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Stereochemistry of the Formation of Endocyclic Sulfoximides from o-Carboxyphenyl Sulfoxides

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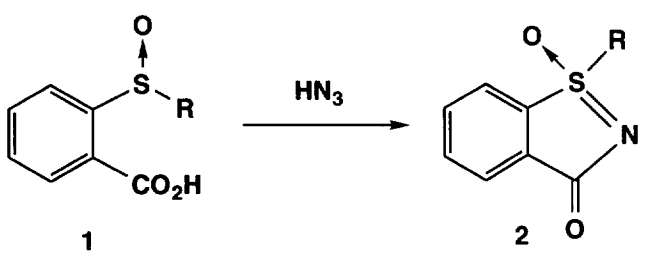
Abstract: The stereochemistry of the amination and subsequent cyclodehydration of optically active 2-(octylsulfinyl)benzoic acid to yield the corresponding endocyclic sulfoximide (1-octyl-3-oxo-benzo[d]-isothia(IV)azole 1-oxide) was studied using two different amination reagents, viz. hydrazoic acid and O-(mesitylenesulfonyl)hydroxylamine (MSH), respectively. It was found that while the reaction with hydrazoic acid yielded a partially racemized product having the same sign of optical rotation as the sulfoxide precursor, MSH gave essentially complete formation (>94%) of enantiopure product with the opposite sign of rotation. This difference in stereochemistry is likely to be caused by a neighbouring carboxyl group participation taking place in the strong acid medium used in the first case.

The endocyclic sulfoximides **2** can be obtained via reaction of the corresponding o-carboxyphenyl sulfoxides (**1**) with hydrazoic acid[1] (Scheme 1).

This reaction proceeds in two separate steps, *viz.* amination at sulfur followed by cyclodehydration of the free (open) sulfoximide intermediate. In simple alkyl aryl sulfoxides the amination step has been shown[2] to involve the protonated hydrazoic acid (H_2N-N_2^+), which undergoes nucleophilic substitution with free nitrogen as the leaving group, giving the aminated sulfoxide (protonated sulfoximide). Other aminating reagents have been used, notably O-(mesitylenesulfonyl)hydroxylamine (MSH), which liberates mesitylenesulfonic acid (anion) upon substitution.[3]

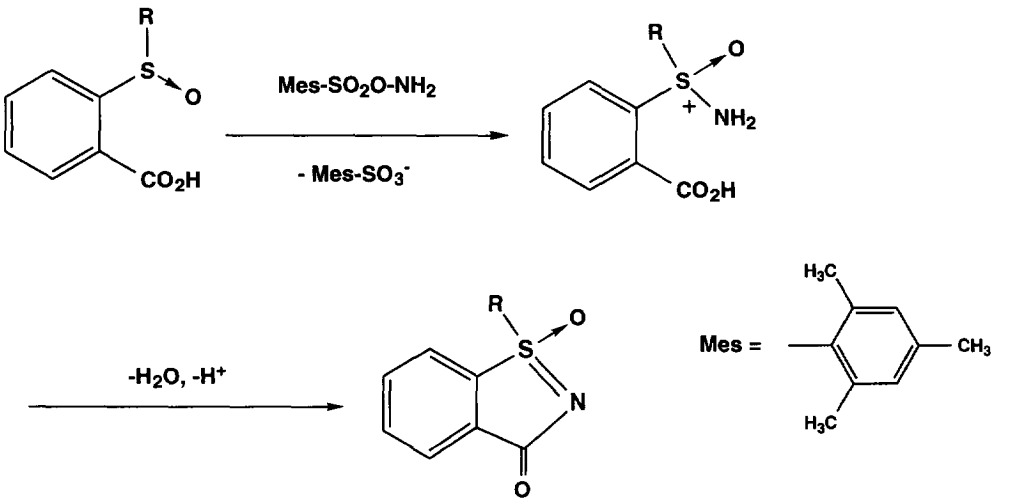


1 2

Scheme 1

In the simple alkyl aryl sulfoxides, these reactions have been shown to proceed with retention of configuration at sulfur,[3] although the reaction with hydrazoic acid is accompanied with partial racemization, which is thought to take place in the sulfoxide used as starting material through acid catalysis. The stereochemistry of the reaction shown in Scheme 1 has never been investigated, however. Recently we reported[4] the first optically active endocyclic sulfoximide of structure **2**, formed from an enantiopure sulfoxide precursor via the reaction of Scheme 1. It was then found that (+)-(R)-2-(octylsulfinyl)benzoic acid (**1**, R=C_8H_{17}-) predominantly gave (+)-**2** (R=C_8H_{17}-) of unknown configuration. It was suggested, however, on the basis of the results from amination of alkyl aryl sulfoxides, that this product also had a retained configuration at sulfur.

Interestingly, however, we found that when the reaction is carried out with MSH[5] as the aminating reagent (Scheme 2) rapid cyclization to compound **2** also takes place and no free sulfoximide can be isolated.[6] In this case, however, an opposite stereochemical result was obtained with optically active **1** as starting material. The reaction stereochemistry was determined by enantioselective liquid chromatography,[7] which permitted enantiomeric compositions to be precisely determined on the reaction product isolated by extraction. Starting with (-)-(S)-**1** (R=C_8H_{17}-), reaction with MSH[6] gave (+)-**2** in 89% e.e. (Fig. 1).



Scheme 2[a]

[a] Conditions: 1,2-dichloroethane, 55-60°C, 4 h.

Since the cyclization reaction does not involve the stereogenic centre, the stereochemistry of the product is determined by the electrophilic amination step. It has been shown[3] that normally this step is a direct nucleophilic substitution at nitrogen, thus not causing any stereoinversion at the sulfur atom. The opposite stereochemical results obtained in our case with the two aminating reagents therefore point to a deviating behaviour of the sulfoxide used due to the presence of the carboxyl substituent. Since carboxyl group participation, leading to inversion at sulfur has been observed previously in acid-catalyzed reactions,[8] it seems likely that the strong acid medium used in the reaction with hydrazoic acid favours a path involving an

acyloxysulfonium ion intermediate and leading to inversion and partial racemization due to the strong acid present. The mechanistic elucidation clearly requires further studies, however. Since compounds **2** have not been obtained in optically active form previously, chiroptical data is lacking and there is no reliable way to deduce absolute configurations by methods of comparison. Even though it seems most reasonable that the reaction with MSH gives a product with retained configuration as opposed to the reaction with hydrazoic acid, a definite proof by means of established absolute configurations is desirable and work in this direction is in progress.

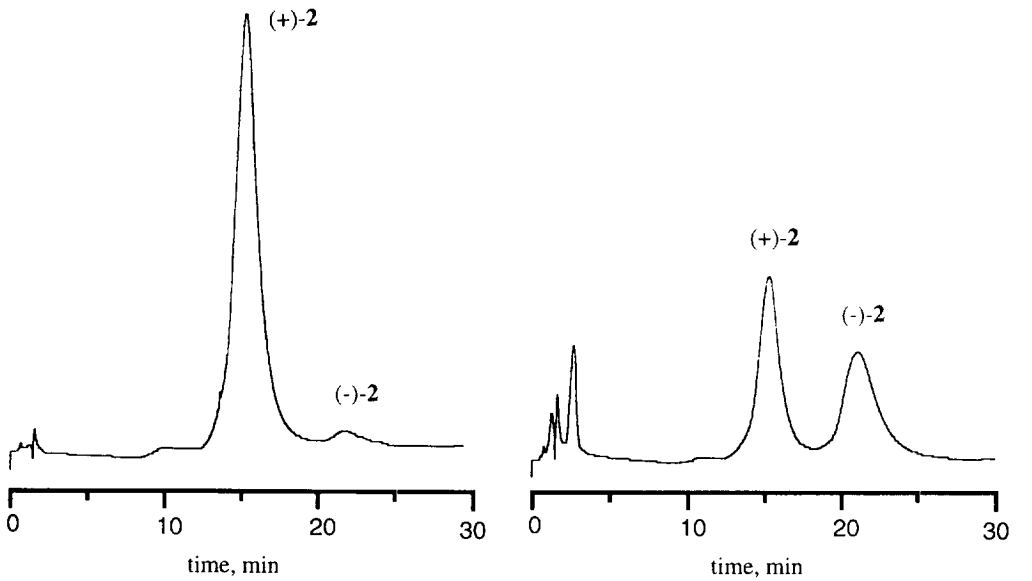


Figure 1. Chromatographic appearance of compound **2** (R=C_8H_{17}-) obtained from the MSH reaction. Left: From (-)-(S)-**1**; right: From (±)-**1**.

The opposite stereochemistries found provide convenient routes for the syntheses of both enantiomers of compounds **2** from a single enantiomer of the sulfoxide precursor. Resolution of sulfoxides of the general structure **1** should be possible on a comparatively large scale via classical resolution procedures[9] as well as by preparative enantioselective liquid chromatography.[10,11]

Acknowledgement. This work was supported by grants from the Swedish Natural Science Research Council (K-AA/KU 02508-321).

References and Notes

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2. Johnson, C.R.; Janiga, E.R. *J. Am. Chem. Soc.* **1973**, *95*, 7692.
3. Johnson, C.R.; Kirchhoff, R.A.; Corkins, H.G. *J. Org. Chem.* **1974**, 39, 2458.
4. Allenmark, S.; Andersson C.; Widell, P. *Chirality* **1995**, 7, 541.
5. MSH was prepared via acid hydrolysis of ethyl O-(mesitylenesulfonyl)acetohydroxamate (see: (a) Tamura, Y.; Minamikawa, J.; Sumoto, K. Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239. (b) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1) using the modified method described by Johnson (see ref. 3).
6. MSH (160 mg) was dissolved in 5 ml of 1,2-dichloroethane, the solution was dried with magnesium sulfate and then filtered. The filtrate was placed in a water-bath at 55°C and a solution of (-)-(S)-**1** (142 mg, 0.5 mmol) in 3 ml of 1,2-dichloroethane was then added dropwise under stirring. After the addition heating (to 60°C) was continued for 3 h. After cooling the reaction mixture was poured into 25 ml of 1 M sodium carbonate solution and shaken. The lower organic phase was washed with water, dried ($MgSO_4$), filtered and the solvent evaporated, which yielded a crystalline product (81 mg, 57%) identified as (+)-**2** in 94.3% stereochemical yield (89% e.e.).
7. An HPLC system incorporating an analytical (4.6 mm ID x 150 mm) column packed with a chiral sorbent based on crosslinked BSA (see: Allenmark, S.; Andersson, S. *Chromatographia* **1991**, *31*, 429) was used. The mobile phase consisted of 16 mM phosphate buffer (pH 8.0) containing 12% (v/v) acetonitrile as retention modifier at a flow rate of 1.2 ml/min. UV-detection at 230 nm was used throughout. Peak areas were determined by a Millipore/Waters mod. 740 integrator interfaced with the detector.
8. (a) Allenmark, S.; Hagberg, C.-E. *Acta Chem. Scand.* **1970**,*24*, 2225. (b) Allenmark, S. *Int. J. Sulfur Chem.* **1973**, *8*, 127. (c) Bohman, O.; Allenmark, S. *Tetrahedron Lett.* **1973**, 405. (d) Bohman, O.; Allenmark, S. *Chem. Scr.* **1973**, *4*, 202.
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10. Allenmark, S., Andersson, S., Möller, P., Sanchez, D. *Chirality* **1995**, *7*, 248.
11. Resolution of (±)-**1** was was achieved by a single load of 0.98 g racemate on a 50 mm i.d. x 250 mm axially compressed Prochrom column containing a chiral sorbent made from crosslinked N,N'-diallyl L-tartardiamide (DATD) bis-(3,5-dimethylbenzoate) immobilized to 10 μm 150 Å Kromasil and elution with hexane/THF (80/20 v/v) containing 0.05% TFA. This gave 0.35g of (+)-(R)-**1** in 99.8% e.e. and 0.38 g of (-)-(S)-**1** in 97.1% e.e.

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