Synthesis, X-Ray Crystal Structure, Equilibration Studies and Anion Chemistry of *trans*-1,3-Dithiane 1,3-Dioxide

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trans-1,3-Dithiane 1,3-dioxide, prepared by stereoselective oxidation of 1,3-dithiane has been found to be thermodynamically more stable than the *cis*-isomer by equilibration studies using N_2O_4 and has been found to undergo highly selective (20:1) aldol type reactions with benzaldehyde.

1,3-Dithiane is a very useful synthon in organic synthesis since it represents a masked carbonyl group with umpolung reactivity.[1] Its importance in synthesis has prompted a number of conformational and synthetic studies of substituted dithianes[2] and dithiane S-oxide.[3,4]

Substituted dithianes without a mirror plane (*e.g.* 4,4,6-trimethyl-1,3-dithiane 1) and dithiane S-oxide 3 are chiral and, therefore, their corresponding 2-metallated moieties represent chiral formyl anion equivalents. In practice it has proved difficult to separate the diasteroisomers 2 that result from reactions of 1 with aldehydes[5] and little is known about the stereochemical course of the addition of 3 to aldehydes.[6] One of the problems associated with these systems is that two new chiral centres are created in the reaction resulting in four possible diastereoisomeric products and this gives rise to difficulties in analysis and separation. However, if the chiral dithiane moieties possessed C_2 symmetry only one new chiral centre would be created in its addition reactions with aldehydes, resulting in only one pair of diastereoisomers. This would greatly simplify analyses of product mixtures. In order to test the feasibility of this idea we decided to prepare substrate 5 and also more lipophilic analogues 6,7. These compounds are potential formyl anion equivalents and in light of recent reports in this area[7] we present our own initial studies.

5,5-Disubstituted 1,3-dithianes 12,13 were prepared as shown in Scheme 1. The starting diols 8,9 were converted into the dithiols[8]

1   2   3   4

R = Me 6
R = Et 7

5
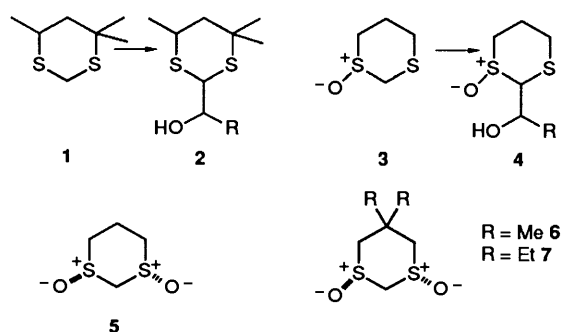
10,11 which were, in turn, converted into the corresponding 1,3-dithianes[9] 12,13.

1,3-Dithiane has been oxidised with MCPBA to furnish the *cis* dioxide 14[10] in low yield. No indication of the relative ratio of *cis* and *trans* dioxides was given and so we repeated this reaction. Other oxidising agents were also tried and the results are summarised in Table 1.

Of all the oxidants, $NaIO_4$ was found to be the most selective for 1,3-dithiane, whilst ozone was most selective for 5,5 disubstituted 1,3-dithiane in favour of the required *trans* diastereoisomer. It has been suggested that the stereochemistry of periodate oxidations is governed by product development

R = Me **8**
R = Et **9**

10 38%
11 48%

12 100%
13 100%

14
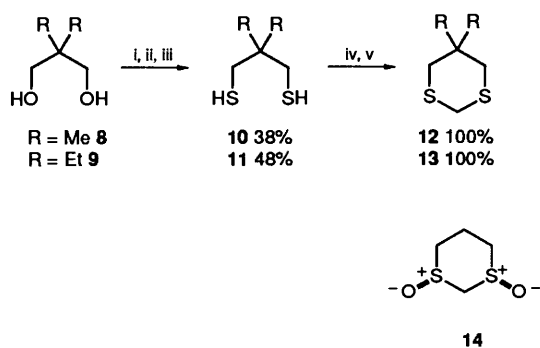
Scheme 1 Reagents and conditions: i, MsCl, py; ii, Na_2S, S, DMF; iii, $LiAlH_4$, Et_2O; iv, $(MeO)_2CH_2$; v, $BF_3 \cdot OEt_2$
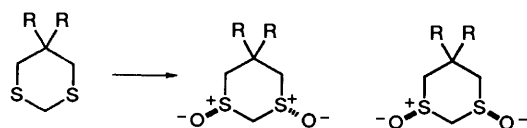
Table 1

	R = H trans:cis	R = Me, Et[a] trans:cis
MCPBA, CH_2Cl_2	-78 °C	45:55 (26% cis[b])	23:77
H_2O_2, CH_2Cl_2	0 °C $\longrightarrow$ RT	78:22	27:73
$NAIO_4$, MeOH	50 °C	86:14 (58% trans[b])	20:80 (60% cis[b])
Ozone, MeOH	-78 °C	57:43	58:42 (35% trans[b,c])
Bu^{t}OCl[d]	0 °C	0[e]	0[e]

[a] Both dimethyl and diethyl substituted dithianes gave similar results. [b] Isolated, recrystallised yields. [c] Based on recovered monosulphoxide (29%). [d] Literature data[11] suggested that this reaction would give highest ratios of the required trans dioxide. [e] Attempted oxidation of dithiane and dithiane S-oxide caused decomposition.

control[11] and the high selectivity for the trans isomer **5*** suggest that this isomer is thermodynamically more stable than the cis isomer **14**.

Attempted equilibration studies with HCl–dioxane[13] or heat[14] on trans and cis dithiane dioxides **5**,**14** caused only decomposition. However, equilibration could be effected using N_2O_4[15] and the results obtained are shown in Table 2. N_2O_4 forms a 1:1 addition complex with sulphoxides and so equilibration studies with N_2O_4 can only give thermodynamic ratios of the sulphoxide–N_2O_4 complex.[16] However, the results obtained using N_2O_4 are often closely related to thermodynamic ratios obtained by other means.[16] A further complication in the analysis of these results was the observation of slow formation of the sulphoxide–sulphone **15**, possibly via disproportionation of the bis sulphoxide to the sulphide–sulphone[17] followed by oxidation. Nevertheless, the results obtained show that the trans dioxide **5** is thermodynamically more stable than the cis isomer **14**. This finding was corroborated using molecular mechanics

* High stereoselectivity for the trans dioxide during periodate oxidation of 1,3-dithiolane monosulphoxide has been observed.[12]
† Compound **5** crystallised (methanol) in space group $P2_1/a$ with $a = 8.026(2)$, $b = 8.415(2)$, $c = 9.789(1)$ Å, $\beta = 97.52(1)°$ and $D_{calc} = 1.54$ g cm^{-3} for $Z = 4$. Data were collected at room temperature on a Hilger and Watts Y290 diffractometer. The structure was solved using 893 unique reflections with $I > 3\sigma(I)$, and refined to a final $R = 5.78%$ for unit weights.
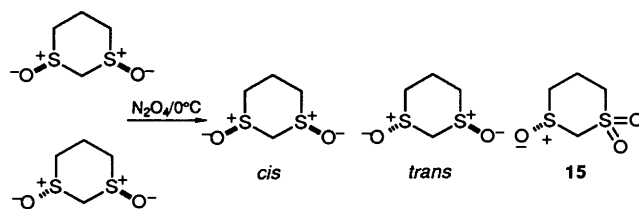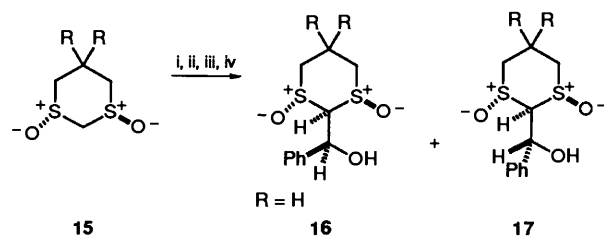

Table 2

| Time	cis:trans:15
0 min	100:0:0
35 min	87:5:8
9 h	34:56:10
18 h	23:59:18
72 h	0:59:18
0 min	0:100:0
35 min	12:86:2
9 h	12:84:4
72 h	8:74:18

R = H
15
16
17

| R = H | Solvent = py / THF (1.5:1) | 5 : 95 (87%) |
| R = Et | Solvent = THF | 8 : 92 |

Scheme 2 Reagents and conditions: i, solvent; ii, NaHMDS, 0 °C; iii, PhCHO, 0 °C; iv, 2M HCl (0.2 ml) in EtOH

calculations[18] and the trans sulphoxide was 0.8 kcal mol^{-1} more stable than the cis isomer.

The enhanced stability of the trans isomer is thought to arise from a favourable dipole–dipole interaction between the two sulphoxide groups and evidence for this effect is found in the X-ray crystallographic analysis of **5**† which reveals a distortion of the axial sulphinyl oxygen towards the equatorial sulphoxide. The calculations successfully reproduced this X-ray crystal structure including the bending of the axial sulphoxide towards the equatorial sulphoxide.

ORTEP view of **5**
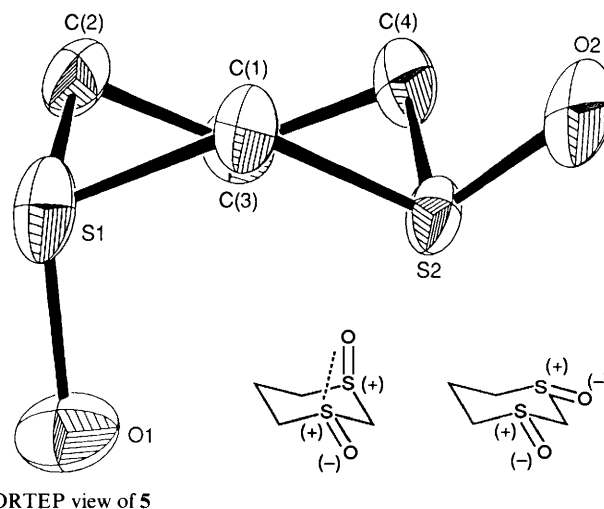
As expected, **5** was much more polar than **7** and only soluble in very polar solvents, whereas **7** was soluble in THF. Preliminary results showed that the sodium anion of **5**, suspended in pyridine–THF (1.6:1),[19] reacted with benzaldehyde to give a 5:95 ratio of diastereoisomers. Similarly, the sodium anion of **7** in pure THF reacted with the same aldehyde to give a similar ratio of diastereoisomers. In both cases the reaction was under thermodynamic control. At −78 °C, the reaction was under kinetic control and only gave a 2:1 ratio of diastereoisomers. The origin of this remarkably high selectivity under thermodynamic conditions and the scope of the reaction are under current investigation.

Experimental

trans-1(RS)-3(RS)-1,3-*Dithiane* 1,3-*Dioxide* **5**.—1,3-Dithiane (15 g, 0.12 mol) was suspended in methanol (410 ml) and water (40 ml). To this was added sodium periodate (66.7 h, 0.31 mol) and the suspension stirred at room temperature for 96 h. Dimethyl sulphide (8.7 ml, 0.12 mol) was added, stirring continued for 0.5 h before the solvents were evaporated under reduced pressure. The resulting white solid was filtered through a short pad of silica gel with acetone–ethanol (5:1) as eluent and fractions containing the *cis* and *trans* isomers were combined. After evaporation the mixture was purified by flash chromatography using acetone as eluent and recrystallisation of the *trans* isomer from methanol gave the *dioxide* as colourless blocks (11.2 g, 58%) m.p. 170–171 °C, R_f(acetone) 0.2; ν_{max}(Nujol)/cm^{-1} 1300, 1210 and 1040–1000s (S–O); δ_H(DMSO)* 4.35 (2 H, s, 2-H), 3.21 (2 H, ddd, J 12.9, 6.4 and 5.9, 4-Heq and 6-Hax), 2.96 (2 H, ddd, J 12.9, 6.0 and 5.1, 4-Hax and 6-Heq) and 2.38 (2 H, tt, J 6.4 and 5.3, 5-H); δ_C(DMSO) 61.6 (C-2), 47.5 (C-4 and C-6) 14.9 (C-5); m/z (EI) 152 (20%, M$^+$), 103 (M–SOH), 90 (20, $C_3H_6SO^+$), 73 (30), 63 (30) and 41 (100, $C_3H_5^+$) (Found: C, 31.6; H, 5.3. $C_4H_8O_2S_2$ requires C, 31.7; H, 5.46%).

1(α-RS,1'-RS,3'-RS)-α-(1',3'-*Dithian-2-yl)benzyl Alcohol* S', S'-*Dioxide*.—Compound **5** (0.1 g, 0.657 mmol) was dissolved in pyridine (5 ml) with warming and the solution diluted with THF (3 ml) before cooling to 0 °C, under nitrogen. To this was added a solution of NaHMDS in THF (1.0 mol dm^{-3}; 0.99 ml, 0.99 mmol). Stirring was continued at 0 °C for 30 min. An excess of benzaldehyde (0.1 ml) was then added in one portion. Stirring was continued for 30 min at 0 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (15 ml) and aqueous HCl (2 mol dm^{-3}; 1.6 ml, 3.2 mmol) at 0 °C. The mixture was evaporated under reduced pressure and the resulting white solid recrystallized from ethanol to give a colourless solid **9a** (0.13 g, 77%). The mother liquor was then subjected to flash chromatography on silica gel eluting with 90–100% acetone–petroleum to afford **17** which was recrystallized from ethanol to give the *adduct* as colourless needles (0.017 g, 10%). Total yield of **17** 0.147 g (87%), m.p. 187–188 °C; R_f(acetone 0.25; ν_{max}(Nujol)/cm^{-1} 3200 (OH), 1045 and 1010 (SO); δ_H(DMSO) 7.5–7.25 (5 H, m, Ph), 6.07 (1 H, d, J 4.3, OH), 5.49 [1 H, br t, J 4.4 (α-H/2'-H), 4.3 (α-H/OH) α-H], 4.16 [1 H, d, J 4.3 (2-H/α-H) 2'-H], 3.53 [1 H, ddd, J 12.0 (4'-Heq/4'-Hax), 4.8 (4'-Heq/5'-Heq), 1.5 (4'-Hax/5'-Hax) 4-Heq], 3.09 [1 H, ddd, J 12.0 (4'-Hax/4'-Heq), 12.0 (4'-Hax/5'-Hax), 2.3 (4-Hax/5-Heq) 4'-Hax], 3.0–2.6 (2 H, m, 6'-Heq and 6'-Hax), 2.55 (1 H. m, 5'-Hax) and 2.22 (1 H, m, 5'-Heq); δ_C(DMSO) 141.5 (–C–, Ar),

128.4 (2 × CH, Ar), 127.7 (–C–, Ar), 126.7 (2 × CH, Ar), 79.0 (CH, C-2), 67.8 (CH, α-C), 51.5 (CH$_2$, C-4 or C-6), 45.9 (CH$_2$, C-4 of C-6), 15.3 (CH$_2$, C-5); m/z (ci) 259 (10%, M + 1), 153 (50, $C_4H_8O_2S_2$ + 1) and 107 (100, PhCHOH$^+$).

Note added in proof. Since submission of this manuscript a report on the oxidation of 1,3-dithiane with MCPBA and NaIO$_4$ to give the corresponding *cis* and *trans* 1,3-dioxides has appeared. Crystal structures of these dioxides were also reported (S. Bien, S. K. Celebi and M. Kapon, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1987). However the results reported for the oxidation experiments are different from ours and having double checked our results we confirm that they are correct. We have noted that further oxidation of the 1,3-dioxides is possible under the reaction conditions and that the *cis* dioxide oxidises at a faster rate than does the *trans* dioxide. Hence *cis:trans* ratios are potentially variable depending on the extent of over oxidation.

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* *J* Values in Hz.