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Rearrangement of Allylic Sulfoximines to Allylic Sulfinamides

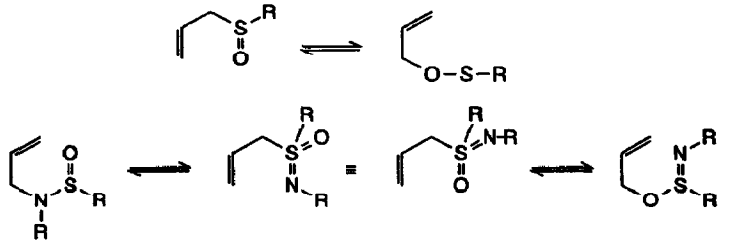
Hans-Joachim Gais,* Matthias Scommoda, and Dirk Lenz

Institut für Organische Chemie der RWTH Aachen, Prof.-Pirlet-Straße 1, 52056 Aachen, Germany

Abstract: Thermolysis of the enantiomerically pure allylic sulfoximines **3a,b** leads to their partial rearrangement to the isomeric allylic sulfinamides **5a,b** and **6a,b**, respectively, with complete retention of configuration at the S-atom. Racemization of the allylic sulfoximines **3a,b** at the S-atom does not occur.

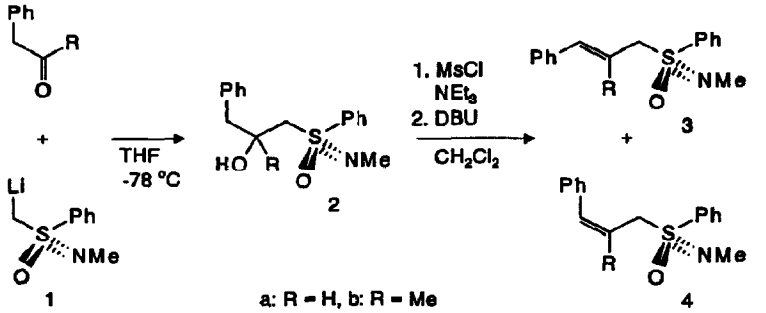
Allylic sulfoximines, which are readily accessible enantiomerically pure from aldehydes or ketones and (*S*)- or (*R*)-S-lithiomethyl-N-methyl-S-phenylsulfoximine (**1** or *ent*-**1**)[1,2] through an addition-elimination-isomerization sequence (*vide infra*, Scheme 2),[3-6] are a new promising class of chemical chameleons endowed with a chiral carbanion stabilizing nucleofuge.[3,7-10] In the substitution of allylic sulfoximines with copper-organyls[3,10b,c,e] as well as in the reaction of metallated allylic sulfoximines with electrophiles[7-9] the sulfonimidoyl group imparts considerable asymmetric induction, and its chirality is retained when acting as a nucleofuge.[3] Allylic sulfoximines bear some resemblance to the synthetically well established allylic sulfoxides whose characteristic feature is their thermal racemization through a reversible [2,3]-sigmatropic rearrangement to the corresponding allylic sulfinates (Scheme 1).[11]

Scheme 1



It was now of special interest for a general synthetic application of allylic sulfoximines to see if they would undergo a similar rearrangement to allylic sulfinamides or sulfinic acid ester imides (Scheme 1) and, most importantly, if such a rearrangement would be accompanied by a racemization at the S-atom. MNDO calculations by Harmata *et al.*[7] and Pyne *et al.*[9] indicated that allylic sulfinamides are thermodynamically much more stable than allylic sulfoximines. However, Tamura *et al.*,[12] Harmata *et al.*,[7] and Pyne *et al.*[9] did not observe a rearrangement of racemic allyl sulfoximines to the corresponding allyl sulfinamides upon heating the former in toluene solution to reflux for several hours.[13] In our ongoing study of the asymmetric γ-substitution of allylic sulfoximines with organocopper compounds we were led to synthesize the allylic sulfoximines **3a,b** and **4b** (Scheme 2).

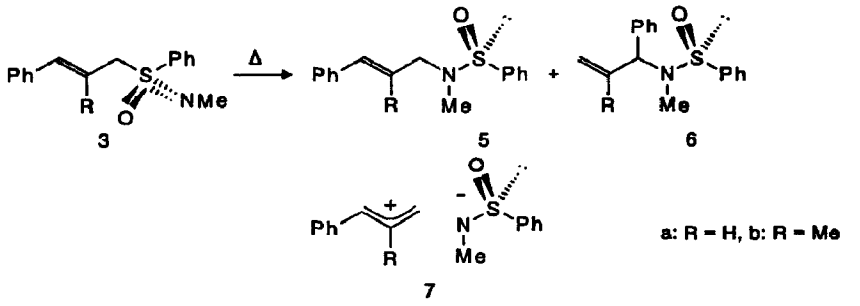
Scheme 2



Addition of the lithiomethyl sulfoximine **1** to phenyl acetaldehyde gave the β-hydroxy sulfoximine **2a** as a mixture of diastereomers in 67% yield. Synthesis of the enantiomerically pure (*E*)-configurated allylic sulfoximine **3a** was achieved in 57% yield in an one-pot version from **2a** via its conversion to the corresponding mesylate and elimination/isomerization with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[14,15] Similarly the β-hydroxy sulfoximine **2b**, which was obtained from phenyl acetone and **1** in 80% yield as a mixture of diastereomers, was transformed to the allylic sulfoximines **3b** and **4b**, which could be separated by chromatography, in 51% and 32% yield, respectively.

We found that the allylic sulfoximine **3a** suffered a partial rearrangement to the allylic sulfinamide **5a** upon heating neat for 15 h to 80 °C (Scheme 3).[16]

Scheme 3



Chromatography of the dark brown reaction product gave the allylic sulfinamide **5a** in 26% yield and the allylic sulfoximine **3a** in 52% yield. The ^{1}H NMR spectrum of the crude reaction product from the thermolysis of the sulfoximine **3a** in toluene at 110 °C for 20 h showed besides the signals of **3a** and **5a** further signals which were tentatively assigned to the sulfinamide **6a** (as mixture of diastereomers). Similarly, the allylic sulfoximine **3b** upon heating in 1,2-dichloroethane solution for 50 h to 85 °C led to its partial rearrangement as shown by the isolation of the isomeric allylic sulfinamides **5b** and **6b** (as a 1:1-mixture of diastereomers) in 11% and 10% yield, respectively, and the recovery of the allylic sulfoximine **3b** in 62% yield.[16,17] The structure of the sulfinamides **5a,b** and **6b** is supported by their analytical and spectroscopic data.[17] Furthermore, the structure of the sulfinamide **5a** was verified by an independent synthesis starting from 3-phenyl-allylamine[18a,10d] and that of the sulfinamide **6b** through its hydrolysis to methyl-(2-methyl-1-

phenyl)-allylamine.[18b,10e] The recovered allylic sulfoximines **3a,b** and the isolated allylic sulfinamides **5a,b** and **6b** all were enantiomerically pure,[19] and we assume that the rearrangement occurs under retention of configuration at the S-atom. Thermolysis of the allylic sulfinamides **5a,b** at 85 °C did not lead to the formation of the allylic sulfoximines **3a,b**, respectively. According to ^{1}H NMR spectroscopy **5a,b** remained unchanged under the above reaction conditions. In order to gain more insight into this rearrangement the thermolysis of **3a,b** neat and in different solvents at various temperatures was studied (Table 1).

Table 1. Thermolysis of the allylic sulfoximines **3a,b**.

3	solvent	T (°C)	t (h)	3/5/6(%)[a]
a	neat	80	15	52/26/-[b,c]
a	neat	100	15	44/56/-[b]
a	CH_2Cl_2	40	120	82/18/-[b]
a	toluene	110	20	26/74/-[b]
b	toluene	85	50	95/ 5/-[b]
b	1,2-$C_6H_4Cl_2$	85	50	84/ 5/11
b	$ClCH_2CH_2Cl$	85	50	74/15/11
b	$ClCH_2CH_2Cl$	85	112	62/11/10[c]
b	CH_3CN	85	50	90/10/-[b]

[a] Ratios were determined by ^{1}H NMR spectroscopy. [b] Amount of **6** not determined. [c] Ratio was determined by isolation.

A significant dependency of the rearrangement on the solvent polarity[20] does not exist. The experimental data available allow one so far only to speculate about the mechanism of this rearrangement. The formation of **5** and **6** from **3** could be explained by a dissociation-recombination mechanism involving the ion pair **7** (Scheme 3).[11] In order to explain the formation of **5** and **6** as the result of sigmatropic rearrangements one would have to invoke a [2,3]-sigmatropic rearrangement involving the S=N-group[12] for the formation of **6**, and for the formation of **5** a combination of a [2,3]-sigmatropic rearrangement involving the S=O-bond[11] to the corresponding sulfinic acid ester imide followed by its [3,3]-sigmatropic rearrangement (Scheme 1). By the route of Scheme 2 we have prepared a large number of acyclic as well as endocyclic primary allylic sulfoximines.[3,10] Up to now we observed only in the case of the acyclic allylic sulfoximines **3a,b** this rearrangement which represented however in no case a problem in regard to their synthesis on a preparative scale and synthetic application.

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16. Rearrangement of the allylic sulfoximines **3a,b** to a minor extend was observed also when they were kept for several months at -20 °C as oils but not as crystals.
17. A solution of the allylic sulfoximine **3b** (697 mg, 2.44 mmol; $[\alpha]_D$ 48.1° (*c* 2.44, THF)) in dry 1,2-dichloroethane (30 ml) was heated to 85 °C for 112 h. Removal of the solvent and chromatography (silica gel, gradient 33% ethyl acetate-*n*-hexane, 33% *n*-hexane-ethyl acetate) of the residue gave the allylic sulfinamides **5b** (79 mg, 11%; $[\alpha]_D$ 31.0° (*c* 0.80, THF)) and **6b** (70 mg, 10%; as 1:1-mixture of diastereomers), and the allylic sulfoximine **3b** (435 mg, 62%). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm, TMS): **3b**: 1.94 (d, ^4J = 1.35 Hz, 3 H, CH_3), 2.77 (s, 3 H, NCH_3), 3.97 (s, 2 H, $C\underline{H}_2S$), 5.97 (m, 1 H, Ph-C<u>H</u>=C), 7.01-7.04 (m, 2 H, *o*-Ph-Ch=), 7.16-7.31 (m, 3 H, *m*-, *p*-Ph-CH=), 7.49-7.62 (m, 3 H, *m*-, *p*-PhS), 7.83-7.87 (m, 2 H, *o*-PhS). **5b**: 1.87 (d, ^4J = 1.01 Hz, 3 H, CH_3), 2.52 (s, 3 H, NCH_3), 3.66 (d, ^2J = 13.76 Hz, 1 H, CH_2-N), 3.85 (d, ^2J = 13.76 Hz, 1 H, CH_2-N), 6.47 (m, 1 H, Ph-C<u>H</u>=C), 7.20-7.37 (m, 5 H, Ph-CH=), 7.45-7.55 (m, 3 H, *m*-, *p*-PhSO), 7.68-7.73 (m, 2 H, *o*-PhSO). **6b**: 1.75 (m, 3 H, CH_3), 2.24 (s, 3 H, NCH_3), 2.39 (s, 3 H, NCH_3), 4.90 (m, 1 H, C<u>H</u>(Ph)), 4.98 (m, 1 H, C<u>H</u>(Ph)), 5.07-5.10 (m, 2 H, $=CH_2$), 5.14 (m, 1 H, $=CH_2$), 5.37 (m, 1 H, $=CH_2$), 7.27-7.56 (m, 8 H, Ph, *m*-, *p*-PhS), 7.64-7.67 (m, 2 H, *o*-PhS), 7.70-7.74 (m, 2 H, *o*-PhS).
18. (a) The racemic sulfinamide **5a** was prepared by the treatment of lithium 3-phenyl-allylamide with PhS(O)Cl in THF at 0 °C followed by the methylation of the isolated racemic benzene sulfinic acid 3-phenyl-allylamide through deprotonation with NaH in THF-*n*-hexane and treatment with MeI in 23% overall yield. (b) The sulfinamide **6b** was cleaved to the amine (60%) by methanolysis in the presence of CF_3COOH at room temperature for 30 min.
19. The *ee*-value of the sulfinamides **5a,b** and **6b** was determined by ^{1}H NMR spectroscopy in the presence of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol (3 equiv) (Pirkle, W. H.; Sikkenja, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384): **5a**: ΔΔδ(Me) = 0.012, ΔΔδ(2-H) = 0.032, ΔΔδ(3-H) = 0.032; **5b**: ΔΔδ(Me) = 0.006, ΔΔδ(N-Me) = 0.008, ΔΔδ(3-H) = 0.018, **6b**: ΔΔδ(N-Me) = 0.018, ΔΔδ(N-Me) = 0.02 ppm.
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