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STEREOSELECTIVE SYNTHESIS OF ENANTIOMERICALLY PURE 1-(E)-ALKENYLSULFOXIMINES

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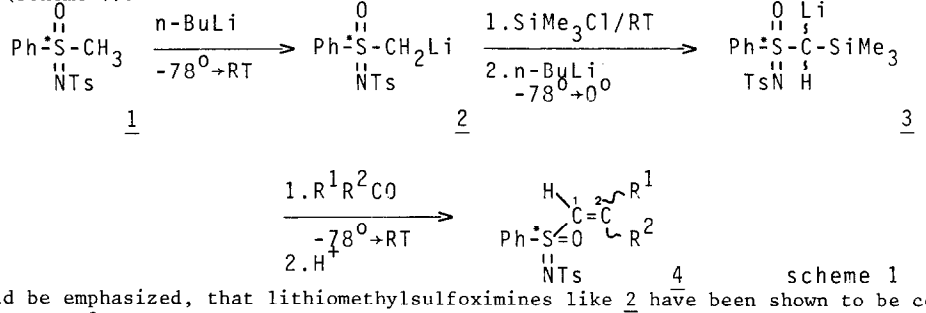
Summary: Optically active (E)-N-tosyl-S-(1-alkenyl)-S-phenylsulfoximines 4 are synthesized stereoselectively in a one pot sequence from readily available 1 via C-silylation, metallation and reaction of the corresponding lithiosulfoximine 3 with various carbonyl compounds. The El-MS spectra of the so prepared alkenylsulfoximines 4 show unexpected fragmentations, pointing to a new, unusual S-O-migration of the 1-alkenyl moiety.

Despite their potential as chiral intermediates in asymmetric synthesis 1-alkenyl sulfoximines have received only very little attention[1]. Broader investigations aimed at the utilization of the sulfoximine group as temporary, chiral auxiliary, e.g. in diastereofacial cycloadditions or organometallic ß-additions to the 1-alkenyl double bond are hampered by a lack of suitable methods for their synthesis in optically active form[1c,2].

Herein we wish to report the first general synthesis of enantiomerically pure (E)-N-tosyl-S-(1-alkenyl)sulfoximines 4 from carbonyl compounds through Peterson Olefination and their interesting MS fragmentation pattern.

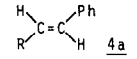
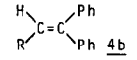
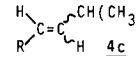
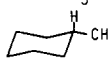
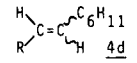
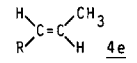
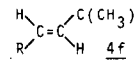
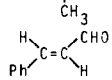
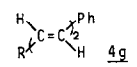
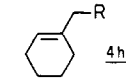
Reaction of one equivalent of n-butyllithium (n-BuLi) with readily available (S)-S-methyl-S-phenyl-N-tosylsulfoximine 1 in tetrahydrofuran (THF) gives lithiosulfoximine 2[3]. Dropwise addition of 2 to one equivalent trimethylchlorsilane in THF at room temperature, followed by n-BuLi at -78°C and Peterson reaction of the thus formed new α-silyllithiosulfoximine 3[4] with aldehydes or ketones results in the formation of 1-alkenylsulfoximines 4 in overall yields ranging from 63% to 76% (scheme 1).[5]



1 2 3 4 scheme 1

It should be emphasized, that lithiomethylsulfoximines like 2 have been shown to be configurationally stable[3]. Consequently, the olefination procedure takes place with retention of configuration at the chiral S-atom. Therefore, this method can be successfully applied to the synthesis of mono-, di-, and trisubstituted enantiomerically pure 1-alkenylsulfoximines of both absolute configurations at the S-atom, essential for their planned utilization in asymmetric synthesis.

Tab. 1 Synthesis of 1-Alkenylsulfoximines 4 through Peterson Olefination

entry	carbonyl compound	product	E:Z[e]	yield[a)b)c)]
1	PhCHO	 4a	>98:2	68% (85%)
2	PhCOPh	 4b	-	63%
3	CH_3-CH(CH_3)-CHO	 4c	94:6	76%[d)]
4		 4d	93:7	68%[d)] (81%)
5	CH_3CHO	 4e	>98:2	72%[d)]
6	CH_3-C(CH_3)$_2$-CHO	 4f	>98:2	63%
7		 4g	>98:2	65%
8		 4h	-	23%

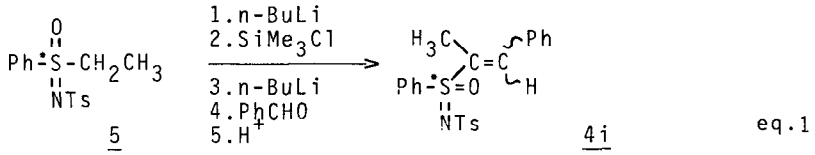
a) Overall yields of isolated pure products.
b) All products exhibited the expected ^{1}H NMR (300 MHz) and MS characteristics consistent with the assigned structure. Satisfactory CHN analysis (except 4h) was obtained for each compound.
c) Values in parenthesis refer to optimized yields obtained on a 50 mmol scale.
d) The reaction mixture was kept 2-3 h at -78°C after the addition of the carbonyl compound before quenching. Otherwise the product contained a considerable quantity of the isomerized allylsulfoximines.
e) E/Z-ratio determined by 300 MHz ^{1}H NMR.

The examples in table 1 show, that the reaction is quite general. The procedure succeeds equally well with sterically hindered carbonyl compounds like t-butyl-aldehyde (entry 6), and α,β-unsaturated aldehydes, like cinnamaldehyde (entry 7), where only the formation of 4g resulting from an initial 1,2-addition was observed. ^{1}H NMR-spectroscopic examination of the crude reaction mixture showed no trace of products derived from a 1,4-addition.

The stereoselective formation of the E-configurated double bond (≥ 93:7) in unsymmetrical products (entries 1, 3-7) is significant. In contrast, the comparable synthesis of 1-alkenylsulphones through Peterson Olefination[6] gave unselective E/Z-mixtures for unsymmetrical products.

As expected, the reaction was unsatisfactory with enolizable ketones like cyclohexanone (entry 8). Evidently, the enolization of the ketone through 3 takes place to a large extent and prevents the olefination reaction[7].

Our version of the "in situ Peterson reaction" also provides an access to trisubstituted N-tosyl-S-(1-alkenyl)sulfoximines, when α-substituted sulfoximines (e.g. S-ethyl-S-phenyl-N-tosylsulfoximine 5) are chosen as starting materials. The same one pot sequence as described above afforded directly, in 79 % overall yield, the highly substituted 1-alkenylsulfoximine 4i (E/Z = 86:14) (eq. 1).

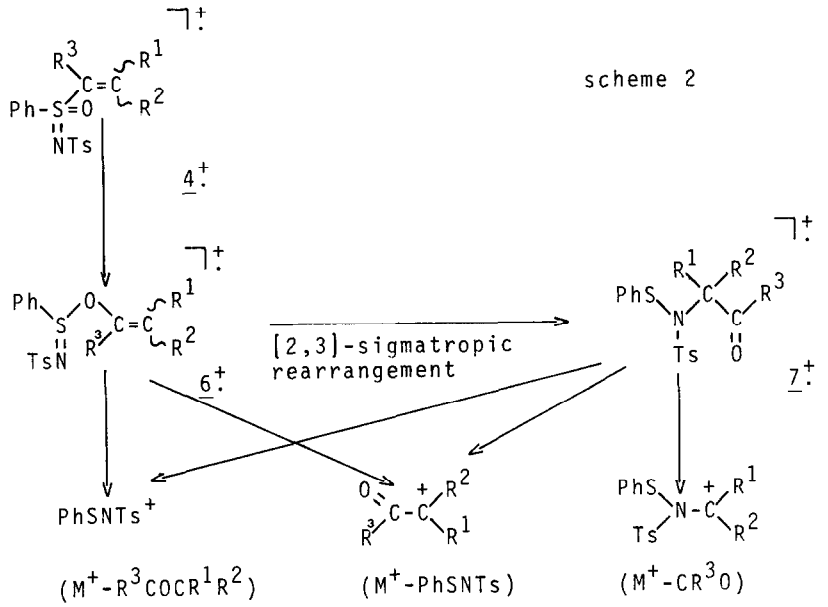


5 4i eq.1

During the EI-MS examination of the 1-alkenylsulfoximines 4 we observed striking fragmentations. First, in the high-mass region besides the weak M^+ a fragmentation was registered according to M^+-CR^3O.[8] Second, for all compounds the fragment $PhSNTs^+$ is found, but not the expected mass of $PhSONTs^+$. Third, and most surprising, all compounds gave the fragment $M^+-PhSNTs$.[8]

These findings suggest that a fast migration of the 1-alkenyl group from S to O in $4^{+\cdot}$ to $6^{+\cdot}$ followed at least in part by a [2,3]-sigmatropic rearrangement leading to $7^{+\cdot}$ must have taken place before fragmentation (scheme 2).

scheme 2



A significant correlation between the relative intensities of $PhSNTs^+$ and $M^+-PhSNTs$ depending on the ability of the substituents R^1, R^2 to stabilize carbocations, was observed, e.g. in the mass spectrum of 4b the fragment $PhSNTs^+$ was registered with 2 %, but that of $M^+-PhSNTs$ with 100 % intensity, whilst 4f gave $PhSNTs^+$ with 32 %, and $M^+-PhSNTs$ only with 3 % intensity. Besides these findings, the examination of 1-deuterated 1-alkenylsulfoximine 4a (R^3=D) supports this mechanism, which showed no scrambling, but a complete incorporation of deuterium only in the fragment $M^+-PhSNTs$.

The nature of this unusual and so far unknown migration of a sp^2-C-atom in 1-alkenylsulfoximines unter MS-EI conditions will be under further investigation.

General Procedure: A solution of 1.55 g (S)-1 (5 mmol, $[\alpha]_D^{25}$= +132°;c=1, acetone) in 30 ml dry THF at -78°C was treated with one equivalent of n-BuLi. Then the mixture was allowed to warm to room temperature. The so prepared yellow solution of 2 was added dropwise to 0.63 ml (5 mmol) trimethylchlorsilane in 15 ml dry THF. After stirring for 1 h at room temperature, the mixture was cooled down to -78°C, one equivalent of n-BuLi was added and the orange solution warmed up to 0°C. Then 0.64 g (6 mmol) benzaldehyde in 2 ml dry THF was added at -78°C. After stirring for 1 - 2 h at room temperature, the mixture was quenched with 50 ml 2N HCl, extracted with ethyl acetate, washed first with 70 ml bicarbonate solution and then with brine. After drying ($MgSO_4$), evaporating of the solvent, and flash chromatography on silicagel (n-hexane/ethyl acetate 1:1), 1.35 g (68%) 4a was isolated as colourless needles (mp = 134°C; $[\alpha]_D^{25}$= -56°; c= 1.5, acetone).
^{1}H-NMR (300 MHz, $CDCl_3$): δ= 2.38 (s, 3H), 6.96 (d, J= 15 Hz, 1H, H-1), 7.25-8.09 (m, 14H), 7.66 (d, J= 15 Hz, 1H, H-2). MS (EI, 70 eV): m/z (%) = 368 (M^+-CHO, 12), 278 ($PhSNTs^+$, 9), 214 (9), 155 (10), 139 (100), 125 (33), 119 (M^+-PhSNTs, 22), 116 (11), 91 (100), 77 (42), 65 (22), 51 (25), 39 (14).

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3. C.R. Johnson, R.A. Kirchhoff, R.J. Reischer, and G.F. Katekav, J. Am. Chem. Soc. 95 (1973) 4287; (S)- and (R)-1 are obtained via racemate separation of rac-S-methyl-S-phenylsulfoximine with 10-campher sulfonic acid of which both enantiomers are commercially available (Aldrich).

4. The corresponding (S)-N-tosyl-S-phenyl-S-(trimethylsilyl)methylsulfoximine could be isolated quantitatively by quenching of 3 with 2N HCl and extractive work up as a yellow brown oil, which crystallizes with n-hexane/methanol yielding a colourless powder with m.p. below room temperature. ^{1}H-NMR (60 MHz, $CDCl_3$): δ= 0.18 (s, 9H), 2.38 (s, 3H), 2.78 (d, J= 14 Hz, 1H), 3.28 (d, J= 14 Hz, 1H), 7.18-8.17 (m, 9H); MS (EI, 70eV): m/z (%) = 381 (M^+, 7), 366 (12), 300 (12), 294 (71), 290 (22), 228 (50), 167 (22), 155 (20), 149 (23), 147 (43), 139 (52), 125 (16), 91 (100), 77 (32), 73 (80), 65 (31), 51 (21), 39 (16). $[\alpha]_D^{25}$= +152° (c= 3.0, $CHCl_3$).
Anal. calcd for $C_{17}H_{23}NO_3S_2Si$: C, 53.51; H, 6.07; N, 3.67.
Found C, 53.82; H, 6.08; N, 3.63.
This compound is fairly stable in solution, but desilylates in substance at room temperature within a couple of days to 1.

5. The alternative route to 4 via addition of 2 to R^1R^2CO and elimination of the thus obtained ß-hydroxy compounds is not feasible because of their rapid elimination to epoxides; C.R. Johnson, Compr. Org. Chem. 3 (1979) 223.

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7. 1-Alkenylsulfoximines from enolizable ketones, e.g. cyclopentanone, can be synthesized in high yield by "inverse Peterson Olefination": I. Erdelmeier and H.-J. Gais, to be published.

8. Determined by high resolution mass spectrometry.

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