ROLE OF HETEROCYCLES ON THE STEREOSELECTIVE REACTIONS OF α-SULFINYL CARBANIONS USING OPTICALLY ACTIVE 2-PYRIDYLMETHYL p-TOLYL AND 2-(N-METHYLIMIDAZOLYL)METHYL p-TOLYL SULFOXIDES WITH ALDEHYDES

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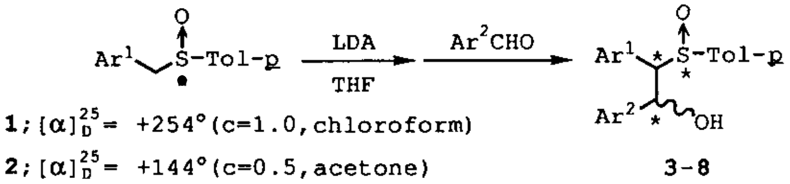
Abstract---Optically active 2-pyridylmethyl p-tolyl (**1**) and 2-(N-methylimidazolyl)methyl p-tolyl sulfoxides (**2**) were synthesized and the reactions of their chiral α-sulfinyl carbanions with aldehydes afforded stereoselectively the condensation products. The absolute configurations of the products were determined by X-ray crystallographic analysis and chemical reactions. The mechanism for the reactions is described.

Chiral α-sulfinyl carbanions have been widely utilized for asymmetric synthesis.[1] Simple dialkyl or alkyl aryl sulfoxides have been employed as common chiral sources, however a few optically active sulfoxides bearing heterocycles have attracted attention.[2,3] Recently, we reported highly stereoselective methylation using optically active α-sulfinyl carbanion of pyridylmethyl p-tolyl sulfoxide with iodomethane.[4]

In order to investigate the role of heterocycles in the stereoselective reactions, several optically active sulfoxides bearing heterocycles were prepared and subjected to react with aldehydes. This paper describes representative results on the reactions of α-sulfinyl carbanions of 2-pyridylmethyl p-tolyl (**1**) and 2-(N-methylimidazolyl)methyl p-tolyl sulfoxides (**2**) with aldehydes. Optically active sulfoxides (**1**) and (**2**) were prepared by the Andersen's procedure[5] using 2-methylpyridine or 1,2-dimethylimidazole. The absolute configuration of **1** has been reported to have an R configuration by X-ray crystallographic analysis.[4] The condensation reactions of α-sulfinyl carbanions of **1** and **2** with aldehydes were carried out in *tetrahydrofuran (THF) using LDA (lithium* diisopropylamide) as a base under argon atmosphere at either -78 °C or 0 °C. After usual work-up, the conceivable four products (**a-d**) were separated by column chromatography and their ratios were determined by measuring the peak areas of the doublet peaks of the α-CH in the product mixture by ^{1}H-nmr (500 MHz). The results are shown in Scheme 1 and Table 1.



1; $[\alpha]_D^{25}$= +254°(c=1.0,chloroform)

2; $[\alpha]_D^{25}$= +144°(c=0.5,acetone)

3-8

Scheme 1

Table 1, Reactions of α-lithio sulfoxides with aldehydes

Subst. Ar^1	Electrophile Ar^2	Temp. (°C)	Product	Yield (%)	Diastereomeric Ratio c) **a**	**b**	**c**	**d**
2-Py a) (**1**)	Phenyl	-78	(**3**)	84	14.6	2.5	3.5	1.0
		0		83	1.0	7.6	1.2	2.0
	p-Tolyl	-78	(**4**)	88	14.0	3.0	2.8	1.0
		0		85	1.4	6.9	1.0	1.2
	p-Anisyl	-78	(**5**)	98	13.7	4.2	2.7	1.0
		0		99	1.0	9.4	1.6	1.8
	p-ClC_6H_4	-78	(**6**)	85	7.8	1.2	1.0	trace
		0		81	1.4	14.1	1.0	1.5
	p-$CF_3C_6H_4$	-78	(**7**)	92	19.0	2.1	7.1	1.0
		0		92	1.1	2.8	1.2	1.0
N-MeIm b) (**2**)	Phenyl	-78	(**8**)	81	17.1	2.3	3.6	1.0
		0		76	trace	22.0	1.0	trace

a) 2-Pyridyl b) 2-(*N*-methylimidazolyl) c) Determined by ^{1}H-nmr

In the reaction of **1** with benzaldehyde one major diastereomer (**3a**)[6] was obtained together with other three minor isomers in total yield of 84% in a ratio of 14.6:2.5:3.5:1.0. Interestingly, when the reaction was carried out at 0 °C, the product ratio was changed dramatically to 1.0:7.6:1.2:2.0 and **3b**[6] became the major diastereomer. The absolute configuration of **3b** was determined by X-ray crystallographic analysis as shown in Figure 1 indicating that **3b** has $R_SR_{C\alpha}S_{C\beta}$.[7] In the crystals of **3b**, two aromatic and pyridine rings take a Gauche conformation in each other as shown in Figure 1 suggesting that phenyl-pyridyl stacking effect may play a significant role for approaching the aldehyde to the carbanion. Since the carbanions of methylpyridines at -78 °C have been analyzed by ^{1}H-nmr to be nearly sp^2 hybridization[9] and Li cation may be chelated by both the nitrogen of the pyridine ring and the sulfinyl oxygen atom, benzaldehyde approaches to the carbanion of **1** from its *re*-face preferentially giving **3a** as shown in [**A**] in Figure 2, while at higher temperature Li cation may not be chelated enough to be able to fix the conformation like [**A**] and the *si*-face attack of the aldehyde becomes the more prefered transition state or intermediate affording the major product (**3b**) (thermodynamically stable product). Since the absolute configuration of the sulfur atom in **a-d** is R, the configurations of Cα and Cβ in **3a,c,d**, were determined using the following two reactions. When **3a** was treated with n-BuLi (reaction A), an S_N2 type substitution took place on the sulfinyl sulfur atom[8] to give (-)-1-phenyl-2-(α-pyridyl)ethanol (**9**) in 36% yield. On the other hand, the treatment of **3a** with LAH (lithium aluminum hydride) (reaction B) gave both the reduction product (**10a**) in 23% together with (-)-**9** in 34% yield respectively.

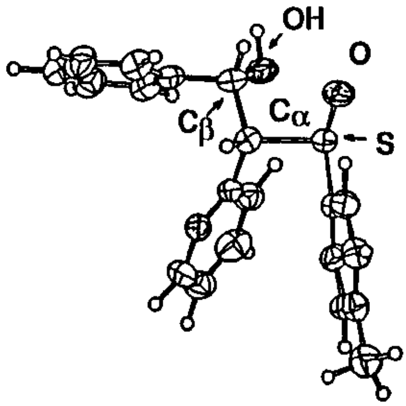
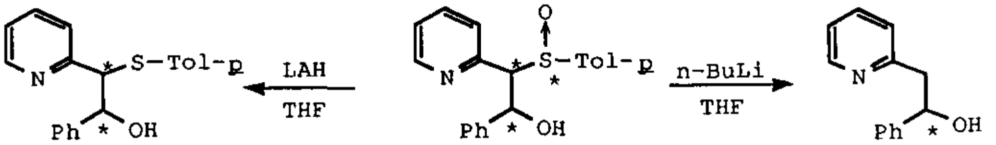


Figure 1. The crystal structure of compound (**3b**)

Similarly other diastereomers (**3b**) and (**3c**) were converted to the corresponding desulfinylation and reduction products. The structures of the products were confirmed by ^{1}H-nmr and their optical rotations . The results are shown in Scheme 2 and Table 2. From these chemical procedures, both **3a** and **3b** gave structurally identical products, namely (-)-**9** or (+)-**9** (from the reaction B) or a mixture of (-)-**9** and **10a** or (+)-**9** and **10b** (from the reaction A). Since the absolute configuration of (+)-**9** is known to be S, the structure of (-)-**9** can be determined to be R and hence **3a** has $R_SS_{C\alpha}R_{C\beta}$. The configuration of **3c** was determined similarly as described above to be $R_SS_{C\alpha}S_{C\beta}$ and hence **3d** should have $R_SR_{C\alpha}R_{C\beta}$. The configuration of sulfoxide (**2**) was determined by comparing the cd spectrum[10] with that of benzyl and 2-pyridyl analogues of the known configurations since in the similar structure, the sign of the Cotton curve



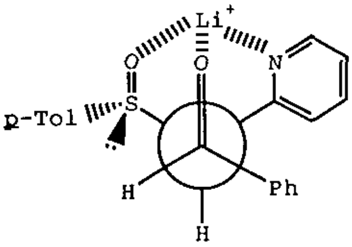
10a-c + (+)or(-)-**9** reaction A **3a-c** reaction B (+)or(-)-**9**

Scheme 2

Table 2, Determination of stereochemistry at Cα and Cβ positions by reduced and desulfinylated compounds of **3**

Subst.	Product	^{1}H-nmr (δ)	$[\alpha]_D^{25}$	Configuration[a)]
3a	(-)-**9**		-20.5°(c=1.6,CHCl$_3$)	$R_SS_{C\alpha}R_{C\beta}$
	10a	5.28(d,J=4.3 Hz,1H,C$_\alpha$H)		
		4.40(d,J=4.3 Hz,1H,C$_\beta$H)		
3b	(+)-**9**		+20.5°(c=1.3,CHCl$_3$)	$R_SR_{C\alpha}S_{C\beta}$
	10b	5.28(d,J=4.3 Hz,1H,C$_\alpha$H)		
		4.41(d,J=4.3 Hz,1H,C$_\beta$H)		
3c	(-)-**9**		+21.0°(c=1.5,CHCl$_3$)	$R_SS_{C\alpha}S_{C\beta}$
	10c	5.42(d,J=4.0 Hz,1H,C$_\alpha$H)		
		4.27(d,J=4.0 Hz,1H,C$_\beta$H)		

a) The configuration of **3d** is $R_SR_{C\alpha}R_{C\beta}$.



[A]

Figure 2

on the cd spectrum is known to give the identical absolute configuration.[11] The sulfoxide (**2**) also gave nearly an identical product distribution in comparison with the reaction of **1** with benzaldehyde. The result is summarized in Table 1. These aldol condensations of α-sulfinyl carbanions of **1** and **2** with aldehydes give higher stereoselectivity than that of the corresponding phenyl derivative.[12] Thus, the optically active sulfoxides having heterocycles as ligands are promissed to become useful reagents for organic synthesis.

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6. **3a**; mp 127-128 °C; ^{1}H-nmr ($CDCl_3$) δ 8.65-8.43 (m, 1H, 6-PyH), 7.87-6.87

(m, 12H, 3,4,5-PyH, ArH), 4.99 (d, J=4.0Hz, 1H, CHSO), 3.98 (d, J=4.0Hz, 1H, CHOH), 2.45 (s, 3H, $PhCH_3$); Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68, N, 4.15. Found: C, 71.39; H, 5.48; N, 4.15. **3b**; mp 143.5-145 °C; ^1H-nmr ($CDCl_3$) δ 8.55-8.35 (m, 1H, 6-PyH), 7.33-6.87 (m, 12H, 3,4,5-PyH, ArH), 5.85 (m, 1H, CHSO), 3.95 (m, 1H, CHOH), 2.31 (s, 3H, $PhCH_3$); Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68, N, 4.15. Found: C, 71.12; H, 5.71; N, 4.08.

7. Crystal data for **3b**: $C_{20}H_{19}NO_2S$, monoclinic, space group $P2_1$, a=12.383(3)b=6.031(1), c=11.840(2) Å, β=100.33(2)°, U=869.8 $Å^3$, Z=2, D_c=1.288 gcm^{-3} Mo-Kα radiation (λ=0.711Å), a Rigaku AFC-5 diffractometer, 1700 reflections (3°≤2θ≤50°), 1410 observed with $F_0 \geq 3\sigma \geq (F_0)$. The value was 0.051($R_w$=0.049)

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10. **2** has two cd bands, one at 254μm ([θ]= +8.0 x 10^4) and another at 227μm ([θ]= -5.7 x 10^4). Detailed results will be published elsewhere.

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