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Stereoselective Addition Reactions of Lithiated 2-Chloro-1,3-Dithiane-1,3-Dioxide to Aldehydes

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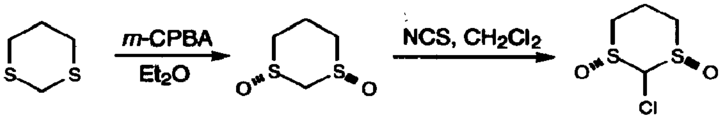
Abstract: *The lithium anion of 2-chloro-1,3-dithiane-1,3-dioxide reacts with aromatic aldehydes with 82:18 to 94:6 diastereoselectivity at the β-position.*

Chiral acid anions are potentially useful synthons for the preparation of homochiral α-substituted carbonyl compounds. Chiral nucleophilic acid anions have been reported; recent examples include a lactic acid derived vinyl lithium[1] and 1-chloroalkyl *p*-tolyl sulfoxide.[2] The former reagent requires very low temperatures to obtain good selectivity in addition reactions with aldehydes and the latter shows high α-selectivity but essentially no β-selectivity.[3] As the stereochemistry at the α-centre is usually destroyed upon removal of the sulfoxide and that at the β-centre retained, separation of the diastereoisomers or further transformations are required to obtain enantiomerically pure products.[4] We have studied the anion chemistry of 1,3-dithiane-1,3-dioxide **1** and found high β-diastereoselectivity in reactions with aromatic aldehydes.[5] We asked whether the 2-chloro analogue would show similar diastereoselectivity, or whether it would give low selectivity as in the case of Yamakawa's α-chlorosulfoxides.[3]

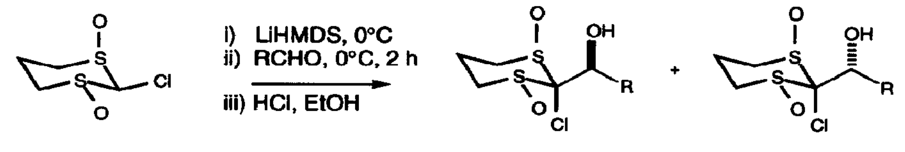
In this communication we report that 2-chloro-1,3-dithiane-1,3-dioxide **2** is indeed highly β-diastereoselective in reactions with aromatic aldehydes. The presence of the Cl- substituent allows further transformations not possible with dithiane dioxide, and greatly extends the potential of this chemistry in asymmetric synthesis.



1 52% **2** 57%

Chlorination at the 2-position of *trans*-1,3-dithiane-1,3-dioxide was achieved, without isomerisation of the sulfoxides, using N-chlorosuccinimide in CH_2Cl_2.[6-8] Deprotonation using LiHMDS and addition to benzaldehyde at -78°C led to the formation of adducts in a 73:27 ratio (3:4), and the reaction was found to be under kinetic control. When the reaction was carried out at 0°C, equilibration occurred and a 8:92 ratio (3:4) was obtained within 2 hours.

A variety of aldehydes were tried under these conditions, and the results are summarised in table 1. It was found that in general, reactions with aromatic aldehydes proceed in good yield with high diastereoselectivity at the β-position. The α-position is not a chiral centre due to the C_2 symmetric nature of dithiane dioxide. In reactions with aromatic aldehydes having electron withdrawing substituents (entry 2) the diastereoselectivity is lower than with electron donating substituents (entries 3, 4); however the proportion of addition products to recovered starting materials is higher (88% conversion of starting material for entry 2, entry 1 69%, entry 3 62%).



2 **3** **4**

Table 1: Summary of Results from Anion Reactions

Entry	Aldehyde	Ratio 3:4[a]	Isolated yield of isomer 4
1	C_6H_5CHO	8 : 92	62% (90%[b])
2	*p*-$NO_2C_6H_4CHO$	18 : 82	50% (55%[b])
3	*p*-$MeOC_6H_4CHO$	6 : 94	49% (71%[b])
4	3,4-$(MeO)_2C_6H_3CHO$	7 : 93	38% (62%[b])
5	*n*-C_4H_9CHO	51 : 49	[71% (81%[b])][c]
6	*i*-C_3H_7CHO	43 : 57	8% (13%[b])

a Ratios determined by ^1H NMR integration of crude reaction mixture
b Yields based on recovered starting material
c Combined yield of 3 and 4; diastereoisomers were inseparable by column chromatography

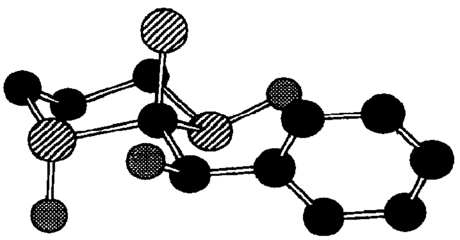
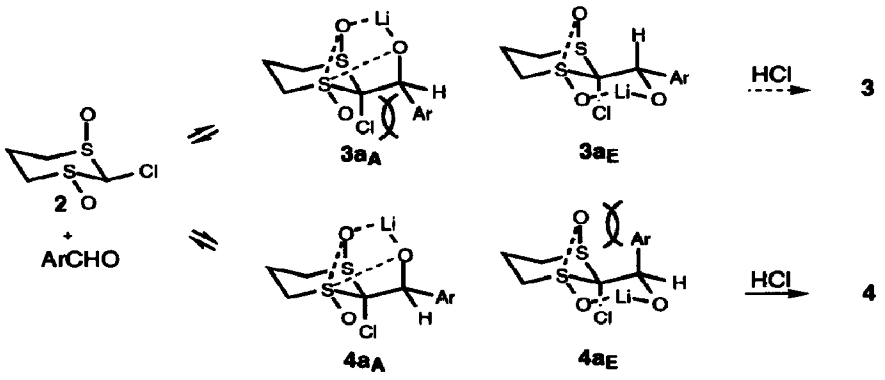


Figure 1: ORTEP diagram of isomer 4

The stereochemistry of isomer 4 was determined for entry 1 by X-ray crystallography.[9]

Reactions with aliphatic aldehydes under the same conditions were not as impressive; very poor selectivities were obtained with unhindered aldehydes, and poor yields with hindered ones. Similarly low diastereoselectivities with aliphatic aldehydes were observed in the anion chemistry of 1,3-dithiane-1,3-dioxide.[5]

In proposing a rationale for the stereochemical outcome of the reactions, only the two lithium alkoxides **3a** and **4a** need to be considered, as the reactions are under thermodynamic control. These alkoxides can each adopt two possible conformations (**3a**$_A$, **3a**$_E$, **4a**$_A$, **4a**$_E$) depending on whether chelation of the lithium counterion occurs with the axial or equatorial sulfoxide. The X-ray crystal structure of 1,3-dithiane-1,3-dioxide itself shows that the axial S-O bond is bent towards the equatorial sulfoxide, the O1-S2 distance being shorter than expected and the S2-S1-O1 angle being 81°.[10] This suggests the possibility of favourable dipole-dipole interactions from the axial sulfoxide to the equatorial sulfoxide. In our adducts, we suggest that chelation of the lithium counterion to the axial sulfoxide (**3a**$_A$, **4a**$_A$) allows two such dipole-stabilising interactions to occur and that this conformation is therefore favoured over chelation to the equatorial sulfoxide (**3a**$_E$, **4a**$_E$) where only one is possible. Of the two diastereomeric alkoxides **3a** and **4a**, isomer **4a** would then be preferred, as electronic repulsion between lone pairs of the equatorial sulfinyl oxygen and π electrons of the aryl group destabilises isomer **3a**. The destabilisation would be expected to be greater for electron rich Ar groups, which may help to explain the increased diastereoselectivity obtained in these cases (entries 3 & 4). The low selectivities observed with aliphatic aldehydes are also consistent with this hypothesis.



In conclusion, 2-chloro-1,3-dithiane-1,3-dioxide is readily prepared from dithiane and shows high selectivity at the β-position in reactions with aromatic aldehydes under equilibrating conditions.

We are currently investigating the further transformations of our addition products in order to determine the scope of this chemistry in asymmetric synthesis.

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7. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130-3136. Yamakawa's alkyl *p*-tolyl sulfoxides racemised on chlorination with NCS in CH_2Cl_2. He found that addition of K_2CO_3 caused the reaction to proceed more slowly and with inversion at sulfur, maintaining optical activity. We found that chlorination of *trans* dithiane dioxide occurred without isomerisation in the absence of K_2CO_3. The chlorinated product was exclusively *trans* and chlorination of the *cis* dioxide occurred much less readily, which suggests that *cis* dioxide is not an intermediate. No reaction occurred in the presence of K_2CO_3.
8. Drabowicz, J. *Synthesis* **1986**, 831-833. This communication states that the choice of solvent has a large effect on the reaction rate in the chlorination of sulfoxides using NCS. Our results were consistent with this; chlorination of dithiane dioxide was successful in CH_2Cl_2 but not in acetonitrile. Another solution to the problem of racemisation during chlorination of alkyl aryl sulfoxides is also provided; the reaction is carried out in the solid phase using silica gel as a support, and again proceeds with inversion at sulfur.
9. Crystal data for $C_{11}H_{13}S_2O_3Cl$; M =292.78, crystallises from chloroform/40-60 pet ether as clear oblongs; crystal dimensions 0.85 x 0.40 x 0.25 mm. Monoclinic, a = 10.540(3), b = 7.656(2), c = 16.212(4) Å, β =102.440(15)° U = 1277.5(6) $Å^3$, Z = 4, D_c = 1.522g cm^{-3}, space group $P2_1/c$ (C_{2h}^5 No.14), Mo-K_α radiation ($\bar{\lambda}$ = 0.71069 Å), μ(Mo-K_α) = 0.618 mm^{-1}, F(000) = 608. Three-dimensional, room temperature X-ray data were collected in the range $3.5 < 2\theta < 40°$ on a Nicolet R3 diffractometer by the omega scan method. The 1195 independent reflections (of 1800 measured) for which $|F|/\sigma(|F|) > 4.0$ were corrected for Lorentz and polarisation effects, but not for absorption. The structure was solved by direct methods and refined by full matrix least squares on F^2. Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final R=0.0337 (wR2=0.0853, 154 parameters, mean and maximum δ/σ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density -0.183 and 0.181e A^{-3}. A weighting scheme $w = 1/[\sigma^2(Fo^2) +(0.0565 *P)^2+0.27*P]$ where $P=(Fo^2+ 2 * Fc^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXTL93 as implemented on the Viglen486dx computer.
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