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Synthesis of chiral β-disulfoxides and their racemization with strong bases

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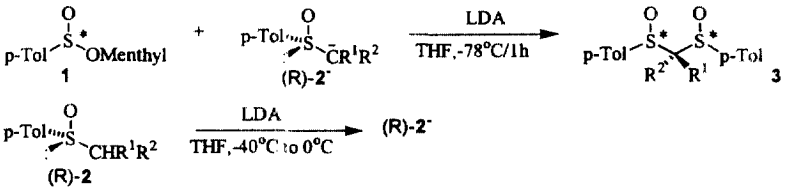
Abstract: β-Disulfoxides can be obtained from different α-sulfinylcarbanions and sulfinates. While α-unsubstituted and monosubstituted β-disulfoxides are configurationally stable in the presence of strong bases, α,α-disubstituted β-disulfoxides epimerize through an intermolecular mechanism. © 1997 Elsevier Science Ltd

Acyclic β-disulfoxides are readily available from sulfinic esters and α-sulfinyl carbanions.[1] These organosulfur compounds are interesting in asymmetric synthesis since they can be used as 1,3-dithiane-1,3-dioxide anions[2] as well as C2-symmetric chiral ligands which carry their chirality in the co-ordinating atom itself.[3] The synthesis of β-disulfoxides has only been accomplished by reacting sulfinates and nonhindered α-sulfinyl carbanions (e.g. **2a**) derived from the corresponding methyl-substituted sulfoxides. In these cases, the reaction proceeds with a full inversion of configuration at the sulfur atom, similar to that which usually occurs in the nucleophilic substitution reaction of sulfinic esters. In view of the utility of β-disulfoxides in asymmetric synthesis, we decided to study the synthetic potential of the reaction of some α-sulfinyl carbanions $\mathbf{2}^-$ with sulfinates **1** with regard to the synthesis of mono- and disubstituted β-disulfoxides in the α position (Figure 1). The preparation of such compounds has been reported previously through the methylation of (S,S)-**3a**, but this procedure is obviously limited to the introduction of alkyl substituents and, in practice, only methyl groups can be incorporated.[3h]



1	(R)-2[4]			3				
	R^1	R^2	comp	comp.	(SS)-%	(RR)-%	*meso*	method
(S)-	H	H	**a**	**a**	87[a]	-	-.	A
(S)-	H	CH_3	**b**	**b**	80	-	-	A
(S)-	CH_3	CH_3	**c**	**c**	12[b]	7[b]	56	A
(R)-	CH_3	CH_3	**c**	**c**	9[b]	9[b]	56	A
(S)-	CH_3	CH_3	**c**	**c**	59	20	-	B

[a]Yield given in reference 1. [b]Enantiomer ratio determined by En(hfc)

Figure 1. [4]

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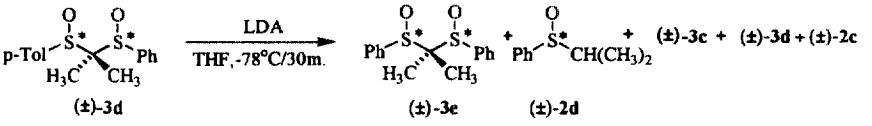
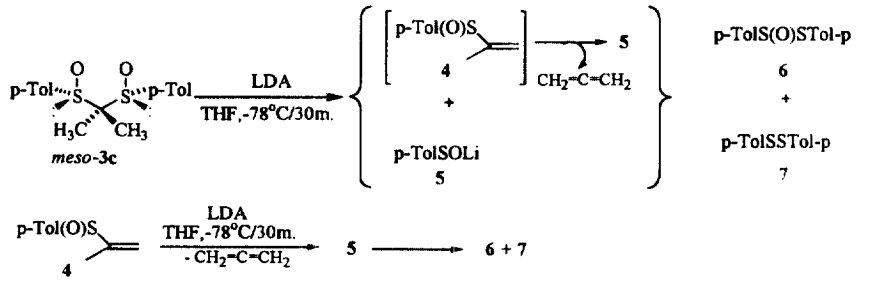
Sulfinate (S)-**1** underwent stereoinvertive conversion with (R)-**2b**$^-$ to give (S,S)-**3b** in 80% yield. Although compound (S,S)-**3b** can be obtained, in two steps, by methylation from commercially available (R)-**2a**, the high cost of (R)-**2a** suggests that it also should be synthesized, and an additional step is then required in the sequence [(S)-**1**→(R)-**2a**→(S,S)-**3a**→(S,S)-**3b**]. On the other hand, using our method, (S,S)-**3b** can be obtained from (S)-**1** in two steps with an overall yield of 73%. When this reaction was performed with (R)-**2c**$^-$ and the sulfinate (S)-**1** under the same conditions (procedure A), (S,S)-**3c** was obtained along with the unexpected stereoisomers *meso*-**3c** and (R,R)-**3c**. A similar result was observed when (R)-**2c**$^-$ was reacted with (R)-**1** (Figure 1). In view of this unprecedented result, we focused our attention on studying the apparent anomalous behaviour of (R)-**2c**$^-$. In a control experiment, (R)-**2c**$^-$ was found to be configurationally stable in basic medium. Thus, our results may be a consequence of either a different reaction mechanism in the reaction of (R)-**2c**$^-$ with sulfinates (S)-**1** and (R)-**1**, or the epimerization of disulfoxides **3c** under basic conditions (0.5 eq excess of LDA is used in procedure A to ensure the total deprotonation of sulfoxide **2c**).

To test the latter hypothesis, *meso*-**3c** was treated with LDA to give a mixture of the three stereoisomers, which is evidence of the epimerization of α,α-disubstituted β-disulfoxides in the presence of LDA. A feasible explanation is that free (±)-**2c**$^-$ promotes the epimerization of **3c** by a sequential addition–elimination mechanism. The free anion (±)-2c$^-$ could be generated by nucleophilic attack of LDA to **3c** to give the corresponding σ-sulfurane,[5] which decomposes to (±)-**2c**$^-$ and N,N-diisopropyl-p-toluenesulfinamide. In fact, the presence of a small amount of (±)-**2c** was detected in the crude reaction mixture by TLC and ^{1}H NMR. To obtain further evidence for this mechanism, we prepared disulfoxide (±)-**3d** from sulfoxide (±)-**2d** and sulfinate (±)-**1**. When disulfoxide (±)-**3d** was treated with LDA (Equation 1), a mixture of (±)-**3c**, (±)-**3d** and (±)-**3e** was obtained in addition to small amounts of (±)-**2c** and (±)-**2d**, which supports the notion that epimerization occurs by the postulated intermolecular mechanism. Moreover, LDA promotes the decomposition of disulfoxide **3c** to give thiosulfinate **6**, disulfide **7**, the formation of which can be explained through the intermediate sulfenic acid generated by elimination, and the olefin **4**, which could not be isolated. In a separate experiment, olefin **4** was synthesized[6] and allowed to react with LDA, which led to thiosulfinate **6** and disulfide **7** as isolable products, most probably through an elimination to give propadiene and sulfenic acid.[7] (Scheme 1)



Equation 1



Scheme 1.

Similar results were obtained when BuLi was used to generate (R)-**2c**$^-$. In this case, di-p-tolylsulfoxide[8] was isolated in addition to the above-mentioned products. Conversely, in the presence of weaker bases such as menthoxide or thiolate anions, disulfoxide **3c** was stable and neither epimerization nor elimination products were observed.

Thus, to obtain **3c** as a single stereoisomer, the presence of unreacted carbanion or other strong bases must be avoided to prevent epimerization and elimination reactions. Inverse addition was carried out (procedure B) using two equivalents of the sulfinate. Under these conditions, (S,S)-**3c** was obtained as the main product and *meso*-**3c** was a byproduct. The formation of *meso*-**3c** in the inverse addition, i.e., with an excess of sulfinate and a low concentration of (R)-**2c**$^-$, could indicate that the reaction of (R)-**2c**$^-$ and (S)-**1** does not proceed with a full inversion of configuration. In fact, the reaction of hindered Grignard reagents with sulfinates proceeds either with a retention of configuration[9] or with predominant inversion.[10]

Based on these results, it is clear that the synthesis of α,α-disubstituted **3c** requires special care to avoid the presence of both unreacted sulfoxide **2c** and LDA. Conversely, with unsubstituted **3a** or α-monosubstituted disulfoxides **3b**, no side reactions occur in the presence of the starting anion or free base, most likely because deprotonation of the α position prevents the nucleophilic attack at sulfur.

Experimental section

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument using $CDCl_3$ as a solvent. Melting points were determined with a Cambridge Instruments apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a Fisons VG Autospec instrument.

Reaction of (R)-2b and (R)-2c with sulfinates (S)-1 and (R)-1. — General procedure A

To a solution of freshly prepared LDA (2.5 mmol) at −40°C was added dropwise the appropriate sulfoxide (2 mmol) in THF (2.5 ml), and the temperature was allowed to reach 0°C. The reaction mixture was then cooled to −78°C, and a solution of the appropriate sulfinate (2 mmol) in THF (5 ml) was added. The solution was allowed to stand for 1 h with stirring at the same temperature, and then quenched with saturated NH_4Cl solution and extracted with AcOEt.

(S,S)-**3b** (Procedure A). Yield: 80%; m.p.: 115–117°C; $[\alpha]_D^{22}$=+216 (c=1, acetone); ^{1}H NMR δ 1.10 (d, 3H, J=7.0 Hz), 2.40 (s, 3H), 2.43 (s, 3H), 3.55 (q, 1H, J=7.0 Hz), 7.64–7.27 (m, 8H); ^{13}C NMR δ 4.0, 21.3, 21.5, 85.0, 124.1, 125.3, 130.0, 130.1, 137.7, 138.4, 141.7, 142.9.

meso-**3c** (Procedure A). Yield: 56%; m.p.: 131°C; ^{1}H NMR δ 1.02 (s, 3H), 1.46 (s, 3H), 2.44 (s, 6H), 7.35 (d, 4H, J=7.5 Hz), 7.59 (d, 4H, J=7.5 Hz); ^{13}C NMR δ 12.6, 13.6, 21.5, 79.7, 126.3, 129.6, 134.9, 142.7.

(S,S)-**3c** From (S,S)-**3b**. To a solution of (S,S)-**3b** (1.35 mmol) in THF (15 ml) at −78°C was added n-BuLi 1.6M in hexane (1.8 mmol). After 30 min, pure MeI (6.75 mmol) was added at the same temperature. Stirring was continued for 30 min and the solution was then quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The solid residue was purified by column chromatography. Yield: 95%; m.p.: 128–129°C; $[\alpha]_D^{22}$=+341 (c=1, acetone) (data not given by Khiar *et al.*[3b]). ^{1}H NMR and ^{13}C NMR parameters were consistent with those given previously.[3b]

Reaction of (R)-2c$^-$ with (S)-1. Procedure B

To a solution of freshly prepared LDA (2 mmol) at −40°C was added the sulfoxide (2 mmol) in THF (2.5 ml), and the temperature was allowed to reach 0°C. The reaction mixture was then cooled to −78°C and added to a solution of the sulfinate (S)-**1** (4 mmol) in THF (5 ml). The solution was allowed to stand for 30 min with stirring at the same temperature, and then quenched with saturated NH_4Cl solution and extracted with AcOEt. Purification by column chromatography using hexane: ethyl acetate gave (S,S)-**3c**. Yield: 59%; m.p: 128–129°C; $[\alpha]_D^{22}$=+341 (c=1, acetone).

(±)-3d From (±)-1 and (±)-2d following procedure A

Yield: 40%; m.p.: 108–110°C; ^{1}H NMR δ 1.09 (s, 6H), 2.42 (s, 3H), 7.66–7.34 (m, 9H); ^{13}C NMR δ 12.7, 21.2, 82.4, 126.3, 128.6, 129.4, 131.8, 134.9, 138.3, 142.5; HMRS: exact mass calcd for $C_{16}H_{18}O_2S_2$ 307.0826, found: 307.0816.

Acknowledgements

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