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One-Pot Synthesis of (*S*)-4-Isopropyl-2-*p*-toluene-4,5-dihydro-[1,2λ^6,3]oxathiazole 2-Oxides: Efficient Precursors of Optically Active Sulfoximines

Michael Reggelin* and Heinz Weinberger

Institut für Organische Chemie, J. W. Goethe-Universität, Niederurseler Hang, W-6000 Frankfurt/Main 50, Germany

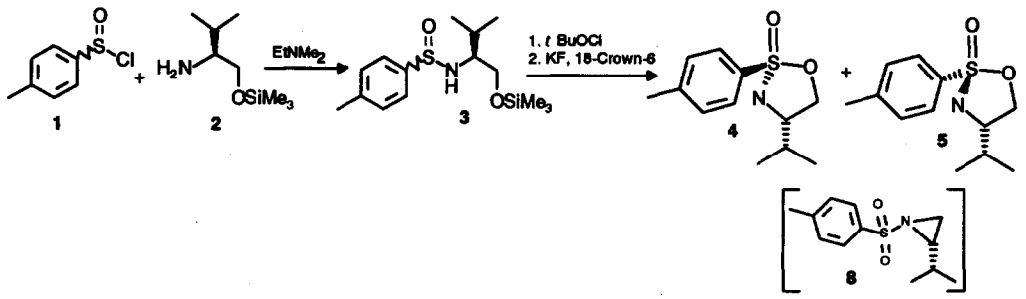
Abstract: The title compounds were prepared from *p*-toluenesulfinyl chloride and (*S*)-*O*-trimethylsilyl valinol without isolation of intermediates. Key step in the synthesis is the fluoride-induced cyclisation of sulfonimidoyl chlorides yielding the crystalline sulfonimidates **4** and **5** as a mixture of enantiomerically pure diastereomers which were easily separable by column chromatography or just simple crystallisation. Their reactions with either organolithium or Grignard reagents offer a convenient entry to enantiomerically pure sulfoximines in high yields.

Sulfoximines as representatives of chiral tetracoordinate, hexavalent sulfur compounds, play an increasing role in asymmetric synthesis.[1] Since the pioneering work of Bentley et al.[2] in 1950, many preparations of sulfoximines have been accomplished by a variety of processes. The most general entry till now is the reaction of sulfonimidoyl fluorides[3] or sulfonimidates[4] with organolithium compounds. More recently, Harmata et al.[5] have reported the preparation of racemic S-allyl sulfoximines by reacting sulfonimidoyl chlorides with allyltributyltin in the presence of aluminium chloride. However, due to the difficult preparation of enantiomerically pure sulfur(VI) electrophiles, all the above mentioned procedures are convenient only for the synthesis of racemic sulfoximines. Optically active sulfoximines have been obtained by oxidative imination of chiral, non-racemic sulfoxides using the quite unstable *O*-mesitylenesulfonyl-hydroxylamine (MSH)[6] or via metalated *N,S*-dimethyl-*S*-phenyl sulfoximine,[1c] which has been prepared by resolution of the racemate.

In this contribution we would like to introduce an effective approach to enantiomerically pure sulfoximines via nucleophilic substitution of the new[7] cyclic sulfonimidates **4** and **5** with organometallic reagents (Scheme 1 and Table 1).

Starting from *p*-toluenesulfinyl chloride **1** and (*S*)-*O*-trimethylsilyl-valinol **2**, sulfinamide **3** was obtained as a 1:1 mixture of diastereomers in almost quantitative yield. Oxidation with *t*-butyl hypochlorite[8] in CCl_4 at 0-5 °C followed by reaction with KF in acetonitrile in the presence of catalytic amounts of 18-crown-6 for 24 hours at room temperature completed the reaction.[9] After chromatographic purification on silica gel the two epimeric sulfonimidates **4** and **5** were isolated as colorless, stable crystals in 70 % overall yield, calculated from the protected valinol. It is important not to exceed the given reaction time to avoid the formation of the rearranged aziridine **8**. The

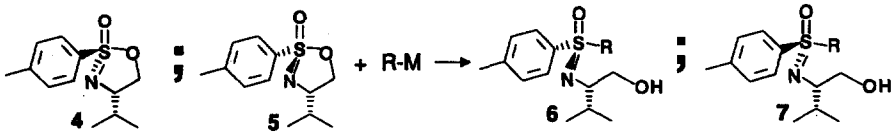
isolation of pure **5** is especially easy due to its much higher bias to crystallisation as compared to the epimer **4**. Its absolute configuration was confirmed by X-ray crystallographic analysis.[10]

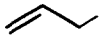
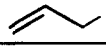
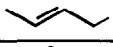
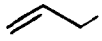


Scheme 1: Synthesis of the title compounds.

Reaction of **4** and **5** with 2 eq of organometallic reagents generated the corresponding sulfoximines in good to excellent yields (Table 1).[11]

Table 1: Reactions of **4** and **5** with Various Organometallic Compounds.



SM[a]	R	M	yield [%]	m.p. [°C]	$[\alpha]_D^{20}$	c [g/100ml][c]
4/5	$-CH_3$	Li	85/90	oil/oil	-151.9/37.0	1.01/1.05
5	$-CH_3$	MgI	quant.	oil	not det.	-
5		MgBr	93	42	102.4	1.01
5		MgBr	94	oil	88.4	1.04
5		MgBr	97	oil	not det.	-
5		Li	89	oil	-7.6	1.26
5		MgBr	89	oil	3.3	0.52
5		MgBr	91	oil	-165.0	1.04
5		MgBr/Cl	0[b]	-	-	-
4		Li	92	60	-105.8	1.41

[a] Starting material, [b] After prolonged reaction times aziridine **8** was isolated in 73 % yield, [c] in CH_2Cl_2

The indicated absolute configuration of the sulfur center in the reaction products is in accordance with D.J. Cram's work on the stereochemistry of the nucleophilic attack on tetracoordinate sulfur compounds.[12] Excess of organometallic reagent was necessary to achieve the yields given in the table. It is worth mentioning that unlike the above described sulfur(VI) electrophiles the oxathiazole 2-oxides do not produce mixtures of sulfoximines and sulfinamides in the reaction with Grignard reagents.[3,12]

It is this nice feature of the title heterocyclic systems that allows for the easy preparation of a variety of alkyl- and 2-alkenyl sulfoximines from the corresponding Grignard reagents, which were much easier to prepare than the corresponding organolithiums. Furthermore, the reaction of the constitutional and configurational inhomogeneous crotylmagnesium bromide yields in a stereoconvergent manner nearly exclusively (*E*:*Z* = 37:1, Table 1) the *E* configurated crotyl sulfoximine.

In summary, the facile preparation of both diastereomers of (*S*)-4-isopropyl-2-*p*-toluene-4,5-dihydro-[1,2λ^6,3]oxathiazole 2-oxide and their clean reaction with Grignard and organolithium compounds offer a versatile entry to a variety of enantiomerically pure sulfoximines. Therefore, the heterocycles **4** and **5** may be regarded as the sulfur(VI) analogues of the popular menthyl-*p*-toluenesulfinate used in sulfur(IV) chemistry to prepare optically active sulfoxides.[13]

We are currently exploring the synthetic potential of 2-alkenyl sulfoximines as asymmetric d^3-building blocks.

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REFERENCES AND NOTES

1. a) Johnson, C.R. *Aldrichim. Acta* **1985**, *18*, 3-10. b) Erdelmeier, I.; Gais, H.-J. *J. Am. Chem. Soc.* **1989**, *111*, 1125-1126. c) Erdelmeier, I.; Gais, H.-J.; Lindner, H.-J. *Angew. Chem.* **1986**, *98*, 912-914; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 935. d) Bund, J.; Gais, H.-J.; Erdelmeier, I.; *J. Am. Chem. Soc.* **1991**, *113*, 1242-1244. e) Pyne, S. G. *J. Org. Chem.* **1986**, *51*, 81-87.
2. Bentley, H.R.; Whitehead, J.K. *J. Chem. Soc.* **1950**, 2081-2082.
3. Johnson, C.R.; Bis, K.G.; Cantillo, J.H.; Meanwell, N.A.; Reinhard, M.F.D.; Zeller, J.R.; Vouk, G.P. *J. Org. Chem.* **1983**, *48*, 1-3.
4. Pyne, S.G. *J. Org. Chem.* **1986**, *51*, 81-87.
5. Harmata, M.; Claassen II, R.J. *Tetrahedron Lett.* **1991**, *32*, 6497-6500.
6. a) Johnson, C.R.; Kirchhoff, R.A.; Corkins, H.G. *J. Org. Chem.* **1974**, *39*, 2458-2459. b) Tamura, Y.; Sumoto, K.; Minamikama, J.; Ikeda, M. *Tetrahedron Lett.* **1972**, 4137-4140.
7. The only hitherto known derivatives of 5-membered ring sulfonimidates were the racemic 4-oxo- and the racemic 4-imino substituted 4,5-dihydro-oxathiazole systems prepared by *G. Lohaus* (Lohaus, G. *Tetrahedron Lett.* **1970**, 127-130.) and *Van Meerssche* (L'abbé, G.; Yu, C.-C.; Declercq, J.-P.; Germain, G.; Van Meerssche, M. *Angew. Chem.* **1978**, *90*, 394-395; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 352.), respectively.
8. Johnson, C.R.; Wambsgans, A. *J. Org. Chem.* **1979**, *44*, 2278-2280.

9. *Synthesis of* (2R,4S)- and (2S,4S)-*4-isopropyl-2-p-toluene-4,5-dihydro-[1,2λ⁶,3]oxathiazole 2-oxide* (**4** and **5**): The sulfinamide **3** was prepared following literature procedures (Krauthausen, E. in *Houben-Weyl, Methoden der Organischen Chemie;* Müller, E. Ed.; G. Thieme: Stuttgart, 1985; Vol. E11, p. 656.) from 7.95 g (45 mmol) sodium *p*-toluenesulfinate and 7.04 g (40.1 mmol) *O*-trimethylsilyl valinol. Deviating from the procedures described we used the volatile ethyldimethylamine as base to avoid acidic workup. The crude sulfinamide was dissolved in 200 ml tetrachloromethane, cooled to 0°C and treated with 6.51 g (60 mmol) *t*BuOCl maintaining the reaction temperature between 0°C and 5°C. The mixture was stirred for 45 min at 0°C, then all volatile components were removed at this temp. *in vacuo* obtaining the crude sulfonimidoyl chloride as a light yellow oil. This was dissolved in 20 ml acetonitrile (dried over CaH_2!) and slowly added to a suspension of 4.56 g (80 mmol) KF and 0.53 g (2.0 mmol, 5 Mol-%) 18-crown-6 in 80 ml CH_3CN. Stirring was continued for exactly 24 h, then the solvent was removed *in vacuo*, the residue suspended in 100 ml ether, filtered and evaporated again. The residue was purified on silica gel (15-40 µm) using ether/hexane (1:3) as eluents, yielding 3.62 g **5** (mp.: 81 °C; $[\alpha]^D_{20}$ = -93.8, c = 1.05, CH_2Cl_2) and 3.07 g **4** (mp.: 62 °C; $[\alpha]^D_{20}$ = +61.5, c = 1.08, CH_2Cl_2; total yield: 6.69 g, 70%) as colorless, crystalline substances.
4: 400 MHz-^{1}H-NMR: δ=0.988, 1.130 (2× d, 4-CH(CH_3)$_2$, 1.913 (dqq, 4-C*H*(CH_3)$_2$), 2.426 (s, *p*-CH_3), 3.905 (ddd, 4-H), 4.165 (dd, 5-H), 4.386 (dd, 5'-H), 7.298 ("d", *m*-H_2), 7.752 ("d", *o*-H_2) ppm; $J_{5,5'}$=7.4 Hz, $J_{5,4}$=7.3 Hz, $J_{5',4}$=7.4 Hz, $J_{4,4\text{-}CH(CH_3)_2}$=7.1 Hz, $J_{4\text{-}CH(CH_3)_2 4\text{-}CH(CH_3)_2}$=6.7 Hz.
62.5 MHz-^{13}C-NMR: δ=18.76, 19.57 (4-CH(CH_3)$_2$), 21.45 (*p*-CH_3), 33.68 (4-C*H*(CH_3)$_2$), 72.75 (4-C), 73.34 (5-C), 127.60 (*o*-C), 129.64 (*m*-C), 136.68 (*ipso*-C), 144.07 (*p*-C) ppm.
5: 400 MHz-^{1}H-NMR: δ=0.946, 1.170 (2× d, 4-CH(CH_3)$_2$, 1.791 (dqq, 4-C*H*(CH_3)$_2$, 2.439 (s, *p*-CH_3), 3.829 (dd, 5-H), 4.019 (ddd, 4-H), 4.663 (dd, 5'-H), 7.312 ("d", *m*-H_2), 7.859 ("d", *o*-H_2) ppm; $J_{5,5'}$=7.6 Hz, $J_{5,4}$=9.0 Hz, $J_{5',4}$=6.0 Hz, $J_{4,4\text{-}CH(CH_3)_2}$=8.3 Hz, $J_{4\text{-}CH(CH_3)_2 4\text{-}CH(CH_3)_2}$=6.7 Hz.
62.5 MHz-^{13}C-NMR: δ=18.43, 20.31 (4-CH(CH_3)$_2$), 21.53 (*p*-CH_3), 34.09 (4-C*H*(CH_3)$_2$), 70.88 (4-C), 75.45 (5-C), 129.10 (*o*-C), 129.67 (*m*-C), 135.02 (*ipso*-C), 144.81 (*p*-C) ppm.
10. *Enraf-Nonius CAD4* diffractometer, Cu-K_α radiation, structure determination by direct methods using the SHELXS program system. Complete results have been deposited and are available on request from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftliche Information mbH, W-7514 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD-56405, the names of the authors and the journal citation.
The crystals of **5** (ether) are orthorhombic, $P2_12_12_1$ (No. 19), a = 6.2494(4) Å, b= 9.5297 (6) Å, c = 21.449(1) Å; V = 1277.4(2) Å^3; Z = 4; ρ_{calc} = 1.244 g/cm^3; hemisphere through 2Θ = 140°; 2416 independent reflections, 2416 with I>0, 214 variables; R(F) = 0.033, R_ω(F)= 0.035. A difference Fourier synthesis showed the position of all H-atoms. The structure refinement on F values using unit weights converged at R(F) = 0.033 and R_ω(F)= 0.035. A refinement of the enantiomorphous structure gave R(F) = 0.049 and R_ω(F)= 0.049. Thus the latter can be rejected.
11. *General Procedure:* To a cold (-78°C) solution of 239 mg (1.0 mmol) **5** in 3 ml of dry THF two equivalents of the corresponding Grignard reagents in ether were added. After 5 min, the reaction mixture was allowed to reach 0°C and stirred for another 45 min at this temperature. Then 2 ml of saturated NH_4Cl solution were added and usual etheral workup, followed by flash chromatographic purification, yields the sulfoximines as colorless oils or solids.
12. Jones, M. R.; Cram, D.J. *J. Am. Chem. Soc.* **1974**, *96*, 2183-2190.
13. Solladié, G. *Synthesis* **1981**, 185-196.

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