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An Efficient Preparation of Coumarins

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Abstract *: o-methoxyaryl-aldehydes (or -ketones) react in solid-phase with Meldrum's acid under mild conditions, to give benzylidene derivatives which are cyclized in high yield, with cold sulfuric acid to substituted 3-carboxycoumarins. Thermal decarboxylation, speed up by copper powder, provided an easy access to numerous coumarins.*

While engaged on work directed towards the synthesis of terpenoids (1), we needed to prepare different natural coumarins associated to sugars or terpenic moieties (2). Despite these compounds are obtained from a variety of ways, some methods show important limitations. For our purpose we considered first the possibility of preparing these molecules by denitro-cyclization of o-nitrobenzylidenemalonic acids **1** using the principle reported a few years ago by Sakakibara (3). Unfortunately we could not obtain good yields with our substrates. Consequently, in this communication, we present our own strategy to prepare coumarins through the use of the Perkin synthesis of pyrone ring, starting from o-methoxy aromatic aldehydes or ketones (4,5).

Our results are illustrated with four examples : daphnetin-7-methylether **2a**, two benzofuranocoumarins **2b** , **2c**, and the 4-methyl-7-methoxycoumarin **2d**.

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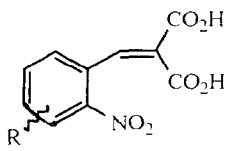
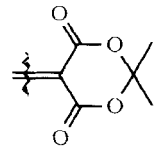
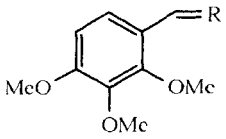


1

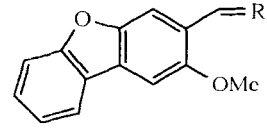
R = 

3a/d or R = O 4a/d



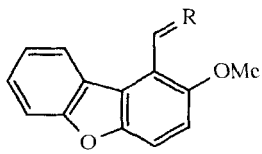
3a

R = O 4a



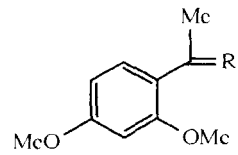
3b

4b



3c

R = O 4c



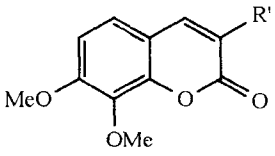
3d

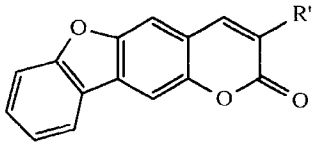
4d

The method consists to prepare compounds **3** (with R=Meldrum's acid radical) by solid phase synthesis (6) in the presence of a large excess of ZnO (7) to promote a clean Knoëvenagel type reaction between Meldrum's acid (8) and the corresponding carbonyl compound **4** (R = O) (9,10). The required 3-carboxycoumarins **5a/d** (R' = CO_2H), resulted from a cyclization of the o-methoxybenzylidene Meldrum's acid derivatives in cold concentrated sulfuric acid, a well-known condensing agent for the von Pechmann reaction. Finally decarboxylation to coumarins **2a/d** were achieved with copper powder (11).

In conclusion, among the great number of different approaches to coumarins that are known in the literature (12), the described synthesis employing common intermediates has the advantage to furnish by a straightforward sequence of reactions,

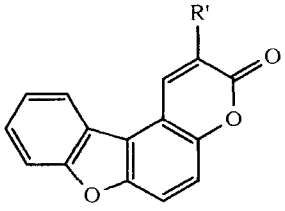
in fair yields and feasible on grams quantities, easily separable crystalline compounds which may be conveniently purified.

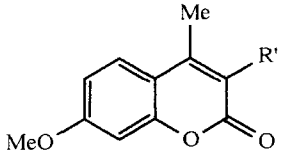




R' = CO_2H **5a** **5b**

R' = H **2a** **2b**





R' = CO_2H **5c** **5d**

R' = H **2c** **2d**

Experimental section

^1H and ^{13}C NMR were recorded with a Varian EM90 (MHz) or a Bruker AC, 400 MHz spectrometer, in $CDCl_3$. Chemical shifts were reported in ppm (δ) relative to tetramethylsilane as internal standard; coupling constants (J) are given in Hz with the following abbreviations for splitting patterns: s = singlet, ps = pseudo-singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Melting point were taken on a Reichert apparatus and are uncorrected. Flash chromatography was performed on 230-400 mesh Merck Silica gel 60. Elemental analyses of new compounds were performed in the *Service de Microanalyse de l'ICSN* (Gif sur Yvette). High resolution mass spectra were recorded with a Varian MAT 311.

Condensation with Meldrum's acid. General procedure for compounds 3 - In a 50 mL flask, 10 mmol of the aldehyde **4a** to **4d** (R = O) (9,10), 2 g of Meldrum's acid (14 mmol) (8) and 10 g of zinc oxide (140 mmol) are mixed together. This mixture, turned to orange yellow, was maintained to 80 °C and stirred from time

to time for 4 hr. After cooling to room temperature the mixture is extracted by CH_2Cl_2 (150 mL). After decantation, the solvent is removed under reduced pressure. Crystallization afforded pure Meldrum's derivatives **3a,d.** Physical and spectroscopic data follow.

2,2-dimethyl-5-[(2,3,4-trimethoxyphenyl)-methylene]-1,3-dioxane-4,6-dione 3a (77%) mp. 128 °C (ethyl acetate/cyclohexane). NMR ^1H (90 MHz) $CDCl_3$, ppm : 1.76 (s, 6H, 2 Me), 3.87; 3.97 and 4.03 (3s, $Me_{(C2')}$ $Me_{(C3')}$ and $Me_{(C4')}$), 6.82 (d, J = 9 Hz, 1H), 8.32 (d, J = 9 Hz, 1H), 8.88 (s, 1 H). Elemental analysis, found C, 59.66; H, 5.52; O, 34.57 %. $C_{16}H_{18}O_7$ requires C, 59.62; H, 5.63; O, 34.75 %.

2,2-dimethyl-5-(3-(2-methoxydibenzofuran)methylene)-1,3-dioxane-4,6-dione 3b - (97%) mp. 198-200 °C (methylene chloride). NMR ^1H (400 Mhz) $CDCl_3$, ppm : 1.83 (s, 6H, 2 CH_3), 4.03 (s, MeO), 7.32-7.39 (m, 1H), 7.41 (s, 1H), 7.49-7.60 (m, 2H), 7.94 (d, J = 8 Hz, 1H), 8.46 (s, 1H), 8.94 (s, $H_{(ethylenic)}$). Elemental analysis, found C, 68.12; H, 4.62; O, 27.40 %. $C_{20}H_{16}O_6$ requires C, 68.18; H, 4.58; O, 27.25 %.

2,2-dimethyl-5-[1-(2-methoxydibenzofuran)methylene]-1,3-dioxane-4,6-dione 3c - (95%) mp. 234-235°C (methylene chloride). NMR ^1H (400Mhz) $CDCl_3$, ppm : 1.93 (s, 6H, 2 CH_3), 3.90 (s, MeO), 7.05 (d, J = 9 Hz, 1H), 7.37 (m, 1H), 7.51 (m, 1H), 7.59 (d, J = 9 Hz, 1H), 7.94 (d, J = 8 Hz, 1H), 8.89 (s, $H_{(ethylenic)}$). Elemental analysis, found C, 68.06; H, 4.72; O, 27.46 %. $C_{20}H_{16}O_6$ requires C, 68.18; H, 4.58; O, 27.25 %.

2,2-dimethyl-5-[(2,4-dimethoxyphenyl)-α-methylmethylene]-1,3-dioxane-4,6-dione 3d - (63%) mp. 117-121°C. NMR ^1H (90 Mhz) $CDCl_3$, ppm : 1.84 (s, 6H, 2 CH_3), 3.79 and 3.87 (2s, MeO and MeO), 6.53 (d, J = 3 Hz, $1H_{(arom.)}$), 6.65 (dd, J = 9 and 3 Hz, $H_{(arom.)}$), 7.22 (d, J = 9 Hz, $H_{(arom.)}$). Elemental analysis, found C, 62.87; H, 5.82; O, 31.57 %. $C_{16}H_{18}O_6$ requires C, 62.74; H, 5.92; O, 31.34 %.

Cyclization of compounds 3 by sulfuric acid. General procedure for compounds 5.

A mixture of **3** (**3a** to **3d**) (6 mmol) and 15 mL of concentrated sulfuric acid is stirred at 3-4 °C (ice bath) for 1.5 hr, then slowly poured on crushed ice. The mixture is cooled with an ice bath for 2 hr during which the corresponding crude acid **5a** to **5d** crystallyzes. **5** is washed with water then crystallized from ethanol/water to give pure **3**. Physical and spectroscopic data follow.

7,8-dimethoxy-2-oxo-2H-1-benzopyran-3-carboxylic acid 5a. (82%) mp. 187-188 °C (ethanol/water). NMR ^1H (90 MHz) DMSO-*d6*, ppm : 4.13 (s, MeO), 4.15 (s, MeO), 7.15 (d, J = 9 Hz, 1H), 7.62 (d, J = 9 Hz, 1H), 9.02 (s, $H_{(ethylenic)}$), 11.45 (bs, CO_2H). Elemental analysis, found : C, 54.90; H, 3.54; O, 40.82 %. $C_{11}H_8O_6$ requires C, 54.94; H, 3.41; O, 40.64 %.

2H-benzofuro[2,3,g]chromene carboxylic acid 5b. (95%) mp. decomp (DMSO). NMR ^1H (400 MHz) DMSO-*d6*, ppm : 7.44-7.52 (m, 1H), 7.63-7.71 (m, 1H), 7.73 (d, J = 8 Hz, 1H) 8.23-8.34 (m, 1H + 1H), 8.90 (s, 1H),11.35 (ps, CO_2H).

2H-benzofuro[2,3,f]chromene carboxylic acid 5c.(96%), mp. : decomp. (DMSO). NMR ^1H (400 MHz) DMSO-*d6*, ppm: 7.46-7.54 (m, 1H), 7.57 (d, J = 7 Hz, 1H), 7.60-7.69 (m, 1H) 7.80 (d, J = 8 Hz, 1H), 8.07 (d, J = 9 Hz, 1H), 8.31 (d, J = 8 Hz, 1H), 9.12 (s, 1H), 10.5 (ps, CO_2H).

4-methyl-7-methoxy-2-oxo-2H-1-benzopyran-3-carboxylic acid 5d. (73%) mp. 179-180°C (ethanol/water). NMR ^1H (90 MHz) acetone-*d6*, ppm : 2.73 (s, Me), 3.99 (1s, 3H, MeO), 4.50-5.50 (m, $1H_{(acid)}$), 6.83-7.23 (m, $2H_{(arom)}$), 7.98 (d, J = 9 Hz, $1H_{(arom)}$). Elemental analysis, found : C, 61.65; H, 4.39; O, 34.02 %. $C_{12}H_{10}O_5$ requires C, 61.54; H, 4.30; O, 34.16 %.

Decarboxylation of acids 5. General procedure for coumarins 2.

A mixture of **5** (5 mmol) and 36 mg of powdered copper placed in a round-bottomed flask (25 mL) fitted with a reflux condenser, is heated under N_2 at 300 °C with a metallic bath for 10 min. After cooling, 80 mL of water are added. Crude **2** is extracted by CH_2Cl_2 (2 * 70 mL). The two phases are separated and the aqueous layer is discarded. The organic layer is dried over anhydrous $MgSO_4$, filtered, and the solvent is removed by evaporation. Crude **2** is purified by crystallization in ethyl acetate/cyclohexane (1:1 vv). Physical and spectroscopic data follow.

7,8-dimethoxy-2H-1-benzopyran-2-one 2a (daphnetin methylether). mp. 118 °C (ethyl acetate/cyclohexane). NMR ^1H (90 MHz) $CDCl_3$, ppm : 4.02 and 4.05 (2s, 6H, 2 MeO), 6.34 (d, J = 9 Hz, 1H), 6.94 (d, J = 9 Hz, 1H), 7.30 (d, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H).

2H-benzofuro[2,3,g]chromenone 2b. (87%) mp. 249-250°C (methylene chloride). NMR ^1H (400 MHz) $CDCl_3$, ppm 6.48 (d, J = 9 Hz, 1H), 7.38-7.43 (m, 1H), 7.53-7.61 (m, 1H+1H), 7.63 (s,1H), 7.82 (d, J = 9 Hz, 1H), 7.86 (s, 1H),

8.10 (d, J = 8 Hz, 1H). Elemental analysis, found : C, 74.66; H, 3.61; O, 20.56 %. $C_{15}H_8O_3$ requires C, 76.27; H, 3.41; O, 20.32 %. HRMS calcd for $C_{15}H_8O_3$ 236.034734; Found 236.0482; (M-CO) calcd 208.05243; Found 208.0513.

2H-benzofuro[2,3,f]chromenone 2c. (85%) mp. 201-203°C (methylene chloride). NMR ^1H (400 MHz) $CDCl_3$, ppm 6.66 (d, J = 10 Hz, 1H), 7.43-7.49 (d, J = 10 Hz,1H+ m,1H), 7.54-7.61 (m, 1H), 7.68 (d, J = 8 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.52 (d, J = 10 Hz, 1H). HRMS calcd for $C_{15}H_8O_3$ 236.03473; Found 236.0479;

4-methyl-7-methoxy-2H-1-benzopyran-2-one 2d. mp. 144 °C. NMR ^1H (90 MHz) $CDCl_3$, ppm : 2.41 (1s, 3H, 1Me), 3.93 (1s, 3H, MeO), 6.19 (s, $1H_{(ethyl)}$), 6.70-7.10 (m, $2H_{(arom)}$), 7.56 (d, J = 9 Hz, $1H_{(arom)}$). Elemental analysis, found : C, 69.80; H, 5.54; O, 25.03 %. $C_{11}H_{10}O_3$ requires C, 69.46; H, 5.30; O, 25.24 %.

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