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Mechanism of Reaction of *S*,*S*-Diphenyl-*S*-methoxythiazyne with Thiols

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Synopsis. The reaction of *S, S*-diphenyl-*S*-methoxythiazyne with various thiols gave methyl sulfides. Kinetic investigations support a mechanism involving an initial protonation of the thiazyne nitrogen with thiol followed by a nucleophilic attack of thiolate anion on the methyl group.

Thiazynes[1] are relatively unusual compounds having an SN triple bond, and their chemistry is mostly unexplored.[2] Only a few fluoro derivatives are known.[2,3] Recently we reported the first preparation of *S,S*-diphenyl-*S*-methoxythiazyne (**1**) from the alkaline hydrolysis of *S,S*-diphenyl-N-bromosulfilimine (**2**) in methanol.[4] The structure of the compound **1** was confirmed by the fact that the compound **1** can readily react with benzenethiol to form methyl phenyl sulfide and *S,S*-diphenylsulfoximine (**3**) quantitatively. Therefore, in order to clarify the mechanism of this interesting methylation reaction, kinetic investigation was carried out.

Results and Discussion

The thiazyne **1** was prepared as a mixture with sulfoximine 3 (**1**:**3**=70:30) by the alkaline hydrolysis of *N*-bromosulfilimine **2** since the thiazyne **1** is hard to be separated.[4] The mixture was allowed to react with substituted benzenethiols, α-toluenethiol, and methyl phenyl sulfide at 30 °C in benzene. The products were analyzed by ^{1}H NMR and gas chromatography and the results are summarized in Table 1.

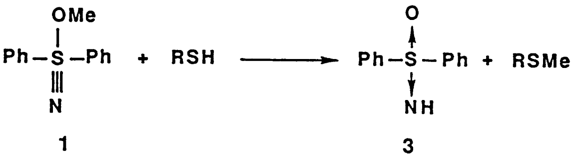
As shown in Table 1, both alkane- and arenethiols gave the corresponding methyl sulfides in high yields but methyl phenyl sulfide showed no reaction. Since the reaction can be readily performed under neutral conditions, this reaction is synthetically useful for methylation of SH groups as is the reaction of diazomethane. Then in order to clarify the mechanism of the reaction, kinetic investigation was carried out in benzene at 20—40 °C using substituted benzenethiols.

The reaction was followed by measuring the increasing GLPC peak of the methyl sulfide formed. The reaction was found to fit the second-order kinetic equation and the results are shown in Table 2.

A small activation energy (29 kJ mol^{-1}) and a large negative activation entropy (−184 JK^{-1} mol^{-1}) were obtained in such nonpolar solvent as benzene suggesting that the reaction involves an ion pair. Contrary to the expectation of negative trend for substituent effect for S$_N$2 reaction involving a nucleophilic attack of the thiol on the methyl group, a large positive ρ-value (2.63) was obtained from the Hammett plot as shown in Fig. 1.

Since methyl phenyl sulfide does not react with the thiazyne **1**, an active proton is required for this reaction.

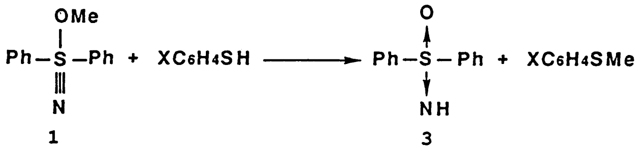
Table 1. Reaction of *S*,*S*-Diphenyl-*S*-methoxythiazyne with Thiols



Thiol	Conditions[a]			RSMe
[RSH]	Time/h	Temp/°C	Solvent	Yield/%[b]
C_6H_5SH	10	30.0	Benzene	95
p-$CH_3C_6H_4SH$	6	30.0	Benzene	77
m-ClC_6H_4SH	7	30.0	Benzene	100
p-ClC_6H_4SH	12	30.0	Benzene	97
p-$CH_3OC_6H_4SH$	16	30.0	Benzene	83
$PhCH_2SH$	28	30.0	Benzene	52
$PhSCH_3$	3 days	50.0	Chloroform	0

a) The reactions were carried out with 2—3 equivalent amounts of thiols. b) Yields of diphenylsulfoximine are all quantitative except for the reaction with methyl phenyl sulfide.

Table 2. Kinetic Data for *S*,*S*-Diphenyl-*S*-methoxythiazyne with Substituted Benzenethiols



X	Temp/°C	k×10^2/dm^3 mol^{-1} s^{-1}	
H	30.0	4.73±0.05	E_a=28.8±3.3 kJ mol^{-1}
H	35.0	6.30±0.16	$\Delta S^{\ddagger}$=−184±8 J K^{-1} mol^{-1}
H	40.0	7.63±0.13	ρ=2.63
p-MeO	30.0	1.58±0.05	k_H/k_D=1.09
p-Me	30.0	2.67±0.06	
p-Cl	30.0	28.3 ±0.14	
m-Cl	30.0	75.2 ±0.14	
(PhSD)	30.0	4.32±0.25	

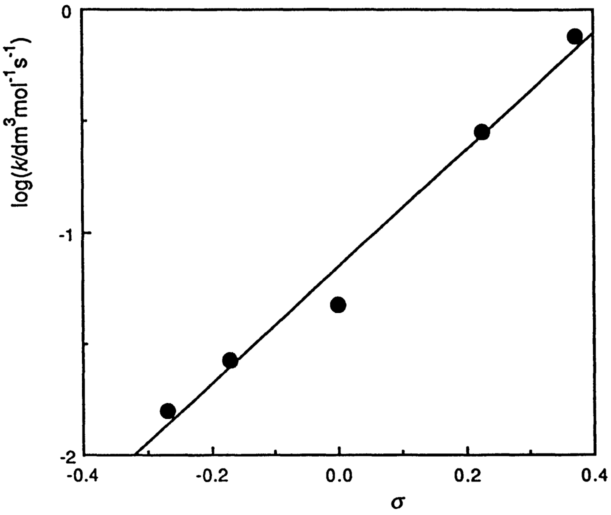


Fig. 1. The Hammett plot for the reaction of *S,S*-diphenyl-*S*-methoxythiazyne (**1**) with substituted benzenethiols.

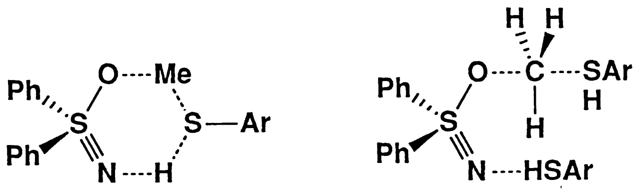
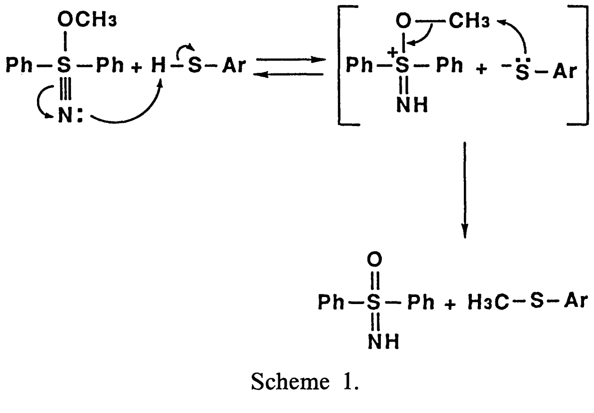


Fig. 2.

The positive ρ-value suggests that the acidity of thiol is more important than nucleophilicity. There are two possible mechanisms. One is a concerted process involving both proton transfer and nucleophilic attack of thiol sufur to the methyl group. Such a process should involve six-membered transition state or two molecules of thiol as shown in Fig. 2.

However, both mechanisms are unfavorable, because the former involves a nonlinear nucleophilic displacement on the methyl group and the latter is not consistent with present second-order kinetic results. The other one is a two-step mechanism involving an initial protonation of thiol to the nitrogen atom of the thiazyne followed by a nucleophilic attack of thiolate anion to the methyl group as shown in Scheme 1.



Scheme 1.

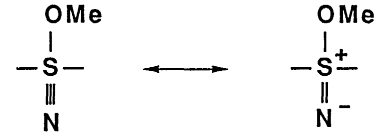


Fig. 3. Resonance structure of methoxythiazyne.

Then in order to examine a possibility of the rate-determining protonation of the nitrogen atom, isotope effect was measured using active proton-deuterated system. The rate constant of the reaction k_D using benzenethiol-*d* was found to be almost the same as k_H ($k_H/k_D=1.09$). Therefore the rate-determining step cannot be the first protonation step but the second nucleophilic substitution. The lack of appreciable kinetic isotope effect is also inconsistent with the concerted mechanism. The substituent effects for the acidity of benzenethiol are known to be $\rho=1.81$[5] in 20% EtOH, $\rho=2.58$[6] in 48% EtOH, and $\rho=3.03$[7] in 95% EtOH. Namely there is a tendency to increase the ρ-value for acidity in less polar solvent and thus the ρ-value of the predissociation in benzene can be estimated to be more than 3.0. Meanwhile, the substituent effect on benzenethiolate anion for the reaction with benzyl bromide in methanol gives relatively small ρ-values from -0.439 to -1.07 depending on the substituents on benzyl bromide.[8] Although substituent effects depend on substrates and solvents, a smaller negative ρ-value may be expected in the second step nucleophilic substitution reaction. If the substituent effect of the second step is assumed to be small, the observed positive ρ-value can be interpreted as a result of combination of a more positive ρ-value for the first equilibrium protonation step with a negative ρ-value in the second step. From the consideration of this mechanism, it is concluded that the nitrogen atom of the methoxythiazyne is basic to accept the thiol proton and to activate the carbon–oxygen bond to promote the methylation. Therefore the SN triple bond is considered to be polarized as shown in Fig. 3.

Experimental

General. IR spectra were taken on a JEOL-810 spectrometer. GLPC was performed on a Hitachi 163 using a 1-m DEGS column with N_2 gas at 50 ml min^{-1} flow rate. ^{1}H NMR spectra were obtained on a Hitachi R-24B (60MHz) in $CDCl_3$ using TMS as an internal standard.

All reagents were obtained from Wako Pure Chemical Industry Ltd., Tokyo Kasei Co., Ltd. or Aldrich Chemical Co. The reagents and solvents used were further purified by usual methods.

Preparation of *S,S*-Diphenyl-*S*-methoxythiazyne (1).[4] To a stirred solution of *N*-bromosulfilimine[9] 2 (0.4 g, 1.4 mmol) in MeOH (50 ml) was added an aqueous solution of 0.8 M-NaOH (50 ml) (1M=1 mol dm^{-3}). After the solution was warmed at 35 °C for 40 min, it was poured into a cold water, and extracted with $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4. The residue obtained by evaporation of the solvent was found to be a mixture of *S,S*-diphenyl-*S*-methoxythiazyne (1) (70%) and *S,S*-diphenylsulfoximine (3) (30%) from the NMR spectral analysis. ^{1}H NMR and IR spectra were the same as those reported previously.[4]

Reaction of *S,S*-Diphenyl-*S*-methoxythiazyne (1) with Sub-

stituted Benzenethiols. To a solution of the thiazyne **1** in $CDCl_3$ in an NMR tube was added benzenethiol and ^1H NMR was taken immediately. The NMR spectrum showed that the methoxy signal (3.7 ppm) was already disappeared and only one methyl signal was observed at 2.35 ppm which was assigned as that of methyl phenyl sulfide. The solution was analyzed by GLPC to show retention time 52 s consistent with that of the authentic sample. (DEGS, 1 m, column temp 120 °C, injection temp 150 °C, flow rate N_2 50 ml min^{-1})

The reaction of the thiazyne **1** with substituted benzenethiols were carried out in benzene under the conditions shown in Table 1. The product sulfides were all identified by comparing their GLPC retention time with those of the authentic samples and their yields were determined by GLPC calibration curves using naphthalene or methyl phenyl sulfide as an internal standard. The solvent was removed in vacuo and residue was chromatographed on silica gel using chloroform as an eluent to give *S,S*-diphenylsulfoximine (**3**) quantitatively.

Kinetics. A benzene solution of thiazyne **1** (6.0×10^{-3} mol dm^{-3}, 10 ml) and a benzene solution of substituted benzenethiol (1.2×10^{-2} mol dm^{-3}, 10 ml) containing an internal standard (naphthalene 1.2×10^{-2} mol dm^{-3} for PhSH, *p*-$CH_3C_6H_4SH$, and *p*-$CH_3OC_6H_4SH$; methyl phenyl sulfide for *m*- and *p*-ClC_6H_4SH) were immersed in a water bath thermostated at the constant temperature (20—40 °C(±0.1 °C)). After five minutes, two solutions were mixed. At an appropriate time interval, a 0.5 ml portion of the reaction mixture was taken out, added to 1 ml of 1 M-HCl, and shaken to decompose the unreacted thiazyne **1**. The benzene solution was analyzed by GLPC (DEGS, 1 m, column temp 120 °C, injection temp 150 °C). The increasing amount of methyl-substituted phenyl sulfide was followed and the second-order rate constant was calculated by a least squares method using the equation

$$kt = \ln((1-fx)/(1-x))/([B]_0-[A]_0)$$

($[A]_0$ is the initial amount of thiazyne **1**, $[B]_0$ is the initial amount of substituted benzenethiol, f is the ratio $[A]_0/[B]_0$, x is the conversion of thiazyne calculated by $(a_t-a_0)/(a_\infty-a_0)$, where a_0 and a_t are the amounts of methyl phenyl sulfide at the initial time and at time t, respectively, and a_∞ is the amount at the infinite time (more than 6 h)).

Isotope Effect. The benzene solution of the thiazyne containing the sulfoximine was shaken with D_2O many times to exchange the NH group to ND and the benzene solution of benzenethiol was also treated similarly with D_2O. The H–D exchange was confirmed by ^1H NMR and IR and the kinetics was carried out similarly.

References

1) The compounds having an SN triple bond are called thiazyl compounds[2)] like thiazyl trifluoride for $F_3S\equiv N$, but this name is not appropriate for the compounds substituted by carbon groups. Meanwhile, the name "thiazyne" is first used by Clifford et al.[3)] for $Ph_2FS\equiv N$ as diphenylfluorothiazyne.

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