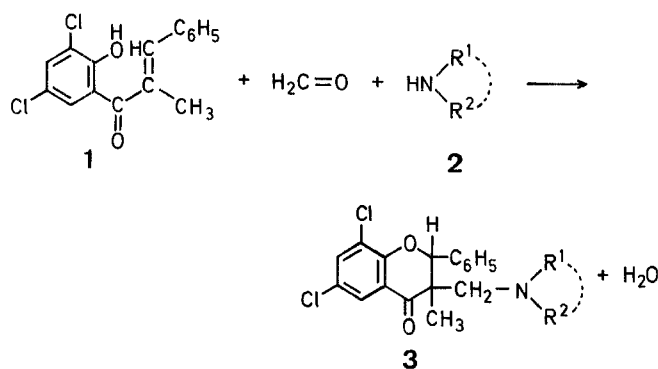


2-Hydroxyketones; XIV¹. A Facile One-Step Synthesis of 3,3,6,8-Tetrasubstituted Flavanones

Alexandru CAȘCAVAL

Department of Organic and Macromolecular Chemistry, Polytechnic Institute of Iassy, R-6600 Iassy, Calea 23 August 22, Romania

The investigation of the syntheses of chromone and chromanone derivatives exhibiting physiological activity has led us to apply some known reactions (Vilsmeier-Harnisch, Mannich-Werner) to a few halogenated alkyl 2-hydroxyphenyl ketones; we have thus developed a versatile synthesis of some new 3,6,8-trisubstituted chromones² and 3,3,6,8-tetrasubstituted 4-chromanones³ which, according to pharmacological screening, act on the smooth muscular system. These results encouraged me to publish a similar one-step synthesis of some new 3,3,6,8-tetrasubstituted flavanones derived from a halogenated chalcone by both cyclization and Mannich reaction: 3,5-dichloro-2-hydroxyphenyl 1-phenylpropen-2-yl ketone (**1**) reacts with aqueous formaldehyde and cyclic secondary amines (**2**) at room temperature (24 h) to afford 3-cycl-aminomethyl-6,8-dichloro-3-methylflavanones (**3**).

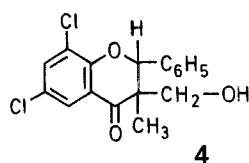


2,3	R ¹	R ²
a	—(CH ₂) ₄ —	
b	—(CH ₂) ₅ —	
c	—CH ₂ —CH ₂ —O—CH ₂ —CH ₂ —	
d	—CH ₂ —CH ₂ —N—CH ₂ —CH ₂ — CH ₂ —CH ₂ —OH	

It is interesting to note that under the same conditions the reaction of chalcone **1** with aqueous formaldehyde and diethylamine yields 6,8-dichloro-3-hydroxymethyl-3-methylflavanone (**4**) which is a possible intermediate in the formation of Mannich bases **3**.

Table. Substituted Flavanones (**3**, **4**) prepared

Product	Yield [%]	m.p. [°C]	Molecular formula ^a	I.R. ν [cm ⁻¹]	¹ H-N.M.R. (CDCl ₃ /TMS _{int}) ^b δ [ppm]
3a	79	162–163°	C ₂₁ H ₂₁ Cl ₂ NO ₂ (389.9)	3000 (CH); 1670 (CO)	7.6–7.8 (dd, 2H); 7.3–7.6 (m, 5H); 5.8 (s, 1H); 2.4–3.0 (m, 6H); 1.5–1.8 (m, 4H); 1.0 (s, 3H)
3b	51	151–152°	C ₂₂ H ₂₃ Cl ₂ NO ₂ (403.9)	3000 (CH); 1680 (CO)	7.6–7.8 (dd, 2H); 7.2–7.5 (m, 5H); 5.8 (s, 1H); 2.1–2.8 (m, 6H); 1.3 (m, 6H); 1.0 (s, 3H)
3c	57	166–167°	C ₂₁ H ₂₁ Cl ₂ NO ₃ (405.9)	3000 (CH); 1685 (CO)	7.6–7.8 (dd, 2H); 7.3–7.6 (m, 5H); 5.85 (s, 1H); 3.4–3.6 (t, 4H); 2.8–3.1 (t, 4H); 2.0–2.5 (m, 2H); 1.0 (s, 3H)
3d	50	167–168°	C ₂₃ H ₂₆ Cl ₂ N ₂ O ₃ (428.9)	3300 (OH); 2900 (CH); 1680 (CO)	7.6–7.8 (dd, 2H); 7.1–7.5 (m, 5H); 5.8 (s, 1H); 3.4 (t, 2H); 3.1 (1H); 3.0–2.2 (m, 12H); 1.0 (s, 3H)
4	66	193–194°	C ₁₇ H ₁₄ Cl ₂ O ₃ (336.9)	3400 (OH); 1690 (CO)	7.6–7.8 (dd, 2H); 7.3–7.6 (m, 5H); 5.8 (s, 1H); 3.4 (2H); 1.5 (s, 1H); 1.0 (s, 3H)

^a The microanalyses were in satisfactory agreement with the calculated values: C, ± 0.25 ; H, ± 0.20 ; N, ± 0.25 ; Cl, ± 0.25 .^b Recorded on a JEOL instrument at 50°C and 60 MHz.

The structures of all new compounds were proven by microanalytical, I.R.-spectral, and ¹H-N.M.R.-spectral data.

3,5-Dichloro-2-hydroxyphenyl 1-Phenylpropen-2-yl Ketone (1):

A solution of benzaldehyde (5.31 g, 50 mmol) in dioxan (25 ml) is added to a vigorously stirred solution of 1-(3,5-dichloro-2-hydroxyphenyl)-1-propanone⁴ (10.96 g, 50 mmol) in aqueous 10% potassium hydroxide (100 ml) + dioxan (25 ml) at room temperature. Stirring is continued for 24 h, the mixture then acidified with dilute hydrochloric acid (100 ml), and the precipitated crude yellow product **1** isolated and recrystallized from ether; yield: 9.37 g (61%); m.p. 137–138°C.

C₁₆H₁₂Cl₂O₂ calc. C 62.56 H 3.91 Cl 23.10
(306.9) found 62.17 4.26 22.86

I.R. (KBr): ν = 3050 (CH); 1620 (C=O) cm⁻¹.

¹H-N.M.R. (CDCl₃/TMS_{int}): δ = 12.3 (s, 1H); 7.7–7.9 (dd, 2H); 7.1–7.5 (m, 5H); 5.9–6.0 (d, 1H); 1.0 ppm (s, 3H).

3-cycl-Aminomethyl-6,8-dichloro-3-methylflavanones (3); General Procedure:

To a solution of chalcone **1** (307 mg, 1 mmol) and the secondary cyclic amine **2** (technical grade; 1.5 mmol) in methanol (25 ml) is added aqueous 30% formaldehyde (0.5 ml, 4 mmol) and the mixture is allowed to stand at room temperature for 24 h. Cold water (100 ml) is then added and the product **3** is extracted with ether (50 ml). The extract is dried with sodium sulfate and evaporated to give the essentially pure product. For purification, products **3** are recrystallized from methanol (Table).

6,8-Dichloro-3-hydroxymethyl-3-methylflavanone (4):

To a solution of chalcone **1** (1 g, 3 mmol) in methanol (50 ml) is added diethylamine (1.5 ml, 15 mmol) and aqueous 30% formaldehyde solution (1.25 ml, 10 mmol). The mixture is allowed to stand at room temperature for 24 h. Then, cold water (100 ml) is added to precipitate the crude product **4** which is isolated and recrystallized from methanol to give the analytically pure product **4**; yield: 0.72 g (66%); m.p. 193–194°C.

The author is thankful to "Alexander von Humboldt-Stiftung", Bad Godesberg (West-Germany), for providing a fellowship at the University of Freiburg i. Br., and also to BASF/Ludwigshafen (West-Germany), for the gift of several compounds.

¹ 2-Hydroxyketones. XIII: A. Caşcaval, *Bul. Inst. Polit. Iaşi*, in press.

² A. Caşcaval, *Liebigs Ann. Chem.* **1980**, 669.

³ A. Caşcaval, *Synthesis* **1983**, 579.

⁴ D. S. Tarbell, Y. Sato, *J. Am. Chem. Soc.* **68**, 1091 (1946).