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Stereochemical Proof for Front Side Deuteride Attack via σ-Sulfurane in the Reductive Desulfinylation of Sulfoxides with Lithium Aluminum Deuteride

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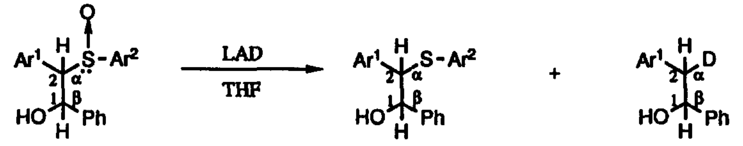
Abstract: Stereochemical results obtained from the concomitant reduction and desulfinylation of 1-phenyl-2-pyridyl-2-(p-tolylsulfinyl)- and 1,2-diphenyl-2-phenylsulfinyl ethanols with lithium aluminum deuteride reveal that the reactions proceed stereospecifically via σ-sulfurane as a common intermediate.

Tricoordinated organic sulfur compounds such as sulfoxides and sulfilimines are readily reduced to sulfides by treatment with various hydrides such as lithium aluminum hydride (LAH).[2] The mechanism accepted proceeds via an initial attack of hydride ion on the sulfinyl sulfur to give σ-sulfurane as an intermediate.

Meanwhile, the reactions of sulfoxides bearing heterocycles have been known to react with Grignard and organolithium reagents to afford not only ligand-coupling but also ligand-exchange products via σ-sulfuranes.[3] Recently, Kim and Oae have proposed that reduction of sulfilimines with LAH also proceeds via ligand-coupling within σ-sulfuranes as intermediates on the basis of substituent effect for the reactions.[4] Furthermore we found that several sulfoxides on treatment with LAH[5] afforded the desulfinylated products together with the sulfides. When lithium aluminum deuteride (LAD) was used in place of LAH, deuterium was incorporated quantitatively and stereospecifically into the α-carbon atom of desulfinylated compounds. In this paper, we describe the stereochemical results for this unusual reductive desulfinylation of the sulfoxides on the basis of ligand-coupling process via σ-sulfurane.

A typical experimental procedure is as follows: A solution of erythro 1-phenyl-2-pyridyl-2-(p-tolylsulfinyl) ethanol (1a)[6] (200 mg, 0.59 mmol) in dry tetrahydrofuran (THF) (10 mL) was slowly added to a suspension of LAD (55 mg, 1.30 mmol) in dry THF at 0 °C under an argon atmosphere, then the mixture was stirred at room temperature for 8 h. After usual work-up, the crude products were separated and purified by column chromatography (silica gel, ethyl acetate : n-hexane = 1 : 1) to give pure 1-phenyl-2-pyridyl-2-(p-tolylthio) ethanol (3a) (54.6 mg, 39 %) and 2-deuterio-1-phenyl-2-pyridyl ethanol (5a) (49.8 mg, 42 %) (Scheme 1).

The configurations of C_α and C_β in the products **3a** and **3b** were confirmed to be identical with those of the starting sulfoxides **1a** and **1b** whose structures had been determined previously[5] and deuterium was not indeed incorporated at the C_α in 3 by inspection of their ^{1}H NMR spectra. Thus, the reduction should proceed at the sulfur atom and not via the Pummerer type reaction involving an initial α-proton elimination by LAD as shown in Scheme 3.



1; Ar^1= 2-Pyridyl, Ar^2 = *p*-Tolyl
2; Ar^1, Ar^2 = Phenyl

3; Ar^1= 2-Pyridyl, Ar^2 = *p*-Tolyl
4; Ar^1, Ar^2 = Phenyl

5; Ar^1= 2-Pyridyl

6; Ar^1= Phenyl

Ar^1	compd (configuration)	compd (Yield)	
2-Pyridyl	**1a** ($R_SR_{C\alpha}S_{C\beta}/S_SS_{C\alpha}R_{C\beta}$)	**3a** (39 %)	**5a** (42 %)
	1b ($R_SS_{C\alpha}S_{C\beta}/S_SR_{C\alpha}R_{C\beta}$)	**3b** (21 %)	**5b** (60 %)
Phenyl	**2a** ($R_SS_{C\alpha}R_{C\beta}/S_SR_{C\alpha}S_{C\beta}$)	**4a** (28 %)	**6a** (52 %)
	2b ($R_SR_{C\alpha}R_{C\beta}/S_SS_{C\alpha}S_{C\beta}$)	**4b** (34 %)	**6b** (47 %)

Scheme 1

On the other hand, the configurations of **5a** and **5b** were determined by ^1H and ^{13}C NMR spectroscopy, while the deuterium contents were determined by mass spectroscopy. Interestingly, since the desulfinylated compounds **5a**, **5b** and **6a**, **6b**[7] were found to be a sole diastereomer, namely either one of the two diastereomers, erythro($R_{C\alpha}S_{C\beta}/S_{C\alpha}R_{C\beta}$) or threo($S_{C\alpha}S_{C\beta}/R_{C\alpha}R_{C\beta}$) form, determined by their ^1H NMR spectra, the desulfinylation reaction at the C_α in **1** or **2** takes place either by an S_N2 like pathway which may give rise to inversion of the configuration or by ligand coupling via σ-sulfurane with retention of the configuration. It is well known that vicinal ^1H-^1H and ^{13}C-^1H coupling constants follow a Karplus type relationship with the dihedral angles[8] so that gauche-coupling constant is expected to be much smaller than trans-coupling constant. The vicinal ^1H-^1H and ^{13}C-^1H coupling constants of **5a** and **5b** are summarized in Table 1.[9]

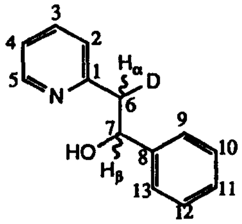
The $^3J_{HH}$ coupling constants of **5a** and **5b** are 9.4 Hz and 1.7 Hz respectively indicating that the relative configuration between two methine protons should take nearly trans in **5a**, while cis in **5b**. Similarly, the $^3J_{CH}$ coupling constants of **5a** and **5b** are also 1.7 Hz indicating that the relative configuration between β-phenyl group and α-proton should take cis in both cases.[10] Thus, the configuration can be determined to be erythro for **5a** and threo for **5b** respectively (Fig. 1).

Furthermore, in order to determine the configurations of **6a** and **6b** obtained, we prepared erythro isomer **6a'** ($R_{C\alpha}S_{C\beta}/S_{C\alpha}R_{C\beta}$) which was readily synthesized from trans-stilbene as shown in Scheme 2.[11] Since the ^1H NMR spectra of **6a'** thus obtained was identical with that of **6a**, the configuration of **6a** was identified

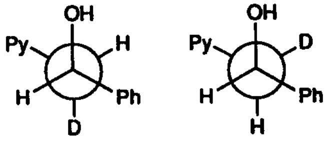
Table 1. The vicinal ^1H-^1H and ^{13}C-^1H coupling constants of **5a** and **5b**.

compd	$^3J_{H\alpha\text{-}H\beta}$ (Hz)	irradiated position	$^3J_{C8\text{-}H10}$ (Hz)	$^2J_{C8\text{-}H\beta}$ (Hz)	$^3J_{C8\text{-}H\alpha}$ (Hz)
5a	9.4	-	-	-	-
	-	H_α	6.9	3.3	-
	-	H_β	6.9	-	1.7
5b	1.7	-	-	-	-
	-	H_β	6.9	-	1.7

$^2J_{C8\text{-}H9}$ and $^4J_{C8\text{-}H11}$ were not observed.

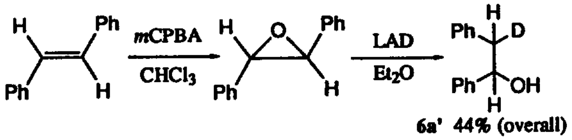


unambiguously as an erythro and hence **6b** as a threo isomer. This result demonstrates rationally that the deuterium atom in **6** was incorporated with complete retention in the desulfinylation via an initial formation of σ-sulfurane as an intermediate.



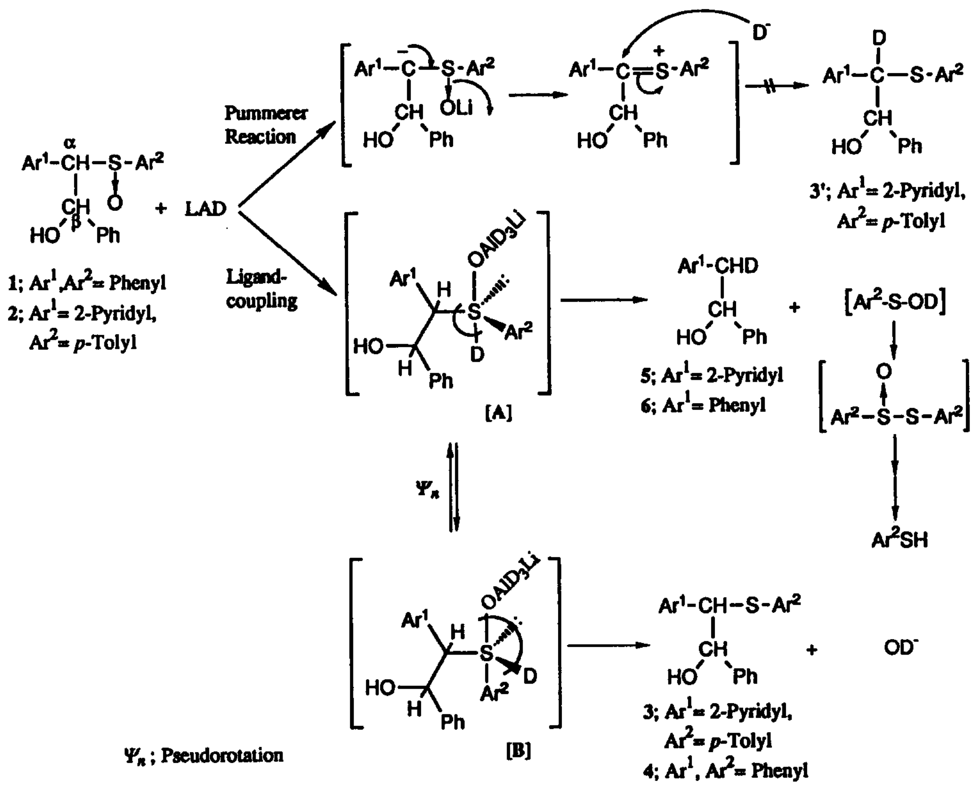
5a, erythro **5b**, threo

Fig. 1



Scheme 2

Consequently, the mechanism in the desulfinylation of sulfoxides **1** and **2** with LAD should proceed via an initial formation of the σ-sulfurane [A] as an intermediate from which the ligand coupling process involving either deuterium atom and α-carbon atom or sulfinyl oxygen atom with retention of configuration as illustrated in Scheme 3.



Ψπ ; Pseudorotation

Scheme 3

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4. K. S. Kim, I. B. Jung, Y. H. Kim, and S. Oae, *Tetrahedron Lett.*, **30**, 1087 (1989).
5. N. Furukawa, T. Sagae, and S. Ogawa, *Heterocycles*, **32**, 679 (1991).
6. Diastereomerically pure pyridyl sulfoxides **1a** and **1b** were prepared using 2-pyridylmethyl p-tolyl sulfoxide with benzaldehyde as described previously.[5]
7. Physical data of **5a**; mp 103-105 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.53 (d, J=4.6 Hz, 1H, 6-PyH), 7.61 (td, J=7.6 Hz, 1.7 Hz, 1H, 4-PyH), 7.42 (d, J=7.1 Hz 2H 2,6-PhH), 7.34 (t, J=7.3 Hz, 2H, 3,5-PhH), 7.26 (t, J=7.3 Hz, 1H, 4-PhH), 7.18 (dd, J=5.2 Hz, 5.1 Hz, 1H, 5-PyH), 7.10 (d, J=7.8 Hz, 1H, 3-PyH), 5.16 (d, J=9.4 Hz, 1H, PyOH), 3.13 (d, J=9.4 Hz, 1H, C$\underline{\mathrm{H}}$OH); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.7, 148.6, 144.4, 136.9, 128.4, 127.3, 126.0, 124.1, 121.8, 73.4, 46.2; MS m/z 200 (M$^+$), deuterium content = 90 %; **5b**; mp 102-104 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.53 (d, J=4.6 Hz, 1H, 6-PyH), 7.61 (td, J=7.6 Hz, 1.7 Hz, 1H, 4-PyH), 7.42 (d, J=7.1 Hz 2H 2,6-PhH), 7.34 (t, J=7.3 Hz, 2H, 3,5-PhH), 7.26 (t, J=7.3 Hz, 1H, 4-PhH), 7.18 (dd, J=5.2 Hz, 5.1 Hz, 1H, 5-PyH), 7.10 (d, J=7.8 Hz, 1H, 3-PyH), 5.15 (d, J=1.7 Hz, 1H, PyOH), 3.10 (d, J=1.7 Hz, 1H, C$\underline{\mathrm{H}}$OH); MS m/z 200 (M$^+$), deuterium content = 89 %; **6a**[11]; mp 63.5-64 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.35-7.17 (m, 10H, PhH), 4.88 (d, J=8.6 Hz, 1H, C$\underline{\mathrm{H}}$OH), 2.97 (d, J=8.6 Hz, 1H, CHD); **6b**[11]; mp 63.5-64 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.35-7.17 (m, 10H, PhH), 4.87 (d, J=4.7 Hz, 1H, C$\underline{\mathrm{H}}$OH), 3.00 (d, J=4.7 Hz, 1H, CHD)
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9. Vicinal ^{13}C-^{1}H coupling constants of **5a** and **5b** were determined from their natural abundance ^{13}C NMR spectra. An complicated coupling pattern at C8 carbon in CDCl$_3$ was observed with non-decoupling mode, then H_α and H_β protons were decoupled respectively.
10. It has been reported that a coupling constant of 1 Hz would be expected for gauche ^{13}C-^{1}H groups, and 8 Hz for trans groups from the plot of $^{3}J_{CH}$ vs. dihedral angle by Lemieux *et al.*[8]
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