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SIMPLE AND COST EFFECTIVE SYNTHESES OF 4-HYDROXYCOUMARIN

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Abstract: Two simple and inexpensive methods for the preparation of 4-hydroxycoumarin from aspirin are described, which should be readily amenable to large scale synthesis.

As part of our synthetic program[1] directed towards the synthesis of 4-hydroxycoumarin derivatives, having potent anticoagulant properties, practical synthesis of 4-hydroxycoumarin (1) was needed for large scale production.

Several syntheses of this compound (1) have been reported in the literature.[2-6] Most of these methods have been based on the Friedel-Crafts acylation of phenol in which Lewis acids such as $ZnCl_2$, $AlCl_3$ and $POCl_3$ are used. These Lewis acids form an intractable solid mass during the reaction which makes the stirring of the reaction mixture and the product isolation considerably difficult. As a consequence, they suffer from drawbacks such as tedious work-up, poor yield

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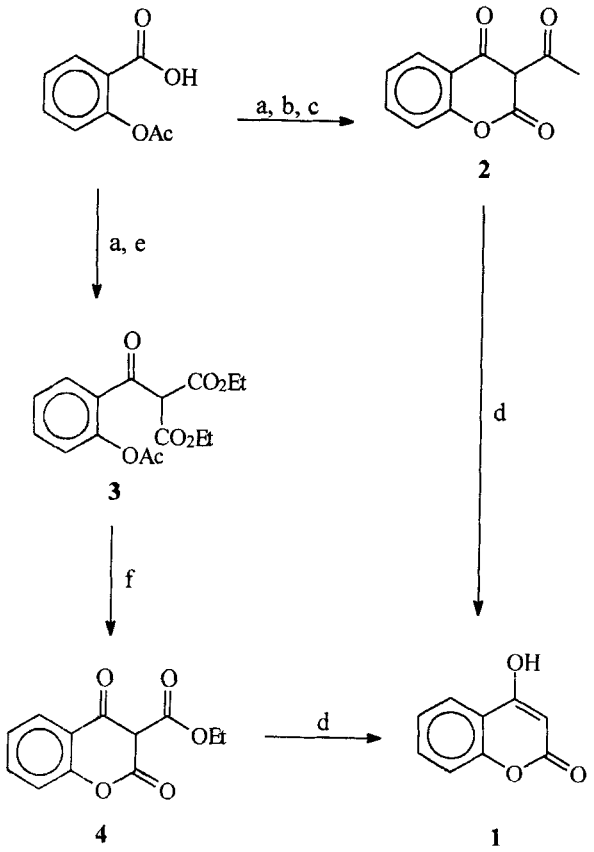


(a) $SOCl_2$, urea/toluene; (b) $CH_3COCH_2CO_2Et$, 40% NaOH; (c) 40% NaOH, 35℃; (d) H_2SO_4; (e) $CH_2(CO_2Et)_2$, Mg, EtOH; (f) 3N-HCl/EtOH or *aq*. $NaHCO_3$/EtOH

Scheme 1

and use of expensive reagents. This prompted us to investigate on the alternative synthesis of this compound (1).

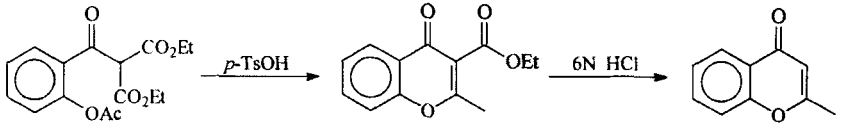
In this paper, we report two simple and inexpensive syntheses of this compound (1), starting from aspirin. The synthetic strategies involve the use of

well known ethyl acetoacetate synthesis and malonic ester synthesis (Scheme 1).

In the first method, aspirin was converted to 2-acetoxybenzoyl chloride by the use of thionyl chloride, which was subsequently treated with the anion of ethyl acetoacetate to give ethyl 2-(2-acetoxy)benzoylacetoacetate. This compound was not isolated and cyclized directly to 3-acetyl-4-hydroxycoumarin (2) under basic condition in 73.6% yield. Further purification of this intermediate (2) was unnecessary for the next reaction. 3-Acetyl-4-hydroxycoumarin (2) was treated with concentrated sulfuric acid to give 4-hydroxycoumarin (1) in 90.2% yield. The overall yield is 66.4%. The whole reaction sequence can be carried out in one-pot from aspirin without isolation of intermediates.

In the second method, the anion of diethyl malonate was treated with 2-acetoxybenzoyl chloride to afford diethyl 2-(2-acetoxy)benzoylmalonate (3) in 88.2% yield. The ring cyclization of this compound (3) was achieved by refluxing with 3N hydrochloric acid or aqueous sodium bicarbonate to produce 3-carbethoxy-4-hydroxycoumarin (4) in 81.1% and 72.4 % yield, respectively. However, the ring cyclization of this compound (3) with *p*-toluenesulfonic acid gave a complex mixture from which we could isolate compound 5[7] in low yield. The hydrolysis and decarboxylation of compound 5 with 6N hydrochloric acid proceeded smoothly to afford 2-methyl-4*H*-4-chromenone (6)[8] in 85.3 % yield (Scheme 2).

The hydrolysis and decarboxylation of compound 4 with concentrated sulfuric acid proceeded smoothly to afford 4-hydroxycoumarin (1) in 90.5% yield. The overall yield is 64.7%.



3 5 6

Scheme 2

In conclusion, we have developed two simple and efficient large scale syntheses of 4-hydroxycoumarin (1) in 66.4% and 64.7% overall yield, respectively, starting from readily available and inexpensive reagents. The reactions are simple, should be easy to scale up and the intermediates do not require further purification.

EXPERIMENTAL SECTION

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F 254 plates from EM reagents and visualized with 254-nm UV light or ceric sulfate-ammonium-molybdate-sulfuric acid spray. Flash chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040~0.063 mm, 230~400 mesh ASTM). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker DPX 300 at 300 MHz and 75.47 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. IR

spectra were obtained on a Jasco FT/IR-300E spectrometer. Mass spectra were recorded on a Shimadzu-LKB 9000 GC/MS system. All mps were uncorrected. When necessary, chemicals were purified according to the reported procedure.[9]

3-Acetyl-4-hydroxycoumarin (2)

14.3 g (120 mmol) of thionyl chloride was added to a well stirred solution of 18.0 g (100 mmol) of 2-acetylsalicylic acid and urea (120 mg) in 14 mL of anhydrous toluene at 10 – 15℃. The reaction mixture was heated in an oil bath at 100 – 110℃ for 3h, then cooled to RT. In a separate, oven-dried, three-necked, round-bottomed flask, equipped with a mechanical stirrer, a reflux condenser and a thermometer was placed ethyl acetoacetate (13.0 g, 100 mmol) under an atmosphere of nitrogen and cooled in an ice-salt bath to 5℃, and a cold solution of 40% NaOH (13.4 mL) was added with vigorous stirring at 5 – 10℃. The former solution was cannulated into the latter. The resulting reaction mixture was stirred at 0 – 5℃ for 1h, then allowed to warm to RT. To it, 40% NaOH (11 mL) was added, warmed to 35℃ and stirred for 1h. 40 mL of water was added. The aqueous layer was saturated with NaCl, the crude product was filtered and washed with water and dried to give a light yellow crystal (15.1 g, 73.6%). m.p. 155～159 ℃; IR (ν_{max}, KBr) 3410, 1682, 1614, 1387 cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 7.91 (dd, *J*=7.68 Hz, *J*=1.27 Hz, 1 H), 7.50～7.44 (m, 1 H), 7.19～7.10 (m, 2 H), 4.09 (s, 1 H) 2.42 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ

197.55, 176.92, 164.32, 153.68, 132.33, 126.09, 123.01, 122.74, 115.98, 102.90, 33.34

4-Hydroxycoumarin (1)

A mixture of 3-acetyl-4-hydroxycoumarin (8.0 g, 39 mmol), concentrated sulfuric acid (24 mL), H_2O (5 mL) and ethanol (12 mL) was refluxed for 1 h. The mixture was cooled to 10℃ and filtered by suction. The product was washed with water, dried in the air to afford a pale yellow crystal. It was recrystallized from ethanol to give a white crystalline solid (5.7 g, 90.2%). m.p. 211～213 ℃ (*lit*. m.p. 205.1 ℃[6] and 206 ℃[10]); IR (ν_{max}, KBr) 3387-2583, 1658, 1599, 1323 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 12.48 (br s, 1 H), 7.82 (d, *J*=7.20, 1 H), 7.67～7.58 (m, 1 H), 7.38～7.30 (m, 2 H), 5.88 (s, 1 H); ^{13}C NMR (CD_3SOCD_3) δ 169.26, 164.97, 156.02, 134.76, 126.15, 125.53, 118.47, 118.20, 92.72

Diethyl 2-(2-acetoxy)benzoylmalonate (3)

23.8 g (200 mmol) of thionyl chloride was added to a well stirred solution of 30.0 g (167 mmol) of 2-acetylsalicylic acid and urea (200 mg) in 25 mL of anhydrous toluene at 10–15℃. The reaction mixture was heated in an oil bath at 100 – 110℃ for 3h, then cooled to RT. The mixture of diethyl malonate (26.7 g, 167 mmol), magnesium (4.2 g, 173 mmol), ethanol (23.4 g, 508 mmol), CCl_4 (1.6 mL) and anhydrous ether (200 mL) was refluxed for 3.5 h and then cooled to 0 – 5℃. The former solution was cannulated into the latter. The resulting reaction

mixture was stirred at RT for 30 min, and then cooled to 0 – 5℃. 120 mL of 1N HCl was added. The organic layer was washed with brine, dried and concentrated at reduced pressure to give crude product (47.3 g, 88.2%). IR (ν_{max}, KBr) 3068, 2985, 1728, 1680, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.69 (br s, 1 H), 7.58～7.55 (m, 1 H), 7.48～7.46 (m, 1 H), 7.32～7.27 (m, 2 H), 4.20～4.15 (m, 4 H), 2.26 (s, 3 H), 1.33～1.18 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 188.10, 171.13, 164.68, 147.59, 134.32, 130.49, 128.79, 126.18, 122.90, 101.84, 61.95, 61.51, 38.72 14.17, 14.05

3-Carbethoxy-4-hydroxycoumarin (4)

Method A A mixture of diethyl 2-(2-acetoxy)benzoylmalonate (24.6 g, 76 mmol), 3N HCl (750 mL) and ethanol (1.0 L) was refluxed for 3 h. The mixture was cooled to 10℃ and filtered by suction. The product was washed with water and dried in the air to afford a pale yellow crystal (16.2 g, 81.1%). m.p. 89～92 ℃; IR (ν_{max}, KBr) 3064, 2979, 1733, 1619, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 14.70 (s, 1 H), 8.01 (d, *J*=7.79 Hz, 1 H), 7.98～7.60 (m, 1 H), 7.35～7.28 (m, 2 H), 4.51 (q, *J*=7.10 Hz, 2 H), 1.47 (t, *J*=7.10 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.81, 172.27, 157.64, 154.79, 135.90, 125.40, 124.89, 117.20, 114.79, 93.43, 63.17, 14.53

Method B A mixture of diethyl 2-(2-acetoxy)benzoylmalonate (20.0 g, 62 mmol), sat. $NaHCO_3$ (70mL) and ethanol (100 mL) / H_2O (50 mL) was refluxed

for 1 h. The mixture was cooled to 10℃ and filtered by suction. The product was washed with water and dried in the air to afford a pale yellow crystal (11.8 g, 72.4%).

4-Hydroxycoumarin (1)

A mixture of 3-carbethoxy-4-hydroxycoumarin (30.0 g, 114 mmol), concentrated sulfuric acid (100 mL), H_2O (20mL) and ethanol (48 mL) was heated in an oil bath at 100 – 105℃ for 1 h. The mixture was cooled to 10℃ and water (500 mL) was added slowly while stirring vigorously. The produced crystal was filtered by suction, washed with water and dried in the air to afford a pale yellow crystal. It was recrystallized from ethanol to give a white crystalline solid (16.8 g, 90.5%).

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7. Repesentative spectral data: ethyl 2-methyl-4-oxo-4*H*-1-benzopyran-3-carboxylate (5): R_f = 0.45 (silicagel, 20% EA in hexanes); m.p. 68～70 ℃; IR (ν_{max}, KBr) 2989, 1729, 1640, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (d, *J*=7.75, 1 H), 7.64 (q, *J*=7.11, 1 H), 7.41～7.36 (m, 2 H), 4.39 (q, *J*=7.12, 2 H), 2.48 (s, 3 H), 1.40 (t, *J*=7.12, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 175.16, 167.47, 165.88, 156.32, 134.79, 126.80, 126.29, 124.08, 117.53, 118.53, 62.52, 20.28, 14.82; MS (m/e) 232 (M^+), 187, 160 (base peak), 121, 67.

8. Repesentative spectral data: 2-methyl-4*H*-4-chromenone (6): R_f = 0.30 (silicagel, 33% EA in hexanes); m. p. 72～74 ℃; IR (ν_{max}, KBr) 2860, 1655, 1457, 1383 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (d, *J*=7.92, 1 H), 7.62 (m, 1 H), 7.35 (m, 2 H), 6.15 (s, 1 H), 2.37 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 178.50, 166.56, 156.76, 133.77, 126.29, 125.22, 123.84, 118.13, 110.84, 20.91

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