Ammonium Chloride-Catalyzed Three-Component Reaction for the Synthesis of Fused 4H-Chromene Derivatives in Aqueous Medium

Suchandra Bhattacharjee, Deb K. Das, Abu T. Khan*
Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India
Fax +91(361)2582349; E-mail: atk@iitg.ernet.in
Received: 17.07.2013; Accepted after revision: 10.10.2013
This work is dedicated to Professor Gautam Barua, former Director of the Indian Institute of Technology, Guwahati for his immense contribution in setting up and developing the Science Department of IIT Guwahati.

Abstract: An efficient one-pot process was developed to synthesize 4H-chromene derivatives using a three-component reaction involving salicylaldehydes, cyclic 1,3-diketones, and thiols in an aqueous medium at room temperature. This protocol was accomplished using the inexpensive and readily available catalyst NH4Cl. The attractive features of this protocol are: use of inexpensive catalyst NH4Cl, good yields, and mild and environmentally benign reaction conditions.

Key words: 4H-chromenes, salicylaldehydes, cyclic 1,3-diketones, thiols, ammonium chloride, aqueous medium, multicomponent reactions (MCRs)

Multicomponent reaction (MCR) offers a remarkable handy protocol to construct new heterocyclic molecules with relevant biological activity.1 Water is truly the nature’s reaction medium playing a crucial role in various life-sustaining processes. Needless to say, water is found in high abundance, hence cost-effective, and is a green solvent in organic transformations2 owing to its nonflammable and nontoxic nature. Further, it exhibits unique properties like high dielectric constant, and its cohesive energy density puts an extraordinary effect on reaction rates with unique selectivity and reactivity.3 Designing MCRs using water as the reaction medium to synthesize heterocyclic scaffolds with medicinal traits is one of the trending research amongst synthetic organic chemists in view of green chemistry.4

The chromene scaffold and its derivatives exhibit useful biological and pharmacological activities such as antibacterial,5 antitumor,6 anticancer,7 anticonvulsant,8 apoptosis inducers,9 Chk1-inhibitors,10 and anti-anaphylactic activities.11 Some of them are found as natural products, for example, the antibacterial rhodomyrtone (I)12 and the gastric antisecretory agent II13 as shown in Figure 1.

Literature search reveals that salicylaldehyde reacts with an active methylene compound such as cyclic 1,3-diketones14 or malononitrile15 to form a Knoevenagel product, which can react with a suitable nucleophile such as thiols, indoles, benzotriazoles, and 4-hydroxycoumarins followed by ring-closure reaction leading to the formation of 4H-chromene compounds. The other methods available for the synthesis of 4H-chromene derivatives are cycloaddition of propargylic alcohols,16a or ketones16b with phenols, reactions of allenic esters and ketones with salicyl-N-tosylimines,17 ring-closing metathesis reaction of aryl vinyl ethers,18 copper-catalyzed intra-19a and intermolecular19b coupling of aryl bromides with 1,3-dicarbonyl compounds, tetrahydrothiophene-catalyzed ylide annihilation reaction,20 organocatalytic sequential one-pot reaction of 1,3-diones with salicylaldehydes,21 and tandem benzylation and cyclization of 1,3-dicarbonyl compounds using benzylalcohols.22 A survey of the literature shows that the majority of the strategies for the synthesis of 4H-chromene derivatives involve either expensive catalysts,16a,b,18,21 or multistep sequences,18,20 prolonged reaction time,19b and harsh reaction conditions,18,19,22 Consequently, there is a need to develop a synthetic method using inexpensive and environmentally benign catalyst.

Ammonium chloride is readily available and is an inexpensive catalyst. In aqueous medium, it is a good proton source, which can activate the carbonyl group through hydrogen bonding.23 Moreover, it can react with carbonyl groups in the presence of amines to form imines, which can act as dienophiles in Diels–Alder reactions.24 Thus, NH4Cl was considered to be a promising catalyst in view of its remarkable ability to catalyze a manifold of organic transformations by way of multicomponent reactions for the synthesis of pyrrolo[3,4-b]pyridin-5-ones,23a di- and tetrapeptides,23a 3,4-dihydroprimidin-2(1H)-ones,23b spirochromenes,23c 4-imino-4H-3,1-benzoazines,24 tetrahydrofuro[2,3-c]pyridine,25c and tetrahydrobenzo[α]xanthen-11-one derivatives.25c

Figure 1 Some natural compounds containing chromene skeleton
In continuation of our investigations on the synthesis of novel heterocyclic compounds under aqueous conditions, we conceived to investigate the synthesis of 4H-chromene compounds using more environmentally benign reaction conditions. We report herein a new, convenient, and highly efficient greener protocol for the synthesis of 4H-chromenes via three-component condensation of salicylaldehydes, cyclic 1,3-dicarbonyl compounds, and aromatic or aliphatic thiols catalyzed by ammonium chloride in water at room temperature as shown in Scheme 1.

In our initial efforts to synthesize 4H-chromene derivative 4b, a reaction was carried out with an equimolar mixture of salicylaldehyde (1a), dimedone (2a), and 4-chlorothiophenol (3a) in water in the absence of catalyst at room temperature. The reaction did not proceed to completion even after 12 hours and resulted in the isolation of product 4H-chromene derivative 4b and 1-oxohexahydroxanthene derivative 5 in 22% and 48% yield (Table 1, entry 1), respectively, which was confirmed from IR and 1H NMR.

Table 1  Optimization of Reaction Conditions for the Synthesis of 3,3-Dimethyl-9-(4-chlorophenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (4b)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>4b</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>H₂O</td>
<td>12</td>
<td>22</td>
<td>48</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>NH₄Cl (10)</td>
<td>H₂O</td>
<td>12</td>
<td>67</td>
<td>7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>NH₄Cl (20)</td>
<td>H₂O</td>
<td>5</td>
<td>78</td>
<td>trace</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>NH₄Cl (30)</td>
<td>H₂O</td>
<td>5</td>
<td>74</td>
<td>trace</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>NH₄Cl (20)</td>
<td>EtOH</td>
<td>5</td>
<td>29</td>
<td>14</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>NH₄Cl (20)</td>
<td>neat</td>
<td>16</td>
<td>46</td>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>NH₄Br (20)</td>
<td>H₂O</td>
<td>6</td>
<td>74</td>
<td>trace</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>TBAB (20)</td>
<td>H₂O</td>
<td>12</td>
<td>37</td>
<td>36</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>TBAI (20)</td>
<td>H₂O</td>
<td>16</td>
<td>38</td>
<td>26</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>BETAC (20)</td>
<td>H₂O</td>
<td>12</td>
<td>42</td>
<td>22</td>
<td>24</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>TBATB (20)</td>
<td>H₂O</td>
<td>12</td>
<td>38</td>
<td>18</td>
<td>42</td>
<td>–</td>
</tr>
</tbody>
</table>

* Reaction conditions: salicylaldehyde (1a), dimedone (2a), and 4-chlorothiophenol (3a) were taken in a 1:1:1 ratio at r.t.

* Isolated yields after column chromatography.
spectra. The same reaction was also carried out in the presence of 10 mol% of NH₄Cl in water, which afforded the product 4b along with the formation of a trace amount of compound 5 in 67% and 7% yield (Table 1, entry 2), respectively. To reduce the formation of the by-products as well to increase the yield of the desired 4H-chromene 4b, a similar reaction was executed using 20 and 30 mol% of NH₄Cl to afford compound 4b in 78% and 74% yield, respectively. It was noted that the yield of the product 4b had increased from 67 to 78% by increasing the amount of catalyst from 10% to 20% with the formation of only a trace amount of product 5, which also shortened the reaction time significantly (Table 1, entry 3). However, increasing the amount of catalyst from 20% to 30% did not improve the yield of the product (Table 1, entry 4). The reactions were very sluggish and incomplete even after 16 hours, when the same reaction was carried out in the presence of 20 mol% of NH₄Cl under solvent-free conditions (Table 1, entry 6).

These results show that the catalyst NH₄Cl has a remarkable effect in suppressing the formation of by-products and controlling the reaction selectivity in water. To examine the efficacy of the catalyst, several reactions were also performed in the presence of other mild acid catalyst such as TBAB, TBAI, BETAC, and TBATB under identical reaction conditions, but all of them delivered poorer results in terms of yield and selectivity toward 4b (Table 1, entries 8–11) and gave 2-{(4-chlorophenyl)thio}methylphenol (6) as another by-product. It is worthwhile to mention that the same reaction gave comparatively similar yields when 20 mol% of NH₄Br was used in water (Table 1, entry 7). Since the yield has not increased significantly and cost of the NH₄Br is higher as compared to NH₄Cl, all the reactions were performed using 20 mol% of NH₄Cl in water.

The above observations indicate that the reaction proceeds well in the presence of 20 mol% of NH₄Cl in aqueous media. The mild reaction conditions and clean TLC pattern are the main advantages of the present reaction in

**Table 2** Substrate Scope for the Synthesis of 4H-Chromene Derivatives 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>R¹</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>Ph</td>
<td>5.0</td>
<td>4a</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2a</td>
<td>4-ClC₆H₄</td>
<td>5.0</td>
<td>4b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2a</td>
<td>4-BrC₆H₄</td>
<td>4.5</td>
<td>4c</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2a</td>
<td>4-MeC₆H₄</td>
<td>4.0</td>
<td>4d</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2a</td>
<td>4-MeOC₆H₄</td>
<td>4.0</td>
<td>4e</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>2a</td>
<td>2-naphthyl</td>
<td>6.0</td>
<td>4f</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2a</td>
<td>Et</td>
<td>5.0</td>
<td>4g</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>2a</td>
<td>Pr</td>
<td>4.5</td>
<td>4h</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>1b</td>
<td>2b</td>
<td>Bn</td>
<td>5.0</td>
<td>4i</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>2b</td>
<td>4-MeC₆H₄</td>
<td>4.0</td>
<td>4j</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>2a</td>
<td>4-ClC₆H₄</td>
<td>4.0</td>
<td>4k</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>1d</td>
<td>2a</td>
<td>Pr</td>
<td>3.0</td>
<td>4l</td>
<td>71</td>
</tr>
<tr>
<td>13</td>
<td>1d</td>
<td>2a</td>
<td>Ph</td>
<td>4.0</td>
<td>4m</td>
<td>79</td>
</tr>
<tr>
<td>14</td>
<td>1e</td>
<td>2a</td>
<td>Ph</td>
<td>4.0</td>
<td>4n</td>
<td>77</td>
</tr>
<tr>
<td>15</td>
<td>1a</td>
<td>2c</td>
<td>Ph</td>
<td>3.0</td>
<td>4o</td>
<td>72</td>
</tr>
<tr>
<td>16</td>
<td>1b</td>
<td>2c</td>
<td>Ph</td>
<td>3.0</td>
<td>4p</td>
<td>69</td>
</tr>
</tbody>
</table>

a Reaction conditions: salicylaldehyde 1, 1,3-cyclic ketone 2, and thiol 3 were taken in a 1:1:1 ratio in the presence of 20 mol% of NH₄Cl in 5 mL of H₂O at r.t.; entries 15 and 16 were conducted at reflux.

b Isolated yields.

© Georg Thieme Verlag Stuttgart · New York
water. With the optimized conditions in hand, we next embarked on an investigation of the substrate scope of the present multicomponent reaction for the synthesis of 4H-chromene derivatives 4 with different salicylaldehydes 1, cyclic 1,3-diketones 2, and thiols 3. Performing the reaction with a mixture of salicylaldehyde, dimedone, and thiophenol under identical conditions, the desired product 4a was obtained in 79% yield (Table 2, entry 1). To explore the synthetic scope and the generality of the present protocol, various reactions were performed with a wide variety of aromatic thiols containing different substituents in the aromatic ring such as Br, Me, and OMe with salicylaldehyde and dimedone. The reaction time and percentage yield of the products 4c–f are shown in Table 2 (entries 3–6). Likewise, aliphatic thiols such as ethane thiol and propane thiol were tested under identical reaction condition to provide the desired 4H-chromene products 4g–h in good yields (entries 7 and 8, Table 2).

For verifying the generality of the present method, other substituted salicylaldehyde derivatives bearing Br, MeO, and OEt substituent in the ring were also examined with dimedone and different aliphatic or aromatic thiols under identical reaction conditions to provide the desired 4H-chromene products 4i–n in moderate to good yields (Table 2, entries 9–14). Furthermore, the reactions with other cyclic 1,3-diketones such as cyclohexa-1,3-dione and cyclopenta-1,3-dione with salicylaldehydes and thiophenol were also performed to give the desired products 4i,j and 4o,p (entries 9, 10 and 15, 16). It was observed that the similar transformation failed in the case of acyclic 1,3-diketone such as acetylacetone and also for malononitrile. The present protocol was further examined by carrying out two consecutive reactions with salicylaldehyde (1a), dimedone (2a), and with a nucleophile such as indole (7a) and β-naphthol (7b), and the desired products 8a and 8b were isolated in 81% and 58% yield, respectively, as shown in Table 3.

Table 3 Substrate Scope for the Synthesis of 4H-Chromene Derivatives 8

<table>
<thead>
<tr>
<th>Entry</th>
<th>NuH</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>indole</td>
<td>5.0</td>
<td>8a</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>2-naphthol</td>
<td>6.0</td>
<td>8b</td>
<td>58</td>
</tr>
</tbody>
</table>

* Reaction conditions: salicylaldehyde (1a), dimedone (2a), and nucleophile 7 were taken in a 1:1:1 ratio in the presence of 20 mol% of NH₄Cl in 5 mL of H₂O. For entry 1, the reaction was carried out at r.t., whereas in the case of entry 2 the reaction mixture was refluxed.

All the synthesized compounds were characterized by IR, NMR, and elemental analysis. The products 4a–p exhibited a diagnostic signal in the range of δ = 4.96–5.38 assignable to H-9 at the point of attachment of 4H-chromene to the thiol moiety depending on the nature of the substituent in salicylaldehydes and thiols. Finally, the structure of one of the representative compounds such as 9-[(4-chlorophenyl)thio]-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydropyrido-1H-xanthen-1-one (4k) was confirmed unambiguously by single crystal X-ray diffraction analysis (Figure 2) (see Supporting Information).

Figure 2 X-ray crystal structure of 4H-chromene 4k

The formation of the product may be explained as follows: The first step is believed to be the condensation reaction between salicylaldehyde 1 with cyclic 1,3-diketone 2 to give a Knoevenagel product 3, which can act as a suitable Michael acceptor. The role of ammonium chloride is a source of proton, which activates carbonyl group through hydrogen bonding. Then a nucleophile such as thiol reacts at the exocyclic benzylidene double bond of the Knoevenagel product 3 to form the intermediate 4, which further undergoes intramolecular ring-closure reaction followed by dehydration to give the desired 4H-chromene compounds 4 as shown in Scheme 2.

In conclusion, we have demonstrated an efficient and eco-friendly protocol for the synthesis of 4H-chromene derivatives by employing the environmentally benign catalyst NH₄Cl via one-pot three-component condensation reaction from wide variety of salicylaldehydes, cyclic 1,3-diketones, and aromatic or aliphatic thiols employing water as the reaction medium. This new method is endowed with advantages such as green reaction medium, environmentally benign reaction conditions with good yields, superior atom economy, the easy accessibility of the catalyst, and its cost effectiveness.

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on PerkinElmer 281 IR spectrophotometer. 1H and 13C NMR spectra were recorded on Varian 400 spectrometer with TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). 1H NMR spectra are reported in the order: multiplicity, coupling constant.
(J value) in hertz (Hz) and number of protons. Standard abbreviations were used to denote signal multiplicities. Mass spectrometry data was collected on Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS spectrometer. Elemental analyses were carried out using PerkinElmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. The X-ray crystal structure was determined with a Siemens P-4 diffractometer.

Elements were used to denote signal multiplicities. Mass spectrometry data was collected on Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS spectrometer. Elemental analyses were carried out using PerkinElmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. The X-ray crystal structure was determined with a Siemens P-4 diffractometer.

**Scheme 2** Proposed NH$_4$Cl-catalyzed formation of 4H-chromene derivatives 4

**4H-Chromene Derivatives 4a–p; General Procedure**

A mixture of salicylaldehyde (1 mmol), cyclic 1,3-diketone (1 mmol), aliphatic or aromatic thiol (3 mmol), and NH$_4$Cl (0.2 mmol) in H$_2$O (5 mL) was stirred at r.t. for 3–6 h in a 25 mL round-bottomed flask. The progress of the reaction was monitored by TLC (eluent: EtOAc–hexane, 1:9). After the completion of the reaction, the crude reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H$_2$O (10 mL), and dried (Na$_2$SO$_4$). The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh, eluent: EtOAc–hexane, 1:9). After the completion of the reaction, the crude reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H$_2$O (10 mL), and dried (Na$_2$SO$_4$). The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh, eluent: EtOAc–hexane, 1:9) to afford the pure products in 55–79% yields (Table 1).

**Yield:** 0.175 g (48%); white solid; mp 219–221 °C.

**9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one (4c)**

Yield: 0.315 g (76%); orange liquid.

**1H NMR** (400 MHz, CDCl$_3$): $\delta$ = 7.29–7.25 (m, 4 H), 7.20–7.12 (m, 6 H), 6.81 (d, J = 7.6 Hz, 2 H), 5.71 (s, 1 H).

**IR (film):** 3208, 2954, 1645 cm$^{-1}$.

Anal. Calcd for C$_{23}$H$_{26}$O$_4$ (366.45): C, 75.38; H, 7.15. Found: C, 75.44; H, 7.12.

**H NMR** (400 MHz, CDCl$_3$): $\delta$ = 195.9, 166.3, 150.6, 136.4 (2 C), 128.0, 129.5, 129.1 (2 C), 128.5, 128.2, 128.0, 122.8, 116.1, 109.8, 50.9, 41.3, 40.7, 32.1, 28.5, 28.4, 21.3.

© Georg Thieme Verlag Stuttgart · New York

Synthesis 2014, 46, 73–80
IR (KBr): 2960, 1662, 1645, 1458, 1380, 1232, 1172, 1030, 758, 533 cm⁻¹.

Yield: 0.270 g (74%); orange solid; mp 107–108 °C.

1H NMR (400 MHz, CDCl₃): δ = 7.29–7.26 (m, 2 H), 7.17–7.12 (m, 1 H), 6.91 (d, J = 8.8 Hz, 2 H), 6.79 (dd, J = 8.1, 1.6 Hz, 1 H), 6.67 (d, J = 8.8 Hz, 2 H), 5.22 (s, 1 H), 3.78 (s, 3 H), 2.39–2.28 (m, 4 H), 1.18 (s, 3 H), 1.07 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 159.4, 158.5, 150.4, 137.8 (2 C), 129.3, 127.7, 124.6, 122.3, 121.9, 115.7, 113.5 (2 C), 109.3, 54.9, 50.5, 49.9, 40.5, 31.7, 28.2, 28.1.


3,3-Dimethyl-9(naphthalen-2-ylthio)-2,3,4,9-tetrahydro-1H-xanthene-1-one (4f)

Yield: 0.220 g (70%); orange liquid.

IR (film): 2928, 1659, 1473, 1410, 1377, 1231, 1166, 1130, 995, 703 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.30–7.18 (m, 7 H), 6.88 (d, J = 8.8 Hz, 1 H), 4.96 (s, 1 H), 3.61 (s, 2 H), 2.43–2.29 (m, 4 H), 1.19–1.18 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 196.4, 167.1, 149.8, 138.5, 132.7, 131.4, 129.0 (2 C), 128.5 (C), 127.1, 124.7, 118.0, 117.7, 111.8, 36.8, 35.1 (2 C), 27.7, 20.0.


5-Methoxy-9-(4-methoxyphenylthio)-2,3,4,9-tetrahydro-1H-xanthene-1-one (4k)

Yield: 0.218 g (62%); orange liquid.

IR (KBr): 2955, 2927, 1654, 1493, 1459, 1339, 1260, 1225, 1198, 1033, 998, 874, 808, 753 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 6.97 (d, J = 8 Hz, 2 H), 6.93 (d, J = 8 Hz, 2 H), 6.75–6.72 (m, 3 H), 5.25 (s, 1 H), 3.77 (s, 3 H), 2.41–2.37 (m, 4 H), 2.32 (s, 3 H), 2.01–2.04 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 196.2, 168.3, 156.7, 144.9, 139.2, 137.0 (2 C), 129.1 (2 C), 128.1, 123.6, 117.0, 115.3, 112.4, 109.9, 55.8, 41.2, 37.0, 27.7, 21.4, 20.4.


5-Methoxy-9-(4-methylphenylthio)-2,3,4,9-tetrahydro-1H-xanthene-1-one (4l)

Yield: 0.235 g (71%); orange solid; mp 128–129 °C.

IR (KBr): 3009, 2955, 1655, 1639, 1523, 1485, 1391, 1271, 1228, 1124, 1094, 764, 734, 544 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.10 (t, J = 8 Hz, 1 H), 6.98 (dd, J = 7.6, 1.2 Hz, 1 H), 6.81 (dd, J = 8.0, 1.2 Hz, 1 H), 5.01 (s, 1 H), 3.78 (s, 3 H), 2.39–2.28 (m, 4 H), 1.19–1.18 (m, 2 H).
5-Methoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (4m)

Yield: 0.292 g (77%); orange liquid.

IR (KBr): 3055, 2958, 1670, 1645, 1583, 1470, 1385, 1274, 1228, 1186, 1124, 1093, 849, 789, 737, 665 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.34–7.27 (m, 1 H), 7.16 (t, J = 7.2 Hz, 2 H), 7.11–7.02 (m, 3 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.76 (d, J = 7.8 Hz, 1 H), 5.30 (s, 1 H), 3.82 (s, 3 H), 2.48–2.28 (m, 4 H), 1.15 (s, 3 H), 1.06 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 195.8, 166.0, 147.4, 140.5, 136.1 (2 C), 131.9, 128.8, 128.2 (2 C), 124.7, 123.5, 120.9, 110.5, 109.6, 56.1, 50.8, 41.3, 38.8, 32.0, 28.4 (2 C).


Anal. Calcd for C₂₀H₁₈O₂N: C, 72.18; H, 6.05. Found: C, 72.18; H, 6.10.

5-Ethoxy-3,3-dimethyl-9-(phenylthio)-2,3,4,9-tetrahydro-1H-xanthen-1-one (4n)

Yield: 0.277 g (81%); orange solid; mp 200–202 °C.

IR (KBr): 3204, 2960, 1655, 1634, 1484, 1431, 1382, 1182, 1143 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.29 (d, J = 6.6 Hz, 1 H), 7.17 (t, J = 7.8 Hz, 2 H), 7.13–7.09 (m, 2 H), 7.02 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.75 (d, J = 8.1 Hz, 1 H), 5.29 (s, 1 H), 4.14–3.92 (m, 2 H), 2.48–2.32 (m, 4 H), 1.38 (t, J = 6.9 Hz, 3 H), 1.16 (s, 3 H), 1.07 (s, 3 H).

13C NMR (150 MHz, CDCl₃): δ = 195.9, 166.2, 146.6, 140.8, 136.1 (2 C), 132.1, 128.6, 128.2 (2 C), 124.6, 123.6, 120.9, 112.3, 109.6, 64.8, 50.8, 41.2, 40.9, 32.1, 28.4, 28.3, 14.7.


Anal. Calcd for C₂₁H₁₈NO₂Na: C, 72.60; H, 6.36. Found: C, 72.68; H, 6.44.

9-(Phenylthio)-2,3-dihydrocyclopenta[b]chromen-1(9H)-one (4o)

Yield: 0.211 g (72%); brown liquid.

IR (film): 3093, 1615, 1454, 1389, 1312, 1249, 1163, 1119, 744, 695 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.51–7.49 (m, 1 H), 7.31–7.27 (m, 1 H), 7.25–7.20 (m, 2 H), 7.14 (t, J = 7.2 Hz, 2 H), 6.94 (d, J = 8 Hz, 2 H), 6.85–6.83 (m, 1 H), 5.13 (s, 1 H), 2.57–2.36 (m, 4 H).

13C NMR (100 MHz, CDCl₃): δ = 201.5, 179.9, 151.3, 136.8 (2 C), 131.0, 130.9, 129.2, 128.8, 128.4 (2 C), 125.8, 122.2, 116.6, 114.0, 115.9, 115.8, 33.6, 25.3.


© Georg Thieme Verlag Stuttgart · New York

Synthesis 2014, 46, 73–80

Acknowledgment

S.B. is thankful to IIT Guwahati for her research fellowship. D.K.D. is thankful to CSIR, New Delhi for his research fellowship. The authors are grateful to the Department of Science and Technology, New Delhi for financial assistance for creating single XRD facility in the Department of Chemistry under FIST program. The authors also acknowledge the Director, IIT Guwahati for providing laboratory facility.
Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/soc/synthesis. Included are X-ray crystallographic data (CIF files) of 4k, spectral data of all compounds and copies of 1H, 13C NMR, and MS spectra of products.

References


(29) Complete crystallographic data of 4k for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 926004. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk].