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Asymmetric Oxidation of Dithiane Derivatives: Enantiomerically Pure 1,3-Dithiane 1-Oxide

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Abstract: Enantiomerically pure 1,3-dithiane 1-oxide may be efficiently prepared in either absolute configuration through a three-step procedure involving a catalytic asymmetric sulphur oxidation.

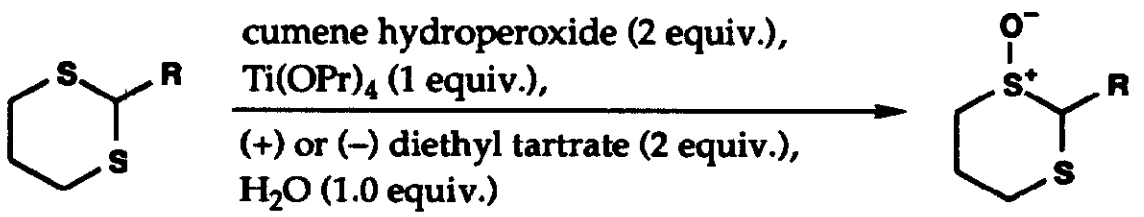
Enantiomerically pure sulphoxides have become very important asymmetric building blocks for enantioselective carbon-carbon bond formation, and a number of methods of varying effectiveness and generality are available for their preparation.[1] 1,3-Dithiane and its derivatives are ubiquitous acyl anion equivalents and are therefore valuable as synthetic intermediates,[2] but the corresponding sulphoxide, a chiral molecule, has seen little use in synthesis, and its potential as a chiral carbonyl group synthon[3] has until recently remained largely unexplored.

Over the last several years we have developed the use of 1,3-dithiane 1-oxides as highly effective chiral auxiliaries or asymmetric building blocks for various types of carbonyl group reactivity, including enolate alkylation,[4] nucleophilic addition,[5] reduction,[6] conjugate addition,[7] cycloaddition,[8] and Mannich reaction.[9] We have prepared the 2-acyl-1,3-dithiane oxide substrates with very high enantiomeric excesses by using the asymmetric sulphoxidation processes developed independently by Kagan and Modena.[10] We have also been able to prepare simple 2-substituted 1,3-dithiane oxides from the corresponding 2-acyl derivatives without loss of optical activity by using a simple deacylation process,[11] as the asymmetric oxidation is poor for 1,3-dithiane substrates with simple alkyl group substitution at C-2, the reaction perhaps requiring the presence of a dipolar grouping within the molecule for some crucial interaction with the reagent system for effective asymmetric induction, in common with the Sharpless epoxidation.

However, until recently we were not able to use this method for the preparation of unsubstituted 1,3-dithiane 1-oxide; while asymmetric sulphoxidation occurs readily for most 2-acyl-1,3-dithianes containing an additional 2-substitutent, no oxidation reaction takes place under our present conditions for several acyl dithianes retaining a proton at C-2. The commercially available 2-carboxyethyl-1,3-dithiane does undergo asymmetric oxidation in around 65% e.e. in our hands, but the monosulphoxide was not easily

crystallized to higher optical purity and did not undergo the necessary subsequent deacylation without decomposition. The 2-cyano derivative, prepared by us in 98% yield by treatment of the tetrafluoroborate salt of 1,3-dithiane[12] with trimethylsilyl cyanide in dichloromethane solution at –20 °C, a new route, was oxidized in at best 33% e.e. We were therefore pleased to discover that both the 2-benzoyl and 2-pivaloyl derivatives do undergo enantioselective sulphur oxidation to give the oxides as *syn/anti* mixtures in reasonable yields and with good to excellent enantiomeric excesses (Table I).[13]

Table I. Asymmetric Oxidation of 1,3-Dithiane Derivatives

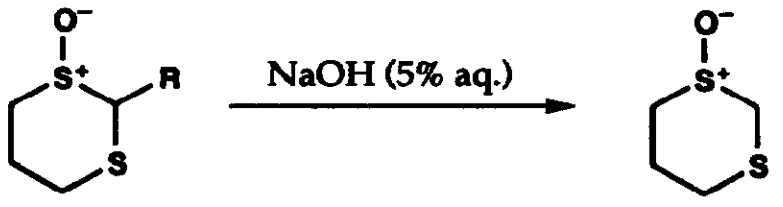


R	Solvent	Temp/°C	Yield/%	e.e.(*anti*)/%	e.e.(*syn*)/%	*anti*:*syn*	tartrate
acetyl	CH_2Cl_2	–20	0	—	—	—	
butyryl	CH_2Cl_2	–20	0	—	—	—	
1-naphthoyl	CH_2Cl_2	–20	0	—	—	—	
cyano	CH_2Cl_2	–20	75	33	33	1 : 1	(+)
CO_2Et	CH_2Cl_2	–20	66	65	65	3 : 1	(+)
benzoyl	CH_2Cl_2	–20	63	66	64	3 : 1	(+)
benzoyl	CH_2Cl_2	–20	60	73	72	3 : 1	(–)
benzoyl	toluene	–42	65	78	72	3 : 1	(–)
pivaloyl	CH_2Cl_2	–42	70	88	90	3 : 1	(–)
pivaloyl	CH_2Cl_2	–37	60	92‡	88‡	1 : 1	(–)
pivaloyl	toluene	–37	65	78	76	1 : 1	(–)

‡ One recrystallization leads to optical purity

Subsequent deacylation of the 2-benzoyl oxide to provide non-racemic dithiane oxide proceeded rapidly in high yield under our normal conditions,[11] but we did not find it possible to crystallize either dithiane oxide itself or the benzoyl derivative to higher e.e. Fortunately the 2-pivaloyl oxide was crystallized to optical purity from *ca.* 90% e.e. in one recrystallization.

Table II. Deacylation of 2-Acyl-1,3-Dithiane 1-Oxides



R	Solvent	Time/h	Yield/%	e.e.(s/m)	e.e.(prod)	*R*/*S*
benzoyl	CH_2Cl_2	1	79	72	72	*R*
benzoyl	CH_2Cl_2	1	80	78	78	*S*
pivaloyl	EtOH§	15	80	88	89	*S*
pivaloyl	EtOH§	15	78	100	100	*S*

§ Deacylation does not occur in dichloromethane

Finally the required deacylation of the recrystallized mixture of *syn* and *anti* *S*-(–)-2-pivaloyl-1,3-dithiane 1-oxides took place in ethanolic solution at reflux over about 15 hours without loss of optical activity at the sulphoxide sulphur atom to provide enantiomerically pure *S*-(–)-1,3-dithiane 1-oxide in 80% yield. Alternatively the unrecrystallized material could be deacylated in similar yields to provide *S*-(–)-1,3-dithiane 1-oxide with 89% e.e. and higher overall conversion (Table II). An experimental procedure is given below.

While 1,3-dithiane 1-oxide has been prepared previously in enantiomerically pure form by resolution and by diastereoselective oxidation of a D-(+)-camphor adduct of 1,3-dithiane followed by cleavage,[3] neither route is ideal for our purposes. We believe the route described here to be the first asymmetric synthesis of enantiomerically pure 1,3-dithiane 1-oxide using an achiral starting material and a chiral reaction medium, in our case a 'fourth generation' asymmetric synthesis.[14] It should further be noted that either optical antipode of 1,3-dithiane 1-oxide is available by appropriate choice of absolute configuration of the tartrate cofactor used in the asymmetric oxidation step; for example, as usual in these systems,[10] use of (–)-tartrate leads to isolation of the acylated *syn* and *anti* sulphoxides each containing the *S* configuration at the sulphoxide sulphur atom, and hence ultimately to *S*-(–)-1,3-dithiane 1-oxide. Examples of the use of each tartrate are given in table I.

Estimation of optical purity was carried out by ^{1}H nmr chiral shift reagent studies at 400 MHz using (*S*)-(+)- or (*R*)-(–)-*N*-(3,5-dinitrobenzoyl)-α-methyl benzylamine, or *S*-(+)- or (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle reagent). Stereochemical assignment to the *anti* or *syn* configuration in acylated materials was carried out by correlation of ^{1}H nmr spectra and chromatographic behaviour with those of compounds previously prepared in our laboratories in racemic form. In addition, X-ray crystallographic data is available for several of our compounds, both acylated and deacylated.

S-(–)-1,3-Dithiane 1-Oxide
Titanium tetraisopropoxide (0.73 ml, 2.45 mmol), D-(–)-diethyl tartrate (1.01 g, 4.90 mmol), and water (0.045 ml, 2.50 mmol) were added to dichloromethane (50 ml) at room temperature under an argon atmosphere, and the mixture was stirred until homogeneous (*ca.* 20 min). A solution of 2-pivaloyl-1,3-dithiane (0.50 g, 2.43 mmol) in dichloromethane (10 ml) was added using a cannula and the mixture cooled to –42 °C. Cumene hydroperoxide (80%, 1.00 ml, 5.41 mmol) was added and the mixture stirred for three days. The mixture was allowed to reach room temperature. 5% Aqueous sodium thiosulphate saturated with brine (5 ml) and 5% aqueous sodium hydroxide saturated with brine (5 ml) were added and the organic solution concentrated onto silica gel. The crude product was purified by flash column chromatography on silica gel to give a mixture of the sulphoxides in *ca.* 1 : 1 *anti* to *syn* ratio (0.38 g, 71%). Recrystallization from ether or ethanol provided a mixture of the sulphoxides in greater than 99% e.e. To a stirred solution of the recrystallized sulphoxide mixture (0.062 g, 0.28 mmol) in ethanol (5 ml) was added 5% aqueous sodium hydroxide (5 ml). The mixture was heated under reflux for 15 hours, evaporated to dryness, partitioned between aqueous ammonium chloride solution and dichloromethane, and the organic layer separated. The aqueous layer was further extracted with dichloromethane (3 x 20 ml) and the combined organic solutions dried over magnesium sulphate and evaporated to dryness *in vacuo*. The product *S*-(–)-1,3-dithiane 1-oxide was isolated as a colourless solid (0.030 g, 78%). $[\alpha]_D^{20}$ –210 (c = 0.97, CH_2Cl_2), confirmed as ≥98% e.e. by 400 MHz ^{1}H NMR studies.

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13. Mono-oxidation of 2-substituted 1,3-dithianes with sodium metaperiodate or MCPBA predominantly furnishes *anti* sulphoxide products. *Anti* isomers display a singlet in their ^{1}H NMR spectra at *ca.* δ 4.7 p.p.m. (2-pivaloyl species) or *ca.* δ 5.4 p.p.m. (2-benzoyl species), each corresponding to the 2-position ring proton. For *syn* substrates the corresponding signals appear at *ca.* δ 5.0 p.p.m. (2-pivaloyl species) or *ca.* δ 5.6 p.p.m. (2-benzoyl species).
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