Regioselective Synthesis of 5-Hydroxychroman-4-ones

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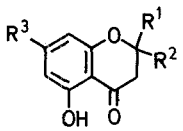
The presently available syntheses of 4-chromanones[1,2,3] are not suitable for the regioselective preparation of 5-hydroxy-4-chromanones (**1**) without formation of the 7-hydroxy isomers (**2**). This is due to the fact that the starting materials are resorcinols which undergo electrophilic acylation in both 2 and 4 positions with simultaneous formation of both **1** and **2** on ring closure.



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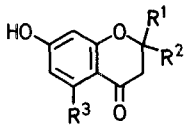
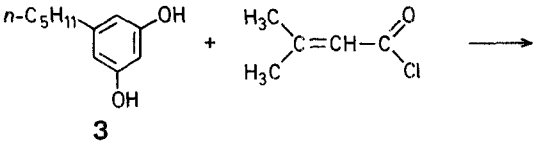


2

Because of the practical importance of some 5-hydroxy-4-chromanones (**1**) a convenient method for their regioselective synthesis would be desirable. 5-Hydroxy-2,2-dimethyl-4-chromanone (**1c**), an intermediate in the synthesis of cannabinoids[4] and of some of their analogs[5,6], has been prepared in admixture with the 7-hydroxy isomer (**2c**) and the 2-oxo isomers **4** and **5** by acylation of the expensive 5-pentylresorcinol (**3**, olivetol) with 3-methyl-2-butenoic acid in the presence of boron trifluoride, the ratio **1c**/**2c** being 1/3 or 2/1, depending on the reaction temperature. The formation of the undesired Michael products **4** and **5**[7] makes chromatographic purification of **1c** unavoidable.



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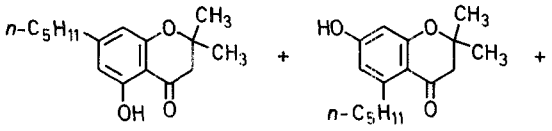
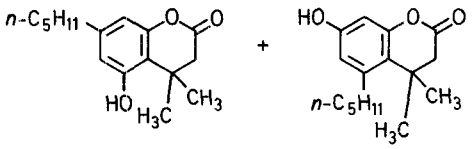
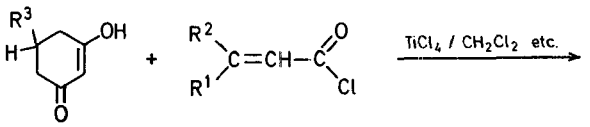


1c **2c**

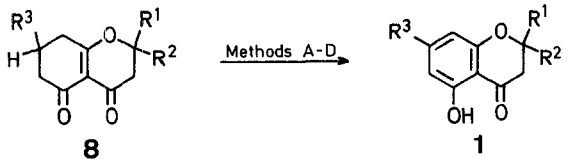


4 **5**

In this report, I describe a regioselective synthesis of 5-hydroxy-4-chromanones (**1**) starting from 1,3-cyclohexanediones (**6**). Whereas the alkylation of these highly enolized and acidic compounds (pK_a: 5.2) in basic medium may afford *C*- or *O*-derivatives, depending on the reaction conditions and the alkylating species[8], their acylation proceeds only at the enolic OH group. The enol esters obtained from diones **6** and 2-alkenoyl chlorides (**7**) in acidic medium undergo Fries rearrangement with ring closure in the presence of certain Lewis acids[9,10] to give 4,5-dioxo-5,6,7,8-tetrahydrochromans (**8**) which can be dehydrogenated to the desired products **1**.



6 **7**



8 **1**

8,1	R^1	R^2	R^3	
a	CH_3	CH_3	H	
b	CH_3	CH_3	CH_3	
c	CH_3	CH_3	n-C_5H_{11}	
d	CH_3	CH_3	C_6H_5	
e	CH_3	H	H	
f	CH_3	H	n-C_5H_{11}	
g	C_6H_5	H	H	no product
h	C_6H_5	H	C_6H_5	no product

Table 1. 4,5-Dioxo-2,3,5,6,7,8-hexahydro-4*H*-chromenes (**8**) prepared

8	Ratio $TiCl_4$/6	Solvent	Reaction Temperature and Time [°C], [h]	Yield[a] [%]	m.p. [°C] (solvent)	Molecular Formula[b] or m.p. [°C] reported	M.S. (M^+) *m/e*	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	1.2	CH_2Cl_2	20°, 20	61	97–98° (cyclohexane)	95°[9]	194	1.45 (s, 6H, 2 CH_3); 1.9–2.2 (m, 2H, 7-CH_2); 2.3–2.7 (6H)
b	1.2	CH_2Cl_2	20°, 20	60	134–135° (cyclohexane)	$C_{12}H_{16}O_3$ (208.25)	208	1.1 (d, 3H, 7-CH_3); 1.4 (s, 3H, 2-CH_3); 1.45 (s, 3H, 2-CH_3); 2.0–2.8 (5H); 2.55 (AB, 2H, 3-CH_2)
c	1.2	CH_2Cl_2	20°, 20	79	89–90° (hexane)	$C_{16}H_{24}O_3$ (264.35)	264	0.86 (t, 3H, CH_2—CH_3); 1.15–1.50 (9H); 1.4 (s, 3H, 2-CH_3); 1.47 (s, 3H, 2-CH_3); 1.9–3.0 (6H)
d	1.2	CH_2Cl_2	20°, 20	62	96–97° (cyclohexane/toluene 2/1)	$C_{17}H_{18}O_3$ (270.3)	270	1.5 (s, 3H, 2-CH_3); 1.58 (s, 3H, 2-CH_3); 2.55–2.95 (6H); 3.25–3.6 (m, 1H, 7-CH); 7.15–7.55 (m, 5H)
e	1.2	CH_2Cl_2	40°, 30	21	89° (cyclohexane)	91°[9]	180	1.5 (d, 3H, 2-CH_3); 1.9–2.9 (8H); 4.7 (m, 1H)
f	1.2	CH_2Cl_2	40°, 30	20	oil	$C_{15}H_{22}O_3$ (250.3)	250	0.9 (t, 3H, CH_2—CH_3); 1.1–1.35 (8H); 1.4 (d, 3H, 2-CH_3); 1.9–2.9 (7H); 4.25–4.9 (m, 1H, 2-CH)
	2.2	CH_2Cl_2	40°, 30	30				
	1.2	$ClCH_2$—CH_2Cl	83°, 11	15[c]				
	1.2	Cl_2CH—$CHCl_2$	140°, 2	10				
[g]	1.2	CH_2Cl_2	20°, 20	0				
[h]	1.2	CH_2Cl_2	20°, 20	0				

[a] Yield of isolated product. The yields were not optimized in most cases.

[b] The microanalyses showed the following maximum deviations from the calculated values: C ±0.43 (**8f**); H ±0.28.

[c] Plus 25% of the open-chain compound **9f**.

Table 2. Reaction of 1,3-Cyclohexanediones (**6**) with 2-Alkenoyl Chlorides in the Presence of Lewis Acids

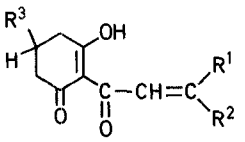
R^3 in **6**	7		Lewis Acid	Yield of **8**[a] [%]
	R^1	R^2		
H	CH_3	CH_3	$TiCl_4$	**8a**: 61
			$AlCl_3$	20
			$FeCl_3$	–[b]
n-C_5H_{11}	CH_3	H	$TiCl_4$	**8f**: 20
			$AlCl_3$	–[b]

[a] Yield of isolated product.

[b] Compound **8** was not detected in the reaction mixture by T.L.C. after a reaction time of 24 h in dichloromethane at 20°C.

The use of titanium(IV) chloride[10] was found to give much better results in the reaction leading to compounds **8** than the reported[9] use of aluminum chloride. The satisfactory results obtained with titanium(IV) chloride can be rationalized by its high affinity to oxygen and its high chelating capability and are in accord with similar successful applications in aldol reactions between enol silyl ethers and aldehydes or ketones[10] and in alkylations of enol silyl ethers with alkyl halides[10]. The 2-alkenoyl chloride (**7**) is added to the preformed red complex of dione **6** and $TiCl_4$ in dichloromethane, 1,2-dichloroethane, or 1,1,2,2-tetrachloroethane. It is worthy of note that tetronic acids[11], tetramic acids[12], and 4-hydroxy-6-methyl-2-pyrone[13] are *C*-acylated in the presence of Lewis acids.

In some cases, the uncyclized *C*-acylation products **9** were isolated as by-products in low yield. With cinnamoyl chloride (**7**, $R^1 = C_6H_5$, $R^2 = H$), no product could be isolated.



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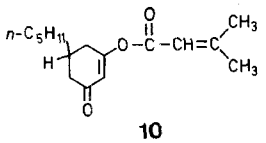
There is a striking difference between the results obtained with 3-methyl-2-butenoyl chloride, which is substituted in position 3, on the one hand and with the 3-unsubstituted 2-butenoyl and cinnamoyl chlorides on the other hand, satisfactory yields of products **8** being obtained only with 3-methyl-2-butenoyl chloride (Table 1). To gain better insight into the reaction mechanism, the reactions of 5-pentyl-1,3-cyclohexanedione (**6**, $R^3 = n$-C_5H_{11}) with 3-methyl-2-butenoyl chloride (**7**, $R^1 = R^2 = CH_3$) and with 2-butenoyl chloride (**7**, $R^1 = CH_3$, $R^2 = H$) in $CDCl_3$ using $TiCl_4$ as catalyst were monitored by ^{1}H-N.M.R. spectrometry. In the solvent used ($CDCl_3$), 5-pentyl-1,3-cyclohexanedione exists as an equilibrium mixture of 20% enol and 80% diketone. The addition of 1.1 mol equiv of $TiCl_4$ shifts the equilibrium completely to the side of the enol form and the signal of the vinylic proton is shifted downfield from $\delta = 5.43$ to $\delta = 6.56$ ppm. After the addition of 3-methyl-2-butenoyl chloride, the formation of the *C*-acylation product **9c** proceeds rather fast and is followed by the rather slow ring closure to **8c**. A signal of the vinylic proton in ring position 2 of the enol ester **10** is not found. Rearrangement of compound **10** under the same conditions is slow enough to exclude that it is an intermediate in the reaction. In the reactions of 5-pentyl-1,3-cyclohexanedione with 2-butenoyl and cinnamoyl chloride, both *C*-acylation and ring closure were found to proceed much slower.

Table 3. 5-Hydroxy-4-chromanones (**1**) prepared

1	Method	Yield[a] [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	Molecular Formula[b] or Lit. Data	M.S. (M^+) *m/e*	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	A	30	m.p. 74°	m.p. 75–77°[17]	192	1.45 (s, 6H, 2,2-di-CH_3); 2.75 (s, 2H, 3-CH_2); 6.3–6.55 (m, 2H, 6-H, 8-H); 7.2–7.5 (t, 1H, 7-H; 11.7 (s, 1H, OH)
	C	0				
b	B	48	m.p. 23–25°	$C_{12}H_{14}O_3$ (206.2)	206	1.42 (s, 6H, 2,2-di-CH_3); 2.25 (s, 3H, 7-CH_3); 2.7 (s, 2H, 3-CH_2); 6.20, 6.27 (2H, 6-H, 8-H); 11.6 (s, 1H, OH)
c	C	78	b.p. 100–105°/0.01	m.p. 23–27°[4]	262	0.9 [t, 3H, $(CH_2)_4$—CH_3]; 1.1–1.7 (6H); 1.45 (s, 6H, 2,2-di-CH_3); 2.5 (t, 2H, C—CH_2—C_4H_9); 2.7 (s, 2H, 3-CH_2); 6.25, 6.33 (2H, 6-H, 8-H); 11.7 (s, 1H, OH)
	D	96				
d	A	37	m.p. 126–128° (cyclohexane)	$C_{17}H_{16}O_3$ (268.3)	268	1.5 (s, 6H, 2,2-di-CH_3); 2.7 (s, 2H, 3-CH_2); 6.6–6.8 (m, 2H, 6-H, 8-H); 7.3–7.7 5H_{arom}); 11.65 (s, 1H, OH)
	B	90				
e	C	53	oil	m.p. 30–33°[18]	178	1.5 (d, 3H, 2-CH_3); 2.6–2.8 (2H, 3-CH_2); 4.5 (m, 1H, 2-CH); 6.3–6.6 (2H, 6-H, 8-H); 7.3 (t, 1H, 7-H); 11.8 (s, 1H, OH)
f	C	60	oil	$C_{15}H_{20}O_3$ (248.3)	248	0.9 [t, 3H, $(CH_2)_4$—CH_3]; 1.0–1.7 (6H); 1.5 (d, 3H, J = 6 Hz, 2-CH_3); 2.4–2.8 (6H); 4.3–4.8 (m, 1H, 2-H); 6.2–6.4 (2H, 6-H, 8-H); 11.6 (s, 1H, OH)

[a] Yield of isolated product.

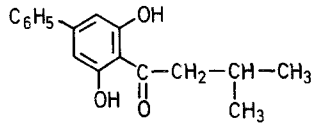
[b] The microanalyses showed the following maximum deviations from the calculated values: C ±0.37; H ±0.19.



10

It is also possible that the formation of insoluble complexes of **8** with $TiCl_4$ has a favourable effect on the yields by shifting the equilibrium toward the cyclic compounds **8**.

Dehydrogenation with aromatization of compounds **8** may be carried out by various methods (Table 4), however, with different results in the individual cases. Thus, Method C is not applicable to the dehydrogenation of compound **8a**, and application of Method A to the dehydrogenation of **8d** affords only 37% of **1d** together with 15% of product **11** formed by disproportionation of **8d**.



11

Melting points are uncorrected. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6D mass spectrometer or on a Finnigan 4021 mass spectrometer equipped with INCOS Data System. ^{1}H-N.M.R. spectra were recorded with a Varian EM-390 (90 MHz) or a Bruker WP 80 Sy (80 MHz) spectrometer.

Column chromatographies were run on silica gel Merck 60 (230–400 mesh). Anhydrous benzene was distilled on sodium and kept on molecular sieves. Dichloromethane, chloroform, tetrachloromethane, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane were distilled from P_2O_5 and kept on molecular sieves. All other commercial products were used without further purification.

5-Methyl-1,3-cyclohexanedione[14], 5-pentyl-1,3-cyclohexanedione[15], and 5-phenyl-1,3-cyclohexanedione[16] were synthesized by known procedures.

4,5-Dioxo-5,6,7,8-tetrahydrochromans (8); General Procedure:

A solution of the 1,3-cyclohexanedione (**6**; 26 mmol) in dichloromethane (30 ml) is added dropwise to a stirred solution of titanium(IV) chloride (5.692 g, 30 mmol) in dichloromethane (10 ml) at 5 °C under nitrogen. The mixture becomes orange and red and a viscous oil separates. After 10 min, the 2-alkenoyl chloride (**2**, 28 mmol) is added and stirring is continued overnight at room temperature until a yellow precipitate separates. The mixture is then hydrolyzed with cold 5% hydrochloric acid (60 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic layers are dried and concentrated in vacuo. The product **8** is obtained from the crude residue by crystallization or column chromatography. Deviations from this procedure are noted in Tables 1 and 2.

5-Hydroxy-2,2-dimethyl-4-chromanones (1) by Dehydrogenation of Compounds 8; General Procedure:

Method A: Compound **8** (5 mmol) is refluxed with 10% palladium on carbon (50 mg) in diethyleneglycol dimethyl ether (20 ml) and the reaction monitored by T.L.C. The mixture is then filtered, dried, and evaporated, and compound **1** is purified by column chromatography.

Method B: Analogous to Method A, but using cyclohexene as a solvent.

Method C: Compound **8** (5 mmol) and DDQ (5 mmol) are refluxed 1 h in toluene (20 ml). The mixture is filtered, the filtrate concentrated, and the residue chromatographed to give compound **1**.

Method D: A solution of compound **8** (9 mmol), *N*-bromosuccinimide (1.96 g, 11 mmol), and dibenzoyl peroxide (10 ml) in tetrachloromethane (25 ml) is heated for 2 h on a water bath. Succinimide is then filtered off and the solvent evaporated. To the crude residue, *N*,*N*-diethylaniline (3 ml) is added and the mixture is heated on a water bath for 3 h. The solution is then diluted with petroleum ether (15 ml), washed with 6 normal hydrochloric acid (2 × 10 ml), dried with sodium sulfate, and evaporated. The product **1** thus obtained is purified by distillation or crystallization.

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[1] I.M. Lockhart, in: G.P. Ellis, *Chromenes, Chromanones, and Chromones*, John Wiley & Sons, New York, 1977, p. 207–428.

[2] F. Camps et al., *Synthesis* **1980**, 725.

[3] H.J. Kabbe, A. Widdig, *Angew. Chem.* **94**, 254 (1982); *angew. Chem. Int. Ed. Engl.* **21**, 247 (1982).

[4] K.E. Fahrenholtz, M. Lurie, R.W. Kierstad, *J. Am. Chem. Soc.* **89**, 5934 (1967).

[5] L. Chiodini, M. Di Ciommo, L. Merlini, *J. Heterocycl. Chem.* **18** 23 (1981).

[6] L. Chiodini, M. Di Ciommo, L. Merlini, *Heterocycles* **16**, 1899 (1981).
[7] Unpublished result from our laboratory.
[8] H.O. House, *Modern Synthetic Reactions*, 2nd Ed., W.A. Benjamin Inc., New York, 1972, p. 520.
[9] S. Gelin, B. Chantegrel, *C.R. Acad. Sci.* **273**, 635 (1971).
[10] T. Mukaiyama, *Angew. Chem.* **89**, 858 (1977); *Angew. Chem. Int. Ed. Engl.* **16**, 817 (1977).
[11] S. Gelin, P. Pollet, *J. Heterocycl. Chem.* **12**, 787 (1975).
[12] R.C.F. Jones, S. Sumaria, *Tetrahedron Lett.* **1978**, 3173.
[13] Y. Shizuri et al., *J. Chem. Soc.* [C] **1969**, 2774.
[14] R.M. Anker, A.H. Cook, *J. Chem. Soc.* **1945**, 311.
[15] A. Focella, S. Teitel, A. Brossi, *J. Org. Chem.* **42**, 3456 (1977).
[16] K.W. Rosenmund, H. Herzberg, H. Schutt, *Chem. Ber.* **87**, 1258 (1954).
[17] J. Nickl, *Chem. Ber.* **92**, 1989 (1959).
[18] D.C. Allport, J.D. Bu'Lock *J. Chem. Soc.* **1960**, 654.