SILICA SUPPORTED PERCHLORIC ACID: AN EFFICIENT AND RECYCLABLE CATALYST FOR SYNTHESIS OF BENZIMIDAZOLO[2,3-b]QUINAZOLINONES


Keywords: 2-Aminobenzimidazole; benzimidazolo[2,3-b]quinazolinones; heterogeneous catalyst; perchloric acid; silica.

Synthesis of benzimidazolo[2,3-b]quinazolinone derivatives has been reported in excellent yields by using silica-supported perchloric acid (HClO4-SiO2) as a mild and reusable heterogeneous catalyst. The procedure is simple, environmentally benign and has the advantage of high atom economy. Furthermore, the catalyst can be recovered and reused several times efficiently without substantial loss of catalytic activity.

*Corresponding author
Tel: +91 0240 2334577; Fax: +91 0240- 2334430
E-Mail: rppawar@yahoo.com, kkpravin@gmail.com
[a]  Department of Chemistry, Deogiri College, Aurangabad, 431005, MS, India.
[b]  Department of Health Sciences, Central University of Technology, Free State, South Africa.

INTRODUCTION

Heterogeneous catalysis is an interesting area of research from an industrial point of view. It has the advantages of thermal stability, high selectivity, better activity, ease of separation, recyclability and long life.1-4 Solid acid catalysts play an important role in organic transformations due to many advantages such as simplicity in handling, decreased reactor corrosion problems and more environmentally safe disposal of the catalyst.5-7 Quinazolinones and their derivatives have been reported to possess interesting pharmacological activities, such as antibacterial,8-9 antihypertension,10 antihistaminic,11 analgesic, anti-inflammatory,12 anticancer,13 and anti-HIV.14 Moreover, a variety of quinazolinones derivatives with different biological activities were synthesized by medicinal chemistry researchers. These derivatives also have a long history of applications in agrochemicals and the pharmaceutical industry as herbicides and active pharmaceuticals. Awareness about environmental hazards in chemical industries becomes a significant concern due to the generation of waste products that leads to the development of environment-friendly synthetic processes. Heterocyclic compounds constitute comprehensive examples in pharmaceutical and chemical industries. Because of their potent physiological properties, they resulted in numerous applications.15

Several methods have been reported for the synthesis of substituted benzimidazolo-quinazolinones. The most common method is the reaction of substituted aldehydes with 2-amino benzimidazole and dideion using various basic and acidic catalysts under reflux conditions,15-16 ionic liquids17 and heteropolyacids.18

EXPERIMENTAL

Preparation of HClO4-SiO2 catalyst:

Aqueous perchloric acid (70 %, 1.8g, 12.5 mmol) was added to a suspension of SiO2 (230-400 mesh, 23.7 g) in...
ether (70 ml). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to give HClO4-SiO2 (0.5 mmol g⁻¹) as free-flowing powder.22


Silica supported perchloric acid (10 wt.%) was added to a mixture of 2-aminobenzimidazole (1 mmol), aldehyde (1 mmol) and dimedone (1 mmol) in 1:1 ethanol: water (5 mL). The mixture was heated at 100 °C for 72 h under vacuum to give HClO4-SiO2 (0.5 mmol g⁻¹) as free-flowing powder.22

Similarly, the other derivatives were also synthesized using the same method (Table 1). Spectral data of the synthesized compounds is mentioned below:

3,3-Dimethyl-12-phenyl-1,2,3,4,5,12-hexahydrobenzo[4,5]-imidazo[2,1-b]quinazolin-1-one (4a)

M.p. 270-280 °C; IR (KBr): 2869, 1681, 1612, 1518 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ H = 1.06 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.19 (s, 2H, CH₂), 2.35 (s, 2H, CH₂), 6.90 (s, 1H, CH), 7.25-8.10 (m, 4H, Ar-H), 7.25-8.10 (m, 2H, Ar-H), 6.93-7.38 (m, 9H, Ar-H), 11.12 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2,4-dichlorophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4b)

M.p. 315-330 °C; IR (KBr): 3085, 2930, 1615, 1520 cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz): δ H = 1.0 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 2.11 (s, 2H, CH₂), 2.49 (s, 2H, CH₂), 3.69 (s, 6H, OCH₃), 3.75 (s, 3H, OCH₃), 6.35 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2,4,6-methoxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4c)

M.p. 280-290 °C; IR (KBr): 3243, 2961, 1641, 1612, 1589, 1566 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ H = 1.03 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 2.06-2.15 (m, 2H, CH₂), 2.25-250 (m, 2H, CH₂), 3.66 (s, 3H, OCH₃), 6.35 (s, 1H, H-12), 6.73-7.42 (m, 8H, Ar-H), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2,4,6-methoxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4d)

M.p. 292-302 °C; IR (KBr): 3210, 2969, 1690, 1590, 1312, 1258 cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz): δ H = 1.09 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 2.11 (s, 2H, CH₂), 2.49 (s, 2H, CH₂), 3.69 (s, 6H, OCH₃), 3.75 (s, 3H, OCH₃), 6.30 (s, 1H, CH), 6.55 (s, 2H, Ar-H), 6.73-7.42 (m,4H, Ar-H), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-((4-fluoro)phenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4e)

M.p.285-295 °C; IR (KBr): 3465, 2945, 1670, 1619, 1560, 1566 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ H = 1.06 (s,3H, CH₃), 1.17 (s,3H, CH₃), 2.04 (s,2H, CH₂), 2.40 (s,2H, CH₂), 6.49 (s,1H,CH), 6.90-7.90 (m, 8H, Ar-H), 10.90 (s, 1H, NH) ppm.

3,3-Dimethyl-12-((4-chloro)phenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4f)

M.p.285-295 °C; IR (KBr): νmax = 3465, 2945, 1670, 1619, 1560, 1566 cm⁻¹. ¹H NMR (DMSO-d₆, 300 MHz): δ H = 1.06 (s,3H, CH₃), 1.17 (s,3H, CH₃), 2.04 (s,2H, CH₂), 2.40 (s,2H, CH₂), 6.49 (s,1H,CH), 6.90-7.90 (m, 8H, Ar-H), 10.90 (s, 1H, NH) ppm.

3,3-Dimethyl-12-((4-methoxy)phenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4g)

M.p. 280-290 °C; IR (KBr): 3243, 2961, 1680, 1641, 1612, 1589, 1566, 1258 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ H = 1.03 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 2.06-2.15 (m, 2H, CH₂), 2.25-250 (m, 2H, CH₂), 3.66 (s, 3H, OCH₃), 6.35 (s, 1H, H-12), 6.73-7.42 (m, 8H, Ar-H), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-((4-methoxy)phenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4h)

M.p. 250-260 °C; IR (KBr): 3085, 2925, 1600, 1575, 1262 cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz): δ H =1.06 (s, 3H, CH₃), 1.11 (s, 3H, CH₃), 1.90 (s, 2H, CH₂), 2.45 (s,2H, CH₂), 3.72 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 6.20 (s, 1H, CH), 6.54-7.44 (m, 3H, Ar-H), 6.58 (t, 1H, Ar-H), 7.44 (d, 1H, Ar-H), 7.00-7.50 (m, 4H, Ar-H), 11.21 (s, 1H, NH) ppm.

3,3-Dimethyl-12-((4-hydroxy)phenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4i)

M.p. 270-275 °C; IR (KBr): 3469, 2962, 1754, 1264 cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz): δ H = 1.06 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 2.04 (s,2H, CH₂), 2.43 (s,2H, CH₂), 6.19 (s,1H, CH), 6.60-7.35 (m, 8H, Ar-H), 8.9-32 (s, 1H, OH), 11.01 (s, 1H, NH) ppm.
3,3-Dimethyl-12-(3-hydroxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4k)
M.p. 287-292 °C; IR (KBr): 3090, 2950, 1572, 1249 cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz): δ H =1.07 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 1.95 (s, 2H, CH₂), 2.50 (s, 2H, CH₂), 6.23 (s, 1H, CH), 6.69-7.00 (m, 3H, Ar–H), 7.52 (d, J = 5.69, Hz, 1H, Ar-H), 7.30-7.70 (m, 4H, Ar-H), 9.20 (s, 1H, OH), 11.30 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-methylphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4l)
M.p. 260-270 °C; IR (KBr): 3085, 2930, 1570, 1253 cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz): δ H = 1.10 (s, 3H, CH₃), 1.12 (s, 3H, CH₃), 2.15 (s, 2H, CH₂), 2.40 (s, 2H, CH₂), 2.70 (s, 3H, CH₃), 6.35(s, 1H, H –12), 6.60 -7.35 (m, 8H, Ar –H), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2-nitrophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4m)
M.p.275-280 °C; IR (KBr): 3400, 2995, 1589, 1320, 1258, 749 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δH = 1.07 (s, 3H, CH₃), 1.11 (s, 3H, CH₃), 2.19 (s, 2H, CH₂), 2.70 (s, 2H, CH₂), 6.45 (s, 1H, CH), 7.05 (d , 1H, Ar –H), 7.20-7.35 (m, 1H, Ar-H), 7.15-7.44 (m, 1H, Ar-H), 7.44 (d, J  = 8.15 Hz, 1H, Ar –H), 7.44 (d, J = 8.15 Hz, 1H, Ar-H), 7.15-7.44 (m, 1 H, Ar-H), 7.44 (d, J  = 8.15 Hz, 1H, Ar –H), 7.50-7.90 (m, 4H, Ar- H), 11.29 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2-methoxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (4n)
M.p. 245-255 °C; IR (KBr): 3089, 2895, 1589, 1248, 740 cm⁻¹; ¹H-NMR (DMSO-d₆, 300 MHz): δH = 1.09 (s, 3H, CH₃), 1.14 (s, 3H, CH₃), 1.99 (s, 2H, CH₂), 2.45 (s, 2H, CH₂), 3.72 (s, 3H, OCH₃), 6.29 (s, 1H, CH), 6.90-7.35 (m, 4H, Ar-H), 7.15-7.64  (m, 4H, Ar-H), 7.15-7.64 (m, 4H, Ar- H), 11.27 (s, 1H, NH) ppm.

RESULTS AND DISCUSSION

We developed a new method for the synthesis of benzimidazolo[2,3-b]quinazolinone derivatives in good yields by using HClO₄-SiO₂ as a mild and reusable heterogeneous catalyst in water:ethanol (1:1) solvent. The procedure is environment-friendly, operationally simple and thus has the advantage of high atom economy. Furthermore, the catalyst can be recovered and reused several times efficiently without substantial loss of activity. We also studied the reaction in aqueous medium only, but the reaction proceed ed very slowly and the product formation was also very poor. When we used ethanol:water (1:1) solvent system, the reaction proceed ed faster with a high yield of the corresponding product.

The effect of temperature on yield of the product 4a was studied by carrying the reactions at different temperatures (30, 55, 80 and 100 °C) as shown in Table 2. By raising the reaction temperature from room temperature to 100 °C gradually, the yield of reactions was found to be increased.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes (2)</th>
<th>Products (4)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
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<td>4a</td>
<td>30</td>
<td>85</td>
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<tr>
<td>2</td>
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<td>90</td>
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<tr>
<td>3</td>
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<td>4c</td>
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<td>85</td>
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<tr>
<td>4</td>
<td>O</td>
<td>4d</td>
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<tr>
<td>5</td>
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<td>90</td>
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<tr>
<td>12</td>
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<td>4l</td>
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<td>90</td>
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<tr>
<td>13</td>
<td>O</td>
<td>4m</td>
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<td>90</td>
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<tr>
<td>14</td>
<td>O</td>
<td>4n</td>
<td>20</td>
<td>90</td>
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</table>

**Reaction conditions:** Aldehyde (1.0 mmol), dimeredone (1.0 mmol), 2-aminobenzimidazole (1.0 mmol), HClO₄–SiO₂ (10 wt%) 20-40 min reflux.

**Table 1.** Synthesis of 3,3-dimethyl-12-(un)substituted phenyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-ones using silica supported perchloric acid.
At 80 °C temperature, the reaction completed in 25 minutes affording 90 % of product yield. Similarly, increasing the reaction temperature to 100 °C does not affect the yield of the product significantly. Thus, we confirmed that 80 °C was the optimum temperature for the transformation. Under these optimized conditions, various aldehydes were reacted with dimedone and aminobenzimidazoles, whose results are summarized in Table 1.

Table 2. Effect of temperature on the preparation of 3,3-dimethyl-12-phenyl-1,2,3,4,5,12-hexahydrobenzo[4,5]-imidazo[2,1-b]quinazolin-1-one (4a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp., °C</th>
<th>Time, min</th>
<th>Yield, %</th>
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</tr>
<tr>
<td>4</td>
<td>100</td>
<td>25</td>
<td>90</td>
</tr>
</tbody>
</table>

Reusability of the catalyst

Solid silica-based perchloric acid works under heterogeneous conditions. It is an inexpensive and non-hazardous solid acid catalyst which can be easily handled and separated from the reaction mixture by simple filtration. The recovered catalyst was reused thrice for consecutive runs with a minimum variation of yields of the products. After completion of the reaction, the catalyst was filtered, thoroughly washed with ethanol and dried at 100 °C for 2 hr and reused for subsequent runs (Table 3). This reusability demonstrates the high stability and turnover of solid silica-based perchloric acid under operating conditions.

Table 3. Reusability of catalyst for the synthesis of 3,3-dimethyl-12-phenyl-1,2,3,4,5,12-hexahydrobenzo[4,5]-imidazo[2,1-b]quinazolin-1-one (4a)

<table>
<thead>
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</tr>
<tr>
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</tr>
<tr>
<td>3</td>
<td>Second time</td>
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<tr>
<td>4</td>
<td>Third time</td>
<td>70</td>
<td>85</td>
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</table>

Conclusions

A convenient method has been developed by the reaction of 2-aminobenzimidazole, dimedone and aldehyde catalyzed by the silica-supported perchloric acid catalyst. Use of inexpensive and reusable catalyst, enhanced reaction rates, readily available starting materials, high yield and easy purification of the products are the key features of this method.

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References


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