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Diastereoselective Alkylation of Ketone Enolates using a 1,3-Dithiane 1-Oxide Auxiliary

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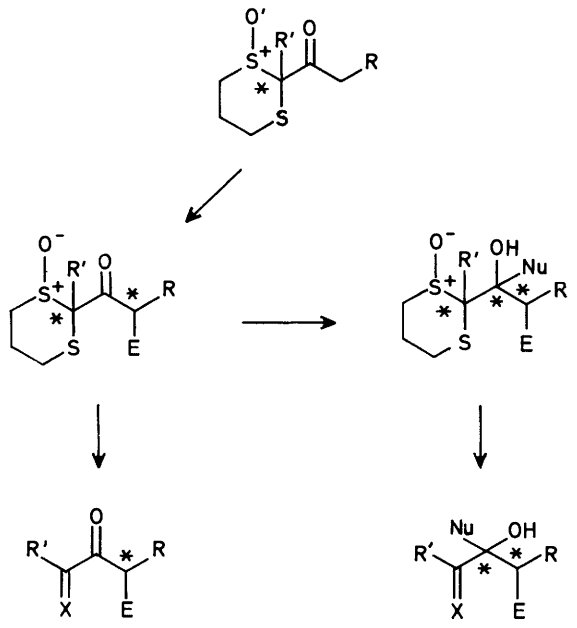
Acyldithiane 1-oxides readily undergo deprotonation to give chelated metal enolates which react with iodomethane to give alkylated products with good selectivity.

Procedures for the enantio- and diastereo-control of enolate alkylation and aldol reactions are currently of great interest.[1] Most methods which do not rely upon asymmetric alkylating agents hinge upon a derivatisation of the ketonic substrate with an enantiomerically pure auxiliary which has no other function and which must subsequently be removed. Such methods include the use of chiral dihydro-oxazoles,[2] hydrazones,[3] acyloxazoles,[4] and acyl iron complexes.[5] A pleasingly different approach involves asymmetric deprotonation with enantiomerically pure chiral bases.[6]

We are investigating a system which we believe will provide a method for diastereo- and enantio-selective enolate alkylation and aldol reactions using a simple heterocyclic acyl derivative at the α' carbon atom as the controlling element. This method would also have the potential for control of reactions other than alkylation and for removal or modification of the heterocycle to expose a second synthetically useful group with existing chirality (Scheme 1). An ideal system for our requirements

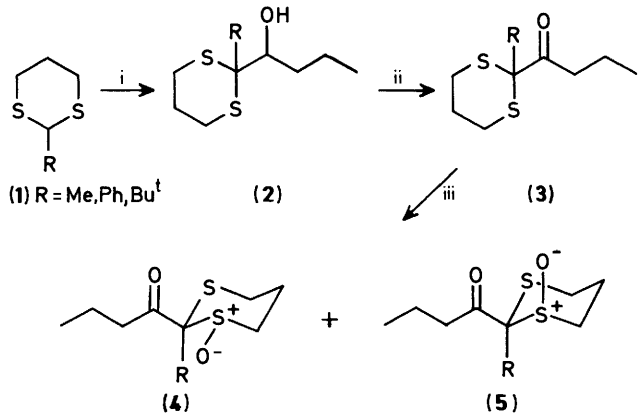


Scheme 1.

should be amenable to stereoselective preparation and should be readily removable. It should be inexpensive, stable, and easily prepared. Both enantiomers should be available and unfamiliar or experimentally difficult chemistry should not be involved. All these requirements are fulfilled by the 2-acyl-1,3-dithiane 1-oxide grouping, and our initial results in this area are presented below.

The 2-acyl-1,3-dithiane 1-oxide system is simple to obtain and may be prepared with high stereoselectivity. The 1,3-dithiane 1-oxide grouping may be removed under a variety of reaction conditions.[7] The sulphoxide unit might be expected to influence the transition state geometry of the enolate, perhaps by chelation to the metal counter ion, and hence control the stereochemistry of alkylation. Indeed, this controlling group has recently been employed for the resolution of racemic ketones.[8]

Our early studies have centred on the diastereoselective alkylation of racemic 2-acyl-2-alkyl-1,3-dithiane 1-oxide systems, prepared as shown in Scheme 2. Deprotonation of 2-



Scheme 2. *Reagents:* i, BuLi, THF, −78 °C; butanal; ii, DMSO, $(CF_3CO)_2O$, CH_2Cl_2, −50 °C; Et_3N; iii, $NaIO_4$

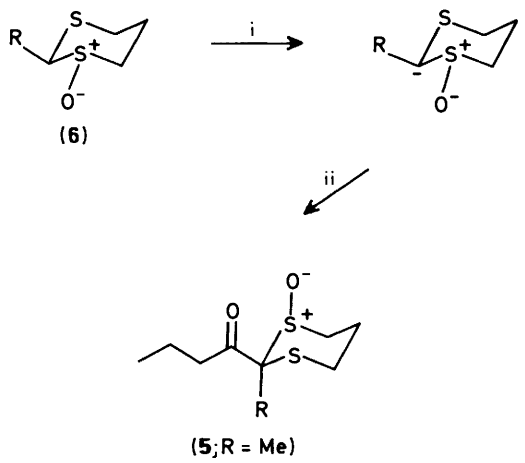
alkyl-1,3-dithianes (**1**) with butyl-lithium (1.1 equiv.) in tetrahydrofuran (THF) solution at −40 °C followed by acylation with butanal (1.1 equiv.) at −78 °C gave the alcohols (**2**) which were converted into the ketones (**3**) by the method of Swern.[9] Construction of the auxiliary was completed by mono-oxidation to the corresponding sulphoxides with sodium metaperiodate[10] (1 equiv.). The mixture of *syn*-(**5**) and *anti*-(**4**) 2-acyl-2-alkyl-1,3-dithiane 1-oxides was readily separable in each case by flash column chromatography on silica gel. This route gives convenient access to both types of diastereoisomers (**4**) and (**5**) in good yield and with diastereoselectivities ranging from 1:2 (R = Bu^t) to 3:1 (R = Ph).

Structural assignments of (**4**) and (**5**) were made by comparisons of ^1H n.m.r. and i.r. spectra with the products arising from direct acylation of *anti*-2-methyl-1,3-dithiane 1-

Table.

Entry	Substrate	Product type	Base	Temp. (°C)	Ratio of isomers
a	(**4**; R = Me)	7	LHMDS	−78	2:1
a	(**4**; R = Me)	7	KOBu^t	25	1:1.7
c	(**4**; R = Ph)	7	LHMDS	−78	2:1
d	(**4**; R = Ph)	7	KOBu^t	25	1:1.4
e	(**4**; R = Ph)	7	KHMDS	−78	1:1.3
f	(**5**; R = Me)	8	LHMDS	−78	23:1
g	(**5**; R = Me)	8	KOBu^t	25	1:1.2
h	(**5**; R = Me)	8	KHMDS	−78	1:1.1
i	(**5**; R = Ph)	8	LHMDS	−78	1:1
j	(**5**; R = Ph)	8	KOBu^t	25	1:1.7

oxide (**6**),* and by analogy with an alkylated material (**9**) the structure of which was solved by *X*-ray analysis (*vide infra*). Treatment of (**6**) with lithium di-isopropylamide (1 equiv.) in THF solution at −78 °C gave the configurationally stable anion[10] which reacted with ethyl butyrate exclusively to give (**5**; R = Me) in good yield (Scheme 3).



Scheme 3. *Reagents:* i, LDA, THF; iii, ethyl butyrate

Deprotonation of systems (**4**) and (**5**) to give the corresponding enolates was carried out typically using lithium (LHMDS) or potassium hexamethyldisilazide (KHMDS) (1.1 equiv.) in THF solution at −78 °C or potassium t-butoxide (1.1 equiv.) in THF solution at 25 °C for up to 30 min. The enolates were quenched at the reaction temperature with iodomethane or chlorotrimethylsilane followed by aqueous work-up using saturated aqueous ammonium chloride or sodium hydrogen carbonate. The crude products were directly analysed by ^{1}H n.m.r. spectroscopy. Yields of alkylated products (**7**) and (**8**) are generally near quantitative, simple rapid purification using a short silica-gel column being necessary in some cases. The product ratios for selected experiments are summarised in the Table.

Examination of trimethylsilyl enol ethers by ^{1}H n.m.r. spectroscopy at 250 MHz indicates that essentially one enolate is generated in each case irrespective of the base used or the temperature of action; we are as yet unable to assign the enolate stereochemistry.

We find that in all cases changing the counter ion from lithium to potassium results in a change in the sense of the

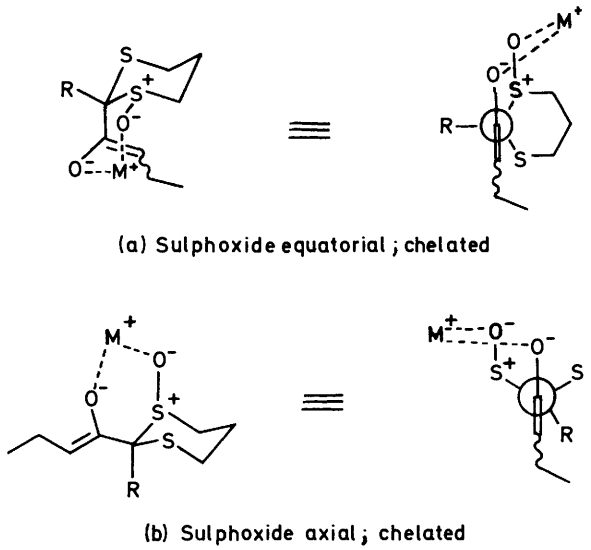
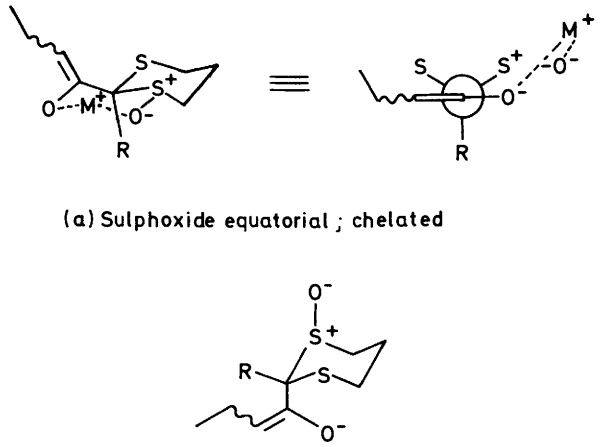


Figure 1. System 5



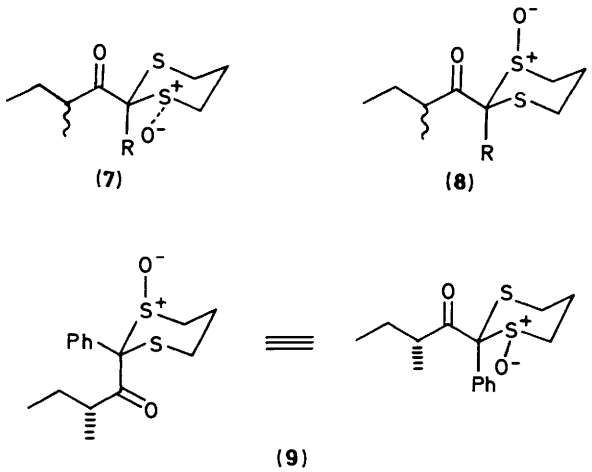


Figure 2. System 4

* Prepared by sodium metaperiodate oxidation of 2-methyl-1,3-dithiane followed by recrystallisation from diethyl ether–dichloromethane.[10]

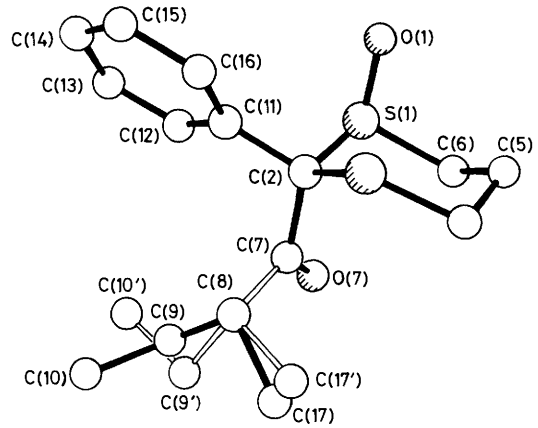


Figure 3. The molecular structure of (**9**) giving the crystallographic numbering scheme. The two different orientations of the ethyl and methyl substituents on C(8) are shown by heavy and open bonds. Selected bond distances (Å): S(1)–O(1) 1.480(3), S(1)–C(2) 1.875(3), S(1)–C(6) 1.808(4), S(3)–C(2) 1.808(3), and S(3)–C(4) 1.805(4)

preferred diastereoselection.[11] ^{1}H N.m.r. analysis of the derived trimethylsilyl enol ethers indicates that the same enolates are involved.

Thus, for example, for system (**5**) when R is small the diastereoisomeric ratio is high, at 23:1 (entry f), when lithium is the counter ion; this would be consistent with a chelated chair transition state, in which the sulphoxide occupies an equatorial position, and the bulky dithiane ring provides a much greater steric restriction than the methyl group (Figure 1a). When R is phenyl a more equally crowded transition state would be expected and indeed a ratio of *ca.* 1:1 is observed (entry i). When R is t-butyl no *C*-alkylation occurs, presumably due to steric hindrance, although some *O*-alkylation was detected by ^{1}H n.m.r. analysis. The alternative chair conformation (Figure 1b) in which the sulphoxide occupies the axial position would not be expected to produce any diastereoselection from inspection of open or closed transition states. With potassium as counter ion the diastereoselectivity is reversed and is generally poor and independent of temperature, perhaps consistent with a dipolar (open), less rigid, transition state geometry.[12]

For system (**4**) a chelated chair transition state would require R to be in an axial position and to provide the only steric bulk for any observed diastereoselectivity upon alkylation (Figure 2a). Indeed, when R is methyl only poor selectivity is obtained. However, as R becomes larger no improvement in selectivity is obtained, possibly due to a transition state geometry where R is in an equatorial position (Figure 2b). This would eliminate any chelation control and would provide little chance of any diastereoselectivity *via* the open transition state. Figure 3 depicts an *X*-ray crystal structure of the major product (**9**) from the reaction of (**4**; R = Ph), using lithium as the counter ion.* Such a structure would be consistent with a transition state as in Figure 2a, employing a *cis* enolate.

The results presented here provide a preliminary insight into the utility of these species and their potential as chiral auxiliaries. It is clear that the nature of the R substituent in the 2-position and the metal counterion have a crucial role to play in determining the stereochemistry of the transition state and the ensuing diastereoselection.

Acknowledgements

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* *Crystal Data*—$C_{15}H_{20}O_2S_2$, M = 296.5, monoclinic, a = 12.568(6), b = 8.718(3), c = 13.967(5) Å, β = 94.07(4), U = 1526 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.29 g cm^{-3}, μ(Cu-K_α) = 31 cm^{-1}, F(000) = 632. 2066 Independent reflections ($\theta \Sigma 58°$) were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. Of these 1944 had $|F_0| > 3\sigma(|F_0|)$ and were considered to be observed. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The ethyl and methyl substituents on C(8) are disordered and have been resolved into two discrete orientations, each of 50% occupancy. Refinement converged to give R = 0.067, R_w = 0.076 [$w^{-1} = \sigma^2(F) + 0.000\,50F^2$]. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See 'Instructions for Authors (1989),' *Perkin Trans. 1*, 1989, Issue 1.

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