A Facile Synthesis of 4-Hydroxycoumarin and 4-Hydroxy-2-quinolone Derivatives

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Coumarin derivatives possessing diverse biological activities play important roles as versatile building blocks for the synthesis of natural products and biologically active compounds. In particular, 4-hydroxycoumarin derivatives, such as 4-hydroxycoumarin and 4-hydroxythiocoumarin, have been used as useful intermediates for the synthesis of anticoagulants, herbicides, and anticancer agents. Recent reports show 4-hydroxy-2-quinolone derivatives are selective glycine site antagonists related to several central nervous system disorders including stroke, epilepsy, schizophrenia, Parkinson’s disease, and Alzheimer’s disease. Furthermore, coumarin derivatives, possessing a heterocyclic skeleton with a ring oxygen on a carbonyl group, are well-known fluorescence dyes for their high photoluminescence quantum efficiencies. A number of coumarins have been synthesized and explored the possibility of their application to electro-optic materials, such as laser dyes, organic scintillators, and photoelectronic sensitizers.

The Pechman reaction is the method widely applied, in a practical sense, for synthesizing coumarins as it involves the condensation of phenols with β-ketoesters in the presence of a variety of Lewis acid catalysts and gives good yields of 4-substituted coumarins. In variation, 4-hydroxythiocoumarins were prepared by heating excess thiophenol and malonic acid with POCl₃ at 110-115 °C and cyclizing the resulting dithiophenylmalonic esters in the presence of AlCl₃ at 180-190 °C. Also, 4-hydroxycoumarins and 4-hydroxy-2-quinolones were similarly prepared from diarylmalonates (ZnCl₂ and POCl₃, 30 h, 202-204 °C) and dianilides (AlCl₃ and NaCl, 250 °C; polyphosphoric acid, 158-160 °C), respectively. This method suffers from several disadvantages such as harsh reaction conditions; use of excess substrate like thiophenol, a large amount of promoters, elevated reaction temperature and long reaction time. Recently, 2-mercapto-benzoic acid or 2’-mercaptoacetophenone has been used for the synthesis of 4-hydroxythiocoumarin derivatives utilizing multi-steps or expensive reagents, respectively.

We envisioned that preparation of half malonic acid 3a-c would offer most concise synthetic route to 4-hydroxycoumarin derivatives 4a-c, as shown in Scheme 1. Amination of Meldrum’s acid 2 with aniline would give the monoanilide 3a in 86% and the monoester 3b in 92% isolated yield, respectively, under solvent-free conditions at 85-90 °C. However, the yield of 3c was quite low due to the rapid formation of dithiophenyl ester in the initial conditions, while the rate was very sluggish in the lower temperatures. Hence the influence of bases or additives on the hydrolysis of 2 in varying solvents was investigated. The addition of bases/additives (K₂CO₃ or Cs₂CO₃; DMAP or CsF) was proven to be useless, while facilitated the formation of dithioester. As shown in Table 1, aprotic polar solvents such as THF or 1,4-dioxane were found to be efficient to suppress the formation of dithioester. However, DMF exclusively facilitated the formation of dithioester. The best choice was found to be 1,4-dioxane in term of yield of 3c (entry 6).

Previously, 4-hydroxythiocoumarins were prepared by

![Scheme 1](image_url)

Table 1. Preparation of half malonic acid 3a-c

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>Conditions</th>
<th>Product (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>aniline</td>
<td>85 °C, 9 h</td>
<td>3a (86%)</td>
</tr>
<tr>
<td>2a</td>
<td>phenol</td>
<td>90 °C, 4 h</td>
<td>3b (92%)</td>
</tr>
<tr>
<td>3a</td>
<td>thiophenol</td>
<td>90 °C, 4 h</td>
<td>3c (24%)</td>
</tr>
<tr>
<td>4</td>
<td>thiophenol</td>
<td>toluene, reflux, 7 h</td>
<td>3e (35%)</td>
</tr>
<tr>
<td>5</td>
<td>thiophenol</td>
<td>THF, reflux, 6 h</td>
<td>3e (43%)</td>
</tr>
<tr>
<td>6</td>
<td>thiophenol</td>
<td>1,4-dioxane, reflux, 4 h</td>
<td>3e (67%)</td>
</tr>
</tbody>
</table>

*aSolvent-free conditions. bSignificant amount of dithiophenylmalonic ester (entry 3, 21%; entry 4, 15%) was isolated. cIn both cases, ~5% of dithioester was isolated.
heating of dithiophenylmalonate with aluminium chloride and/or phosphorus oxychloride at the elevated temperature with elimination of one mole of thiophenol. This condensation proceeds probably by way of a half malonic acid intermediate, in turn, which successfully cyclized to 4-hydroxycoumarin. The use of Lewis acids, such as AlCl₃ and ZnCl₂, was not effective, even though, at the elevated temperature. However, half malonic acid readily transformed to the 4-hydroxycoumarin derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Eaton’s reagent, 60 °C, 5 h 4a (74%)</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>116% PPA, 140 °C, 4 h 4a (70%)</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>Eaton’s reagent, 70 °C, 1 h 4b (75%)</td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>116% PPA, 120 °C, 15 h 4b (48%)</td>
</tr>
<tr>
<td>5</td>
<td>3c</td>
<td>Eaton’s reagent, 70 °C, 8 h 4c (38%)</td>
</tr>
<tr>
<td>6</td>
<td>3c</td>
<td>116% PPA, 120 °C, 8 h 4c (67%)</td>
</tr>
</tbody>
</table>

Notes

- Polyphosphoric acid.
- Phenylsulfanylcarbonyl acetic acid 3c (Entry 6, Table 2). A mixture of thiophenol (110 mg, 1 mmol) and Meldrum’s acid (2, 144 mg, 1 mmol) in anhydrous 1,4-dioxane (1 mL) was heated to reflux for 4 h. After cooling to room temperature, the reaction mixture was partitioned with ethyl acetate and sat’d NaHCO₃ solution. The aqueous layer was acidified to pH = 1-2 with conc. HCl and extracted with methylene chloride several times. The combined extracts were dried over MgSO₄ and concentrated to give 132 mg (67%) of 3c. An analytical sample was obtained by recrystallization (C₉H₈O₄). Mp 72-73 °C (lit. 13 74.0-75.5 °C); ¹H NMR (300 MHz, DMSO-d₆) δ 12.95 (s, 1H), 7.54-7.37 (m, 5H), 3.78 (s, 2H); EIMS m/z (rel intensity) 161 (M⁺, 42), 119 (74), 104 (32), 91 (100), 77 (40), 63 (96), 51 (55).

- 4-Hydroxy-2-quinolone 4a (Entry 1, Table 2). A mixture of 3a (89 mg, 0.5 mmol) and Eaton’s reagent (1.5 mL) was stirred at 60 °C for 5 h and then water was added to this mixture while stirring vigorously. The precipitate was filtered by suction, washed with H₂O, and dried in the air to give a solid. It was recrystallized from acetic acid to afford 60 mg (74%) of 4a, as a pale pink crystal. Mp 132-320 °C (lit. 106 320 °C); ¹H NMR (300 MHz, DMSO-d₆) δ 11.17 (s, 1H), 7.77 (d, 1H, J = 9 Hz), 7.48 (t, 1H, J = 9, 6 Hz), 7.26 (d, 1H, J = 9 Hz), 7.13 (t, 1H, J = 9, 6 Hz), 5.73 (s, 1H); EIMS m/z (rel intensity) 161 (M⁺, 42), 119 (74), 104 (32), 91 (100), 77 (40), 63 (96), 51 (55).

- 4-Hydroxycoumarin 4b (Entry 3, Table 2). A mixture of 3b (180 mg, 1 mmol) and Eaton’s reagent (3 mL) was stirred at 70 °C for 1 h and then water was added to this mixture while stirring vigorously. The precipitate was filtered by suction, washed with H₂O, and dried in the air to give a solid. It was recrystallized from ethanol to afford 122 mg (75%) of 4b, as pale yellow crystal. Mp 206 °C (lit. 108 211-213 °C); ¹H NMR (300 MHz, DMSO-d₆) δ 12.40 (s, 1H), 7.68 (d, 1H, J = 7.2 Hz), 7.53-7.48 (m, 1H), 7.24-7.18 (m, 2H), 5.45 (s, 1H); EIMS m/z (rel intensity) 162 (M⁺, 38), 120 (74), 92 (83), 77 (17), 63 (100), 42 (48).

- 4-Hydroxythiocoumarin 4c (Entry 6, Table 2). A mixture of 3c (98 mg, 0.5 mmol) and 116% PPA (1 g) was stirred at 120 °C for 8 h and then water was added to this mixture while stirring vigorously. The precipitate was filtered by suction, washed with H₂O, and dried in the air to give...
a solid. It was recrystallized from ethanol to afford 60 mg (67%) of 4c, as pale yellow crystal.

Mp 205-207 °C (lit.10b 209-210 °C); 1H NMR (300 MHz, DMSO-\textsubscript{d6}) \( \delta \) 8.15 (d, 1H, \( J = 7.7 \) Hz), 7.63-7.61 (m, 3H), 7.49-7.46 (m, 1H), 6.07 (s, 1H); EIMS \( m/z \) (rel intensity) 178 (M\(^+\), 23), 150 (62), 136 (77), 121 (43), 108 (74), 75 (83), 62 (92), 42 (100).

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References