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CONJUGATE ADDITION TO CHROMONES: SYNTHESIS OF SUBSTITUTED 4-CHROMANONES

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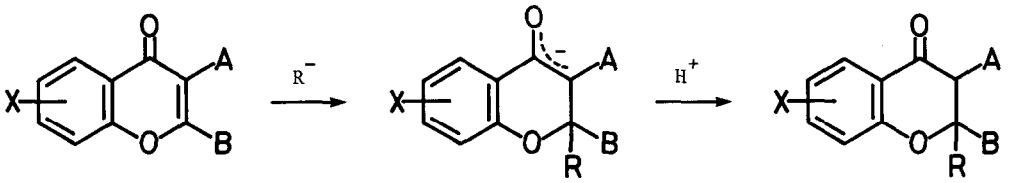
Summary: Chromones activated by carbonyl substituents at C-3 are transformed into the corresponding 2-methyl 4-chromanones by treating with lithium dimethylcuprate

The biological activity of many of the naturally-occurring compounds which incorporate a chroman ring system[1] has resulted in several applications of substituted 4-chromanones in synthesis.[2] In spite of recent advances in the area, methods for preparing these valuable intermediates remain limited.[3] In contrast, chromones are readily prepared by a variety of methods,[4] and could in principle provide 4-chromanones *via* the conjugate addition sequence shown in the Scheme.

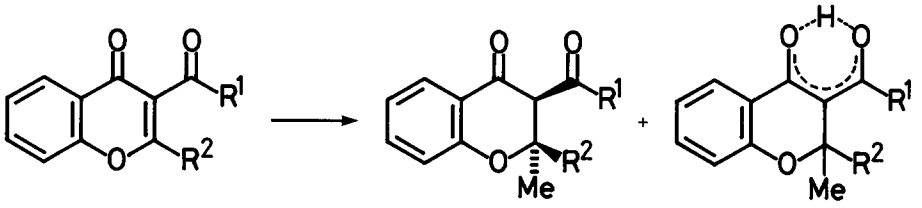


SCHEME

The attractions of such an approach prompted an examination of the reactions of a series of chromones with lithium dimethylcuprate, and the results are herein reported.[5]

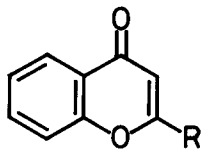
Using a standard procedure, each of the chromones (1) to (10) was treated with lithium dimethylcuprate in ether/tetrahydrofuran at -10°C, and the products examined by ^{1}H-n.m.r. spectroscopy and thin layer chromatography. As the results in Table 1 indicate, conjugate addition products were isolated in useful yields when a carbonyl substituent was incorporated in the 3-position of the chromone. The less activated substrates (7) to (10) gave complex reaction mixtures under the conditions used, and these were not investigated further.

TABLE 1 REACTIONS OF CHROMONES WITH LITHIUM DIMETHYLCUPRATE[6]

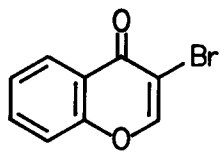


	R^1	R^2		RATIO[a]		% YIELD[b]
(1)[7]	Ph	H	(11a)	9:1	(11b)	77
(2)[8,10]	OMe	H	(12a)	4:1	(12b)	78
(3)[7]	Me	H	(13a)	1:4	(13b)	70
(4)[11]	H	H	-	-	(14)	50[c,d]
(5)[12]	Me	Me	(15)	-	-	42[d]
(6)[13]	OMe	Me	(16)	-	-	74

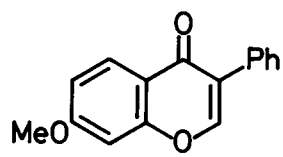
a Estimated by integration of the 60 MHz ^{1}H-n.m.r. spectrum of the mixture
b After isolation by medium pressure chromatography
c Not obtained pure by chromatography and decomposed on distillation
d Starting material remained even when the reaction time was extended to 3 h



(7) R = H
(8)[12] R = Me



(9)[14]



(10)[15]

The products were identified *via* their ^{1}H-n.m.r. spectra (Table 2). Those of the keto forms (11a), (12a), and (13a) include an overlapping double quartet (six lines) at around 5 p.p.m. due to H-2, which is coupled to the 2-methyl group ($J \simeq 6$ Hz) and to H-3 ($J \simeq 12$ Hz). The latter value is consistent with the expected *trans* (equatorial) arrangement of the 2,3-substituents. In the enolic forms (11b), (12b), (13b), and (14), the signal due to H-2 is a simple quartet ($J \simeq 6$ Hz). The difference in chemical shift of the respective H-2 signals allowed the ratio of keto and enol forms in product mixtures to be calculated (Table 1). Subsequent crystallisation of (11ab) and (13ab) gave exclusively the major tautomer in each case, as indicated by ^{1}H-n.m.r. spectroscopy. By contrast, the keto-enol ratio in (12ab) was essentially unaltered after distillation of the analytical sample.

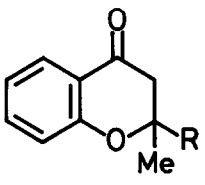
From a synthetic viewpoint the failure of the chromones (7) and (8) to undergo a clean conjugate addition is of little consequence, since a 3-carbomethoxy function in the chromone

TABLE 2 SELECTED ^{1}H-N.M.R. DATA FOR CONJUGATE ADDITION PRODUCTS

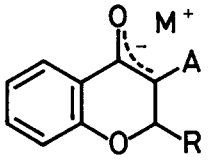
PRODUCT	δ p.p.m. ($CDCl_3$/TMS)[a]			
	2-Me	H-2	H-3	OTHERS
(11a)	1.45 d	5.06 dq	4.61 d	
(11b)	?	5.41 q	-	16.4 bs, 1H
(12a)	1.50 d	4.83 dq	3.60 d	3.80 s, 3H
(12b)	1.34 d	5.35 q	-	12.03 s, 1H
(13a)	?	4.75 dq	3.69 d	
(13b)	1.40 d	5.37 q	-	16.10 s, 1H; 2.13 s, 3H
(14)	1.50 d	5.08 q	-	11.9 bs, 1H
(15)	1.48 s, 1.53 s	-	3.87 s	2.28 s, 3H
(16)	1.53 s, 1.57 s	-	3.74 s	3.77 s, 3H

a Measured at 90 MHz. Values underlined refer to 60 MHz spectra of mixtures.

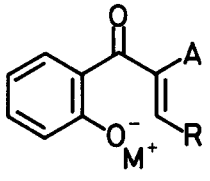
can function as a temporary activating group. Thus treatment of the β-ketoester (16) with sodium chloride in wet dimethylsulphoxide (155°/4h)[16] effected smooth decarbomethoxylation. The product, 2,2-dimethyl-4-chromanone (17), was isolated as the 2,4-dinitrophenylhydrazone,



(17) R = Me
(18) R = H



(19)



(20)

m.p. 223-224° (lit.[17] 220-221°), in 86% overall yield. By an analogous procedure, (12ab) was converted to (18) and isolated as the 2,4-dinitrophenylhydrazone, m.p. 234-236° (lit.[18] 236°), in 77% overall yield.

While the chromanones produced in the above reactions clearly arise *via* conjugate addition, the nature of the intermediate remains unclear. An equilibrium between (19) and (20), for which there is ample precedent,[19] cannot be ruled out and may account for some of the less successful results; enones (20) are *inter alia* potential consumers of the cuprate reagent. Attempts to detect such equilibration, which would limit the potential of these cuprate additions in synthesis, have been initiated using chromones which incorporate chiral activating substituents, and the experiments will be described in due course.

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5 Some of these findings were reported at the Autumn Meeting of The Royal Society of Chemistry, Swansea, September 1983.

6 A solution of the chromone (2 mmol) in THF (10 ml) was added dropwise under N_2 to a stirred solution of Me_2CuLi (3 mmol), prepared by treating CuI (3.05 mmol) in Et_2O (10 ml) with MeLi-LiBr complex in Et_2O (1.2M, 5.0 ml) at -10 to -5°C and stirring until the orange solid had dissolved. After 0.5 h the reaction was quenched by stirring vigorously with sat. aq. NH_4Cl (15 ml) and the products extracted into EtOAc (3 x 20 ml). The extract was washed successively with aq. HCl (2M, 20 ml), H_2O (20 ml), and sat. aq. NaCl (20 ml), and dried on Na_2SO_4. The residue on evaporation was dissolved in a small quantity of CH_2Cl_2 and the solution filtered through a short plug of silica gel (Merck 7736) using CH_2Cl_2. The filtrate was evaporated and examined by 60 MHz ^{1}H-n.m.r. spectroscopy. The major products were isolated by medium pressure chromatography over silica gel (as above) using mixtures of CH_2Cl_2 and petroleum ether, b.p. 40-60°, as eluting solvent. The products were invariably less polar than the starting materials, and fluorescent on GF_{254} t.l.c. plates under U.V. light.

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10 Satisfactory elemental analyses were obtained for the following compounds (melting point/crystallisation solvent or Kugelröhr oven temperature/pressure indicated): (2), 93-94°/EtOAc:petroleum ether, 60-80°, 1:2; (11a), 91-93°/EtOH; (12ab), 115-120°/0.2 mm Hg; (13b), 72-74°/petroleum ether, 40-60°:Et_2O 19:1; (15), 105-110°/0.2 mm Hg; (16), 110-115°/0.2 mm Hg.

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