Tetrahedron Vol. 43, No. 1, pp. 93 to 100, 1987
Printed in Great Britain.

0040-4020/87 $5.00+.00
Pergamon Journals Ltd.

SYNTHESIS OF ETHYL 3-ALKYL-4-OXOCHROMAN-3-CARBOXYLATES AND THEIR CONVERSION TO SOME DERIVATIVES

Bernard LOUBINOUX*, Jean-Luc COLIN, Brigitte ANTONOT-COLIN
Université de Nancy I, Faculté des Sciences, Laboratoire de Chimie Organique 4,
Unité Associée au CNRS n° 486, B.P. 239, 54506 VANDOEUVRE-LES-NANCY Cédex, FRANCE

Lucien LALLOZ
Université de Nancy I, Faculté de Pharmacie

(*Received in France* 22 *September* 1986)

Abstract : A series of ethyl 3-alkyl-4-oxochroman-3-carboxylates 5 was synthesized and some representative reactions were attempted on these compounds. The first step of the synthesis was the condensation of diethyl alkylsodiomalonates on aryloxymethyl chlorides. Hydrolysis of one ester group and treatment with thionyl chloride afforded the mono acyl halides which were cyclized by means of aluminium chloride.

Introduction

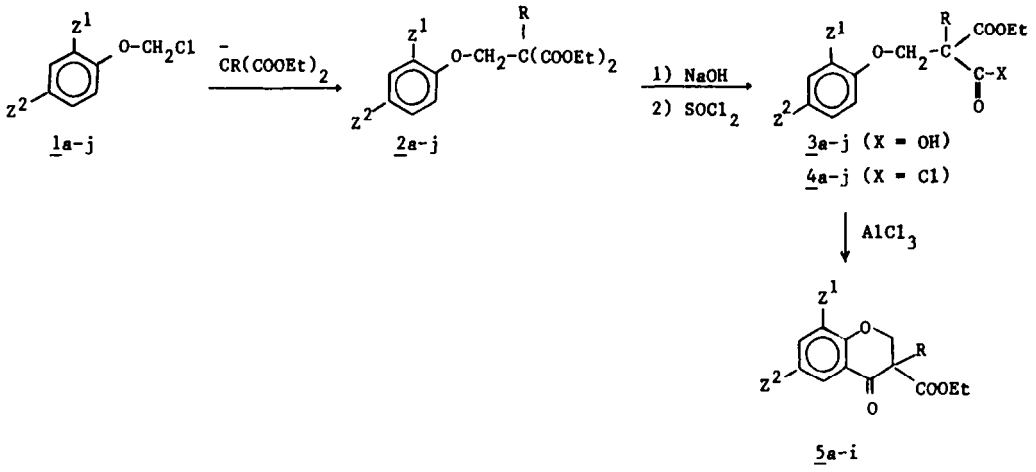
The preparation of 3-substituted 4-oxochromanes by addition reactions to chromones or by direct reactions on the active methylene group of unsubstituted 4-oxochromanes is often difficult with the result that the most widely used method of formation of these compounds is the cyclization of 3-phenoxypropionic acids and related compounds.[1]

Recently, 3-dialkylaminomethyl-4-oxochromanes were prepared from halogenated 2-hydroxypropiophenones[2] whereas the hydroxymethylation of 2-hydroxypropiophenones afforded a good yield of 3-hydroxymethyl-3-methyl-4-oxochromanes[3]. Furthermore, the latter compounds were converted to the corresponding 3-methyl-4-oxochroman-3-acetic acid potential anti-inflammatory agents. The synthesis of two 3-methyl-3-carbethoxychroman-4-ones from the corresponding unsubstituted chromanones has also been described.[4]

As an extension of our previous work[5] on the chemistry of halomethoxy aromatic compounds, we decided to investigate whether they could be employed in the synthesis of substituted oxochromanes 5. The present paper describes the results of our investigations.

Results and discussion

Aryloxymethyl halides have been known for many years and numerous derivatives have been prepared. Several preparations have been described especially for aryloxymethyl chlorides (1) now easily available in good yields[6,7,8]. They react readily with ethyl sodiomalonate in ethanol[8] or in THF, but the only products are the bisaryloxymethanes, the phenols and methylenebismalonic ester. However, as observed by others with chloromethyl ethyl sulfide and β-ketocarboxylic esters[9], we have found that treatment of chlorides 1 by diethyl alkylmalonates, afforded the aryloxymethylmalonates 2 in fair yields. The nucleophilic substitutions were achieved at room temperature in a two phase system containing a phase transfer catalyst, except in the case of methylmalonate where tetrahydrofuran and sodium hydride were used to prevent hydrolysis (Table 1). Attempts to condense acetamidomalonate with 1 led to bisaryloxymethane whereas β-keto esters were O-alkylated.



1-5	Z^1	Z^2	R
a	H	H	Et
b	Cl	H	Et
c	H	Cl	Et
d	Me	Cl	Et
e	Cl	Cl	Et
f	H	Cl	Me
g	Cl	Cl	Me
h	Me	Cl	Me
i	Cl	Cl	$CH_2CH_2CH(CH_3)_2$
j	Cl	Cl	$CH_2CH{=}CH_2$

SCHEME 1

TABLE 1 : YIELDS [a] AND PHYSICAL DATA OF DIETHYL ARYLOXYMETHYLMALONATES 2 [b]

Product 2	Yield [%]	Procedure[c]	b.p. [°C] /3 torr	^{1}H-N.M.R. (CCl_4/TMS int.) δ [ppm]
a	75	A	110-115	0.85 (t, J = 7.3 Hz), 1.2 (t, J = 6.7 Hz), 9 H ; 2.15 (q, J = 7.3 Hz, 2 H) ; 4.15 (q, J = 6.7 Hz), 4.25 (s), 6 H ; 6.7-7.4 (m, 5 H).
b	68	A	140-145	0.9 (t, J = 7.3 Hz), 1.25 (t, J = 6.7 Hz), 9 H ; 2.2 (q, J = 7.3 Hz, 2 H) ; 4.15 (q, J = 6.7 Hz), 4.35 (s), 6 H ; 6.7-7.4 (m, 4 H).
c	81	A	135-140	0.85 (t, J = 7.3 Hz), 1.2 (t, J = 6.7 Hz), 9 H ; 2.1 (q, J = 7.3 Hz, 2 H) ; 4.15 (q, J = 6.7 Hz), 4.25 (s), 6 H ; 6.7-7.4 (m, 4 H).
d	70	A	150-155	0.85 (t, J = 7.3 Hz), 1.2 (t, J = 6.7 Hz), 9 H ; 2.1 (s), 2.15 (q, J = 7.3 Hz), 5 H ; 4.15 (q, J = 6.7 Hz), 4.25 (s), 6 H ; 6.6-7.3 (m, 3 H).
e	72	A	129-135	0.9 (t, J = 7.3 Hz), 1.25 (t, J = 6.7 Hz), 9 H ; 2.2 (q, J = 7.3 Hz, 2 H) ; 4.21 (q, J = 6.7 Hz), 4.35 (s), 6 H ; 6.7-7.4 (m, 3 H).
f	70	B	135-140	1.25 (t, J = 6.7 Hz, 6 H) ; 1.55 (s, 3 H) ; 4.2 (q, J = 6.7 Hz), 4.25 (s), 6 H ; 7.0 (q, J = 9.3 Hz, 4 H).
g	81	B	130-135	1.25 (t, J = 6.7 Hz, 6 H) ; 1.55 (s, 3 H) ; 4.2 (q, J = 6.7 Hz), 4.25 (s), 6 H ; 6.7-7.4 (m, 3 H).
h	70	B	117-120	1.2 (t, J = 6.7 Hz, 6 H) ; 1.55 (s, 3 H) ; 2.1 (s, 3 H) ; 4.15 (q, J = 6.7 Hz), 4.2 (s), 6 H ; 6.7-7.4 (m, 3 H).
i	80	A	145-150	0.95 (d, J = 6 Hz), 1.25 (t, J = 6.7 Hz), 0.8-1.5 (m), 15 H ; 0.9-2.3 (m, 2 H) ; 4.2 (q, J = 6.7 Hz), 4.3 (s), 6 H ; 6.8-7.4 (m, 3 H).
j	65	A	140-145	1.25 (t, J = 6.7 Hz, 6 H) ; 2.9 (d, J = 6.7 Hz, 2 H) ; 4.2 (q, J = 6.7 Hz), 4.3 (s), 6 H ; 4.9-5.9 (m, 3 H) ; 6.85-7.5 (m, 3 H).

[a] Yields of pure products isolated by chromatography (ether/hexane : 3/7) ; [b] IR (CO), ν : 1730 cm^{-1} for all the products (liquid film) ; [c] See experimental section.

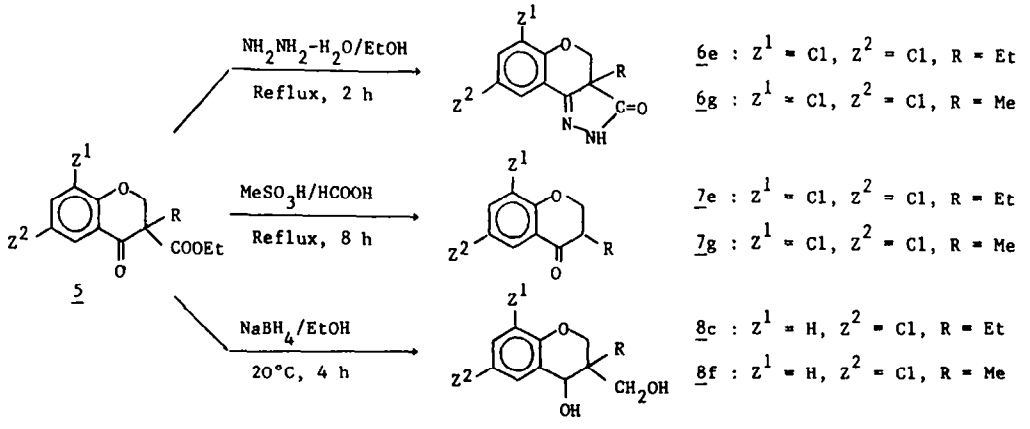
Hydrolysis of 2 in basic conditions[10] afforded the monoacids 3 (Table 2) and the crude acyl halides 4 obtained by treatment of 3 with thionyl chloride gave ethyl 3-alkyl-4-oxochroman-3-carboxylates 5 by reaction with aluminium chloride in methylene chloride (Table 3). In the case of 5j, the cyclization did not proceed without byproducts because the addition of hydrochloric acid across the double bond occured during treatment of 4 by aluminium chloride.

TABLE 2 : PREPARED ACIDS 3

Acid 3	Yield [%][a]	^{1}H-N.M.R. (CCl_4/TMS int.) δ [ppm]
a	75	0.9 (t, J = 7.3 Hz), 1.15 (t, J = 6.7 Hz), 6 H ; 2.2 (q, J = 7.3 Hz, 2 H) ; 4.15 (q, J = 6.7 Hz), 4.35 (s), 4 H ; 6.7-7.4 (m, 5 H) ; 11.5 (s, 1 H).
b	70	0.95 (t, J = 7.3 Hz), 1.25 (t, J = 6.7 Hz), 6 H ; 2.25 (q, J = 7.3 Hz, 2 H) ; 4.2 (q, J = 6.7 Hz), 4.35 (s), 4 H ; 6.7-7.4 (m, 4 H) ; 9.8 (s, 1 H).
c	82	0.95 (t, J = 7.3 Hz), 1.2 (t, J = 6.7 Hz), 6 H ; 2.2 (q, J = 7.3 Hz, 2 H) ; 4.3 (q, J = 6.7 Hz), 4.35 (s), 4 H ; 7.1 (q, J = 9.3 Hz, 4 H) ; 11.05 (s, 1 H).
d	79	0.95 (t, J = 7.3 Hz), 1.25 (t, J = 6.7 Hz), 6 H ; 2.1 (s), 2.15 (q, J = 7.3 Hz), 5 H ; 4.25 (q, J = 6.7 Hz), 4.3 (s), 4 H ; 6.7-7.3 (m, 3 H) ; 9.5 (s, 1 H).
e	73	0.95 (t, J = 7.3 Hz), 1.15 (t, J = 6.7 Hz), 6 H ; 2.15 (q, J = 7.3 Hz, 2 H) ; 4.15 (q, J = 6.7 Hz), 4.25 (s), 4 H ; 6.8-7.4 (m, 3 H) ; 11.0 (s, 1 H).
f	84	1.25 (t, J = 6.7 Hz, 3 H) ; 1.6 (s, 3 H) ; 4.25 (q, J = 6.7 Hz), 4.3 (s), 4 H ; 7.1 (q, J = 9.3 Hz, 4 H) ; 11.3 (s, 1 H).
g	72	1.2 (t, J = 6.7 Hz, 3 H) ; 1.6 (s, 3 H) ; 4.15 (q, J = 6.7 Hz), 4.25 (s), 4 H ; 6.7-7.4 (m, 3 H) ; 10.95 (s, 1 H).
h	70	1.25 (t, J = 6.7 Hz, 3 H) ; 1.6 (s, 3 H) ; 2.1 (s, 3 H) ; 4.15 (q, J = 6.7 Hz), 4.25 (s), 4 H ; 6.7-7.4 (m, 3 H) ; 11.0 (s, 1 H).
i	70	0.8-1.6 (m, 12 H) ; 2.0-2.5 (m, 2 H) ; 4.25 (q, J = 6.7 Hz), 4.45 (s), 4 H ; 6.8-7.4 (m, 3 H) ; 11.1 (s, 1 H).
j	75	1.25 (t, J = 6.7 Hz, 3 H) ; 2.95 (d, J = 6.7 Hz, 2 H) ; 4.25 (q, J = 6.7 Hz), 4.40 (s), 4 H ; 4.9-5.9 (m, 3 H) ; 6.85-7.35 (m, 3 H) ; 10.25 (s, 1 H).

[a]Yield of crude products, which were used without further purification.

4-Oxochromanes have served as precursors to several series of biologically active compounds ; as an extension of our work, we have studied some possibilities of the newly synthesized products. Only some representative reactions were performed ; they are described as example in this paper.



5

SCHEME 2

TABLE 3 : YIELDS AND PHYSICAL DATA OF ETHYL 3-ALKYL-4-OXOCHROMAN-3-CARBOXYLATES 5[a]

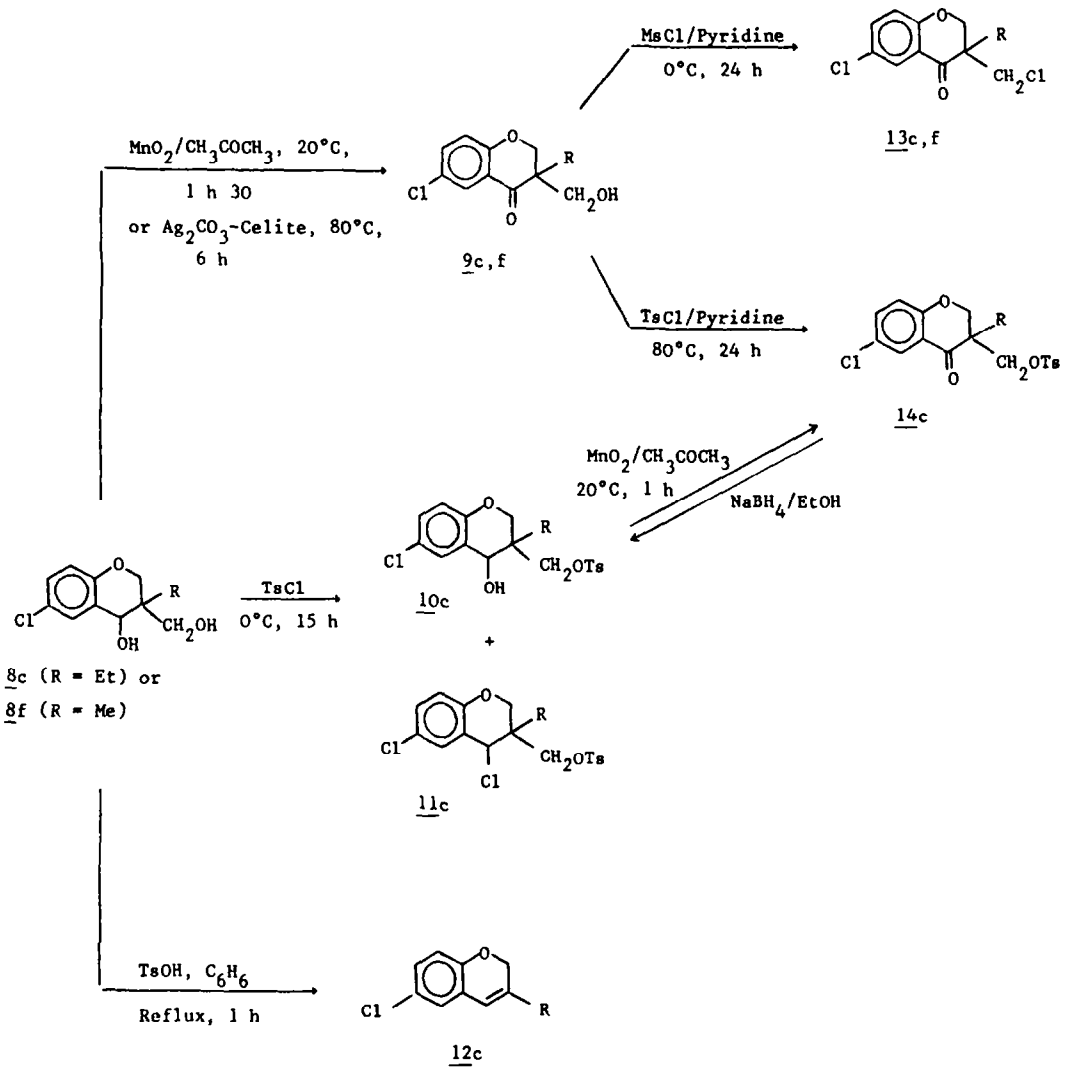
Product 5	Yield[b] [%]	m.p. [°C] (solvent)	^{1}H-N.M.R. (CCl_4[c] or $CDCl_3$[d]/TMS int.) δ [ppm]
a	75	liq.	[c] 1.0 (t, J = 7.3 Hz), 1.15 (t, J = 6.7 Hz), 6 H ; 1.6-2.2 (m, 2 H) ; 4.1 (q, J = 6.7 Hz), 4.45 (q, J = 11.3 Hz), 4 H ; 6.7-8.0 (m, 4 H).
b	67	liq.	[c] 1.0 (t, J = 7.3 Hz), 1.2 (t, J = 6.7 Hz), 6 H ; 1.6-2.1 (m, 2 H) ; 4.2 (q, J = 6.7 Hz), 4.65 (q, J = 11.3 Hz), 4 H ; 6.9-7.8 (m, 3 H).
c	88	liq.	[c] 1.0 (t, J = 6.7 Hz), 1.2 (t, J = 6.7 Hz), 6 H ; 1.6-2.2 (m, 2 H) ; 4.15 (q, J = 6.7 Hz), 4.5 (q, J = 11.3 Hz), 4 H ; 7.15 (q, J = 8.65 Hz, 2 H) ; 7.8 (d, J = 2.7 Hz, 1 H).
d	80	liq.	[c] 0.95 (t, J = 7.3 Hz), 1.15 (t, J = 6.7 Hz), 6 H ; 1.6-2.1 (m, 2 H) ; 2.2 (s, 3 H) ; 4.15 (q, J = 6.7 Hz), 4.5 (q, J = 11.3 Hz), 4 H ; 7.25 (d, J = 2.7 Hz, 1 H) ; 7.65 (d, J = 2.7 Hz, 1 H).
e	77	76-78 (hexane)	[c] 1.0 (t, J = 7.3 Hz), 1.25 (t, J = 6.7 Hz), 6 H ; 1.6-2.2 (m, 2 H) ; 4.2 (q, J = 6.7 Hz), 4.65 (q, J = 11.3 Hz), 4 H ; 7.55-7.95 (m, 2 H).
f	85	liq.	[c] 1.15 (t, J = 6.7 Hz, 3 H) ; 1.35 (s, 3 H) ; 4.1 (q, J = 6.7 Hz), 4.4 (q, J = 11.3 Hz), 4 H ; 7.15 (q, J = 8.65 Hz, 2 H) ; 7.8 (d, J = 2.7 Hz, 1 H).
g	66	120-121 (hexane)	[d] 1.15 (t, J = 6.7 Hz, 3 H) ; 1.40 (s, 3 H) ; 4.15 (q, J = 6.7 Hz), 4.5 (q, J = 11.3 Hz), 4 H ; 7.5 (d, J = 2.6 Hz, 1 H) ; 7.7 (d, J = 2.6 Hz, 1 H).
h	83	90-92 (hexane)	[d] 1.20 (t, J = 6.7 Hz), 1.45 (s), 6 H ; 2.2 (s, 3 H) ; 4.15 (q, J = 6.7 Hz), 4.5 (q, J = 10.65 Hz), 4 H ; 7.3 (d, J = 2.7 Hz, 1 H) ; 7.7 (d, J = 2.7 Hz, 1 H).
i	78	65-67 (hexane)	[d] 0.9 (d, J = 5.2 Hz), 1.2 (t, J = 7.3 Hz), 0.7-2 (m), 14 H ; 4.2 (q, J = 7.3 Hz), 4.7 (q, J = 12 Hz), 4 H ; 7.6 (d, J = 2.6 Hz, 1 H) ; 7.8 (d, J = 2.6 Hz, 1 H).

[a] IR (C=O), ν : 1695, 1730 cm^{-1} for all the products ; [b] Yields of pure products isolated by chromatography (silica gel, ether/hexane : 3/7).

Treatment of the ethyl 3-alkyl-6,8-dichloro-4-oxochroman-3-carboxylates 5e and 5g with hydrazine hydrate in dry ethanol gave the 5-oxopyrazoles analogues (6e, 6g) in good yields. Phenylhydrazine did not react under the same conditions. The deethoxycarbonylation of 5 into 7 occurs readily by treatment with methanesulfonic acid in formic acid. When the β-keto-esters 5c and 5f were treated with sodium borohydride the corresponding diols 8 were obtained. Similar reduction of the ester group by sodium borohydride was observed by others on ethyl 2,2-dimethyl-4-oxochroman-3-carboxylate. This reduction is considered to be a result of intramolecular delivery from alkoxyborohydrides initially formed by reduction of the keto group[11].

Attempts to convert 5 by standard procedures into their imines, oxime, acetal and thioacetal were unsuccessful. Furthermore reductions of the keto group into a methylene group also failed.

Other derivatives of 4-oxochromanes can be readily obtained from diols 8. For instance, they were converted into the ketols 9, the chlorides 13 and the tosylate 14, these products being starting compounds of interest for further syntheses. We also found that treatment of the β-keto-alcohols 9 with p.toluenesulfonic acid in refluxing benzene gives the corresponding 3-alkyl-4-oxochromanes 7 in good yields by a retro-aldol reaction.


MsCl/Pyridine
0°C, 24 h
13c,f
MnO2/CH3COCH3, 20°C,
1 h 30
or Ag2CO3-Celite, 80°C,
6 h
9c,f
TsCl/Pyridine
80°C, 24 h
14c
MnO2/CH3COCH3
20°C, 1 h
NaBH4/EtOH
TsCl
0°C, 15 h
10c
+
11c
8c (R = Et) or
8f (R = Me)
TsOH, C6H6
Reflux, 1 h
12c

SCHEME 3

TABLE 4 : DERIVATIVES OF PREPARED ETHYL 3-ALKYL-4-OXOCHROMAN-3-CARBOXYLATES 5

Derivatives	Yield[a] [%]	b.p. [°C] /torr or m.p. [°C] (solvent)	IR ν [cm^{-1}]	^{1}H-N.M.R.[b] δ [ppm]
6e	88	205-207 (CCl_4)	1670, 1720, 3160	0.85 (t, J = 7.3 Hz, 3 H) ; 1.95 (q, J = 7.3 Hz, 2 H) ; 4.35 (q, J = 10.6 Hz, 2 H) ; 7.7 (s, 2 H) ; 11.9 (s, 1 H).
6g	92	170-172 (CCl_4)	1670, 1720, 3160	1.5 (s, 3 H) ; 4.35 (q, J = 10.64 Hz, 2 H) ; 7.4 (d, J = 2.7 Hz, 1 H) ; 7.6 (d, J = 2.7 Hz, 1 H) ; 9.7 (s, 1 H).
7e	90	51-53 (hexane)	1700	1.0 (t, J = 7.3 Hz, 3 H) ; 1.5-2 (m, 2 H) ; 2.2-2.8 (m, 1 H) ; 4.1-4.8 (m, 2 H) ; 7.4 (d, J = 2.7 Hz, 1 H) ; 7.6 (d, J = 2.7 Hz, 1 H).
7g	90	86-87 (hexane)	1700	1.15 (d, J = 6.7 Hz, 3 H) ; 2.5-3.1 (m, 1 H) ; 4.0-4.8 (m, 2 H) ; 7.4 (d, J = 2.7 Hz, 1 H) ; 7.6 (d, J = 2.7 Hz, 1 H).
8c	90	126 (ether/ hexane 1/9)	3600	0.95 (t, J = 7.3 Hz, 3 H) ; 1.4 (q, J = 7.3 Hz, 2 H) ; 3.45 (s), 3.6-4.2 (m), 3.85 (s), 6 H ; 4.6 (s, 1 H) ; 6.6-7.4 (m, 3 H).
8f	80	160 (ether/ hexane 1/9)	3600	1.2 (s, 3 H) ; 3.5 (s), 3.4-4.2 (m), 3.8 (s), 6 H ; 4.6 (s, 1 H) ; 6.7-7.5 (m, 3 H).
9c	90[c] 70[d]	110/0.1	1690, 3500	1.0 (t, J = 6.7 Hz, 3 H) ; 1.7 (q, J = 6.7 Hz, 2 H) ; 3.1 (s, 1 H) ; 3.4-4.8 (m, 4 H) ; 6.7-7.7 (m, 3 H).
9f[e]	85[c] 60[d]	110/0.1	1690, 3500	1.2 (s, 3 H) ; 3.3 (s, 1 H) ; 3.2-4.7 (m, 4 H) ; 6.7-7.7 (m, 3 H).
10c	40[f] 98[g]	80 (hexane)	3500	0.65 (t, J = 6.7 Hz, 3 H) ; 1.5 (q, J = 6.7 Hz, 2 H) ; 2.2 (s, 1 H) ; 2.4 (s, 3 H) ; 3.7-4 (m, 4 H) ; 4.4 (s, 1 H) ; 6.5-8 (m, 7 H).
11c	20	-	-	0.9 (t, J = 6.7 Hz, 3 H) ; 1.4 (q, J = 6.7 Hz, 2 H) ; 2.4 (s, 3 H) ; 3.8-4.2 (m, 4 H) ; 4.85 (s, 1 H) ; 6.6-7.8 (m, 7 H).
12c	50	-	-	1.25 (t, J = 7.3 Hz, 3 H) ; 2.2 (q, J = 7.3 Hz, 2 H) ; 4.7 (s, 2 H) ; 6-6.2 (m, 1 H) ; 6.5-7.1 (m, 3 H).
13c	90	-	1690	0.8 (t, J = 7.3 Hz, 3 H) ; 1.8 (q, J = 7.3 Hz, 2 H) ; 3.7 (s, 2 H) ; 4.4 (s, 2 H) ; 6.8-7.8 (m, 3 H).
13f	55	-	1690	1.3 (s, 3 H) ; 3.4-4.7 (m, 2 H) ; 6.8-7.8 (m, 3 H).
14c	80[h] 95[i]	-	1690	0.7 (t, J = 7.3 Hz, 3 H) ; 1.8 (q, J = 7.3 Hz, 2 H) ; 2.5 (s, 3 H) ; 4.2 (s, 2 H) ; 4.5 (s, 2 H) ; 6.8-8 (m, 7 H).

[a]Yields of pure products ; [b]Spectra were recorded in CCl_4, except for 6e (d_6 DMSO), 6g ($CDCl_3$), 8c and 8f (d_6 acetone) ; [c]Oxidation of 8 by MnO_2 ; [d]Oxidation of 8 by Ag_2CO_3/celite ; [e]Physical data in agreement with literature[3] ; [f]Tosylation of 8 ; [g]Reduction of 14 ; [h]Tosylation of 9 ; [i]Oxidation of 10.

EXPERIMENTAL SECTION

IR spectra were measured as films for oils or as KBr discs for solids on a Perkin Elmer 580 B spectrometer. NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Perkin Elmer R 12B spectrometer. Mps were taken on a Kofler hot stage uncorrected. Microanalyses were determined by "Service Central de Microanalyses du C.N.R.S. de Solaize". All products synthetized gave satisfactory analytical results.

Diethyl (aryloxymethyl)alkylmalonates (2).

Procedure A. The aryloxymethylhalide (10 mM) in toluene (10 ml) is added to stirred aqueous 50 % sodium hydroxide (5 g) containing diethyl alkylmalonate (11 mM) and tetrabutylammonium hydrogenosulfate (1.1 mM). The mixture is vigorously stirred for one hour at room temperature. The organic phase is then separated, washed with water, dried with magnesium sulfate and concentrated in vacuo. Products 2 are purified by distillation under reduced pressure.

Procedure B. Diethyl alkylmalonate (11 mM) is added dropwise to a suspension of sodium hydride (11 mM) in THF (10 ml). When the gas evolution ceases, the aryloxymethylhalide (10 mM) in THF (10 ml) is added dropwise. The mixture is then stirred at 50°C for 4 h. After cooling, water is added and the product is extracted with ether. The ether phase is dried with magnesium sulfate and concentrated in vacuo. The products 2 are purified by distillation under reduced pressure.

Monoethyl (aryloxymethyl)alkylmalonates (3).

The malonic esters 2 (25 mM) and potassium hydroxide (25 mM) in 20 ml of a mixture ethanol/water (9:1) are stirred for 40 hours at room temperature.

The solvent is then evaporated and water is added. After extraction with ether, the aqueous phase is acidified with 3N hydrochloric acid. The product is extracted with ether. The ether phase is dried with magnesium sulfate and concentrated in vacuo. The products 3 are used without further purification.

Ethyl 3-alkyl-4-oxochroman-3-carboxylates (5).

A mixture of the acid 3 (10 mM) and thionyl chloride (30 ml) is refluxed until the gas evolution ceases. The excess of thionyl chloride is evaporated. Dichloromethane (20 ml) is then added. The reaction mixture is cooled to 0°C and $AlCl_3$ (30 mM) is added portionwise, the temperature being maintained below 10°C.

After completion of the reaction, the mixture is poured into ice. The organic phase is washed with aqueous sodium hydroxide and water, dried with magnesium sulfate and concentrated in vacuo. The products 5 are purified by column chromatography on silica gel eluting with ether/hexane (3:7).

5-Oxopyrazoles (6e and 6g).

A mixture of 5 (0.5 g) and hydrazine hydrate (1 ml) in ethanol (3 ml) is refluxed for five hours. Dichloromethane is added. The organic phase is washed with water, dried with sodium sulfate and concentrated in vacuo. The crude product is purified by column chromatography eluting with a mixture ether/hexane (1:1) to yield 0.41 g (92 %) of 6.

3-Alkyl-4-oxochromanes (7e and 7g).

The keto-ester 5 (1 g) and methanesulfonic acid (0.4 ml) in aqueous formic acid 90 % are refluxed for 6 hours. After cooling, ether is added to the mixture. The organic phase is washed with water, 2N sodium hydroxide, water, is dried with magnesium sulfate and evaporated to dryness to give pure product 7.

Diols (3-alkyl-6-chloro-3-hydroxy-4-hydroxymethyl-chromanes 8c and 8f) and diol monotosylate (10c) (reduction).

Sodium borohydride (120 mM) is added portionwise to the keto-ester 5 (60 mM) dissolved in ethanol (50 ml) and the mixture is stirred at room temperature. The course of the reaction is followed by T.L.C. on silica gel. When the reaction is over, the ethanol is evaporated. The product is extracted with ether. The organic phase is washed with water, dried with magnesium sulfate and concentrated in vacuo. The crude product is crystallised from ether/hexane (1:9) to yield pure 8. The same procedure is used to convert 14c into 10c which is purified by washing with hexane.

Hydroxy-ketones, 3-alkyl-6-chloro-3-hydroxymethyl-4-oxochromanes (9c and 9f).

Oxidation of 8c and 8f by Ag_2CO_3/celite

A suspension of silver carbonate on celite (18 g) and diol (5 ml) in benzene (80 ml) is stirred in a flask fitted with a Dean-Stark apparatus. 20 ml of benzene are distilled off and the mixture is refluxed for 6 hours. After cooling, the solid is filtered. The product is purified by column chromatography on silica gel eluting with ether/hexane (4:6).

Oxidation of 8c and 8f by MnO_2

Diol (1 g) in acetone (10 ml) is added to a suspension of freshly prepared manganese dioxide (5.5 g) in acetone (20 ml). The mixture is stirred at room temperature under nitrogen. When the reaction is over (T.L.C. on silica gel), the solid is filtered and the acetone is evaporated. The pure product is obtained after purification by column chromatography on silica gel eluting with ether/hexane (4:6).

Tosylation and mesylation (10c, 11c, 13c, 14c).

A solution of methanesulfonyl chloride (12.5 mM) or p.toluenesulfonyl chloride (25 mM) in anhydrous pyridine (15 ml) is cooled to 0°C under nitrogen. The substrate 8 or 9 (5 mM) dissolved in pyridine (15 mM) is then added dropwise. The mixture is stirred at 0°C (8) or 80°C (9). When the reaction is over (T.L.C. on silica gel), the pyridine is evaporated, water is added and the product is extracted with dichloromethane. The organic phase is dried with magnesium sulfate and concentrated on a rotary evaporator. The products are purified by column chromatography on silica gel, eluting with dichloromethane/hexane (1:1) for 10c and 11c or with ether/hexane (2:8) for 13c,f and (3:7) for 14c.

6-Chloro-3-ethyl-2H-chromene (12c).

A solution of the diol 8c (2.15 mM) and p.toluenesulfonic acid (6.5 mM) in benzene (30 ml) is refluxed for one hour. The benzene is evaporated, water is added and the product is extracted with ether. The ether phase is washed with aqueous sodium hydroxide, dried with magnesium sulfate and concentrated on a rotary evaporator. The product is purified by column chromatography on silica gel, eluting with ether/hexane (3:7).

REFERENCES

[1] Ellis, G.P., The chemistry of heterocyclic compounds : Chromenes, Chromanones, and Chromones, Chapter 4, John Wiley and Sons, New York, 1977.

[2] Cascaval, A., Synthesis (1983), 579.

[3] Barlocco, D. ; Cignarella, G. ; Curzu, M., Synthesis (1985), 876.

[4] Kasturi, T.R. ; Arunachalam, T., Indian J. Chem., (1970), 203-209.

[5] Loubinoux, B. ; Colin, J.L. ; Tabbache, S., J. Heterocycl. Chem., 21, 1669, (1984) ; Colin, J.L. ; Loubinoux, B., Synthesis (1983), 568.

[6] Gross, H. ; Burger, W., Org. Synth. Coll. Vol. V, 221, (1973).

[7] Beneche, T. ; Undheim, K., Acta Chem. Scand., Ser. B, 37, 93, (1983).

[8] Barber, H.J. ; Fuller, R.F. ; Green, M.B. ; Zwartouw, H.T., J. Appl. Chem. (1953), 266.

[9] Böhme, M. ; Mundlos, E., Chem. Ber., 86, 1414, (1953).

[10] Corey, E.J., J. Am. Chem. Soc., 74, 5897, (1952).

[11] Anastasis, P. ; Brown, P.E., J. Chem. Soc. Perkin Trans. I, (1983), 197.