Diastereoselective Conjugate Addition to 3-(*p*-Tolylsulphinyl)chromone: a Route to Chiral 2-Substituted Chroman-4-ones

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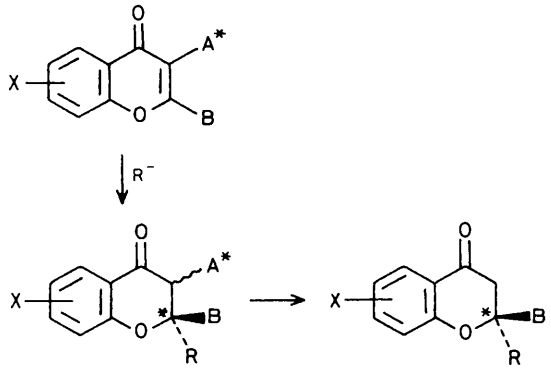
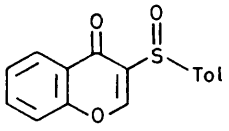
Conjugate addition of lithium dimethylcuprate to 3-(*p*-tolylsulphinyl)chromone (**1**) proceeds with at least 90% diastereoselectivity, and the products from (*S*)-(**1**) can be converted into chiral 2-methylchroman-4-one (−)-(**16**).

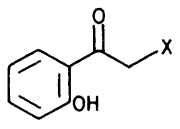
A route to 2-substituted chroman-4-ones based on the conjugate addition of organocopper reagents to chromones was recently established[1] and shown to be general.[2] In order to develop the method for synthetic purposes we required a means of inducing chirality at C-2, and were attracted by the protocol shown in Scheme 1, in which the substituent A serves both as an activating group and chiral auxiliary. The successful use of a *p*-tolylsulphinyl substituent in a similar role by Posner *et al.*[3] prompted us to examine the reactions of 3-(arylsulphinyl)chromones with lithium dimethylcuprate, and the results of a study using the *p*-tolylsulphinyl system (**1**) are herein described.



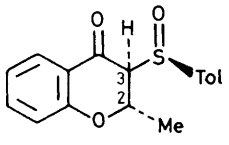
Scheme 1



(1)



(2) X = S.Tol
(3) X = S(O)Tol



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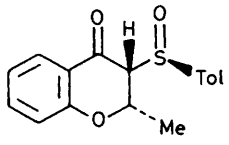

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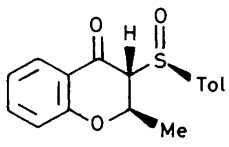

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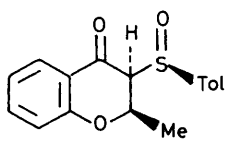

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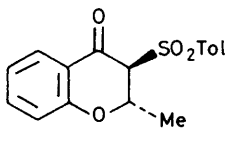

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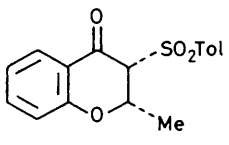
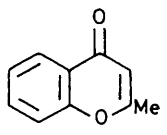


(9)

To prepare the racemic chromone (**1**),† 2-bromo-2′-hydroxyacetophenone[4] was treated with the sodium salt of *p*-thiocresol (ethanol-dioxane, room temp., 1 h), giving 2′-hydroxy-2-(*p*-tolylthio)acetophenone (**2**)‡ in 83% yield. Oxidation of (**2**) with *m*-chloroperbenzoic acid (MCPBA) (1.3 equiv., dichloromethane, 0 °C, 5 h) gave the ketosulphoxide (**3**), 94%, m.p. 118—119 °C (diethyl ether–dichloromethane). Treatment of (**3**) with acetic–formic anhydride[5] and sodium formate (70—75 °C, 3 h) gave the chromone (**1**), 56%, m.p. 175—176 °C (diethyl ether–dichloromethane). Treatment of (**1**) with lithium dimethylcuprate [3 mol. equiv., diethyl ether–tetrahydrofuran (THF), −78 °C, 1 h, then to 0 °C over 1 h] gave a mixture which was analysed by high field n.m.r. spectroscopy. Only two of the four possible diastereoisomeric products (**4**)—(**7**) were readily apparent, together with some starting material. The products were identified as (**4**) [δ_H ($CDCl_3$, 400 MHz) 1.46 (3 H, d, *J* 7 Hz, 2-Me), 3.53 (1 H, d, *J* 2 Hz, 3-H), and 5.50 (1 H, dq, *J* 2, 7 Hz, 2-H)] and (**5**) [δ_H ($CDCl_3$, 400 MHz) 1.92 (3 H, d, *J* 6.7 Hz, 2-Me), 3.44 (1 H, d, *J* 2.7 Hz, 3-H), and 4.93 (1 H, dq, *J* 2.7, 6.7 Hz, 2-H)], ratio *ca.* 6:1 (total 87%), after making a series of chemical correlations. Thus, oxidation of the mixture of (**4**) and (**5**) with MCPBA (1.4 equiv., dichloromethane, 0 °C, 1 h) gave, in the same ratio, two sulphones (**8**) [m.p. 118—119 °C (light petroleum–diethyl ether); δ_H ($CDCl_3$, 60 MHz) 1.44 (3 H, d, *J* 7 Hz, 2-Me)] and (**9**) [δ_H ($CDCl_3$, 60 MHz) 1.93 (3 H, d, *J* 7 Hz, 2-Me)], total 85%, indicating that the original sulphoxides differed in their C-2/C-3 relative stereochemistry and were not merely sulphur epimers. Thermolysis of the mixture of (**4**) and (**5**) (0.15 M in $CDCl_3$, 80 °C) led to the progressive disappearance over three hours of the major component and the concomitant formation of 2-methylchromone (**10**). This established that the major (labile) component of the mixture was either (**4**) or (**6**), since the transition state for *syn*-elimination leading to (**10**) is not readily accessible to the 2,3-*cis* isomers (**5**) and (**7**). Significantly, thermolysis of the mixture of (**4**) and (**5**) at 140 °C for one hour led to the consumption of both components. This is presumably due to thermal equilibration of the two isomers *via* the enol tautomer (**11**), and the isolated yield of the chromone (**10**) (98%) indicates that the sulphoxide (**1**) may be of general use in approaches to 2-substituted chromones.



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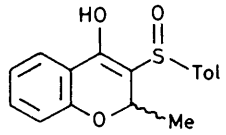

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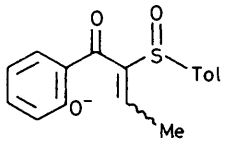
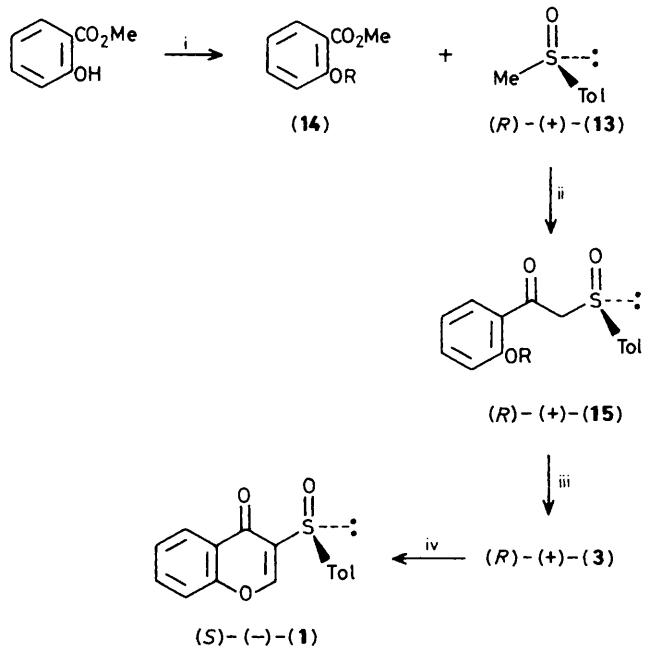


(12)

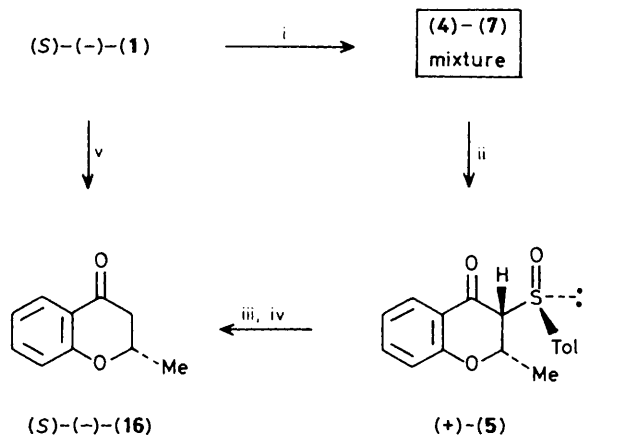
To determine whether the two cuprate adducts possessed the same relative stereochemistry with respect to sulphur and C-2, the *trans*-isomer (**4**), m.p. 114—115 °C, was isolated by flash chromatography[6] and fractional crystallisation from methanol. After confirmation of its homogeneity by 360 MHz ^1H n.m.r. spectroscopy, a deuteriochloroform solution of (**4**) was treated with a drop of [$^2H_5$]pyridine, whereupon signals attributable exclusively to the previously observed *cis*-isomer (**5**) became evident. It is reasonable to assume that this equilibration, which leads to a (**4**) : (**5**) ratio of 87 : 13 after 16 h at room temperature, proceeds *via* the anion of the enol (**11**), and therefore confirms that (**4**) and (**5**) differ in stereochemistry only at C-3. Equilibration of (**4**) under more forcing conditions (2 equiv. sodium methoxide, THF, room temp., 14 h, aq. HCl quench) produced a mixture of four compounds (total 82%), assigned by n.m.r. spectroscopy as (**4**), (**5**), (**6**)

† All figures represent racemic materials unless signs of optical rotation are indicated in the text. Tol = *p*-Tolyl.

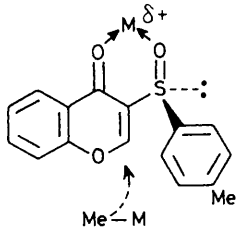
‡ All new compounds gave satisfactory spectroscopic, microanalytical, and mass spectral data.



Scheme 2. *Reagents:* i, 3,4-Dimethoxybenzyl chloride, K_2CO_3, Me_2CO, reflux, 30 h (85%); ii, lithium di-isopropylamide (1.6 equiv.), THF, −78 °C, 0.5 h, then 0 °C, 1 h (72%); iii, $Ph_3C^+BF_4^-$ (1.1 equiv.). CH_2Cl_2, 0 °C, 2 h, room temp., 0.5 h (95%); iv, AcOCHO, HCO_2Na, 70–75 °C, 3 h (86%).



Scheme 3. *Reagents:* i, Me_2CuLi (5 mol. equiv.), Et_2O–THF, −78 °C, 2 h, then to 0 °C, 1 h (90%); ii, flash chromatography, crystallisation (EtOH, trace of pyridine) (27%); iii, Al–Hg (15 equiv.), THF–H_2O, 0 °C, 0.5 h, room temp., 14 h; iv, PDC (5 equiv.), CH_2Cl_2, room temp., 4 h (59% over two steps); v, as i, iii, and iv (65% over three steps).



(17)

[δ_H ($CDCl_3$, 360 MHz) 1.465 (3 H, d, *J* 6.8 Hz, 2-Me), 3.90 (1 H, d, *J* 2.5 Hz, 3-H), and 5.25 (1 H, dq, *J* 2.5, 6.8 Hz, 2-H)], and (**7**) [δ_H ($CDCl_3$, 360 MHz) 1.88 (3 H, d, *J* 6.8 Hz, 2-Me), 3.89 (1 H, d, *J* 3 Hz, 3-H), and 5.00 (1 H, dq, *J* 3, 6.8 Hz, 2-H)] in a ratio of 54.6 : 7.7 : 19.2 : 18.5. The lability of (**6**) at 80 °C confirmed the 2,3-*trans* arrangement as was the case with (**4**). Having located (**6**) and (**7**), presumably formed *via* an elimination–addition process involving (**12**), in the ^1H n.m.r. spectrum of the original cuprate addition mixture, it was possible to estimate the diastereoisomeric excess of (**4**) + (**5**) by integration as at least 90%.

The absolute stereochemical course of the cuprate addition was established using the optically active sulphoxide (*S*)-(−)-(**1**), prepared as shown in Scheme 2. Acylation of (*R*)-(+)-methyl *p*-tolyl sulphoxide (**13**)[7] with the protected salicylate (**14**) gave (*R*)-(+)-(**15**), which was deprotected to furnish the ketosulphoxide (*R*)-(+)-(**3**), m.p. 125—126 °C (diethyl ether–dichloromethane), $[\alpha]_D^{20}$ +156° (*c* 1, $CHCl_3$). Formylation of (*R*)-(+)-(**3**) gave the chromone (*S*)-(−)-(**1**), m.p. 174—175 °C (decomp.) (diethyl ether–dichloromethane), $[\alpha]_D^{21}$ −278° (*c* 1, $CHCl_3$). Treatment of (*S*)-(−)-(**1**) with lithium dimethylcuprate gave the expected mixture of chromanones from which the *cis* isomer (+)-(**5**), m.p. 147—148 °C (decomp.) (ethanol), $[\alpha]_D^{21}$ +720° (*c* 0.1, $CHCl_3$), was isolated in 24% overall yield by flash chromatography and crystallisation from ethanol containing a trace of pyridine§ (Scheme 3). The sulphoxide substituent was removed from (+)-(**5**) by treatment with aluminium amalgam,[8] and the resulting chromanols oxidised with pyridinium dichromate (PDC)[9] to give the chromanone (*S*)-(−)-(**16**), m.p. 39—40 °C, $[\alpha]_D^{22}$ −50° ±4° (*c* 1.2, $CHCl_3$). The configuration at C-2 of (−)-(**16**) was assigned using c.d. spectroscopy, there being an established relationship between the signs of the Cotton effects due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of such carbonyl systems and their absolute stereochemistry.[10] The respective positive ($\Delta\varepsilon_{310}$ = + 4.85) and negative ($\Delta\varepsilon_{342}$ = − 4.15) values for (−)-(**16**) are consistent with the (2*S*) stereochemistry depicted. Repeating the desulphurisation sequence using an unresolved mixture of methylcuprate adducts from (*S*)-(−)-(**1**) gave another sample of (*S*)-(−)-(**16**), $[\alpha]_D^{22}$ −44° ±2° (*c* 2, $CHCl_3$) (65% yield), which confirms the viability of this method as a source of chiral 2-substituted chroman-4-ones.

Mechanistically, the above results are consistent with the model (**17**), in which chelation of the oxygen atoms by a metallic species M causes shielding of the *re* face of the substrate by the tolyl substituent.[3] The incoming methyl group therefore tends to approach from the relatively unhindered *si* face, with the consequence that (2*S*) chirality is induced.

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§ Without the pyridine to effect equilibration at C-3, this crystallisation yielded only a few percent of (+)-(**5**), while in the racemic series crystallisation from methanol had yielded the major isomer (±)-(**4**) without difficulty.

Sheffield), I. H. Sadler (University of Edinburgh), and S. R. Challand (Wellcome Research) for high field n.m.r. spectra.

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