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SYNTHESIS OF 2-SUBSTITUTED CHROMONES, CHROMANONES, AND THEIR THIO ANALOGUES USING ORGANOCOPPER REAGENTS

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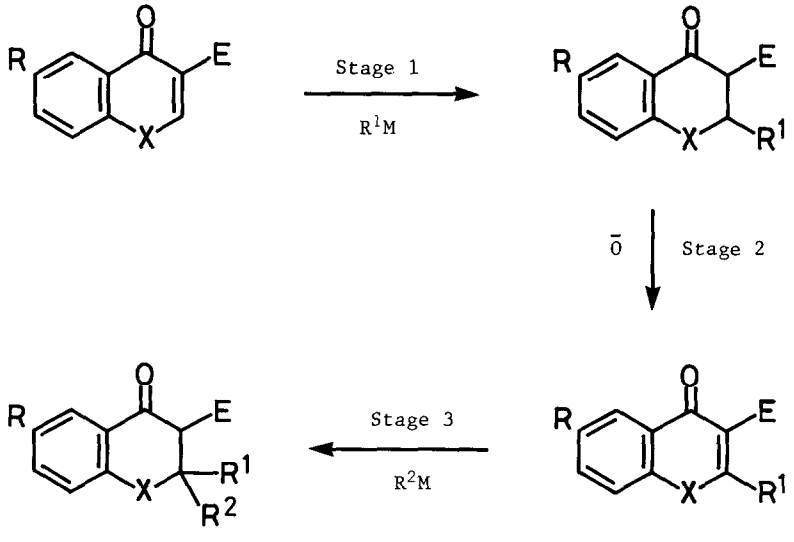
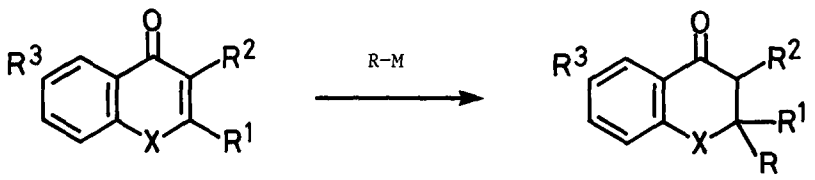
Summary: *Improved use of organocopper reagents provides a general route to unsymmetrical 2,2-dialkylchromanones and thiochromanones from chromones and thiochromones* via *a simple addition - oxidation - addition sequence*

Organocopper reagents have been shown to effect 1,4-additions to various α,β-unsaturated carbonyl compounds,[1] and it was recently demonstrated that chromones activated by carbonyl substituents at C-3 can be transformed into 2-methyl-4-chromanones by treatment with lithium dimethylcuprate.[2] We now describe further experiments which show that the alternative use of methylcopper - boron trifluoride[3] increases the efficiency of the conjugate addition both to unactivated chromones and to thiochromones, and that the scope of the lithium dialkylcuprate addition permits chromanones and thiochromanones bearing two different substituents at C-2 to be conveniently prepared via the addition - oxidation - addition sequence shown in the Scheme.



SCHEME E = Electron Withdrawing Group

TABLE 1 Reactions of Chromones and Thiochromones with Organocopper Reagents.



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2 R = Me

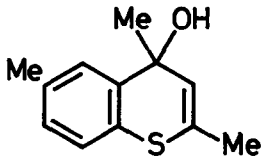
3 R = Bu^n

	X	R^1	R^2	R^3	R	Method	Equivs.	Product[a]	Yield %
1a	O	Me	H	H	Me	A[4]	1.5	2a	16
1a					Me	A	6	2a	23
1a					Me	B[5]	6	2a	76
1b	O	Me	H	Me	Me	A	1.5	2b	19
1b					Me	A	6	2b	23
1b					Me	B	1.5	2b	18
1b					Me	B	6	2b	33
1c	O	Me	COMe	Me	Me	A	1.5	2c	69
1c					Bu^n	C[6]	3	3c	71
1d	O	H	CO_2Me	OMe	Me	A	3	2d	98
1d					Bu^n	C	3	3d	94
1e	O	Me	CO_2Me	OMe	Bu^n	C	3	3e	97
1f	O	Bu^n	CO_2Me	OMe	Me	A	3	2f	63
1g	O	CO_2Et	H	CO_2Et	Me	B	1.5	2g	55
1h	S	Me	H	Me	Me	B	6	2h	56
1i	S	H	CO_2Et	Me	Me	A	1.5	2i	44
1i					Me	A	4	2i	77
1i					Bu^n	C	3	3i	81
1j	S	Me	CO_2Et	Me	Bu^n	C	1.5	3j	71
1k	S	Bu^n	CO_2Et	Me	Me	A	1.5	2k	75
1l	S	CO_2Et	H	Me	Me	B[b]	1.5	2l	12

[a] All new products were characterised by ^{1}H-n.m.r., i.r., u.v., m.s., and elemental analysis. Yields refer to isolated, chromatographically homogeneous materials. Most products exhibited keto-enol tautomerism, as noted previously.[2]

[b] Reaction of the thiochromone 1l under condition A gave the reduced[7] thiochromanone (2l, R = H) in 82% yield.

The results of a series of experiments comparing different conjugate addition procedures are shown in Table 1. Although 2-methylchromone (1a) did not react cleanly with lithium dimethylcuprate,[2] using methylcopper-BF_3 was more effective, providing 2,2-dimethylchromanone in 76% yield. Similarly, 2,6-dimethylchromone (1b) was directly converted into the trimethyl chromanone (2b) in 33% yield. Use of the alkylcopper-BF_3 reagent also improved the yield of conjugate methyl addition to the chromone diester (1g) to give the chromanone (2g) (55%), and it smoothly converted the unactivated thiochromone (1h) into the corresponding thiochromanone (2h) in 56% yield. This latter reaction contrasted sharply with that between (1h) and lithium dimethylcuprate, which afforded a mixture (76%) of the thiopyranols (4) and (5), derived respectively from 1,2-addition and allylic rearrangement, the latter presumably



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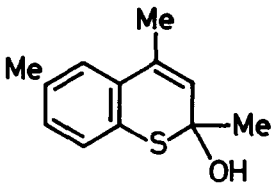

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occurring during the aqueous ammonium chloride work-up. Conjugate additions using lithium di-n-butylcuprate and the activated substrates (1c, 1d, 1i, and 1j) were predictably clean.

The second stage in the Scheme, oxidation of the 2-monosubstituted chromanones and thiochromanones to the corresponding chromones and thiochromones was smoothly effected using 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ).[8] Thus the chromanones (2d) and (3d) gave the chromones (1e) and (1f), while the thiochromones (1j) and (1k) were obtained on oxidation of the respective thiochromanones (2i) and (3i) (Table 2).

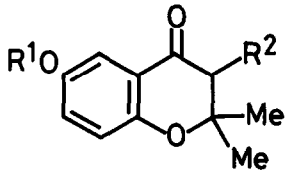
TABLE 2 Oxidations of Chromanones and Thiochromanones using DDQ.

Substrate	Product	M.p. (°C)	Yield %
2d	1e	129-130	56
3d	1f	184-185	64
2i	1j	129-130	61
3i	1k	77-78	64

The final stage in the Scheme involves conjugate addition to the 2-substituted chromone or thiochromone obtained by oxidation, and the results (Table 1) show that conjugate methyl addition to (1f) and n-butyl addition to (1e) both produce the chromanone (2f ≡ 3e) in good yield, while in the thio series methyl addition to (1k) and n-butyl addition to (1j) both give the thiochromanone (2k ≡ 3j). The equivalence of these pairs of products obtained via alternative sequences of conjugate addition is apparent from their identical spectra, and is

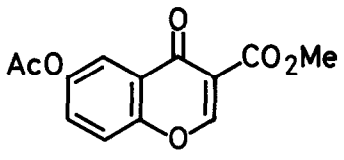
a predictable consequence of thermodynamic control during protonation of the intermediate metalloenolate formed via conjugate addition. It is assumed that the most stable product in each case has the large n-butyl and ester substituents in a trans-diequatorial orientation.

The above results combine to extend considerably the scope of conjugate addition to chromones. For example, the sequence provided a route to the naturally occurring chromanone (6a),[9] which was readily prepared from the ester (7) via two methyl additions followed by deacetylation and demethoxycarbonylation of the resulting intermediate (6b). Similar routes leading to various naturally occurring chromans[10] and thiochromans are under investigation.



6 a $R^1 = R^2 = H$

b $R^1 = Ac$ $R^2 = CO_2Me$



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4 General Procedure A: To a stirred suspension of $Me_2S{\cdot}CuBr$ (1.5, 3, or 6 equivs.) in dry ether (20 ml) under N_2 at -10°C was added MeLi in ether (3, 6, or 12 equivs.). The colourless solution was cooled to -40°C and the substrate (2 mmol) in ether (20 ml) added dropwise. The temperature was maintained between -40° and -30°C for 30 min., and sat. aq. NH_4Cl (15 ml) added dropwise. The product was extracted with EtOAc (3 x 20 ml) and the extract washed successively with water and brine. The residue on drying and evaporation was flash chromatographed on Aldrich Davisil (230-400 mesh) under N_2 to yield the product in pure form.

5 General Procedure B: To a stirred suspension of $Me_2S.CuBr$ (3 or 12 mmol) in dry ether (20 ml) under N_2 at -10°C was added MeLi in ether (3 or 12 mmol). The resulting yellow suspension was cooled to -70°C and $BF_3.Et_2O$ (3 or 12 mmol) added. After 5 min., the substrate (2 mmol) in ether (20 ml) was added dropwise. The mixture was allowed to warm to room temperature for 14 h and then quenched by dropwise addition of sat. aq. NH_4Cl (15 ml). The product was isolated as above (reference 4).

6 General Procedure C: As reference 4, using n-BuLi in hexane (3 or 6 mmol) at -20°C in place of MeLi at -10°C, and cooling the dark red solution to -40°C prior to adding the substrate (2 mmol).

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