Heterogeneous catalyst: Silica sulfuric acid catalyzed synthesis of 9, 10-dihydro-12-aryl-8H-benzo[a]xanthen-11(12H)-one derivatives under solvent-free conditions

G M Nazeruddin*, Mahesh S Pandharpatte & Khudbudin B Mulani

Department of Chemistry (P.G. Centre), Poona College of Arts, Science & Commerce, Pune 411 001, India
E-mail: gnmazeruddin@yahoo.co.in

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Silica sulfuric acid (SSA) as an efficient and reusable heterogeneous catalyst has been used for the preparation of 9,10-dihydro-12-aryl-8H-benzo[a]xanthen-11(12H)-one derivatives from the three-component condensation reaction of β-naphthol, cyclic 1,3 dicarbonyl compounds and aromatic aldehydes under solvent-free conditions in good to excellent yields and short reaction times.

Keywords: Silica sulfuric acid, heterogeneous catalyst, solvent-free conditions, xanthene

There continues to be considerable interest and growing expertise in converting homogenous catalytic process to heterogeneous ones with significant economical and environmental advantages. The main advantage of using heterogeneous catalyst is the relative ease of catalyst separation from the product stream. The use of heterogeneous catalysts in different areas of the organic synthesis has now reached significant level, not only for the possibility to perform environmentally benign synthesis, but also for good to excellent yields.

Acidic catalysts have been used mainly in industry, for producing more than $1 \times 10^8$ Mt/year of products. Among acidic catalysts, the most commonly used are HF, H$_2$SO$_4$, HClO$_4$, HSO$_3$Cl, CH$_3$SO$_3$H, and H$_3$PO$_4$ (in liquid form or supported on Kieselguhr). Solid acids have many advantages such as ease of handling, decreasing reactor and plant corrosion problems and environmental compatibility. Also, wastes and by-products can be minimized or avoided by developing benign synthetic routes. It makes reaction processes convenient, more environmentally benign and economical. In addition, there is a general interest in heterogeneous systems because of its importance in industry and in developing technologies.

Note

Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in the industrial context. During recent years, the use of silica sulfuric acid as a catalyst in organic synthesis has attracted great interest from many chemists. Silica sulfuric acid can enhance the reactivity and selectivity of many types of reactions, such as oxidation, carbon-carbon bond formation, cycloaddition, and protection and deprotection.

Xanthenes and benzoxanthenes have attracted considerable interest because they possess various pharmaceutical activities such as anti-bacterial, anti-inflammatory, and anti-viral. These structural motifs have also found a niche as antagonists for paralyzing the action of zoxazolamine and demonstrate efficacy in photodynamic therapy. In addition, these compounds have been employed as dyes and pH-sensitive fluorescent materials for visualization of biomolecular assemblies and utilized in laser technologies. Thus a broad utility range has made xanthenes as a prime synthetic candidate thereby accentuating the need to develop newer synthetic routes for scaffold manipulation of xanthene derivatives. The synthesis of 9,10-dihydro-12-aryl-8H-benzo[a]xanthen-11(12H)-one derivatives has been reported in the presence of strontium triflate, indium trichloride, phosphorus pentaoxide, NaHSO$_4$-SiO$_2$ under reflux in halogenated solvents for long hours. However, these methodologies suffer from one or more disadvantages such as low yields, lack of easy availability of the starting materials, prolonged reaction time (16 hr), use of toxic organic solvents, requirement of excess of reagent catalyst, and special apparatus. Thus, there is a need for development of an alternative route to synthesize the xanthene derivatives. In this context, we decided to investigate the possibility of synthesizing 9,10-dihydro-12-aryl-8H-benzo[a]xanthen-11(12H)-one derivatives through one-pot three-component condensation reaction strategy of β-naphthol with aldehydes and cyclic 1,3-dicarbonyl compounds using silica sulfuric acid as a catalyst under solvent free conditions.

Results and Discussion

The condensation of β-naphthol, cyclic dicarbonyl compounds and aryl aldehydes (carrying both
electron-withdrawing and electron-donating groups), in the presence of silica sulfuric acid as a heterogeneous catalyst under solvent-free conditions yielded the desired 9,10-dihydro-12-aryl-8H-benzo[α]xanthen-11(12H)-one derivatives in high purity with good to excellent yields. As expected, satisfactory results were observed. The reaction is depicted in Scheme I and results are summarized in Table I. It was found that silica sulfuric acid shows better catalytic activity and is reusable. To choose optimum conditions, first we tried to prepare 9,10-dihydro-12-phenyl-8H-benzo[α]xanthen-11(12H)-one, 3a from the reaction of benzaldehyde (1.2 mmol), dimedone (1.1 mmol) and β-naphthol (1.1 mmol) as a model in the absence and presence of silica sulfuric acid under thermal solvent-free conditions Table II. As shown in Table III, this transformation requires 0.08 g of silica sulfuric acid as a catalyst at 80°C under solvent free conditions.

**Effect of catalyst concentration and temperature**

The effect of catalyst concentration and temperature on the reaction were also studied, and the results are shown in Table III. It is observed that 0.08 g of catalyst and optimum temperature 80°C is enough to obtain excellent yield. Further increase in temperature to 100 and 120°C, has no significant change in the rate of reaction. Therefore, the reaction temperature was kept at 80°C to furnish good to excellent yields. To optimize the amount of silica sulfuric acid as a catalyst, the reaction was carried out by varying the amount of the catalyst and maximum yield was obtained with 0.08 g of catalyst. It was observed that at 80°C, the reaction proceeded smoothly and completion of the reaction was accomplished. The catalyst was recovered after each run and washed three times with acetone, dried in an oven at 100°C for 10 min prior to use as a catalyst. The same procedure was repeated for three runs to

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**Scheme I — Preparation of 9, 10-dihydro-12-aryl-8H-benzo[α]xanthen-11(12H)-one derivatives**

**Table I — Preparation of 9,10-dihydro-12-aryl-8H-benzo[α]xanthen-11(12H)-one derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Time (min)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>m.p. °C</th>
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</thead>
<tbody>
<tr>
<td>3a</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>60</td>
<td>83</td>
<td>150-52</td>
</tr>
<tr>
<td>3b</td>
<td>4-OMe C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>100</td>
<td>87</td>
<td>204-05</td>
</tr>
<tr>
<td>3c</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>80</td>
<td>90</td>
<td>174-76</td>
</tr>
<tr>
<td>3d</td>
<td>2-OMe C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>130</td>
<td>81</td>
<td>163-65</td>
</tr>
<tr>
<td>3e</td>
<td>4-OH C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>180</td>
<td>76</td>
<td>223-25</td>
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<tr>
<td>3f</td>
<td>2-Cl C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>70</td>
<td>81</td>
<td>179-80</td>
</tr>
<tr>
<td>3g</td>
<td>4-Cl C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>50</td>
<td>89</td>
<td>180-82</td>
</tr>
<tr>
<td>3h</td>
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<td>Me</td>
<td>210</td>
<td>75</td>
<td>193-94</td>
</tr>
<tr>
<td>3i</td>
<td>2-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>90</td>
<td>82</td>
<td>223-25</td>
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<tr>
<td>3j</td>
<td>2-OH C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>H</td>
<td>15</td>
<td>91</td>
<td>225-27</td>
</tr>
<tr>
<td>3k</td>
<td>2-OH C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHO</td>
<td>Me</td>
<td>15</td>
<td>88</td>
<td>205-07</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield
test the catalytic activity of catalyst. It was observed that the catalyst displayed very good reusability. The generality of this reaction was examined using several types of aldehydes. In all cases, the reactions gave the corresponding products in good to excellent yields.

Mechanistic pathway

The suggested mechanism of the silica sulfuric acid catalyzed transformations is depicted in Scheme II. It is interesting to note that in case of 2-hydroxy benzaldehyde (salicylaldehyde) reaction\(^{24}\), there is formation of the desired xanthene without further cyclization. This was confirmed by NMR which showed an exchangeable proton as depicted in Scheme III.

**Experimental Section**

All reagents were purchased from Merck and Loba and used without further purification. Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra, \(^1\)H NMR, and elemental analyses. IR spectra were recorded on Perkin-Elmer FT-IR-1710 instrument. \(^1\)H NMR was recorded on Bruker AC-200 MHz, Bruker MSL-300 MHz and Bruker DRX-500 MHz instrument using TMS as an internal standard. Elemental analyses were determined by an elemental analyser (CHNS-O, EA 1108-elemental analyser, Carlo Erba instruments).

**General procedure for the synthesis of 9,10-dihydro-12-aryl-8H-benzo[α]xanthlen-11(12H)-one derivatives**

Aldehyde (1.0 mmol), β-naphthol (1.0 mmol) 5,5-dimethyl-1,3-cyclohexanone, 1,3-cyclohexanedione (1.1 mmol), and silica sulfuric acid (0.08 g) were taken in a 25 mL round-bottom flask fitted with an air condenser. The mixture was heated in an oil bath at 80°C for the time given in Table I. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to RT followed by addition of 15 mL of chloroform and then warmed for 5 min. The catalyst was filtered and the filtrate was evaporated to furnish the crude product which was further purified by usual crystallization procedure in absolute ethanol. Catalyst can be reused by washing with acetone and drying the same in oven at 100°C for 10 min.

**Table II** — Optimum conditions for the preparation of 9,10-dihydro-9,9-dimethyl-12-phenyl-8H-benzo[α]xanthlen-11(12H)-one under solvent-free thermal conditions at 80°C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (min)</th>
<th>Yield (%)(^a)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>SiO(_2)</td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>H(_2)SO(_4)</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Silica sulfuric acid</td>
<td>50</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield

**Table III** — Effect of temperature and catalyst concentration for the preparation of 9,10-dihydro-9,9-dimethyl-12-phenyl-8H-benzo[α]xanthlen-11(12H)-one derivatives using silica sulfuric acid as catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (g)</th>
<th>Temperature °C</th>
<th>Time (min)</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>120</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>0.03</td>
<td>100</td>
<td>80</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>80</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>0.08</td>
<td>80</td>
<td>60</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>0.08</td>
<td>50</td>
<td>2 hr</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>0.04</td>
<td>RT</td>
<td>24 hr</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>80</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield
for C_{25}H_{21}NO_3: C, 75.17, H, 5.30, N, 3.51. Found: C, 75.18, H, 5.19 N, 3.47%.

9,10-Dihydro-12-(2-methoxyphenyl)-9,9-dimethyl-8H-benzo[α]xanthen-11(12H)-one, 3d: White solid, m.p. 163-65°C; 1H NMR (300 MHz, CDCl_3): δ 8.0 (d, 1H), 7.85-7.7 (m, 2H), 7.5-7.25 (m, 5H), 7.1 (t, 1H), 6.9 (t, 1H), 6.62-6.57 (m, 2H), 5.75 (s, 1H), 3.74 (s, 3H), 2.58 (s, 2H), 2.32 (d, 1H), 2.22 (d, 1H), 1.12 (s, 3H), 1.00 (s, 3H); IR (KBr): 2926, 1646, 1376, 1231, 1169, 1049, 827 cm^{-1}. Anal. Calcd for C_{26}H_{24}O_3: C, 81.22; H, 6.29. Found: C, 81.16 H, 6.32%.

Scheme II — Suggested mechanism for the silica sulfuric acid catalyzed preparation of 9, 10-dihydro-12-aryl-8H-benzo[α]xanthen-11(12H)-one derivatives

9,10-Dihydro-12-(4-hydroxyphenyl)-9,9-dimethyl-8H-benzo[α]xanthen-11(12H)-one, 3e: White solid, m.p. 223-25°C; 1H NMR (300 MHz, CDCl_3): δ 7.98 (d, 1H), 7.78-7.73 (m, 2H), 7.2 (s, 1H), 7.45-7.15 (m, 5H), 6.61 (d, 2H), 5.63 (s, 1H), 2.56 (s, 2H), 2.34 (d, 1H), 2.27 (d, 1H), 1.12 (s, 3H), 0.97 (s, 3H); IR (KBr): 2961, 1618, 1484, 1380, 1232, 1030 cm^{-1}. Anal. Calcd for C_{25}H_{22}O_3: C, 81.06, H, 5.99. Found: C, 81.16, H, 6.32%.

Scheme III — Formation of the desired 9,10-dihydro-12-(2-hydroxyphenyl)-9, 9-dimethyl-8H-benzo[α]xanthen-11(12H)-one without further cyclization.

12-(4-Chlorophenyl)-9,10-Dihydro-9,9-dimethyl-8H-benzo[α]xanthen-11(12H)-one, 3g: White solid, m.p. 180-82°C; 1H NMR (300 MHz, CDCl_3): δ 7.90 (d, 1H), 7.79-7.75 (m, 2H), 7.45-7.11 (m, 7H), 5.67 (s, 1H), 2.56 (s, 2H), 2.34 (d, 1H), 2.26 (d, 1H), 1.12 (s, 3H), 0.96 (s, 3H); IR (KBr): 2952, 1649, 1371,
1226, 1185, 1093 cm\(^{-1}\). Anal. Calcd for C\(_{25}\)H\(_{25}\)ClO\(_2\): C, 77.21; H, 5.44. Found: C, 76.05 H, 5.25%.

9,10-Dihydro-12-(4-hydroxy-3-methoxyphenyl)-9,9-dimethyl-8H-benzo[a]xanthen-11(12H)-one, 3h: White solid, m.p. 193-94\(^{\circ}\)C; \(^1\)H NMR (200 MHz, DMSO-d\(_6\)): δ 8.80 (s, 1H), 6.68-6.55 (m, 3H), 4.43 (s, 1H), 3.69 (s, 3H), 2.32 (d, 1H), 2.0 (d, 1H), 1.04 (s, 3H), 0.92 (s, 3H); IR (KBr): 3406, 2956, 1665, 1325, 1286, 1100, 900, 777 cm\(^{-1}\). Anal. Calcd for C\(_{25}\)H\(_{25}\)O\(_2\): C, 78.0, H, 6.0. Found: C, 78.12, H, 5.93%.

9,10-Dihydro-9,9-dimethyl-12-(2-nitrophenyl)-8H-benzo[a]xanthen-11(12H)-one, 3i: Pale yellow solid, m.p. 223-25\(^{\circ}\)C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): 8.85 (d, 1H), 7.86-7.77 (m, 3H), 7.46-7.03 (m, 6H), 6.58 (s, 1H), 2.60 (d, 1H), 2.52 (d, 1H), 2.29 (d, 1H), 2.19 (d, 1H), 1.11 (s, 3H), 0.86 (s, 3H); IR (KBr): 2962, 1652, 1528, 1373, 1225, 1170, 1026, 823 cm\(^{-1}\). Anal. Calcd for C\(_{25}\)H\(_{21}\)NO\(_4\): C, 78.17; H, 5.30; N, 3.51. Found: C, 78.29; H, 5.51; N, 3.60%

9,10-Dihydro-12-(2-hydroxyphenyl)-9,9-dimethyl-8H-benzo[a]xanthen-11(12H)-one, 3j: White solid, m.p. 225-27\(^{\circ}\)C; \(^1\)H NMR (200 MHz, DMSO-d\(_6\)): δ 9.6 (s, 1H, Exchangeable with D\(_2\)O), 8.32 (d, 1H), 7.9-7.86 (t, 2H), 7.7-7.4 (m, 5H), 7.01 (d, 1H), 6.90 (t, 2H), 6.74-6.63 (m, 5H), 5.77 (s, 1H), 2.7 (d, 1H), 2.63 (d, 1H), 2.33 (d, 1H), 2.16 (d, 1H), 1.1 (s, 3H), 0.96 (s, 3H); IR (KBr): 2961, 1632, 1382, 1215, 1179, 1028, 755 cm\(^{-1}\). Anal. Calcd for C\(_{25}\)H\(_{25}\)O\(_2\): C, 81.06, H, 5.99. Found: C, 81.10, H, 5.93%

9,10-Dihydro-12-(2-hydroxyphenyl)-8H-benzo[a]xanthen-11(12H)-one, 3k: Pale brown solid, m.p. 205-207\(^{\circ}\)C; \(^1\)H NMR (200 MHz, DMSO-d\(_6\)): δ 9.59 (s, 1H), 8.21 (d, 1H), 7.84-7.80 (t, 2H), 7.7-7.35 (m, 5H), 6.90 (t, 2H), 6.74-6.63 (m, 5H), 5.78 (s, 1H), 2.77 (d, 1H), 2.5 (d, 1H), 2.37 (d, 1H), 2.03 (d, 1H); IR (KBr): 3340, 2924, 1629, 1590, 1481, 1377, 1229, 1187, 1127, 817, 755 cm\(^{-1}\). Anal. Calcd for C\(_{25}\)H\(_{25}\)O\(_3\): C, 80.70, H, 5.26. Found: C, 80.67, H, 5.31%

Conclusion

In summary, an efficient and environmentally benign strategy for the preparation of 9,10-dihydro-12-aryl-8H-benzo[a]xanthen-11(12H)-one derivatives has been developed. The reactions were carried out under thermal solvent-free conditions with short reaction times and gave the corresponding products in good to excellent yields. The methodology is safer than those using conventional catalysts like H\(_2\)SO\(_4\), HClO\(_4\), and H\(_3\)PO\(_4\) with respect to the amount, hazard and reaction conditions. The method offers several advantages including high yield of products and short reaction time. Moreover, the catalysts could be successfully recovered and recycled at least for five runs without significant loss in activity.

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References