tr>
<td>5</td>
<td>4-Br</td>
<td>1</td>
<td>90</td>
<td>199-200</td>
<td>193-198 [20]</td>
</tr>
<tr>
<td>6</td>
<td>4-(CH₃)₂CH</td>
<td>2</td>
<td>90</td>
<td>158-161</td>
<td>158-161 [24]</td>
</tr>
<tr>
<td>7</td>
<td>2-Cl</td>
<td>0.5</td>
<td>90</td>
<td>206-208</td>
<td>206-208 [16]</td>
</tr>
<tr>
<td>8</td>
<td>4-Cl</td>
<td>0.8</td>
<td>95</td>
<td>193-194</td>
<td>200-204 [20]</td>
</tr>
<tr>
<td>9</td>
<td>2,4-(Cl)₂</td>
<td>1.2</td>
<td>80</td>
<td>165-169</td>
<td>166-169 [24]</td>
</tr>
<tr>
<td>10</td>
<td>2,4-(MeO)₂</td>
<td>1</td>
<td>60</td>
<td>185-187</td>
<td>185-187 [24]</td>
</tr>
</tbody>
</table>

Aldehyde (1 mmol), 2-aminobenzamide (1 mmol, 0.136 g), PSSA (0.1 g) and ethanol (3 ml) were used. Isolated yield.
explored for the synthesis of quinazolinone derivatives (Scheme 2, Table 2). The aromatic aldehydes containing electron releasing or electron withdrawing groups react in this protocol with high yields.

CONCLUSIONS

In this study, we demonstrate a simple method for the synthesis of quinazolinones in the presence of a catalytic amount of polystyrene sulfonic acid in ethanol under reflux condition. This project has some advantages such as high efficiency, short reaction times, simple separation of catalyst, and easy workup. Finally, on the basis of our observations and the above mentioned advantages, we suggest that the described PSSA has a potential for industrial productions.

ACKNOWLEDGMENTS

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REFERENCES
