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New Stereocontrolled Synthesis of Cyclic Sulfonimidates

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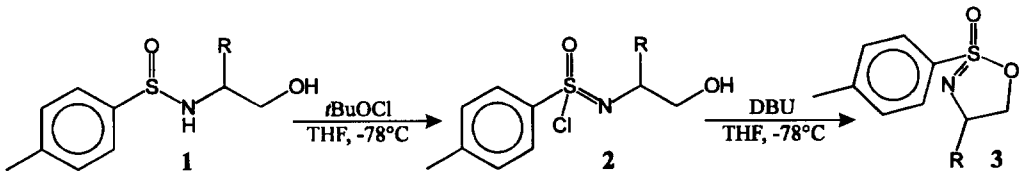
Abstract: Cyclic sulfonimidates **3** can be synthesised in enantiomerically pure form from amino alcohols by 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) induced oxidative cyclisation of sulfinamides **1**. The very rapid intramolecular reaction of the intermediate sulfonimidoylchlorides **2** allows for complete chirality transfer with overall inversion of configuration at sulfur.

Chiral, aracemic sulfoximines have proven to be useful synthetic intermediates for a variety of asymmetric transformations.[1,2] Despite of this fact, there are only few methods known to yield them in enantiomerically pure state. Recently we reported the synthesis of optically active sulfoximines via ring-opening of the cyclic sulfonimidates **3a** and *epi*-**3a** (Scheme 1, Table 1) with organolithium and magnesium compounds.[3] For *allylic* sulfoximines, which have been proven to be excellent solutions for asymmetric d^3-synthons,[2] this method represents the only general entry to this class of compounds. The alternative electrophilic imination of allylic sulfoxides[4] suffers from the rapid [2.3] sigmatropic shift leading to racemisation. Other methods, starting from ketones, work well only for symmetric cycloalkanones.[1b,5] As published earlier the synthesis of **3a**/*epi*-**3a** via fluoride induced cyclisation[3] leads to a mixture of diastereomers whose separation by crystallisation is hampered by the fact that *both* diastereomers are crystalline. Guided by the observation that the diastereomers of the unprotected sulfinamides **1a** (crystalline, S_S, 4*R*)/*epi*-**1a** (oil, R_S, 4*R*) can be separated by crystallisation much easier then the corresponding cyclic sulfonimidates, we investigated possibilities for their stereocontrolled oxidative cyclisation. We now report an improved synthesis of **3** starting from isomerically pure sulfinamides **1** with overall inversion of configuration at the sulfur atom (Scheme 1).[6]



Scheme 1

It is known, that sulfinamides can be oxidised with *t*butyl hypochlorite to yield imidoylchlorides such as **2** with retention of configuration at low temperatures.[7] But usually they are not configurationally stable at the elevated temperatures necessary for a subsequent reaction with nucleophiles.[7a] Here, in contrast, the *intra*molecular attack of the alcohol in presence of a bulky base is rapid enough even at low temperatures, so that the isomeric purity of the starting material can be conserved in the product. The reaction has been carried out successfully with up to

75 mmol of **1a** and with various other sulfinamides (as pure diastereomers or as mixtures), which were synthesised from the corresponding amino alcohols following standard procedures.[3] It is worth mentioning here that no concurrent oxidation of the primary alcohol by *t*butyl hypochlorite occurs.

The separation of the *S*-epimers of **1** is achieved by crystallisation from *t*butyl methyl ether (R = *i*Pr) or ethyl acetate (R = Ph). The oily or slowly crystallising epimer remaining in the mother liquor can be cyclised as well, yielding the epimer of the corresponding sufonimidate.

Table 1: Oxidative Cyclisations of Sulfinamides **1** to 4-Substituted 4,5-Dihydrooxathiazole 2-oxides **3**

Compound	R	Configuration	Yield [%]	*ds* [%]	mp [°C]	$[\alpha]_D^{20}$	R_f[c)]
3a	*i*Pr	S_S, 4*R*[a)]	89	>98	82	+83.9	0.43
epi-**3a**	*i*Pr	R_S, 4*R*[a)]	92	96	61	-56.6	0.36
3b	Ph	S_S, 4*R*	91	>98	87	+127.4	0.32
epi-**3b**	Ph	R_S, 4*R*	92	98	123	-126.7	0.24
3c	*i*Bu	R_S, 4*S*	74	b)	58	-105.7	0.37
epi-**3c**	*i*Bu	S_S, 4*S*	61	b)	72	-38.4	0.31
3d	Me	R_S, 4*S*	69	b)	113	-76.4	0.24
epi-**3d**	Me	S_S, 4*S*	47	b)	90	+58.7	0.20

a) Absolute configuration derived from X-ray structural analysis[3]. All other configurations were tentatively assigned by extrapolating the observation that the *lk*-diastereomer *epi*-**3a** is the more polar one. b) Cyclisation without prior separation of the sulfinamides, thus conserving their diastereomeric ratio. c) R_f-values of **3a-c** taken in ether/hexane = 1:1, the one from **3d** in ethyl acetate/hexane = 1:1.

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6. *General procedure:* To the solution of 240 mg (1.0 mmol) sulfinamide **1a** (S_S) in 5 ml of THF at -78°C is added 120 mg (1.1 mmol) *t*butyl hypochlorite. After stirring at this temperature for 30 min, 305 mg (2.0 mmol) of DBU are added and the mixture is stirred for another 15 min. The reaction is quenched with saturated, aqu. NH_4Cl, the aqueous layer washed with ether three times and the combined extracts dried over $MgSO_4$. The resulting crude sulfonimidate is recrystallised from ether/hexane to yield 213 mg (89%) of pure *epi*-**3a**.
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