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Studies on the formation of a tricyclic C_2-symmetric sulfide

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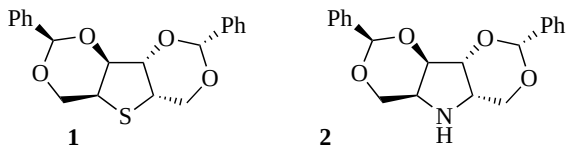
Abstract—Attempts to synthesise chiral sulfide **1** from the dimesylate precursor **5**, via a cyclisation reaction using sodium sulfide in dimethyl sulfoxide, led to the unexpected formation of an unsymmetrical furan derivative **8**. Studies were made into the effect of changing the leaving group, and changing the solvent of reaction. The desired compound could be synthesised in good yields from the xanthate **9** using a radical-mediated procedure.

Compound **1** was the target molecule in a study of chiral sulfur compounds, which have been shown to be useful in asymmetric synthesis,[1] and was related to the C_2-symmetric polyhydroxylated pyrrolidine (**2**), the synthesis and potential applications of which have been reported in the literature[2] (Fig. 1).

The synthetic route towards **1** initially involved dibenzylidene protection of D-mannitol **3** followed by mesylation of the resulting diol, **4**. Dimesylate **5** was then expected to undergo cyclisation via an S_N2 substitution reaction in the presence of sodium sulfide nonahydrate, with inversion occurring at each reacting centre to afford the enantiopure compound **1**.

Acetal formation was based on the method of Baggett and Stribblehill,[3] although it was shown that the yield could be improved to give 86% product without loss of selectivity on increasing the reaction time to 5 days (after 3 days, as described in the literature, the yield was approximately 50%). Mesylation also proceeded in good yield (82% after 16 h) but cyclisation using sodium sulfide nonahydrate in dimethyl sulfoxide at 80°C for 16 h afforded a compound in 43% yield, and approximately 20% of the starting material. This new compound had an ^{1}H NMR spectrum similar to that expected for **1**, except that some of the peaks were doubled, showing that it was not symmetrical.



1 **2**

Figure 1.

The unsymmetrical nature of the product could have been due to epimerisation at one of the benzylidene acetal centres. However, DIBALH reduction of the benzylidene acetals afforded an unsymmetrical product, as did reduction of the analogous *para*-methoxybenzylidene acetals, which were prepared by a similar route. Therefore, it could be concluded that epimerisation had not occurred in this position, but that there had been a retention of stereochemistry at one of the carbon centres adjacent to the mesylate during the cyclisation reaction.

Mass spectrometry and elemental analysis showed that the compound was not an unsymmetrical thiophene derivative, but a furan derivative, **8**, in which there had been retention of configuration at one of the stereocentres adjacent to the oxygen in the five-membered ring (Scheme 1).

Full NMR characterisation[4] showed that the product was furan derivative **8** in which the stereochemistry at one of the carbon centres adjacent to the oxygen had undergone inversion, while the other had retained its stereochemistry. It was shown that sodium sulfide nonahydrate was necessary for this reaction to occur; when the reaction was repeated in the absence of the sulfide, the starting material was recovered in near quantitative yield. It is proposed, therefore, that the mechanism of reaction involves attack of the sulfide anion onto the sulfur atom of the mesylate, leaving an oxygen anion which can undergo intramolecular attack onto the carbon atom bearing the second mesylate group in an S_N2 fashion.

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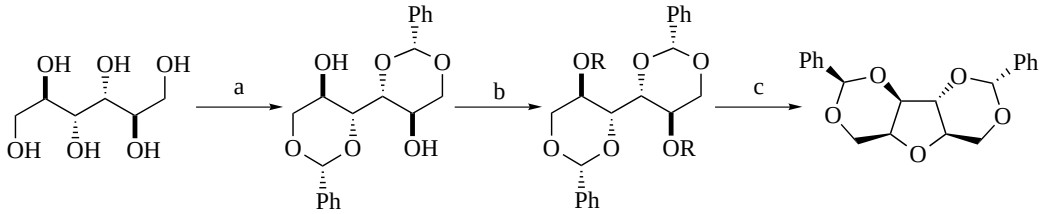


Scheme 1. *Reagents and conditions*: (a) PhCHO, DMF, H_2SO_4, rt, 120 h (86%); (b) either: Et_3N, DCM, MsCl, 0°C, 16 h (82% of **5**); or: TsCl, Py, rt, 16 h (70% of **6**); or: Tf_2O, Py, THF, rt, 16 h (62% of **7**); (c) $Na_2S{\cdot}9H_2O$, DMSO, 80°C, 16 h (43% from **5**, 51% from **6**, 6% from **7**).

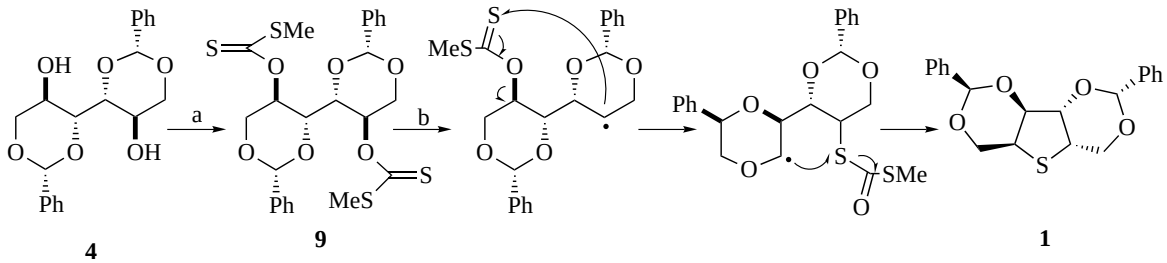
Investigations were then carried out to see whether different leaving groups resulted in the formation of the same product. The corresponding ditosylate (**6**)[3] and ditriflate (**7**)[5] were prepared according to literature methods, and cyclisation afforded the same unsymmetrical product, **8**, in 51% and 6% respectively, with none of the expected compound, **1**.

Solvent effects were also examined. Cyclisation of the mesylate was carried out in a 9:1 mixture of ethanol:*iso*-propanol at 80°C for 16 h, and afforded the unsymmetrical furan compound in 67% yield. On heating with sodium sulfide in dimethylformamide at 150°C for 40 h, it was possible to isolate the desired sulfide, **1**, in 10% yield, recovering approximately 40% of the starting material. The harsh reaction conditions led to decomposition of the starting material with some benzaldehyde being recovered from the reaction mixture.

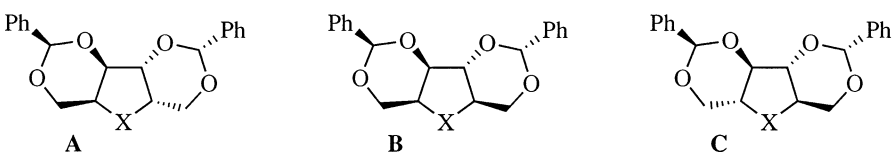
The sulfide, **1**, could be synthesised by a radical-mediated route from the xanthate using tributyl tin hydride in toluene with α,α-diazoisobutyronitrile as an initiator, following the method of Rama Rao.[6,7] The xanthate could be prepared in excellent yields (90%) from the dibenzylidene acetal. This reaction affords a single C_2-symmetric, diastereomeric product in which there is inversion at each of the carbon centres adjacent to the sulfur atom (Scheme 2).

MacroModel MM2* calculations[8,9] showed that the symmetrical sulfide, **1**, was the thermodynamically preferred diastereoisomer (Fig. 2, structure **A**), and this may explain the single diastereomeric product from the radical cyclisation. The global minimum conformation of **1** is shown in Fig. 3.

The tetrahydrofuran diastereoisomer which formed, **8** (Fig. 2, structure **B**), was of a much higher energy than the symmetrical diastereoisomer, and so cannot form under thermodynamic control. The strain energies in the sulfides, relative to tetrahydrothiophene, are higher than in the furans, relative to tetrahydrofuran, for diastereoisomers **A** and **B**.



Scheme 2. *Reagents and conditions*: (a) NaH, THF, CS_2, MeI, rt, 19 h (90%); (b) Bu_3SnH, AIBN, toluene, 80°C, 16 h (78%). The modified Barton–McCombie mechanism illustrated is based on that described in Rama Rao's papers.[6,7]



	X = *S*	*X* = *O*
A	0.00	-42.05
B	9.77	1.54
C	17.68	26.00

All energies in kJ mol^{-1}

For X=S, energy relative to **A**. For X =O, energy relative to **A**, plus the energy of tetrahydrofuran, minus the energy of tetrahydrothiophene.

Figure 2. Energies of the diastereomers.

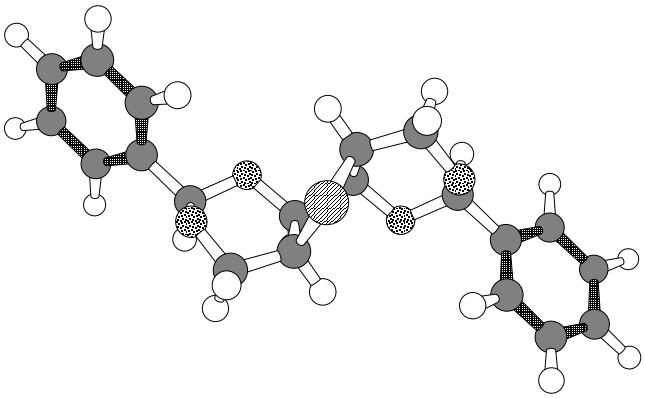


Figure 3. Global minimum conformation of **1**.

Acknowledgements

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4. Data for compound **8**: $[\alpha]_D$ −106.8 (*c* 0.81, $CHCl_3$); mp 133–135°C; ^{1}H NMR (C_6D_6, 400 MHz): δ (4H, dd, J= 7.3, 1.4, PhH), 7.31–7.21 (6H, m, PhH), 5.48 (1H, s, OCHOPh), 5.30 (1H, s, OCHOPh), 4.47 (1H, t, J=6.4, CHO), 4.35 (1H, dd, J=4.5, 9.6, H_{eq}O), 4.11 (1H, dd, J=4.4, 12.1, H_{eq}), 3.99 (1H, dd, J=6.0, 9.7, CHO), 3.81 (1H, dd, J=5.1, 12.1, $CH_{ax}O$), 3.66–3.60 (2H, m, CH_{ax}, CHO), 3.39 (1H, td, J=4.5, 9.9, CHO); ^{13}C NMR (C_6D_6, 400 MHz): δ 139.5, 137.8, 128.8, 128.7, 128.2, 128.0, 126.6, 126.2, 102.4, 98.1, 87.3, 75.9, 73.8, 70.9, 70.8, 65.0; HRMS (+EI) calcd for $C_{20}H_{20}NaO_5$: 363.1209; found: 363.1208 (MNa^+). Elemental analysis found: C, 70.39; H, 5.87. $C_{20}H_{20}O_5$ requires: C, 70.56; H, 5.93%.
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