

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

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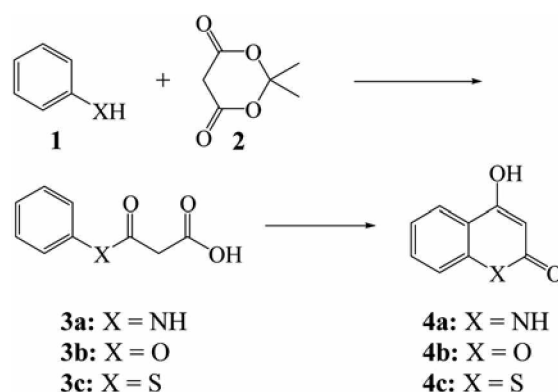
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Coumarin derivatives possessing diverse biological activities play important roles as versatile building blocks for the synthesis of natural products and biologically active compounds.¹ In particular, 4-hydroxycoumarin derivatives, such as 4-hydroxycoumarin² and 4-hydroxythiocoumarin,³ have been used as useful intermediates for the synthesis of anti-coagulants, 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.⁴ 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.⁵

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.⁶ 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.⁷ Also, 4-hydroxycoumarins and 4-hydroxy-2-quinolones were similarly prepared from diarylmalonates⁸ (ZnCl₂ and POCl₃, 30 h, 202-204 °C) and dianilides⁹ (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.¹⁰

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. Aminolysis of Meldrum's acid **2**¹¹ with aniline would give the half acid **3a**, which cyclize in the presence of Lewis acid to afford 4-hydroxy-2-quinolone **4a**. Herein, we report a facile synthesis of 4-hydroxycoumarin derivatives starting from cheap materials, such as phenol and malonic acid.



Scheme 1

Ring opening of Meldrum's acid **2** with aniline and phenol gave the monoanilide **3a** in 86% and the monoester **3b**¹² 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,¹³ 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

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

Entry	1	Conditions	Product (yield, %)
1 ^a	aniline	85 °C, 9 h	3a (86%)
2 ^a	phenol	90 °C, 4 h	3b (92%)
3 ^a	thiophenol	90 °C, 4 h	3c (24%) ^b
4	thiophenol	toluene, reflux, 7 h	3c (35%) ^b
5	thiophenol	THF, reflux, 6 h	3c (43%) ^c
6	thiophenol	1,4-dioxane, reflux, 4 h	3c (67%) ^c

^aSolvent-free conditions. ^bSignificant amount of dithiophenylmalonic ester (entry 3, 21%; entry 4, 15%) was isolated. ^cIn both cases, ~5% of dithioester was isolated.

Table 2. Preparation of 4-hydroxycoumarin derivatives **4a-c**

Entry	3	Conditions	Product (yield, %)
1	3a	Eaton's reagent, ^a 60 °C, 5 h	4a (74%)
2	3a	116% PPA, ^b 140 °C, 4 h	4a (70%)
3	3b	Eaton's reagent, 70 °C, 1 h	4b (75%)
4	3b	116% PPA, 120 °C, 15 h	4b (48%)
5	3c	Eaton's reagent, 70 °C, 8 h	4c (38%)
6	3c	116% PPA, 120 °C, 8 h	4c (67%)

^a7.7 wt. % Phosphorus pentoxide in methanesulfonic acid solution.
^bPolyphosphoric acid.

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.^{7,8b,14} The use of Lewis acids, such as AlCl₃ and ZnCl₂, was not effective, even though, at the elevated temperature. However, half malonic acid **3a-c** was readily transformed to the 4-hydroxycoumarin derivatives **4a-c** under Eaton's reagent or polyphosphoric acid (PPA) in a moderate yield, as shown in Table 2. While Eaton's reagent was proven to be effective for the Friedel-Crafts acylation of **3a** and **3b**, PPA gave better yield of **4c** than Eaton's reagent. It is noteworthy that this route is quite general and practical for the synthesis of 4-hydroxycoumarin derivatives from half malonic acid.

In summary, we have developed a simple and efficient modification of Pechmann condensation leading to 4-hydroxycoumarin derivatives from half malonic acids, which easily prepared from Meldrum's acid with phenol, thiophenol, and aniline, respectively.

Experimental Section

N-Phenyl-malonamic acid 3a (Entry 1, Table 1). A mixture of aniline (186 mg, 2 mmol) and Meldrum's acid (**2**, 288 mg, 2 mmol) was stirred at 85 °C for 9 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 308 mg (86%) of **3a**. An analytical sample was obtained by recrystallization (EtOH).

Mp 132-134 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.65 (s, 1H), 7.59-7.56 (m, 2H), 7.34-7.28 (m, 2H), 7.08-7.03 (m, 1H), 3.35 (s, 2H); EIMS *m/z* (rel intensity) 179 (M⁺, 2), 119 (1), 93 (80), 77 (9), 64 (72), 42 (100); Anal. Calcd for C₉H₉NO₃: C, 60.33; H, 5.06; N, 7.82; O, 26.79. Found: C, 61.40; H, 5.13; N, 7.31; O, 27.89%.

Malonic acid monophenyl ester 3b (Entry 2, Table 1). A mixture of phenol (1.88 g, 20 mmol) and Meldrum's acid (**2**, 2.88 g, 20 mmol) was stirred at 90 °C 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 3.31 g (92%) of **3b**. An analytical sample was obtained by recrystallization (C₆H₆).

Mp 68-69 °C (lit.¹² 71 °C); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.96 (s, 1H), 7.47-7.42 (m, 2H), 7.31-7.26 (m, 1H), 7.14-7.12 (m, 2H), 3.68 (s, 2H); EIMS *m/z* (rel intensity) 180 (M⁺, 2), 94 (100), 77 (6), 65 (25), 43 (97); Anal. Calcd for C₉H₈O₄: C, 60.00; H, 4.48; O, 35.52. Found: C, 59.06; H, 4.32; O, 37.50%.

Phenylsulfanylcarbonyl acetic acid 3c (Entry 6, Table 1). 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 (C₆H₆/C₆H₁₄).

Mp 72-73 °C (lit.¹³ 74.0-75.5 °C); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.95 (s, 1H), 7.54-7.37 (m, 5H), 3.78 (s, 2H); EIMS *m/z* (rel intensity) 196 (M⁺, 2), 152 (1), 109 (100), 87 (14), 82 (15), 64 (39), 42 (62); Anal. Calcd for C₉H₈O₃S: C, 55.09; H, 4.11; O, 24.45; S, 16.34. Found: C, 55.25; H, 4.01; O, 25.29; S, 17.83%.

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 318-320 °C (lit.^{10b} 320 °C); ¹H NMR (300 MHz, DMSO-*d*₆) 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.^{10b} 211-213 °C); ¹H NMR (300 MHz, DMSO-*d*₆) 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-*d*₆) δ 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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