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Stereoselectivity in the Conjugate Addition of Lithium Organocuprate Reagents to α,β-Unsaturated 2-Acyl-2-alkyl-1,3-dithiane 1-Oxides

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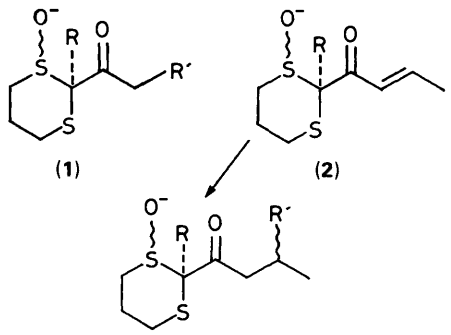
α,β-Unsaturated 2-acyl-2-alkyl-1,3-dithiane 1-oxides undergo diastereoselective conjugate addition by lithium organocuprate reagents. Diastereoisomeric ratios of up to *ca.* 10:1 have been observed in the product mixtures.

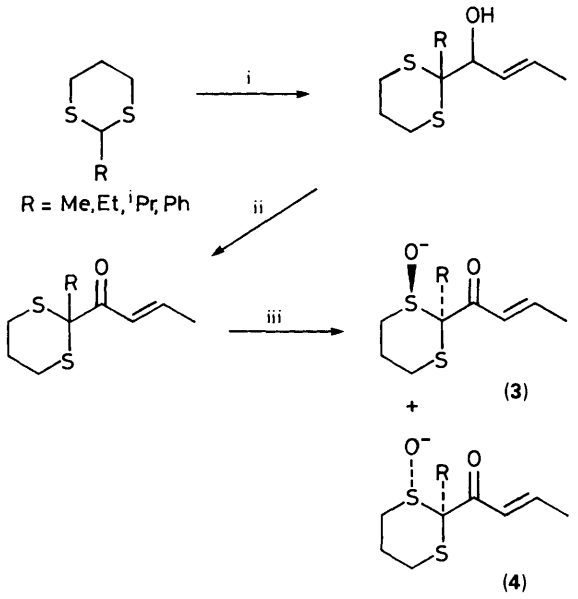
The conjugate addition of organocopper reagents to α,β-unsaturated acyl derivatives is a most important synthetic transformation,[1] and a number of methods for the asymmetric control of these reactions have been developed.[2–4] We have recently shown that 2-acyl-2-alkyl-1,3-dithiane 1-oxides (**1**) undergo very highly diastereoselective enolate alkylation[5,6] and Grignard addition[7] reactions. We are now able to report that racemic α,β-unsaturated 2-acyl-2-alkyl-1,3-dithiane 1-oxides (**2**) undergo conjugate addition with interesting levels of diastereoselectivity. This method has the potential to provide



for asymmetric control of conjugate addition by the use of the dithiane oxide auxiliary/building block in optically pure or enriched form. We are currently examining the enantioselective sulphoxidation of acyl dithianes in our laboratories.[8,9]

A range of *syn* and *anti* α,β-unsaturated 2-acyl-2-alkyl-1,3-dithiane 1-oxide conjugate addition substrates were prepared by deprotonation of the appropriate 2-alkyl-1,3-dithiane using butyl-lithium and subsequent reaction with crotonaldehyde, followed by manganese dioxide oxidation and peracid sulphoxidation (Scheme 1). The *syn* (**3**) and *anti* (**4**) products were readily separated by chromatography. Conjugate addition reactions were carried out using a variety of reagents and reaction conditions; but typically with lithium dibutyl- or diphenyl-cuprate (1 equiv.) in ethereal solution at −78 °C. Ratios of diastereoisomers obtained in a selection of conjugate addition reactions are given in the Table. Product mixtures were analysed after work-up by ^1H and ^{13}C NMR spectroscopy; separation of the diastereoisomers was not usually possible.

As a result of our earlier investigations,[5–7] we anticipated that rapid complexation should occur between the organometallic reagent and the enone substrate involving bidentate co-



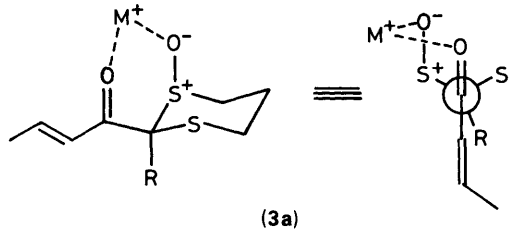
Scheme 1. *Reagents:* (*i*) 1 equiv. BuLi, THF, −20 °C; crotonaldehyde; (*ii*) 15 equiv. MnO_2, CH_2Cl_2, room temp.; (*iii*) 1 equiv. MCPBA, CH_2Cl_2, 0 °C.

ordination of the sulphoxide and carbonyl group oxygen atoms to the counter-ion; d,π_3*-complexation of copper could then occur selectively at the less hindered face of the π-system, resulting in a stereoselective conjugate addition.[10] Inspection of molecular models suggests that while conformations containing equatorial sulphoxides should be selective in reactions of both *syn* and *anti* substrates, the conformation of the *syn* substrates containing axial sulphoxide (**3a**) would not be expected to show much selectivity, and in the case of the *anti* substrates no chelation is possible in the conformation containing axial sulphoxide (**4a**). For the *syn* system, in the equatorial sulphoxide conformation (**3b**), the bulk of the dithiane ring effectively shields one face of the π-system, the other face being exposed unless a very large 2-alkyl group is present (Scheme 2). For the *anti* system (**4b**), only the 2-alkyl substituent is available to hinder reagent approach and selectivity should rise as this group becomes larger (Scheme 3). However, while rationales based upon such transition state models have helped to explain

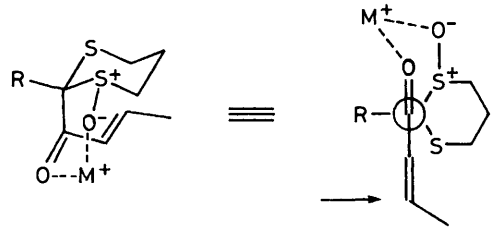
Table. Conjugate addition to 2-acyl-2-alkyl-1,3-dithiane 1-oxides.

Entry	Substrate type	2-Alkyl group	Reagent	Yield	Ratio of isomers *
a	*syn*	Me	Bu_2CuLi	84	4.3:1
b	*syn*	Me	Ph_2CuLi	95	2.3:1
c	*syn*	Et	Bu_2CuLi	73	10.5:1
d	*syn*	Et	Ph_2CuLi	67	3.2:1
e	*syn*	Ph	Bu_2CuLi	80	6.6:1
f	*syn*	Ph	Ph_2CuLi	70	3.4:1
g	*anti*	Me	Bu_2CuLi	84	2.0:1
h	*anti*	Me	Ph_2CuLi	83	1.2:1
i	*anti*	Et	Bu_2CuLi	50	2.0:1
j	*anti*	Et	Ph_2CuLi	87	4.0:1
k	*anti*	Ph	Bu_2CuLi	75	2.0:1
l	*anti*	Ph	Ph_2CuLi	60	2.3:1

* Measured by ^1H and/or ^{13}C NMR spectroscopy.

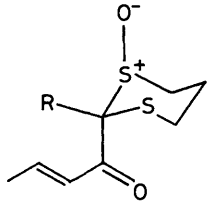


(3a)

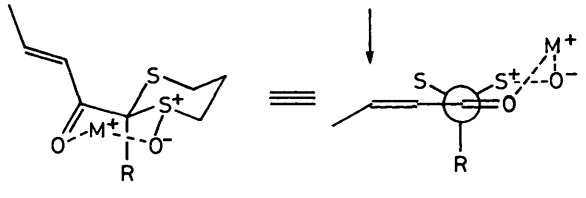


(3b)

Scheme 2.



(4a)



(4b)

Scheme 3.

patterns of selectivity observed in other reactions of 2-acyl-2-alkyl-1,3-dithiane 1-oxides,[5–7] such clear trends are not found in conjugate addition. While selectivity is poor and shows little variation with the 2-alkyl substituent for the *anti* series (**4**) (invariant at *ca.* 2:1 for butyl addition), some variation is seen

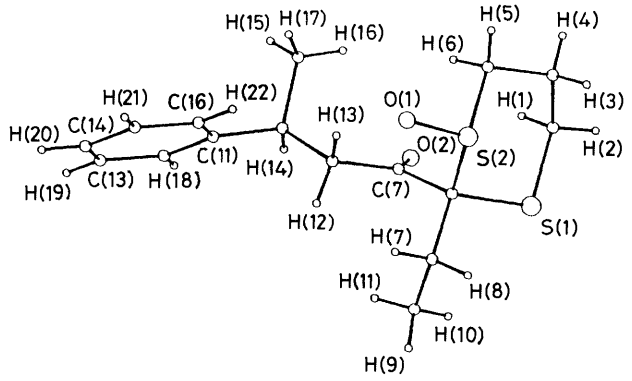
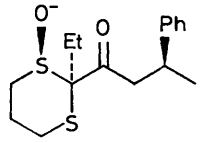


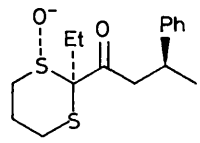
Figure 1. The molecular structure of compound (**5**), the major product of lithium diphenylcuprate to *syn*-2-but-2-enoyl-2-ethyl-1,3-dithiane 1-oxide, giving the crystallographic numbering scheme.

for the *syn* series (**3**), the best result (10.5:1) being observed for butyl addition to the 2-ethyl derivative.

Figures 1† and 2‡ show the molecular structures of (**5**) and (**6**), the major products of addition of lithium diphenylcuprate



(5)



(6)

to the 2-ethyl *syn* (entry d) and *anti* (entry j) substrates respectively, determined by single-crystal X-ray analysis. The relative stereochemistry indicated in Figure 1 corresponds to preferential attack at the least hindered side of a transition state as illustrated in (**3b**), containing a *transoid* enone conformation. The relative stereochemistry of Figure 2 would follow from a corresponding attack of (**4b**), but with a *cisoid* enone conformation. However, such a change in preferred reactive enone conformation seems unlikely, and indeed inspection of molecular models suggests that *transoid* enone conformations should be disfavoured in our systems. Further experiments which may shed more light on the mechanisms of these reactions are underway.

In both structures the C_6H_5 groups were refined with idealised geometry.

† *Crystal Data for Figure* 1.—$C_{16}H_{22}O_2S_2$, M = 310.47, triclinic, a = 9.107(1), b = 10.629(1), c = 8.548(1) Å, α = 85.78(1), β = 92.63(1), γ = 100.09(1)°, U = 811.97 Å^3, space group $P\bar{1}$, Z = 2, D_c = 1.27 g cm^{-3}, μ(Mo-K_α) = 3.13 cm^{-1}, F(000) = 332. 2 847 Independent reflections ($\theta \leqslant 25°$) were measured on a Nonius CAD-4 diffractometer with Mo-K_α radiation (graphite monochromator) using $\omega/2\theta$ scans. Of these 1 702 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The structure was solved by direct methods; the non-hydrogen atoms were refined anisotropically and the hydrogen atoms isotropically. Refinement converged to give R = 0.0576, R_w = 0.0690 [$w^{-1} = \sigma^2(F) + 0.0005F^2$].

‡ *Crystal Data for Figure* 2.—$C_{16}H_{22}O_2S_2$, M = 310.47, monoclinic, a = 11.407(1), b = 11.329(1), c = 12.798(1) Å, β = 93.23(4)°, U = 1 651 Å^3, space group $P2_1/C$, Z = 4, D_c = 1.25 g cm^{-3}, μ(Cu-K_α) = 28.59 cm^{-1}, F(000) = 664. 2 800 Independent reflections ($\theta \leqslant 65°$) were measured on a Nonius CAD-4 diffractometer with Cu-K_α radiation (nickel filter) using $\omega/2\theta$ scans. Of these 2 253 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The structure was solved by direct methods; the non-hydrogen atoms were refined anisotropically and the hydrogen atoms isotropically. Refinement converged to give R = 0.0421, R_w = 0.0706 [$w^{-1} = \sigma^2(F) + 0.001\,885F^2$].

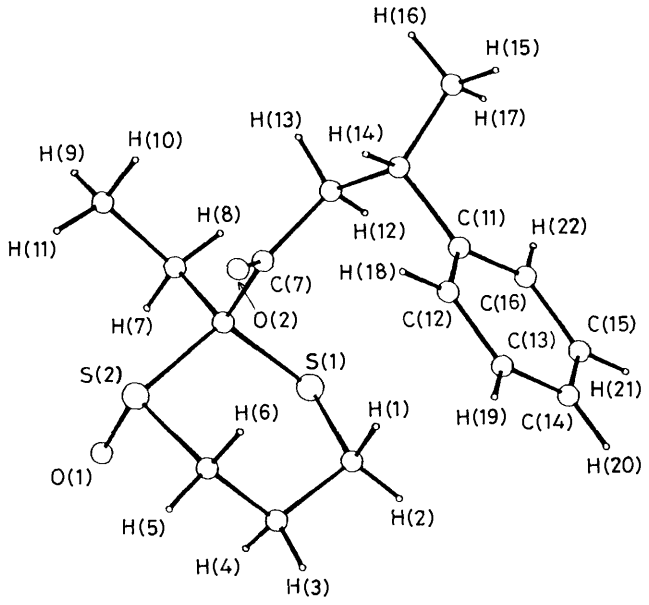


Figure 2. The molecular structure of compound (**6**), the major product of lithium diphenylcuprate to *anti*-2-but-2-enoyl-2-ethyl-1,3-dithiane 1-oxide, giving the crystallographic numbering scheme.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See 'Instructions for Authors (1990),' *Perkin Trans. 1*, 1990, Issue 1.

Acknowledgements

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