

A One-Pot Synthesis of Coumarins from Dipotassium *O*-Methoxybenzylidene-malonates

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o-Methoxybenzylidenemalonates **1**, which are available from *o*-methoxybenzaldehydes and diethyl malonate, were hydrolysed to the dipotassium malonates **2**. Treatment of the salts **2** with trifluoroacetic acid–trifluoroacetic anhydride gave the title coumarins by a demethylative ring-closure reaction in 60–80% yield.

Recently we demonstrated that various dipotassium arylidene-malonates could be prepared conveniently by treatment of the diethyl esters with potassium hydroxide in ethanol followed by filtration of the precipitated salts. The corresponding malonic acids are highly water soluble and therefore their isolation requires cumbersome operations such as treatment of the dipotassium malonates with hydrogen chloride gas in acetic acid.¹ We therefore felt it of interest to examine various dipotassium malonates, rather than the isolated acids, as potential starting materials for the preparation of diverse compounds. As part of our investigations we report herein a convenient synthesis of the coumarins **5** by using the dipotassium *o*-methoxybenzylidenemalonates **2** as starting materials.

Our wish to investigate the dipotassium *o*-methoxybenzylidenemalonate system was also stimulated by the fact that in spite of the copious literature dealing with coumarin synthesis using *ortho*-hydroxy² or protected *o*-hydroxycinnamic acids³ the demethylative variant using *o*-methoxycinnamic acid derivatives has been largely neglected.^{4,5}

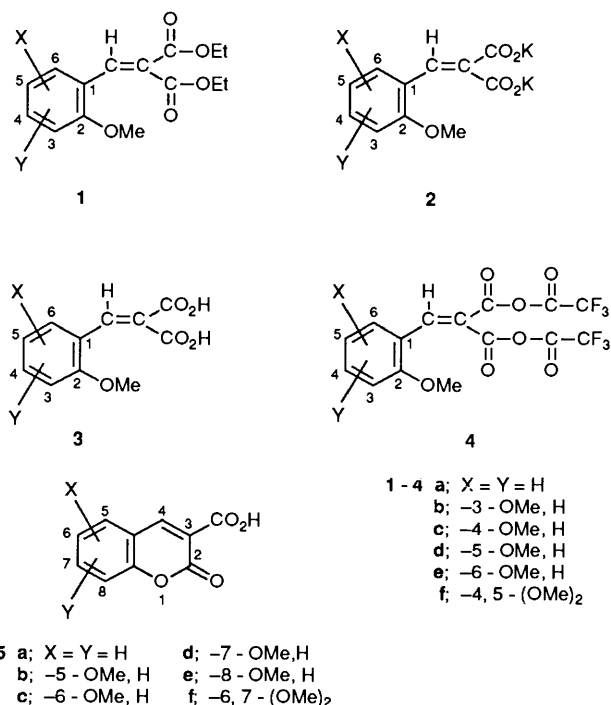
Coumarins are of interest because they constitute a class of naturally occurring compounds, many of which exhibit useful biological activity. The majority of the naturally occurring coumarins are highly oxygenated.⁶

Results and Discussion

The diethyl *o*-methoxybenzylidenemalonates **1** were available from Knoevenagel reaction⁷ between diethyl malonate and the appropriate *o*-methoxybenzaldehydes and no attempts were made to improve the yields of these steps. The aldehydes were commercially available.

Hydrolysis of the esters **1** with potassium hydroxide (2 mol equiv.) in ethanol produced the salts **2** in 60–80% yield.

The remaining step to produce the coumarins **5** from salt **2** required demethylative cyclization. We first tested the action of conc. sulphuric acid on dipotassium 2, 4, 5-trimethoxybenzylidenemalonate **2f** because the reaction between conc. sulphuric acid and the 2,4,5-trimethoxybenzylidene derivative of Meldrum's acid is reported to give an excellent yield of 6,7-dimethoxycoumarin-3-carboxylic acid **5f**.⁴ We found that the reaction produced the desired product but in our hands the yield was only moderate (37%). When we generated 2,4,5-trimethoxybenzylidenemalononic acid **3f** from the corresponding dipotassium salt and trifluoroacetic acid (TFA) in the absence of dehydrating agents such as conc. sulphuric acid we did not observe any ring closure. We believed that one possible cause of the failure to obtain high yields in conc. sulphuric acid was that the carbonyl carbon atoms of the acids **3** do not develop a sufficiently high degree of positive charge to allow the



demethylative cyclization to occur (*cf.* a suggested transition state in β -substituted *o*-methoxybenzylidenemalononitrile systems, ref. 5). We thus reasoned that the yields of the coumarins could be enhanced simply by changing the acid group to an anhydride or an acid chloride function, because anhydrides and acid chlorides are more reactive acylating agents than are acids.

Since TFA is a stronger acid than malonic acid, and since malonic acid derivatives are reported to produce mixed anhydrides on treatment with trifluoroacetic anhydride (TFAA),⁸ we were attracted to the use of TFA as solvent to produce the mixed anhydrides **4** *in situ* from the salts **2** and TFAA *via* the acids **3**.

We found that the reaction involving use of TFA on dipotassium 2,4,5-trimethoxybenzylidenemalonate **2f** produced the intermediate 2,4,5-trimethoxybenzylidenemalononic acid **3f**, and the treatment of the acid with TFAA cleanly converted the salt into the desired coumarin **5f**. The yield was enhanced from 37 to 77%. The approach was uniformly successful and the yields of the coumarins **5** varied between 60–80% and the overall yields of coumarins **5** from substrates **1** varied between 40–60%.

Experimental

M.p.s are uncorrected and were determined on a Gallenkamp melting point apparatus. ^1H NMR spectra were measured with JEOL 90Q or PMX 60 spectrometers and the chemical shifts are reported relative to internal Me_4Si . IR spectra were obtained on a Perkin-Elmer 297 spectrometer and the wave numbers are reported in cm^{-1} . Mass spectra were recorded on a VG 7070E instrument.

*Preparation of the O-Methoxybenzylidenemalonates 1 by use of the Knoevenagel Procedure.*⁷—Diethyl 2-methoxybenzylidenemalonate **1a**. Yield 46%; m.p. 51–52 °C (lit.,⁹ b.p. 193–195 °C/14 mmHg); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.20 (3 H, t, J 7.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 1.38 (3 H, t, J 7.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 3.83 (3 H, s, OMe), 4.30 (2 H, q, J 7.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 4.35 (2 H, q, J 7.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 6.75–7.15 (total 2 H, ArH), 7.20–7.55 (total 2 H, ArH) and 8.18 (1 H, s, =CH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$, 1730s, 1630w, 1600w, 1300–1000 (several bands), 765w and 750w; m/z M^+ , 278.1154 (83%). [Calc. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: M , 278.1154], 247 (46), 233 (84), 219 (17), 204 (19), 186 (64), 173 (100), 132 (76), 131 (40), 118 (21), 89 (18) and 77 (22).

Diethyl 2,3-dimethoxybenzylidenemalonate **1b**. Yield 45%; m.p. 27 °C; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.25 (3 H, t, J 7.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 1.33 (3 H, t, J 8.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 3.8 (6 H, s, OMe), 4.22 (2 H, q, J 7.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 4.28 (2 H, q, J 8 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 6.90 (3 H, s, ArH) and 7.93 (1 H, s, =CH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1730s, 1630m, 1580m, 1380s, 1350m, 1300–1000 (several bands), 790w and 750m; m/z M^+ , 308.1245 (44%). [Calc. for $\text{C}_{16}\text{H}_{20}\text{O}_6$: M , 308.1260], 277 (30), 263 (31), 216 (10), 204 (12), 203 (100) and 162 (11).

Diethyl 2,4-dimethoxybenzylidenemalonate **1c**. Yield 71%; m.p. 51–54 °C; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.30 (3 H, t, J 8.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 1.38 (3 H, t, J 7.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 3.88 (6 H, s, OMe), 4.32 (2 H, q, J 8.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 4.38 (2 H, q, J 7.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 6.40–7.55 (total 3 H, ArH) and 8.15 (1 H, s, =CH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1715s, 1610s, 1570w, 1505w and 1300–1000 (several bands); m/z M^+ , 308.1238 (100%). [Calc. for $\text{C}_{16}\text{H}_{20}\text{O}_6$: M , 308.1260], 263 (57), 234 (13), 216 (13), 203 (33), 162 (55), 161 (15) and 149 (20).

Diethyl 2,5-dimethoxybenzylidenemalonate **1d**. Yield 48%; m.p. 40–41 °C; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.23 (3 H, t, J 7.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 1.30 (3 H, t, J 8.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 3.66 (3 H, s, OMe), 3.75 (3 H, s, OMe), 4.25 (2 H, q, J 7.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 4.25 (2 H, q, J 8.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 6.76–6.98 (total 3 H, ArH) and 7.95 (1 H, s, =CH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1730s, 1630w, 1580w, 1500s and 1300–1000 (several bands); m/z M^+ , 308.1269 (100%). [Calc. for $\text{C}_{16}\text{H}_{20}\text{O}_6$: M , 308.1260], 263 (27), 234 (12), 203 (67), 175 (10), 162 (14) and 161 (11).

Diethyl 2,6-dimethoxybenzylidenemalonate **1e**. Yield of crude product 89%; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.20 (3 H, t, J 7.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 1.30 (3 H, t, J 6.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 3.78 (6 H, s, OMe), 4.1 (2 H, q, J 7.0 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 4.2 (2 H, q, J 6.6 Hz, $\text{CO}_2\text{CH}_2\text{Me}$), 6.32–7.42 (total 3 H, ArH) and 7.83 (1 H, s, =CH).

Diethyl 2,4,5-trimethoxybenzylidene malonate **1f**. Yield 78%; m.p. 99 °C (lit.,¹⁰ 98–99 °C).

Preparation of the Dipotassium O-Methoxybenzylidenemalonates 2.—Dipotassium 2-methoxybenzylidenemalonate **2a**. KOH (85.5%; 1.31 g, 20 mmol) was dissolved in boiling ethanol (30 cm^3). Diethyl 2-methoxybenzylidenemalonate (3.08 g, 10 mmol) was added. The solution was heated and stirred in an oil-bath at 110 °C overnight (12 h). The solution was cooled to room temperature. Filtration with suction gave compound **2a** (1.76 g, 67%).

Other dipotassium benzylidenemalonates prepared using this procedure were:

Dipotassium 2,3-dimethoxybenzylidenemalonate **2b** in 62% yield.

Dipotassium 2,4-dimethoxybenzylidenemalonate **2c**, 67% yield.

Dipotassium 2,5-dimethoxybenzylidenemalonate **2d**, 64% yield.

Dipotassium 2,6-dimethoxybenzylidenemalonate **2e**, 56% yield.

Dipotassium, 2,4,5-trimethoxybenzylidenemalonate **2f**, 78% yield.

Preparation of the Coumarin-3-carboxylic Acids 5.—Coumarin-3-carboxylic acid **5a**. Dipotassium 2-methoxybenzylidenemalonate (1 g) was added in portions to efficiently stirred TFA (10 cm^3) at room temperature. After 5 min, TFAA (5 cm^3) was added. The mixture was stirred overnight (12 h) at room temperature, and was then concentrated on a rotary evaporator. The residue was dissolved in water (10 cm^3), and the product was collected by filtration. The yield of the acid **5a** was 0.43 g (63%), m.p. 185–187 °C (lit.,¹¹ 187 °C).

Other coumarin-3-carboxylic acid prepared using this procedure were as follows:*

5-Methoxycoumarin-3-carboxylic acid **5b**. Yield 63%; m.p. 214–215 °C, darkens at 204 °C (lit.,⁴ 215–216 °C); $\delta_{\text{H}}(\text{CDCl}_3; \text{DMSO})$ 4.03 (3 H, s, OMe), 6.82–7.90 (total 3 H, ArH) and 8.90 (1 H, s, ArH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1815w, 1775s, 1680w, 1615s, 1565m, 1300m, 1230m, 1095m and 800m; m/z [M^+ , 220.0352 (100%)]. Calc. for $\text{C}_{11}\text{H}_8\text{O}_5$: M , 220.0371], 177 (21), 176 (47), 148 (21) and 133 (26).

6-Methoxycoumarin-3-carboxylic acid **5c**. Yield 73%; m.p. 194–196 °C (lit.,⁴ 179–180 °C; cf. compound **5d**); $\delta_{\text{H}}(\text{CDCl}_3; \text{DMSO})$ 3.9 (3 H, s, OMe), 7.36–7.54 (total 3 H, ArH) and 8.83 (1 H, s, ArH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1760s, 1675s, 1620w, 1580s, 1495m, 1410m, 1245m, 1020m and 800m; m/z [M^+ , 220.0355 (100%)]. Calc. for $\text{C}_{11}\text{H}_8\text{O}_5$: M , 220.0371], 176 (30), 161 (32), 148 (25) and 133 (34).

7-Methoxycoumarin-3-carboxylic acid **5d**. Yield 60%; m.p. 176–177 °C (lit.,⁴ 192–193 °C; cf. compound **5c**); $\delta_{\text{H}}(\text{CDCl}_3; \text{DMSO})$ 3.91 (3 H, s, OMe), 6.84–7.92 (total 3 H, ArH) and 8.72 (1 H, s, ArH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1735s, 1690w, 1620m, 1560w, 1505m, 1260w, 1220m, 1015m and 800m; m/z [M^+ , 220.0354 (100%)]. Calc. for $\text{C}_{11}\text{H}_8\text{O}_5$: M , 220.0371], 203 (26), 176 (77), 148 (22) and 133 (34).

8-Methoxycoumarin-3-carboxylic acid **5e**. Yield 66%; m.p. 194–195 °C; $\delta_{\text{H}}(\text{CDCl}_3; \text{DMSO})$, 4.03 (3 H, s, OMe), 7.51 (3 H, s, ArH) and 8.87 (1 H, s, ArH); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1760s, 1675s, 1610s, 1580m, 1285m, 1225m, 1210w, 1205m, 970w and 800m; m/z [M^+ , 220.0348 (100%)]. Calc. for $\text{C}_{11}\text{H}_8\text{O}_5$: M , 220.0371], 203 (16), 176 (44), 133 (23) and 105 (18).

6,7-Dimethoxycoumarin-3-carboxylic acid **5f**. Yield 77%; m.p. 225 °C (decomp.) [lit.,⁴ 240 °C (decomp.)]; $\delta_{\text{H}}(\text{CDCl}_3; \text{DMSO})$ 3.92 (3 H, s, OMe), 4.02 (3 H, s, OMe), 7.31 (1 H, s, ArH), 7.94 (1 H, s, ArH) and 8.92 (1 H, s); $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1745s, 1675m, 1620m, 1570w, 1510s, 1290m, 1260m, 1235w, 1210m, 795w and 720w; m/z [M^+ , 250.0479 (100%)]. Calc. for $\text{C}_{12}\text{H}_{10}\text{O}_6$: M , 250.0477], 206 (21), 191 (18), 163 (20) and 69 (17).

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* DMSO = dimethyl sulphoxide.

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