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SYNTHESIS OF 3-ALKENYLCHROMONES FROM CHROMAN-4-ONES

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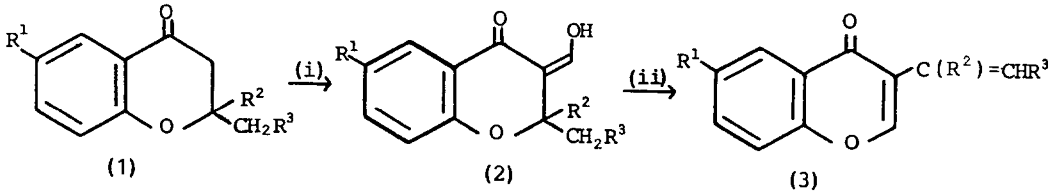
Summary: 3-Hydroxymethylene derivatives of 2-substituted chroman-4-ones rearrange to 3-alkenylchromones under acid-base conditions.

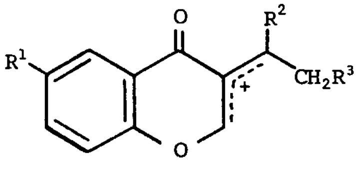
Compounds containing the chromone nucleus are widely distributed in nature and extensive studies have been carried out on their synthesis and reactions.[1] In particular, much attention has been devoted to the 2- and 3-phenyl derivatives, the flavones and isoflavones, respectively.[2] Despite their potential as the diene component in cycloadditions, relatively few examples of simple 2- or 3-alkenylchromones are known.[3]

Although many chroman-4-ones (1) [4,5,6] with a range of substituents at C-2 yielded 3-hydroxymethylene compounds (2) on treatment with sodium methoxide and ethyl formate, spiro[chroman-2,1'-cyclopentan]-4-one (1a) afforded only 3-cyclopentenylchromone (3a), characterised by $\nu_{C=O}$ at 1640 cm^{-1}, within the range expected for chromones [7,8] but outside that normally associated with chromanones,[9] and by an n.m.r. signal at 7.88 for H-2.[10] In the mass spectrum, the base peak is due to the molecular ion and fragments from the loss of carbon monoxide and from ring cleavage by a retro-Diels-Alder reaction are present. The formation of a doubly charged (M-1) ion is also observed, a notable feature in the mass spectra of isoflavones.[11] Recently, the same structure has been proposed for this compound, but without any supporting physical data.[12]

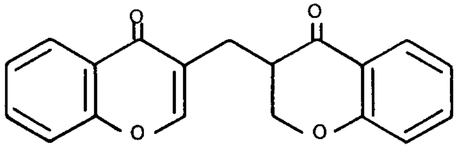


Reagents: (i) $HCOOC_2H_5$, $NaOCH_3$; (ii) pyridine, p-TsOH, reflux

The formation of 3-cyclopentenylchromone (3a) probably arises by ring cleavage of the anion of the 3-hydroxymethylenechromanone (2a) via a retro-Michael reaction. Ring closure of the resulting anion can be envisaged followed by dehydration of the intermediate hemiacetal to the carbocation (4a) during the acidic work-up; proton loss completes the sequence. The formation of (5) from 3-hydroxymethylenechroman-4-one is considered to involve a similar initial ring opening.[13] On this basis, the reaction of 2- and 2,2-substituted derivatives of 3-hydroxy-methylenechroman-4-one under acid-base conditions could provide a general synthesis of 3-alkenylchromones.



(4)



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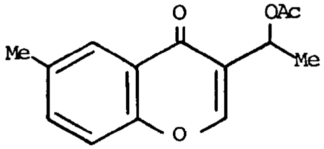

(6)

Upon boiling in acetic acid for several hours with DABCO, compounds (2b-d) yielded the chromones (3b-d). Attempts to extend the reaction to the synthesis of other 3-alkenylchromones were but partially successful. For example, the hydroxymethylene compound (2e) afforded only the acetate (6) (55%), m.p. 74-75°C , although subsequent pyrolysis yielded the alkenylchromone (3e). It appears that the solvent is intercepting the intermediate carbocation (4e) before it can form the alkenic bond by proton loss, for the trifluoroacetate resulted following a change in solvent to trifluoroacetic acid.

The chromanone → chromone conversion was refined by the use of pyridine and *p*-toluenesulphonic acid in place of DABCO and acetic acid. Not only are yields of the alkenylchromone thereby improved, but in addition solvation of (4e) is circumvented, (2e) affording the chromone (3e) directly. The scope of the reaction is not limited by substituents in the aromatic ring and a variety of substituents at C-2 is compatible with the rearrangement (Table). The initial indications are that the alkenylchromones are stable although on prolonged heating they show a tendency to polymerise.

Table

3-Hydroxymethylenechroman-4-ones (2) and 3-alkenylchromones (3)[†]

Compound	R^1	R^2	R^3	2		3	
				Yield (%)	b.p.(^oC/mmHg)* [m.p.(^oC)]	Yield (%)	m.p. (^oC)* [b.p.(^oC/mmHg)]
a	H	$-(CH_2)_3-$		-	-	-	115
b	H	$-(CH_2)_4-$		74	[78-80]	70	94-95
c	H	CH_3	H	62	[51-52]	57	57-59
d	H	CH_3	CH_3	50	140/0.05	85	89-91
e	CH_3	H	H	43	115/0.01	46	[125/0.1]
f	H	H	CH_3	20	130/0.05	67	63
g	H	H	CH_2CH_3	42	150/0.05	65	[150-5/0.1]

[†] Satisfactory elemental and spectral analyses were obtained for all new compounds.

* b.p. refers to Kugelrohr oven temperature at which distillation occurred.

Proton loss from (4) occurs in both a regio- and stereo-specific manner since (2d) yields a single product (t.l.c.). Both ^1H and ^{13}C n.m.r. spectra fully support structure (3d) and consideration of the three-bond ($^{13}C-^1H$) coupling constant $J_{Me(\alpha)-H}$ and the ^{13}C chemical shifts of the α and β methyl groups indicates a Z-configuration. The ^1H n.m.r. spectrum appears to support this view. The formation of a terminal alkene by proton loss from the methyl group of (4d) was not observed.

The hydroxymethylene compounds (2f) and (2g) yield a single geometric isomer in each case. Homo-nuclear spin decoupling experiments enabled measurement of the alkene vicinal coupling constant; a value of 14.9 Hz was observed for both (3f) and (3g) indicating an E-configuration.

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