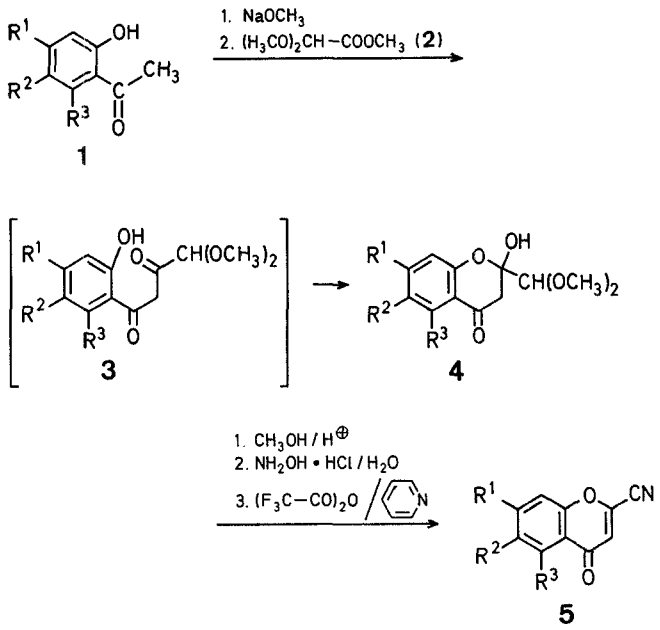

A Simple Route to Chromone-2-carbonitriles

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Chromone-2-carbonitriles **(5)**, key intermediates in the preparation of highly active 2-(tetrazol-5-yl)-chromones, have been synthesized in four steps from the appropriate 2-hydroxyacetophenones **1** via chromone-2-carboxamides[1]. An alternative approach based on the dehydration of the corresponding aldoximes was stated to lack generality because of the inaccessibility of chromone-2-carboxaldehydes[2] and has been used only for the preparation of **5a**[3].

We describe a convenient and general route to products **5** comprising acylation of 2-hydroxyacetophenones **1** to 2-(dimethoxymethyl)-2-hydroxychromanones **4** and subsequent one-pot conversion into **5**. A patented process[4], which has been virtually ignored[5] subsequently, had already mentioned the condensation of **1a, b** with dialkoxyacetic acid esters to give **4** in moderate yields.

In our hands, the original method furnished **4a** in 39% yield but the yields could be improved (≥ 80%) by a simple modification consisting of the successive treatment of **1** with sodium methoxide and methyl dimethoxyacetate **(2)** in refluxing benzene. Sequential one-flask reaction of **4a–f** with acidic methanol, aqueous hydroxylamine hydrochloride under reflux, and trifluoroacetic anhydride/pyridine[6] at room temperature afforded **5a–f** in 75–88% yield.

In contrast to the corresponding 3-carboxaldehydes[7], compounds **4** could not be converted directly into **5** simply by heating with hydroxylamine hydrochloride in acidic ethanol since the resulting aldoximes were stable under these conditions. The conditions chosen by us proved to be critical for the

Table 1. 2-(Dimethoxymethyl)-2-hydroxychromanones **4** prepared

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	M.S. *m/e* (rel. int. %)	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
4a	H	H	H	80	116–117° (methanol)	$C_{12}H_{14}O_5$ (238.2)	3380, 1685	238 (1); 163 (14)	2.83, 3.03 (ABq, 2H, J_{AB} = 16.5 Hz, CH_2); 3.53, 3.65 (2s, 6H, 2 OCH_3); 3.97 (br. s, 1H, OH); 4.42 (s, 1H, CH); 6.95–7.98 (m, 4 H_{arom})
4b	H_3C	H	H	83	89–89.5° (acetone/ hexane)	$C_{13}H_{16}O_5$ (252.3)	3380, 1675	252 (3); 177 (36)	2.31 (s, 3H, CH_3); 2.78, 2.98 (ABq, 2H, J_{AB} = 16.5 Hz, CH_2); 3.52, 3.63 (2s, 6H, 2 OCH_3); 4.13 (br. s, 1H, OH); 4.40 (s, 1H, CH); 6.80–7.86 (m, 3 H_{arom})
4c	H	H_3C	H	86	112–113° (methanol)	$C_{13}H_{16}O_5$ (252.3)	3420, 1680	252 (1); 177 (18)	2.27 (s, 3H, CH_3); 2.82, 2.98 (ABq, 2H, J_{AB} = 16.5 Hz, CH_2); 3.52, 3.63 (2s, 6H, 2 OCH_3); 4.10 (br. s, 1H, OH); 4.40 (s, 1H, CH); 6.83–7.70 (m, 3 H_{arom})
4d	H_3C	H	H_3C	86	149–149.5° (methanol)	$C_{14}H_{18}O_5$ (266.3)	3430, 1665	266 (2); 191 (42)	2.27, 2.60 (2s, 6H, 2 CH_3); 2.77, 2.97 (ABq, 2H, J_{AB} = 16.5 Hz, CH_2); 3.53, 3.65 (2s, 6H, 2 OCH_3); 3.90 (br. s, 1H, OH); 4.38 (s, 1H, CH); 6.67 (br. s, 2 H_{arom})
4e	H_3CO	H	H	83	103–104° (acetone/ hexane)	$C_{13}H_{16}O_6$ (268.3)	3320, 1675	268 (2); 193 (31)	2.80, 2.97 (ABq, 2H, J_{AB} = 16.5 Hz, CH_2); 3.55, 3.67, 3.82 (3s, 9H, 3 OCH_3); 4.05 (br. s, 1H, OH); 4.40 (s, 1H, CH); 6.45–7.92 (m, 3 H_{arom})
4f	H	Br	H	82	115–116° (acetone/ hexane)	$C_{12}H_{13}BrO_5$ (317.1)	3370, 1700	no M^+; 241/3 (3)	2.83, 3.02 (ABq, 2H, J_{AB} = 16.5 Hz, CH_2); 3.53, 3.67 (2s, 6H, 2 OCH_3); 4.00 (br. s, 1H, OH); 4.42 (s, 1H, CH); 6.85–8.05 (m, 3 H_{arom})

[a] Yields of recrystallized product.

[b] Satisfactory microanalyses obtained: C ±0.13, H ±0.23, Br −0.14.

Table 2. Chromone-2-carbonitriles **5** prepared

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C] found	m.p. [°C] reported	I.R. (KBr) ν [cm^{-1}]	M.S. *m/e* (rel. int. %)	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
a	H	H	H	84	132–133°	129–130°[1]	2240[b], 1650	171 (98); 143 (100)	6.83 (s, 1H, 3-H); 7.27–8.28 (m, 4 H_{arom})
b	H_3C	H	H	75	153–154.5°	146–147°[1]	2240[b], 1650	185 (100); 157 (65); 156 (56)	2.50 (s, 3H, CH_3); 6.77 (s, 1H, 3-H); 7.28–8.15 (m, 3 H_{arom})
c	H	H_3C	H	77	160.5–161.5°	160–161°[1]	2240[b], 1655	185 (100); 156 (33)	2.45 (s, 3H, CH_3); 6.78 (s, 1H, 3-H); 7.37–8.02 (m, 3 H_{arom})
d	H_3C	H	H_3C	88	151.5–152.5°	145–146°[1]	2240[b], 1660	199 (100); 170 (23)	2.40, 2.75 (2s, 6H, 2 CH_3); 6.65 (s, 1H, 3-H); 7.03, 7.12 (2 br. s, 2 H_{arom})
e	H_3CO	H	H	81	153.5–154.5°	150–153°[1]	2235[b], 1655	201 (100); 173 (64)	3.92 (s, 3H, OCH_3); 6.75 (s, 1H, 3-H); 6.87–8.18 (m, 3 H_{arom})
f	H	Br	H	77	197.5–198.5°	200–201°[1]	2240[b], 1655	249/51 (100); 198/200 (28)	6.85 (s, 1H, 3-H); 7.40–8.38 (m, 3 H_{arom})

[a] Yields of recrystallized product.

[b] Very weak band; see Ref.[1].

success of the **4** to **5** conversion, a non-trivial remark in view of the well documented complexity[8] of the behaviour of the chromone system towards hydroxylamine. Thus, for instance, the use of anhydrous conditions in the *in situ* preparation of aldoximes resulted in a drastic decrease in the yield of nitriles (≈ 50%). All the other methods known for the one-flask conversion of aldehydes into nitriles[9] furnished complex mixtures. In conclusion, the present procedure provides a concise route to **5** with overall yields comparable to or better than those reported[1].

2-(Dimethoxymethyl)-2-hydroxychromanones 4; General Procedure:
A solution of the 2-hydroxyacetophenone **1** (5 mmol) in dry benzene (10 ml) is added dropwise to a vigorously stirred suspension of sodium methoxide (from 345 mg of sodium, 15 mmol) in dry benzene (10 ml) at room temperature, under nitrogen. The resulting yellow mass is heated under reflux and a solution of methyl dimethoxyacetate (**2**; 1.22 ml, 10 mmol) in dry benzene (2 ml) is added rapidly after 10 min. The yellow suspension turns to a deep red or brown solution soon after the addition of the ester. Stirring is continued under reflux for 30 min, the mixture is allowed to cool to room temperature, acidified with 50% acetic acid, and extracted with ethyl acetate (2 × 100 ml). The organic extract is washed with water until neutral and dried with sodium sulfate. The solvent is evaporated and the residue is crystallized to give pure **4** (Table 1).

Chromone-2-carbonitriles 5; General Procedure:
A solution of **4** (1 mmol) in methanol (4 ml) containing hydrochloric acid (0.08 ml, 1 mmol) is stirred under reflux for 15 min. A solution of hydroxylamine hydrochloride (76 mg, 1.1 mmol) in water (1 ml) is added and stirring is continued for 6 h (12 h in the case of **4f**) under reflux. The mixture is evaporated in vacuo and the residue, dissolved or suspended in dry pyridine (2 ml), is treated with trifluoroacetic anhydride (0.5 ml) of 0 °C. The solution is left at room temperature for 1 h, treated with 2 normal hydrochloric acid (8 ml), and extracted with ethyl acetate (2 × 50 ml). The organic phase is washed with water until neutral, dried with sodium sulfate, and evaporated. The residue is recrystallized from methanol to furnish pure **5** (Table 2).

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