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On the Reaction of Chiral Sulfinimines with Sulfur Ylides: A Novel Route to the Asymmetric Aziridination

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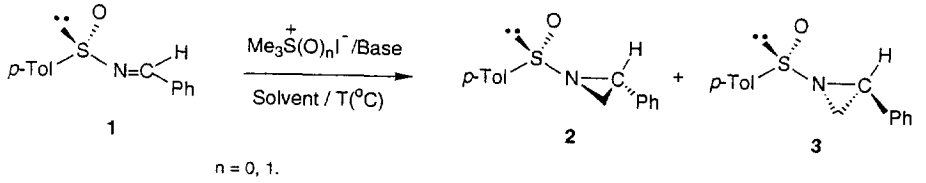
Abstract: The reaction of optically pure N-sulfinyl phenylimine with dimethyloxosulfonium methylide (**A**) and dimethylsulfonium methylide (**B**) yields a mixture of N-sulfinylaziridines, epimers at C-2, which are easily separated. The stereochemical outcome of this aziridination was shown to be dependent on the nature of the methylene transfer reagent. The elimination of the sulfinyl group occurs under mild conditions, leading to optically pure phenyl aziridines.

The seminal work by Corey[1] on the formation of dimethyloxosulfonium methylide (**A**) and dimethylsulfonium methylide (**B**) as methylene transfer reagents has found extensive use in organic synthesis.[2] More recently an application of this reaction to the asymmetric cyclopropanation was reported, using a chiral vinyl sulfoxide as Michael acceptor.[3] Our continued interest in the asymmetric synthesis mediated by chiral sulfinyl groups,[4] prompted us to investigate the stereochemistry and reactivity of these methylene transfer reagents with chiral sulfinimines.[5] This would provide a convenient means, which had been lacking, for preparing non racemic monosubstituted aziridines.[6] The first substrate selected for this study was the optically pure (*S*)-(+)-N-p-tolylsulfinyl phenylamine **1**, whose synthesis and absolute configuration were recently reported.[7]



Scheme 1

The sulfinimine **1** was exposed to dimethylsulfonium and dimethyloxosulfonium methylide under a variety of conditions (temperature and solvent). [8] In table 1 are summarised the most significant results that were obtained in the course of this study.

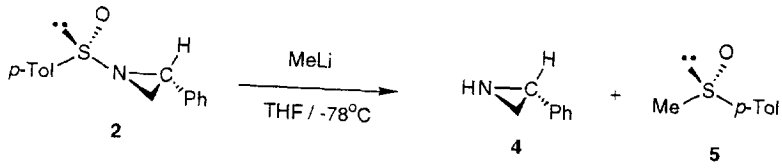
In all cases, the reaction gave rise to a mixture of the two diastereoisomers of N-p-tolylsulfinyl-2-phenylaziridine **2** and **3**, epimers at C-2, in high yield. The diastereoselectivity of the reaction for each run (table 1) was determined by ^{1}H-NMR spectral analysis of the crude material (all signals belonging to aziridine ring protons were quite distinct in **2** and **3**). Both diastereoisomers could be separated and obtained in their diastereomerically pure forms by a simple flash chromatography on silica gel. In Table 1 are indicated the results that were obtained at room temperature and at the lowest temperature in which the reaction occurs.

Two main facts can be deduced from Table 1. Firstly, the nature of the major diastereoisomer is related to the methylene transfer reagent used. Thus, **2** was formed as a major product when dimethyloxosulfonium methylide **A** was used, whereas **3** was predominant when the reagent **A** was substituted by dimethylsulfonium methylide **B**. Secondly, the solvent polarity has a small but significant effect on the stereochemical outcome of this aziridination. When dimethyloxosulfonium methylide (**A**) was employed, a decrease of the solvent polarity resulted in an increase of the diastereoselectivity. The highest **2:3** ratio (73:27, entry 7) was actually observed in toluene at room temperature. The result was just the reverse with dimethylsulfonium methylide (**B**). In this case the best diastereoselectivity was observed in polar solvent such as DMSO (36:64, entry 12). Finally, the ratio of **2** to **3** seems to be independent of the nature of the metal. Thus, substituting sodium hydride by n-BuLi, (entries 5, 6, 17 and 18) during the synthesis of both methylides did not lead to a significant change in the stereochemical outcome of the aziridination. Nevertheless, the yields were higher with BuLi.

Table 1: Reaction of (*S*)-N-sulfinimine (**1**) with dimehyloxosulfonium methylide (**A**) and dimethylsulfonium methylide (**B**) under different conditions.

Entry	Reagent	T (°C)	Solvent	**2:3** ratio	Yield (%)	Entry	Reagent	T (°C)	Solvent	**2:3** ratio	Yield (%)
1	A/NaH	rt.	DMF	58:42	85						
2	A/NaH	rt.	DMSO	57:43	91	11	B/NaH	rt.	DMF	43:57	79
3	A/NaH	rt.	CH_3CN	60:40	83	12	B/NaH	rt.	DMSO	36:64	73
4	A/NaH	rt.	CH_2Cl_2	57:43	85	13	B/NaH	rt.	CH_3CN	No reaction	
5	A/NaH	rt.	THF	70:30	78	14	B/NaH	rt.	CH_2Cl_2	No reaction	
6	A/BuLi	rt.	THF	67:33	80	15	B/NaH	rt.	Toluene	No reaction	
7	A/NaH	rt.	Toluene	73:27	95	16	B/NaH	-20	DMF	33:67	50
8	A/NaH	-20	THF	72:28	85	17	B/NaH	-25	THF	48:52	45
9	A/NaH	0	CH_2Cl_2	72:28	90	18	B/BuLi	-25	THF	46:54	81
10	A/NaH	-40	CH_3CN	72:28	92						

For the assignment of the absolute stereochemistry it was thought convenient to break the sulfur-nitrogen bond, since the absolute configuration of the resulting 2-phenyl aziridine was firmly established. When (+)-N-p-tolylsulfinyl-2-phenylaziridine **2** was treated with a solution of methyl lithium in THF at -78°C, the only compounds isolated and identified after column chromatography were (-)-2- phenylaziridine **4** (76%yield, $[\alpha]_D$=-40.7(EtOH, 0.3)[9] and (-)-methyl-*p*-tolylsulfoxide **5** (77%yield, $[\alpha]_D$=-140(acetone, 0.27)[10]. Thus, the compounds **4** and **5** were assigned as (***R***) and (***S***) and consequently the absolute configuration of (+)-N-p-tolylsulfinyl-2-phenylaziridine **2** was established as (S***S***, 2***R***).



Scheme 2

The change observed in the nature of the predominant diastereoisomer when changing the methylene transfer reagent (**A** and **B**), suggests two different pathways. The result obtained from the reaction of **A** with the sulfinyl imine **1** can be rationalised in terms of an equilibration between two betaines formed as intermediates. The most stable in polar solvents accounts for the formation of **2** as the major compound. Such an equilibration can be attributed to the great stability (lower reactivity) of the ylide deriving from **A**. The fact that the situation was the reverse when **B** was employed excludes the equilibration phenomena between both possible intermediates formed during the reaction. Decreasing the solvent polarity seems to favour the formation of the betaine that leads to the diastereoisomer **3**. One may think on a thermodynamic control in the first case and a kinetic control in the second, but neither of them has been undoubtedly proven.

At this point, it should be pointed out that the N-chiral sulfinyl group, by its presence in these systems, not only controls the diastereoselectivity to a certain extent and allows an easy access to both diastereoisomers in their pure forms, but also provides a distinct feature as a satisfactory protecting group for aziridines. Up to date, the most common way for protecting aziridine was the use of N-arylsulfonyl group, usually introduced before the aziridination process.[11] However, with the exception of the cleavage with samarium iodide reported recently[12] and limited to alkyl-substituted N-(arenesulfonyl)- aziridine, most of the attempts to break N-S bond in those systems had led to failure.[13]

In summary, the study reported herein had led to a short and efficient entry to the 2-arylaziridines family here illustrated with the synthesis of the naturally occurring 2-phenyl aziridine in their both possible configurations. The possibility to invert the stereoselectivity by changing the reagent and to obtain both N-sulfinyl aziridine diastereomers in their optically pure form by a simple flash chromatography compensates the modest diastereoselectivity observed. Finally, these reactions are a new example where reagents **A** and **B** act according to different pathways.

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5. For a recent review on the synthesis and biological importance of aziridine see Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599 and references cited therein.

6. During the preparation of this manuscript, an excellent method to synthesise enantiomerically pure 2,3-disubstituted aziridines, by reaction of the lithium enolate of α-bromo ethyl acetate with sulfinimines has been reported (Davis, F.A.; Zhou, P.; Reddy, G.V. *J. Org. Chem.* **1994**, *59*, 3243)

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8. Aziridination of sulfinimine with dimethyl oxosulfonium methylide in DMSO:
1.23 mmol of prewashed NaH was added portionwise to a solution of 1.23 mmol of dimethyloxosulfonium iodide in 5ml of dry DMSO. The mixture was stirred at room temperature until a completely clear solution was obtained. Sulfinimine **1** (0.41 mmol) was added as a net and the reaction mixture was stirred at room temperature for 3h (in some cases the reaction required more time depending on the temperature and solvent) and then poured onto crushed ice and extracted with ether. The ether layers were washed with NaCl sat., dried over $NaSO_4$ and evaporated under vacuo. The resulting mixture of diastereoisomers was analysed by ^{1}H-NMR and then separated by column chromatography (silica, ethyl acetate:n-hexane 1:15) to give 280 mg of **2** (33 % yield) and 506 mg of **3** (58 % yield).
The reaction with dimethyl sulfonium methylide was treated in similar way.
(+)-(SS,2R)-N-p-tolylsulfinyl-2-phenylaziridine **2**; mp 64-65°C; $[\alpha]_D$= +285(chloroform, 2.2). ^{1}H-NMR ($CDCl_3$, 200 MHz) 7.67-7.63 (m, 9H), 3.44 (dd, J=7.0 and 3.9, 1H, H-2), 2.83 (d, J=7.0Hz, 1H, H-3), 2.43(s, 3H); 1.81(d, J=3.9, 1H, H-3');^{13}C-NMR ($CDCl_3$, 50 MHz) 141.95, 141.84, 137.05, 129.55, 128.47, 127.84, 126.51, 124.86, 36.87, 26.5, 21.43. **Anal. Calcd** for $C_{15}H_{15}SON$: C, 70.01; H, 5.87; N, 5.44; S, 12.46. Found: C, 69.54; H, 5.71; N, 5.29; S, 12.59.
(+)-(SS,2S)-N-p-tolylsulfinyl-2-phenylaziridine **3**; mp 61-62°C; $[\alpha]_D$=-125 (chloroform, 6.3) ^{1}H-NMR ($CDCl_3$, 200MHz) 7.7-6.9 (m, 9H), 3.55 (dd, J=8.3 and 4.1, 1H, H-2), 2.63 (d, J=8.3, 1H, H-3), 2.3 (d. J=4.1, 1H, H-3'); ^{13}C-NMR ($CDCl_3$, 50MHz) 141.84, 141.68, 136.66, 129.49, 128.22, 127.39, 126.63, 124.75, 32.12, 30.86, 1.32 . **Anal. Calcd** for $C_{15}H_{15}SON$: C, 70.01; H, 5.87; N, 5.44; S, 12.46. **Found**: C, 69.67; H, 5.81; N, 5.40; S, 12.66

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