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MECHANISTIC STUDIES OF PUMMERER REACTION IN ACYCLIC SULFOXIDES INDUCED BY O-SILYLATED KETENE ACETALS†

Yasuyuki Kita,* Norio Shibata, Naoki Yoshida, Seiji Fukui, and Chino Fujimori

Faculty of Pharmaceutical Sciences, Osaka University 1-6, Yamada-oka, Suita, Osaka 565, Japan

Abstract: The Pummerer reaction of acyclic sulfoxides with O-silylated ketene acetal has been shown to proceed with high diastereoselective deprotonation of the α-methylene proton. A plausible reaction mechanism involving the *anti* elimination process is proposed from deuterium-labeling experiment.

The asymmetric Pummerer reaction of optically active sulfoxides,[1-5] which is one of the self-immolative-type asymmetric inductions,[6] is of significant interest from both a synthetic and mechanistic point of view. The detailed studies of the Pummerer reaction using ^{18}O tracer experiments [7] showed intermolecular rearrangements to be involved, however, the whole mechanism is still obscure, especially, the reaction of chiral acyclic sulfoxides. In the late 1970's, the first asymmetric Pummerer reaction of chiral acyclic sulfoxides was independently reported by Oae et al.[3] and Mikołajczyk et al.[4] (eq. 1). The extent of asymmetric induction, however, never exceeded 30 % e.e. probably due to the formation of a sulfurane intermediate by the reaction with the generated acetate anion. Although the stereoselectivity was improved up to 70 % ee by the addition of 1,3-dicyclohexylcarbodiimide (DCC) as an effective scavenger of acetic acid, the chemical yield decreased to 10 % [5] and the Pummerer reaction of chiral benzyl tolylsulfoxide (R-1a) in the presence of DCC gave only a racemic adduct via the sulfonium intermediate (eq. 2). [8] Wolfe and Kazmaier studied the diastereotopic
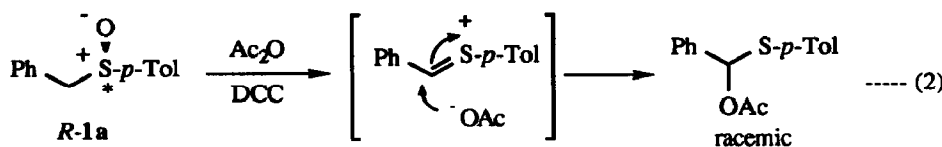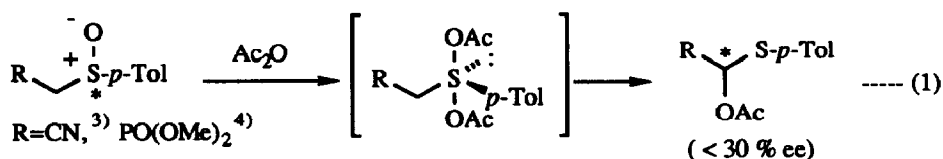

selectivity in the deprotonation step of *syn* and *anti*-α-deuteriobenzyl methyl sulfoxides under normal Pummerer conditions. [9] According to their paper, little selectivity was observed because of competing epimerization at the sulfur via the sulfurane intermediate. Furthermore, regioselectivity was not evident in the reaction, i.e., the Pummerer reaction of benzyl methyl sulfoxide (1b) gave two regioisomers (α-acetoxybenzyl methyl sulfide and α-acetoxymethyl benzyl sulfide) in a ratio of 45:55 in 39% yield (eq. 3). Several years ago, we reported a novel silicon-induced Pummerer-type reaction of sulfoxides using O-methyl-O-*tert*-butyldimethylsilyl ketene acetal (2), which gave α-siloxysulfides under mild conditions[10] and very recently applied this method to the novel highly

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† This paper is dedicated to Professor Yoshifumi Maki on this occasion of his retirement from Gifu Pharmaceutical University in March 1994.

asymmetric induction of some special sulfoxides (R-1c, d, R=CO2Et, CONMe2) leading to chiral α-siloxysulfides (R-3) in high yield (eq. 4).[11]
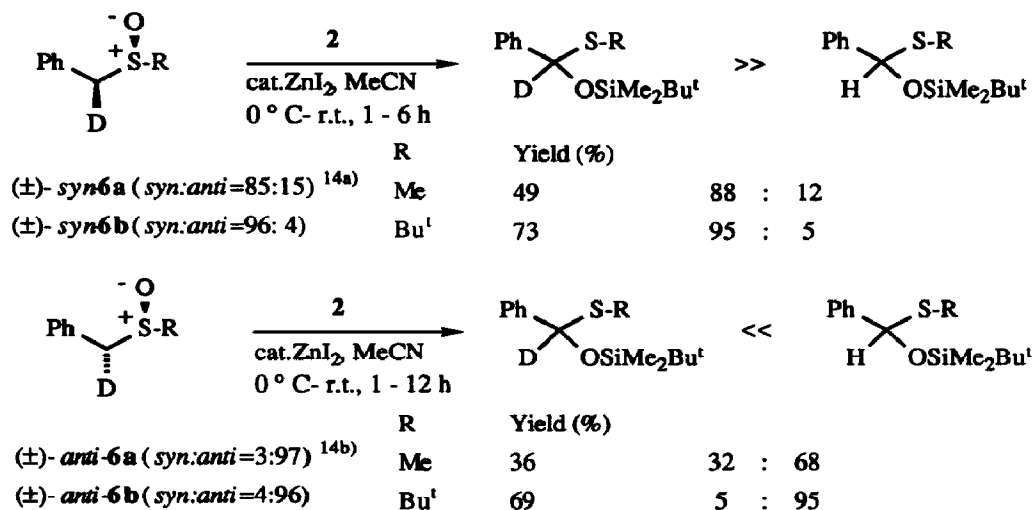
$$\text{(3)}$$

$$\text{(4)}$$
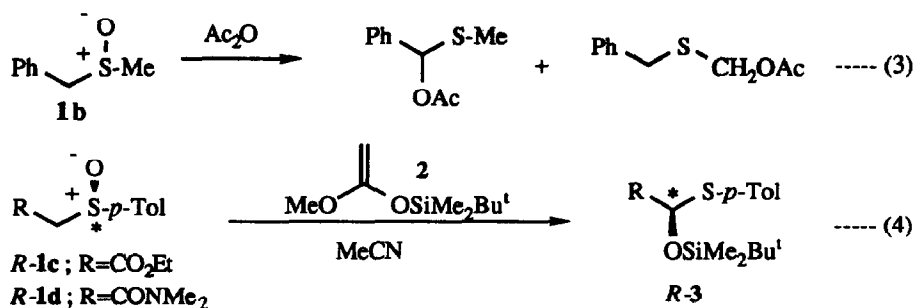
We now found that chiral benzyl tolyl sulfoxide (R-1a) was subjected to our silicon-induced Pummerer-type reaction to give optically active α-siloxysulfide (R-4) with high enantioselectivity (eq. 5). Treatment of R-1a with 2 in the presence of a catalytic amount of ZnI2 in MeCN at 0 °C-r.t. for 3-5 h gave an 87 % yield of the chiral sulfide (R-4) [12] {[α]$_D^{22}$ =+24.6°(acetone)} in about 70 % ee. The optical purity was determined by chiral Daicel AS HPLC column.

$$\text{(5)}$$
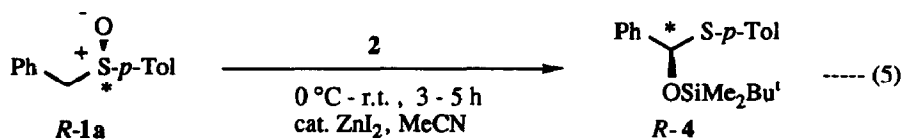
Next, we investigated the reaction of benzyl methyl sulfoxide (1b), benzyl t-butyl sulfoxide (5), and their α-deuteriated compounds (6a, 6b) [13] with 2 and found that the deprotonation of the α-proton occurred with both high regio and diastereoselectivities and that the diastereoselectivity was dependent on the deprotonation step. Treatment of 1b with 2 in the presence of a catalytic amount of ZnI2 in MeCN gave α-siloxysulfide (7a) accompanied by a small amount of regioisomer, α-siloxymethyl benzyl sulfide (8) (eq. 6).

$$\text{(6)}$$

1b ; R=Me
5 ; R=Bu^t

7a ; R=Me, 61 %
7b ; R=Bu^t, 75 %

8 ; 2 %
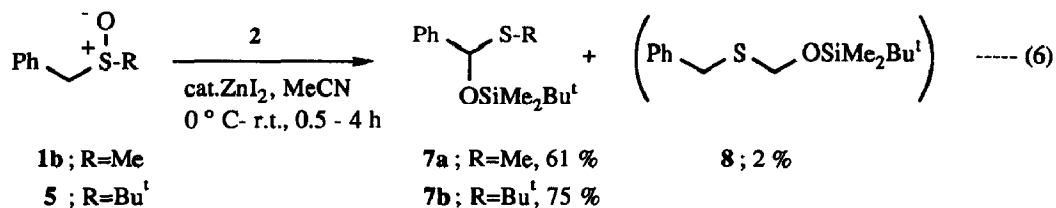
High diastereospecific deprotonation of the α-methylene proton was observed in both syn- and anti-α-deuteriobenzyl methyl-(6a) [13, 14] and α-deuteriobenzyl t-butyl sulfoxides (6b).[13] These results are shown in Scheme 1.
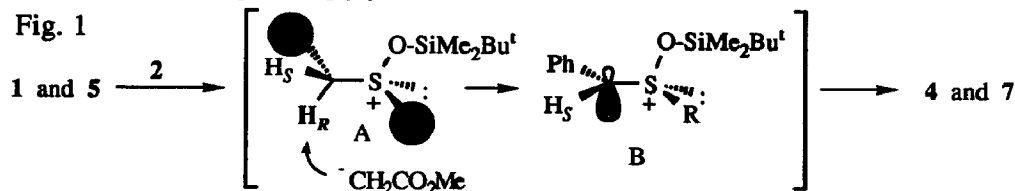
Scheme 1 Silicon-Induced Pummerer Reaction of α-Deuteriated Sulfoxides (6a and 6b)

	R	Yield (%)			
(±)- syn-6a (syn:anti=85:15) [14a]	Me	49	88	:	12
(±)- syn-6b(syn:anti=96: 4)	Buᵗ	73	95	:	5

	R	Yield (%)			
(±)- anti-6a (syn:anti=3:97) [14b]	Me	36	32	:	68
(±)- anti-6b(syn:anti=4:96)	Buᵗ	69	5	:	95

Finally, we applied this reaction to a kinetic resolution. A mixture of chiral sulfoxide (a mixture of isomers, 1a:1e:1f:1g= 15: 50:24: 11[15]), prepared from R-1a with n-BuLi / D₂O) was reacted with 2 under the same conditions. The reaction was monitored by T.L.C. and stopped at about 50 % conversions. The recovered sulfoxides were found to have a different ratio of isomers, 1a:1e:1f:1g= 3:15:50:32 and the deuterium content of 4 was 77 %. In this experiment, discrimination was observed between the two monodeuteriated sulfoxides 1e and 1f. The isotope effect leads to a decrease in the rate of α-hydrogen abstraction of 1f thus allowing a kinetic resolution. This result suggested that 4 was produced with complete loss of the sulfinyl pro-R hydrogen in R-1a (Scheme 2).

Scheme 2 Kinetic Resolution of 1 with 2
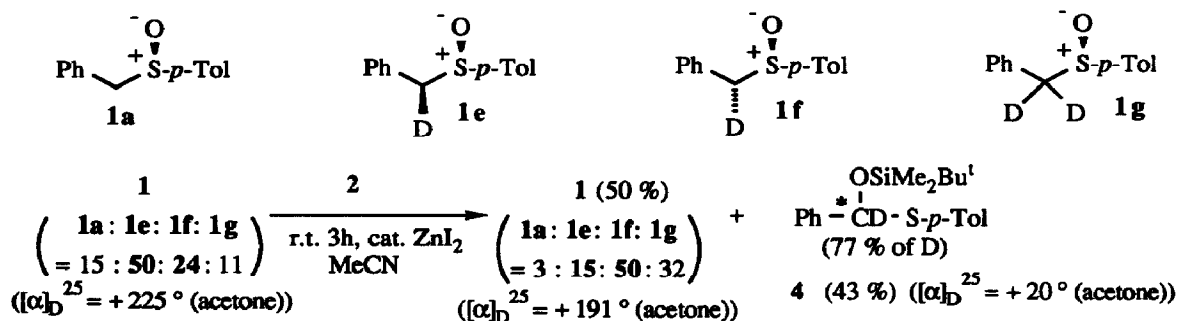
The following mechanism is proposed to explain the present results (Fig. 1). Silylation of sulfoxides with 2 affords an intermediate (A). Thus, A may yield an anion intermediate (B) through abstraction of the pro-R* hydrogen (anti-periplanar hydrogen) with a generated ester enolate from the opposite face of the sulfoxide oxygen, and the siloxy group may be forced to attack the α-position as soon as the anion intermediate (B) undergoes anti-elimination to result in the α-siloxysulfides. Although the exact reaction process for the attack of

siloxy anion to the α-carbon is not clear, it might be explained by the attack on the same face of the sulfinyl oxygen as discussed in our preceding paper.[11)]

Fig. 1

1 and 5 $\xrightarrow{2}$ [A] $\longrightarrow$ [B] $\longrightarrow$ 4 and 7

In conclusion, the first selective deprotonation from acyclic sulfoxides[16)] was observed via our silicon-induced Pummerer-type reaction. Further details of the relationship between a selective deprotonation and a chirality transfer from sulfur to the α-carbon are currently under investigation.

References and Notes

1. a) McCormick, J. E.; McElhinney, R. S. *Chem. Commun.* **1969**, 171; b) Glue, S.; Kay, I. T.; Kipps, M. R. *ibid.* **1970**, 1158.

2. a) Stridsberg, B.; Allenmark, S. *Acta Chem. Scand.* **1974**, *B28*, 591; b) Idem *ibid.* **1976**, *B30*, 219; c) Wolfe, S.; Kazmaier, P. M.; Auski, H. *Can. J. Chem.* **1979**, *57*, 2404; Kaneko, T.; Okamoto, Y.; Hatada, K. *J. Chem. Soc. Chem. Commun.* **1987**, 1511.

3. a) Numata, T.; Oae, S. *Tetrahedron Lett.* **1977**, 1337; b) Numata, T.; Itoh, O.; Oae, S. *Chem. Lett.* **1977**, 909.

4. Mikołajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W. *J. Org. Chem.* **1978**, *43*, 2518.

5. a) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett.* **1979**, 1869; b) Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257.

6. Mislow, K. *"Introduction to Stereochemistry"*, **1966**, Benjamin W. A..

7. Reviews, see: a) Oae, S.; Numata, T. "The Pummerer Type of Reactions," in *"Isotopes in Organic Chemistry,"* ed. by Buncel, E.; Lee, C. C. Elsevier, New York, **1980**, Vol. 5. Chapter 2; b) Lucchi, O. D.; Miotti, U.; Modena, G. *Organic Reactions*, **1990**, *40*, 157.

8. Itoh, O.; Numata. T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 266.

9. Wolfe, S.; Kazmaier, P. M. *Can. J. Chem.* **1979**, *57*, 2388, 2397.

10. a) Kita, Y.; Yasuda, H.; Tamura, O.; Itoh, F.; Tamura, Y. *Tetrahedron Lett.* **1984**, *25*, 4681; b) Kita, Y.; Tamura, O.; Yasuda, H.; Itoh, F.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4235; c) Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Miki, T.; Tamura, Y. *ibid.* **1987**, *35*, 562.

11. Kita, Y.; Shibata, N.; Yoshida, N. *Tetrahedron Lett.* **1993**, *34*, 4063.

12. Absolute stereochemistry of R-4 was tentatively assigned from Ref. 11.

13. Nakamura, K.; Higaki, M.; Adachi, S.; Oka, S.; Ohno, A. *J. Org. Chem.* **1987**, *52*, 1414. Deuterium contents of all sulfoxides and α-siloxysulfides were determined by 200, 250, 270 MHz ^{1}H-NMR spectra.

14. a) Small amount of 1b (7 %) and dilabelled 1b (PhCD$_2$S(O)Me, 12 %) were contained. b) Small amount of 1b (19 %) and dilabelled 1b (PhCD$_2$S(O)Me, 6 %) were contained.

15. Stereochemistry of 1e and 1f was determined by the ^{1}H-NMR chemical shift of methylene proton in CDCl$_3$ (1e: 3.96 ppm. 1f; 4.08 ppm.). The *pro-R*-proton in R-benzyl *p*-chlorophenyl sulfoxide appeared at the higher field in CDCl$_3$; Nishio, M. *Chem. Commun.* **1968**, 562.

16. Although, a clear-cut example of *anti*-elimination in the normal Pummerer reaction was suggested by Oae *et al.*, it is limited only to a rigid six-membered thiane 1-oxide; Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 270.