A Convenient Synthesis of 2- and 2,3-Substituted 4*H*-Chromen-4-ones

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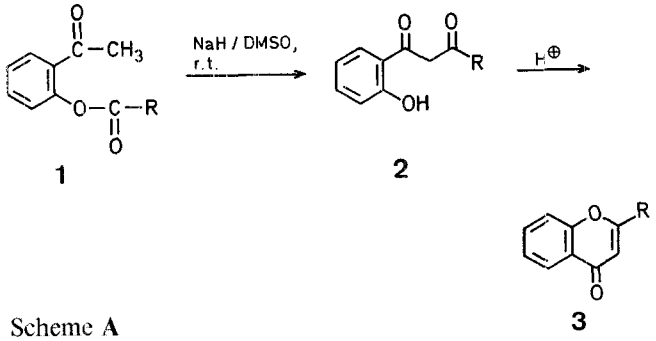
The cyclodehydration of 1-(*o*-hydroxyaryl)-1,3-diketones is one of the most common method for the synthesis of substituted chromones or flavones[1]. The 1,3-diketones, in turn, are synthesized from 1-hydroxy-2-acetylarenes by the acylation with various acylating reagents. In the Baker-Venkataraman synthesis[2,3,4], internal Claisen condensation of 2-aryloxy-1-acetylarenes is employed. The Allan-Robinson synthesis[5] brings about acylation, rearrangement, and cyclization in a single experimental step. As for the synthesis of 2-alkylchromones, the utilization of a large excess of esters as the acylating reagent seems to be the only acceptable method[6]. Recently, flavones were synthesized by the acylation of the dianions of *o*-hydroxyacetophenones with aroyl chlorides[7].

In this communication, a new method for the synthesis of 2- and 2,3-substituted 4*H*-chromen-4-ones is presented, which consists of internal Claisen condensation of 1-acyl-2-acyloxyarenes **1**, **4** or **7** and subsequent cyclization to the corresponding chromones **3**, **6** or **9**. The key step in the synthesis involves the reaction of **1**, **4** or **7** with sodium hydride in dimethyl sulfoxide at room temperature to give **2**, **5** or **8**. Then, the diketones **2**, **5**, or **8** are cyclized to the chromones **3**, **6** or **9** by heating (100 °C) with acetic acid containing a catalytic amount of hydrochloric acid[8].



1 2 3

Scheme A

Table 1. 2-Substituted 4*H*-Chromen-4-ones **3a–f** from *o*-Acyloxyacetophenones **1a–f** (Scheme A)

Substrate No.	R	Method	Product 2			Product 3		
			Yield [%][a]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	Yield [%][a]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]
1a	CH_3	A	–	–	–	41	69–70°	70–71°[6]
1b	C_2H_5	A	–	–	–	55	15–18°	18°[10]
1c	i-C_3H_7	A	–	–	–	69	oil	oil[11]
		B	87	oil	$C_{12}H_{14}O_3$ (206.2)	76		
1d	n-C_9H_{19}	A	–	–	–	68, 58[c]	28.5–29°	$C_{18}H_{24}O_2$ (272.4)
1e	C_6H_5—$(CH_2)_3$—	A	–	–	–	71	34.5–35.5	$C_{18}H_{16}O_2$ (264.3)
1f	C_6H_5	A	–	–	–	83[d]	93–94°	94°[12]
		B	84	117–118°	118°[12]	93		

[a] Yield of isolated product having satisfactory I.R. and ^{1}H-N.M.R. spectra.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.12.
[c] The reaction was carried out with 9 mmol of **1d**.
[d] The reaction was carried out with 15 mmol of **1f**.

Table 2. 2-Substituted Benzochromones **6a–e** from 2-Acetyl-1-acycloxynaphthalenes **4e–e** (Scheme B)

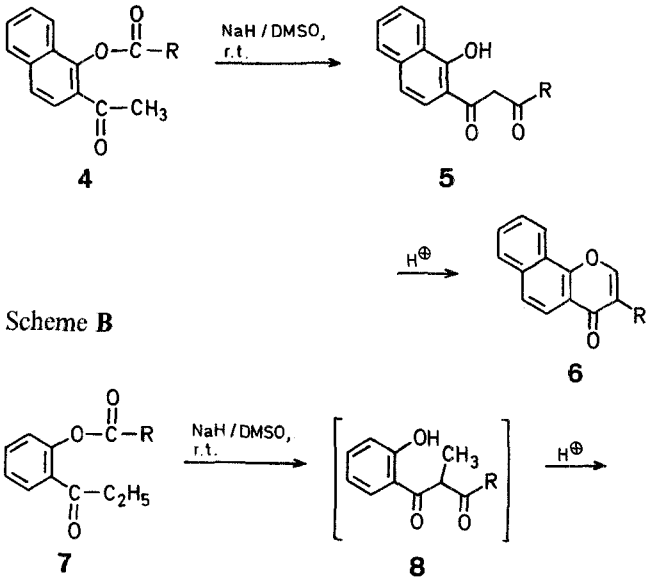
Substrate No.	R	Method	Product 5			Product 6		
			Yield [%][a]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	Yield [%][a]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]
4a	CH_3	B	65	116–117°	117–118°[12]	84	176.5–177°	178–179°[12]
4b	C_2H_5	A	–	–	–	82, 86[c]	110–111°	111°[6]
4c	n-C_9H_{19}	A	–	–	–	72	50.5–51.5°	$C_{22}H_{26}O_2$ (322.4)
4d	C_6H_5	B	90	147–148°	147°[2]	81	153–154°	156–159°[13]
4e	2-H_3C—C_6H_4	B	91	91–94°	$C_{20}H_{16}O_3$ (292.3)	90	159–161°	$C_{20}H_{14}O_2$ (274.3)

[a] Yield of isolated product having satisfactory I.R. and ^{1}H-N.M.R. spectra.
[b] Satisfactory microanalyses obtained: C ±0.38, H ±0.17; exception: **5e**, C −0.61.
[c] The reaction was carried out with 5 mmol of **4b**.

Table 3. 2,3-Disubstituted 4*H*-Chromen-4-ones **9a–d** from *o*-Acyloxypropiophenones **7a–d** (Scheme C)

Substrate No.	R	Method	Yield [%][a] of **9**	m.p. [°C] of **9**	Molecular Formula[b] or Lit. m.p. [°C] of **9**
7a	CH_3	A	56	91–93°	97°[14]
7b	n-C_9H_{19}	A	52	31–32.5°	$C_{19}H_{26}O_2$ (286.4)
7c	C_6H_5	A	75	72–73°	$C_{16}H_{12}O_2$ (236.3)
7d	2-furyl	A	53	110.5–112°	$C_{14}H_{10}O_3$ (226.2)

[a] Yield of isolated product having satisfactory I.R. and ^{1}H-N.M.R. spectra.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.25.



Scheme **B**

Scheme **C**

The reaction conditions are very mild and chromones **3**, **6** or **9** are obtained in good yield (Tables 1, 2, 3). It should also be noted that the method is of general applicability and may be used for 2-mono- and 2,3-disubstituted chromones with various aryl and, especially, alkyl groups.

Table 4. Spectral Data for Compounds **3**, **6**, and **9**

Product	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	1640	2.37 (3H, s); 6.15 (1H, s), 7.2–7.8 (3H, m), 8.0–8.3 (1H, m)
3b	1650	1.30 (3H, t, J = 7 Hz), 2.65 (2H, q, J = 7 Hz), 6.16 (1H, s), 7.1–7.8 (3H, m), 8.0–8.3 (1H, m)
3c	1650	1.30 (6H, d, J = 7 Hz), 2.6–3.1 (1H, m), 6.17 (1H, s), 7.1–7.8 (3H, m), 8.0–8.2 (1H, m)
3d	1655	0.88 (3H, t, J = 5 Hz), 1.1–1.4 (14H, m), 2.50 (2H, t, J = 6 Hz), 6.18 (1H, s), 7.2–7.6 (3H, m), 8.1–8.3 (1H, m)
3e	1650	1.9–2.2 (2H, m), 2.4–2.8 (4H, m), 6.14 (1H, s), 7.20 (5H, s), 7.2–7.8 (3H, m), 8.0–8.3 (1H, m)
3f	1640	6.78 (1H, s), 7.2–8.0 (8H, m), 8.20 (1H, d, J = 7 Hz)
6a	1645	2.52 (3H, s), 6.32 (1H, s), 7.5–8.0 (4H, m), 8.13 (1H, d, J = 8 Hz), 8.3–8.6 (1H, m)
6b	1645	1.42 (3H, t, J = 7 Hz), 2.83 (2H, q, J = 7 Hz), 6.34 (1H, m), 7.5–8.0 (4H, m), 8.14 (1H, d, J = 9 Hz), 8.4–8.6 (1H, m)
6c	1640	0.88 (3H, t, J = 4 Hz), 1.0–2.1 (14H, m), 2.77 (2H, t, J = 7 Hz), 6.33 (1H, s), 7.5–8.0 (4H, m), 8.14 (1H, d, J = 9 Hz), 8.4–8.6 (1H, m)
6d	1630	6.94 (1H, s), 7.5–8.2 (10H, m), 8.5–8.7 (1H, m)
6e	1640	2.54 (3H, s), 6.61 (1H, s), 7.3–7.9 (4H, m), 8.18 (1H, d, J = 8 Hz), 8.3–8.5 (1H, m)
9a	1630	2.02 (3H, s), 2.36 (3H, s), 7.1–7.8 (3H, m), 8.0–8.3 (1H, m)
9b	1630	0.6–1.0 (3H, m), 1.0–1.9 (14H, m), 2.07 (3H, s), 2.71 (2H, t, J = 7 Hz), 7.2–7.6 (3H, m), 8.19 (1H, dd, J = 2, 8 Hz)
9c	1635	2.14 (3H, s), 7.1–7.7 (8H, m), 8.1–8.3 (1H, m)
9d	1620	2.39 (3H, s), 6.62 (1H, dd, J = 2, 3.5 Hz), 7.10 (1H, d, J = 3.5 Hz), 7.2–7.8 (4H, m), 8.22 (1H, d, J = 7 Hz)

The 1,3-diketones **2** or **5** prepared were purified by chromatography over silica gel and were characterized by comparison of their physical and spectral[9] properties with literature data.

2- and 2,3-Substituted 4H-Chromen-4-ones; General Procedure:

Method A: Under a nitrogen atmosphere, a dimethyl sulfoxide (2 ml) solution of the 1-acyloxy-2-acylarene (**1**, **4** or **7**; 0.5–2.0 mmol) is slowly added to a suspension of sodium hydride (3 equiv.) in dimethyl sulfoxide (8 ml). The mixture is stirred for 0.2–2 h, monitoring the reaction by T.L.C. (exceptionally, the reaction of **1d** requires 5 h for the completion). Then, the reaction mixture is slowly added to saturated aqueous oxalic acid (20 ml) at 0 °C. Organic materials are extracted with ethyl acetate (20 ml), washed with water (20 ml) and brine (20 ml) and dried with sodium sulphate. After the solvents have been removed, the crude 1-(*o*-hydroxyaryl)-1,3-diketone **2**, **5** or **8** is dissolved in acetic acid (5 ml) containing several drops of concentrated hydrochloric acid, and the solution is heated at 100–110 °C for 0.3–1.3 h, monitoring the reaction by T.L.C. On cooling, the mixture is diluted with ethyl acetate (20 ml), washed with saturated sodium hydrogen carbonate (2 × 20 ml) and with brine (20 ml), and dried with sodium sulphate. After the solvents have been removed, the residue is chromatographed over silica gel with ethyl acetate/hexane or ether/hexane (for **6a**, **6d**, and **6f**) as eluent.

Method B: The reaction is carried out as described above except that 1,3-diketones **2**, **5** are isolated by chromatography (silica gel) with chloroform/hexane or ethyl acetate/hexane (for **2f**) as eluent.

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