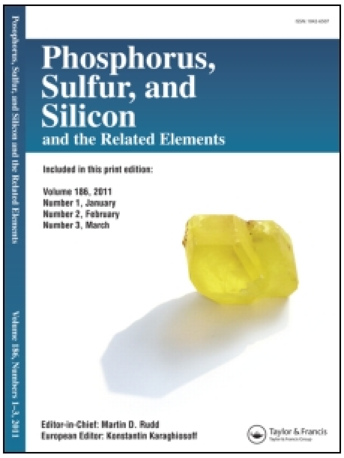

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PUMMERER-TYPE REACTION OF SULFILIMINES WITH ACETIC ANHYDRIDE

Naomichi Furukawa[ab]; Toshiaki Yoshimura[a]; Shigeru Oae[ab]
[a] Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sumiyoshi-ku, Osaka, Japan [b] Department of Chemistry, The University of Tsukuba, Ibaraki, Japan

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PUMMERER-TYPE REACTION OF SULFILIMINES WITH ACETIC ANHYDRIDE

NAOMICHI FURUKAWA,* TOSHIAKI YOSHIMURA and SHIGERU OAE*

Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sugimoto-cho, Sumiyoshi-ku, Osaka, Japan

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Methyl phenyl *N*-*p*-tosylsulfilimine was found to undergo Pummerer type rearrangement affording α-acetoxymethyl phenyl sulfide similar to the corresponding sulfoxide. In order to clarify the mechanism of the reaction of methyl p-substituted phenyl sulfilimines with acetic anhydride, kinetic experiments were carried out. A large negative value of activation entropy, a relatively small value of activation enthalpy and the influence of acetic acid seem to reveal that the initial intermediate, i.e., acetylated sulfilimine, receives the nucleophilic attack of acetate ion to replace imino group, and this substitution reaction is the rate determining step.

Sulfoxides bearing a methyl or methylene group directly attached to sulfur atom readily undergo Pummerer reaction upon reacting with acylating agents. Our earlier papers indicated that the rate determining step of the Pummerer reaction of methyl phenyl sulfoxide is α-proton removal.[1–3] Meanwhile, Pummerer type reaction of sulfilimines has been studied very little. Only recently Swern *et al.* reported Pummerer reaction of dimethyl *N*-acetylsulfilimine with acylating reagent,[4] however the mechanism has not been clarified. Sulfilimine has a semipolar S–N linkage like the S–O linkage in sulfoxides or the S–C linkage in sulfonium ylides. We found recently that a similar Pummerer type reaction takes place with sulfonium ylides. We now have extended a similar reaction to the sulfilimine in order to compare similarities and differences in the Pummerer type reactions of these three different trivalent sulfur species.[5] This paper describes a detail account of the Pummerer type reaction of methyl aryl *N*-*p*-tosylsulfilimine.

RESULTS AND DISCUSSION

A few substituted methyl phenyl sulfilimines and α-trideuterated derivative were synthesized and these sulfilimines were subjected to the Pummerer reaction. The products and yields in the reaction of methyl phenyl *N*-*p*-tosylsulfilimine with excess acetic anhydride at 120°C for 10 hours are shown in Table I.

TABLE I

The Distribution of Products (%) in the Reaction of Methyl Phenyl *N*-*p*-Tosylsulfilimine with Acetic Anhydride

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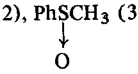
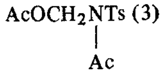
$PhSCH_2OAc$ (65%), TsNHAc (66), recovered (20)
PhSAc (3), PhSSPh (2), $PhSCH_2SPh$ (2),  $PhS(\rightarrow O)CH_3$ (3)
 $AcOCH_2N(Ac)Ts$ (3)

As shown in Table I, the main product is α-acetoxymethyl phenyl sulfide which is presumed to be formed by the Pummerer reaction. Therefore, in order to clarify the mechanism of this reaction, kinetic experiments were carried out and the results are shown in Table II.

As shown in Table II, the effects of substituents as correlated by Hammett σ values give relatively small negative ρ values, and the kinetic isotope effect is also found to be relatively small. These results show that the rate determining step could be neither the acetylation reaction of nitrogen nor the α-proton abstraction reaction of the acetylated sulfilimine. Another conceivable rate determining step is the heterolytic cleavage of the acetyltosylimino group as in the case of the similar Pummerer type reaction of sulfonium ylides (Elcb mechanism).[5] However, unlike the case of the sulfonium ylides, there is no hydrogen-deuterium exchange reaction of methyl group as shown in Table III, thus excluding the Elcb process.

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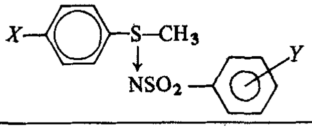
* Present address: Department of Chemistry, The University of Tsukuba, Sakura-Mura, Ibaraki, 300-31, Japan.

TABLE II

Kinetic Data of Pummerer Reaction of Substituted Methyl Phenyl Sulfilimines with Acetic Anhydride



X	*Y*		*k* x 10^5	
H	*p*-CH$_3$	120°C	2.76	$\Delta H^{\neq} = 15.2$ Kcal/mole
		129.8°C	4.46	$\Delta S^{\neq} = -41.2$ e.u.
		139.8°C	7.39	
H	H	120°C	2.07	$\rho_Y = -0.57$
	p-Br		1.45	
	m-NO$_2$		0.891	
CH$_3$	*p*-CH$_3$	120°C	4.08	
OCH$_3$			4.84	$\rho_X = -0.71$
Cl			2.10	
NO$_2$			0.883	
PhSCD$_3$ ↓ NTs		120°C	1.76	$k_H/k_D = 1.57$

TABLE III

H-D Exchange Reaction of Trideuteromethyl Phenyl *N*-*p*-Tosylsulfilimine with Acetic Anhydride in the presence of Acetic Acid

Conditions	Products and yields (%)	*H-D* exchange
120°C 1 hr	Recovered (64)	no
120°C 3 hrs	PhSCD$_2$OAc (41)	no
	PhSCD$_3$ ↓ O (29)	no
	TsNHAc (67)	

In addition, the activation enthalpy is very small and the activation entropy is large and negative as compared with the values of the Pummerer reaction of the corresponding sulfoxide with acetic anhydride (*Ea* = 21.2 Kcal/mole, $\Delta S^{\neq} = -20.7$ e.u.). However, they are of similar magnitude to those of the oxygen exchange reaction of the corresponding sulfoxide with acetic anhydride (*Ea* = 13.1 Kcal, $\Delta S^{\neq} = -45.1$ e.u.).[3]

This seems to support the idea that methyl phenyl-*N,N*-acetyltosyliminosulfonium salt formed in the initial acetylation step undergoes a rate-determining SN2 substitution on sulfur atom to replace the imino group by acetate anion, and this step is faster than the α-proton removal of the acetylated sulfilimine while slower than the following α-proton removal of the acetylated sulfoxide. The formation of a small amount of the sulfoxide shown in Table I and that of a considerable amount in the presence of acetic acid shown in Table III also support this contention. Other supporting evidence may be found in the effect of acetic acid. In the Pummerer reaction of sulfoxides, the rate determining step is the α-proton abstraction reaction and the rate acceleration effect of the addition of acetic acid is substantially small, whereas in the oxygen exchange and recemization reaction, this effect is very large.[3] This was found to be the case in this Pummerer-type reaction of the sulfilimine. Therefore, the over-all mechanistic scheme of the reaction of the sulfilimine with acetic anhydride seems to be as shown below.

Kinetic experiments on the Pummerer reaction of methyl phenyl *N*-*p*-tosylsulfilimine and the corresponding sulfoxide were carried out under the same conditions in the presence of acetic acid. In the case of the sulfilimine, the kinetic pattern became different from the original pseudo first order result; it changed to that of consecutive reaction upon the addition of acetic acid as shown in Figure 2. This seems to reveal that the rate of the substitution reaction of the iminosulfonium salt to the acetoxy-sulfonium salt is accelerated by the addition of acetic acid and becomes close to the rate of the following α-proton abstraction.

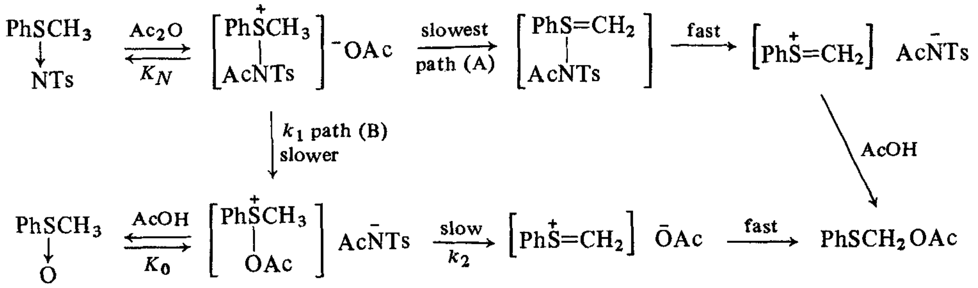


FIGURE 1 Mechanism of the Pummerer Reaction of the Sulfilimine.

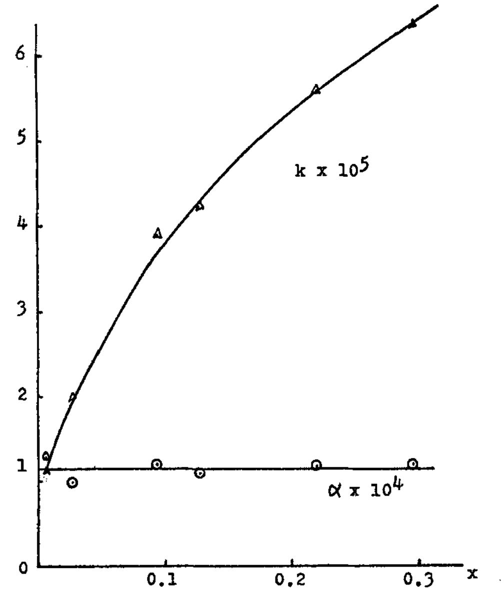


FIGURE 2 Rate constants variation *vs.* conversion. k: pseudo first order rate constant. α: two step consecutive rate constant. [AcOH] = 0.178 mole/l, $\beta = 3.69 \times 10^{-4}$ sec^{-1}.

In Figure 2, α was calculated as follows. The integrated rate equation shown below is based on the assumption of two consecutive reactions which involve the relatively fast equilibrium acetylation reaction of the sulfilimine and the sulfoxide while neglecting the α-proton abstraction reaction of the iminosulfonium salt (path (A)).

$$X = 1 - \frac{\alpha}{\alpha - \beta} e^{-\beta t} + \frac{\beta}{\alpha - \beta} e^{-\alpha t}$$

$$X = [\mathrm{PhSCH_2OAc}] \Big/ \left[\begin{matrix}\mathrm{PhSCH_3}\\ \downarrow\\ \mathrm{NTs}\end{matrix}\right]_0$$

$$\alpha = \frac{K_N k_1}{1 + K_N}, \quad \beta = \frac{K_0 k_2}{1 + K_0}$$

K_0, K_N, k_1 and k_2 are the values as shown in Figure 1. This equation is apparently the same as the one for the two consecutive reactions and β is theoretically the same as the rate constant of the Pummerer reaction of the sulfoxide in the same concentration of acetic acid. Therefore, this α was calculated by the use of the rate constant for the sulfoxide in the same concentration of acetic acid as for the β value in the above equation; α then became constant when plotted against the conversion as shown in Figure 2. Then α values were plotted against the concentration of acetic acid as shown in Figure 3.

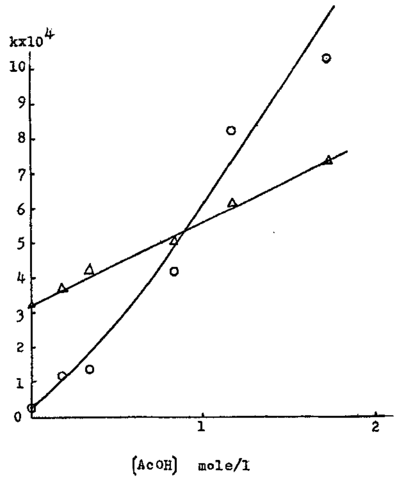


FIGURE 3 The influences of Acetic Acid to the Pummerer reaction of methyl phenyl N-p-tosylsulfilimine and the corresponding sulfoxide, ○: α values, △: β values (for sulfoxide).

As shown in Figure 3, α is very much accelerated by the increase of concentration of acetic acid, similar to the case of oxygen exchange and racemization reactions of the sulfoxide. Thus without acetic acid, the rate determining step should be the substitution reaction on sulfur by acetate anion. Though the kinetic isotope effect seems to show the intervention of the competitive reaction of the path (A), the main path should be the path (B) shown in Figure 1.

EXPERIMENTAL

Material The sulfilimines used in the study were prepared according to the well known method.[6]

Reaction of Methyl Phenyl N-p-Tosylsulfilimine with Acetic Anhydride Methyl phenyl N-p-tosylsulfilimine (0.5 gm.) was dissolved in 5 ml of acetic anhydride, and the mixture was heated at 120°C in a sealed tube for 10 hrs. After the reaction, the solution was decomposed with excess cold water, neutralized with sodium bicarbonate, and was extracted with chloroform. The chloroform extract was separated, washed with water and then dried over anhydrous sodium sulfate. After removing the solvent, the residue was chromatographed through a column packed with silica gel. The products obtained were all identified by comparing their i.r., n.m.r. and g.l.c. with those of the authentic samples prepared. N,N-acetyltosylaminomethyl acetate: m.p. 98.7-99°C; i.r. ν_{CO} 1725, 1750 cm^{-1}; n.m.r. methyl proton 7.56, 7.70, 7.93, methylene 4.15, phenyl protons 2.1-2.8. Anal. Found C: 50.21 H: 5.17 N: 4.71 Calcd. for $C_{12}H_{15}O_5NS$ C: 50.52 H: 5.30 N: 4.91. The yields are shown in Table I.

Kinetic Procedure of the Pummerer-type Reaction Kinetics of the Pummerer type reaction was carried out at a set temperature ranging from 120 to 140°C in sealed tubes into which were placed aliquots of a solution containing methyl p-substituted phenyl sulfilimine (3×10^{-5} mole) in 10 ml of acetic anhydride. From time to time a sealed tube containing more than 1 ml of the reaction mixture was drawn out from the oil bath and cooled in an ice-bath in order to stop the reaction. Then from each sealed tube 1 ml of the reaction mixture was hydrolyzed with 25 ml, 6% of aqueous sodium hydroxide containing 30% of methanol in order to dissolve the unreacted sulfilimine. The rates of the Pummerer reaction were readily followed spectrophotometrically, taking advantage of the difference of UV spectra of the starting and the final hydrolyzed compounds (*p*-substituted phenylmercaptides). All the rate constants quoted in Table II were calculated by the equation for the Pummerer reaction.

$$\log \frac{a_\infty - a_0}{a_\infty - a_t} = \frac{k \cdot t}{2.303} \quad \text{(a: the intensity of resulting mercaptide)}$$

Hydrogen-Deuterium Exchange Reaction of Methyl Phenyl N-p-Tosylsulfilimine in Acetic Anhydride α-Trideuterated methyl phenyl *N*-*p*-tosylsulfilimine (0.2 gm.) was dissolved in 10 ml of acetic anhydride and 0.04 gm. of acetic acid as a proton source, and the reaction was carried out at 120°C in a sealed tube for one or three hours. After the reaction, the solution was treated by the same method as in the above case. Products and their yields are shown in Table III. N.m.r. spectrum showed no H-D exchange reaction.

Effect of Acetic Acid on the Pummerer Reaction of Methyl Phenyl N-p-Tosylsulfilimine and the Corresponding Sulfoxide Kinetics were carried out at 120°C in sealed tubes into which were placed aliquots of a solution containing methyl phenyl sulfilimine (3×10^{-5} mole) or the corresponding sulfoxide in 10 ml of acetic anhydride solution of various concentrations of acetic acid. Following treatments are the same as in the above case.

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