A New Synthesis of Flavones

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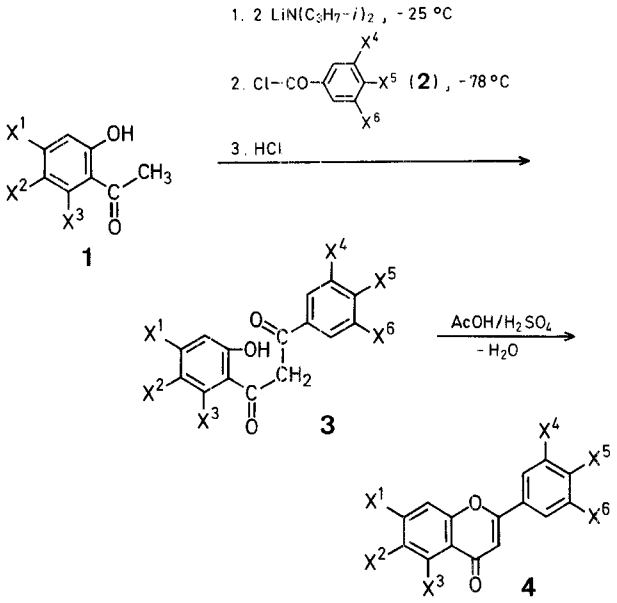
The cyclodehydration of 1-(*o*-hydroxyphenyl)-1,3-diketones is one of the most commonly used methods for the synthesis of substituted chromones and flavones[1]. The basic approach to the synthesis of the diketones consists of the acylation of *o*-hydroxyacetophenones using different acylating agents and experimental conditions[2,3,4]. In the Baker-Venkataraman synthesis, rearrangement (internal Claisen condensation) of *o*-acyloxy- or *o*-aroyloxyacetophenones to β-diketones is utilized[5,6]. The high temperatures used in the Allan-Robinson synthesis bring about acylation, rearrangement, and cyclisation consecutively in a single experimental step[3,4].

In the present communication, a method for the direct aroylation of *o*-hydroxyacetophenones to β-diketones and the subsequent cyclization to the corresponding flavones is reported. The key step in this synthesis involves the reaction of the dianion of an *o*-hydroxyacetophenone (**1**) with an aroyl chloride (**2**) to give the diketone **3**. The reaction conditions are very mild and the β-diketones are obtained in high purity and good yield. The enolates[7] of **1** are generated by treatment of **1** with lithium diisopropylamide in tetrahydrofuran at −25 °C and the smooth reaction of the enolates with the aroyl chlorides **2** is performed at −78 °C. The diketones **3** are readily cyclized to the flavones **4** by heating (100 °C) with acetic acid containing 1% sulfuric acid.



The method is of general applicability and may be used for the synthesis of flavones (**4**) having a variety of substituents

Table 1. 1,3-Dioxo-1,3-diphenylpropanes (**3**, $X^2 = H$) prepared

3	X^1	X^3	X^4	X^5	X^6	Yield [%]	m.p. [°C]	Molecular formula[a] or m.p. reported	M.S. M^+ (*m/e*)	U.V. (CH_3OH) λ_{max} [nm] (log ε)
a	H	H	H	H	H	76	117–118°	117–120°[11]	240	360 (4.16); 250 (3.59); 210 (3.96); 205 (4.01)
b	OCH_3	OCH_3	H	H	H	73	124–125°	$C_{17}H_{16}O_5$ (300.3)	300	365 (3.7); 287 (3.85); 238 (3.68); 220 (3.85); 205 (4.25)
c	OCH_3	H	H	OCH_3	H	94	108–109°	$C_{17}H_{16}O_5$ (300.3)	300	375 (4.32); 385 (4.27); 280 (3.76); 205 (4.15)
d	OCH_3	OCH_3	H	OCH_3	H	73	142°	$C_{18}H_{18}O_6$ (330.3)	330	375 (3.61); 285 (4.09); 210 (4.10); 205 (4.04)
e	OCH_3	H	OCH_3	OCH_3	OCH_3	82	119°	$C_{19}H_{20}O_7$ (360.4)	360	385 (4.18); 270 (3.60); 205 (4.33)
f	OCH_3	OCH_3	OCH_3	OCH_3	H	90	175°	$C_{19}H_{20}O_7$ (360.4)	360	380 (3.6); 290 (4.04); 225 (4.13); 205 (4.21)
g	OCH_3	H	O—CH_2—O		H	89	155°	$C_{17}H_{14}O_6$ (314.3)	314	378 (4.29); 275 (3.66); 225 (3.92); 205 (4.26)

[a] The microanalyses were in good agreement with the calculated values: C, ±0.30; H, ±0.21.

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Table 2. Flavones (**4**, $X^2 = H$) prepared

4	Yield [%]	m.p. [°C]	m.p. [°C] reported or Molecular formula	M.S. M^+ (*m/e*)	U.V. (CH_3OH) λ_{max} [nm] (log ε)
a	84	95°	97°[11]	222	295 (4.58); 250 (4.24)
b	85	147°	143°[13]	282	302 (3.91); 262 (4.32)
c	90	145°	144°[12]	282	320 (4.35); 255 (3.86); 230 (4.15)
d	91	156°	156°[14]	312	320 (4.29); 262 (4.25)
e	88	190–191°	191°[10]	342	310 (4.18); 230 (4.16)
f	87	190–191°	192°[14]	342	330 (4.07); 265 (3.86); 240 (4.01)
g	91	202°	$C_{17}H_{12}O_5$[a] (296.3)	296	335 (4.26); 235 (4.37)

[a] calc. C 68.92 H 4.08
found 68.90 4.10

on rings A and B. The reaction is clean, easy to perform, the starting materials are readily accessible, and the products are of high purity.

The diketones **3** prepared were purified by column chromatography or recrystallization and were characterized by comparison of their physical and spectral[8] properties with literature data.

1,3-Dioxo-1-(2-hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propane (3e); Typical Procedure:

A solution of 2-hydroxy-4-methoxyacetophenone (**1**, $X^1 = OCH_3$, $X^2 = X^3 = H$; 790 mg, 4.75 mmol) in tetrahydrofuran (10 ml) is added to a stirred solution of lithium diisopropylamide[9] (10 mmol; from diisopropylamine and butyllithium) in tetrahydrofuran at −25 °C. The mixture is stirred (1 h) at −25 °C, then cooled to −78 °C, and a solution of freshly distilled 3,4,5-trimethoxybenzoyl chloride (**2**, $X^4 = X^5 = X^6 = OCH_3$; 1.15 g, 5 mmol) in tetrahydrofuran (10 ml) is added. The mixture turns yellow soon after the addition of the acyl chloride. Stirring is continued at −78 °C for 3 h, the mixture allowed to warm to room temperature (20 °C), and set aside overnight. It is then diluted with ethyl acetate (50 ml) and acidified to pH 3 with dilute hydrochloric acid. The organic layer is dried with sodium sulfate and the solvents are removed to give **3e** as a crystalline solid. The product is recrystallized from ethyl acetate/pentane; yield: 1.4 g (82%); m.p. 119 °C. Compound **3e** gives a positive reaction with iron(III) chloride; it dissolves in 1 normal aqueous sodium hydroxide with a yellow color.

$C_{19}H_{20}O_7$ (360.4) calc. C 63.33 H 5.59
found 63.61 5.62

U.V. (CH_3OH): $\lambda_{max} = 385$ (log ε = 4.18); 270 (3.60); 205 nm (4.33).

7,3′,4′,5′-Tetramethoxyflavone (4e); Typical Procedure:

Compound **3e** (100 mg) is dissolved in glacial acetic acid (10 ml), conc. sulfuric acid (0.1 ml) is added, and the mixture is heated at 100 °C for 3.5 h [completion of the cyclodehydration is checked by T.L.C. analysis and by the iron(III) chloride test]. The mixture is poured onto ice (50 g), the resultant precipitate isolated by suction, dried in vacuum and recrystallized from acetone; yield: 85 mg (88%); m.p. 190–191 °C (Ref.[10], m.p. 191 °C).

U.V. (CH_3OH): $\lambda_{max} = 310$ (log ε = 4.18); 230 nm (4.16).

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