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

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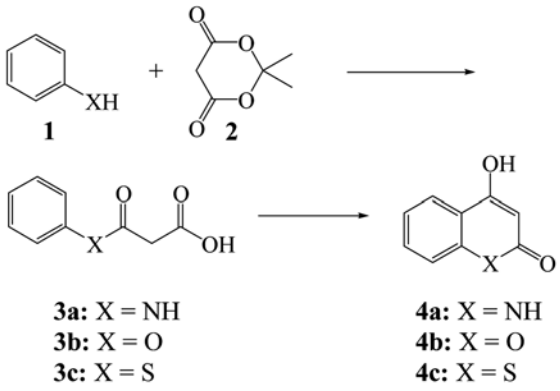
Coumarin derivatives possessing diverse biological activities play important roles as versatile building blocks for the synthesis of natural products and biologically active compounds.[1] In particular, 4-hydroxycoumarin derivatives, such as 4-hydroxycoumarin[2] and 4-hydroxythiocoumarin,[3] have been 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.[4] Furthermore, coumarin derivatives, possessing a hetrocyclic 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 photoelectonic 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 $POCl_3$ at 110-115 °C and cyclizing the resulting dithiophenylmalonic esters in the presence of $AlCl_3$ at 180-190 °C.[7] Also, 4-hydroxycoumarins and 4-hydroxy-2-quinolones were similarly prepared from diarylmaonates[8] ($ZnCl_2$ and $POCl_3$, 30 h, 202-204 °C) and dianilides[9] ($AlCl_3$ 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-mercaptobenzoic 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 (K_2CO_3 or Cs_2CO_3; 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]

[a]Solvent-free conditions. [b]Significant amount of dithiophenylmalonic ester (entry 3, 21%; entry 4, 15%) was isolated. [c]In 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%)

[a]7.7 wt. % Phosphorus pentoxide in methanesulfonic acid solution. [b]Polyphosphoric 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 $AlCl_3$ and $ZnCl_2$, 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 $NaHCO_3$ solution. The aqueous layer was acidified to *p*H = 1-2 with conc. HCl and extracted with methylene chloride several times. The combined extracts were dried over $MgSO_4$ and concentrated to give 308 mg (86%) of **3a**. An analytical sample was obtained by recrystallization (EtOH).

Mp 132-134 °C; ^{1}H 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 $C_9H_9NO_3$: 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 $NaHCO_3$ solution. The aqueous layer was acidified to *p*H = 1-2 with conc. HCl and extracted with methylene chloride several times. The combined extracts were dried over $MgSO_4$ and concentrated to give 3.31 g (92%) of **3b**. An analytical sample was obtained by recrystallization (C_6H_6).

Mp 68-69 °C (lit.[12] 71 °C); ^{1}H 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 $C_9H_8O_4$: 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 $NaHCO_3$ solution. The aqueous layer was acidified to *p*H = 1-2 with conc. HCl and extracted with methylene chloride several times. The combined extracts were dried over $MgSO_4$ and concentrated to give 132 mg (67%) of **3c**. An analytical sample was obtained by recrystallization (C_6H_6/C_6H_{14}).

Mp 72-73 °C (lit.[13] 74.0-75.5 °C); ^{1}H 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 $C_9H_8O_3S$: 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 H_2O, 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); ^{1}H 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 H_2O, 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); ^{1}H 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 H_2O, 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); ^{1}H 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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