

Kinetic Support for the Generation of a Phenylsulfenium Ion Intermediate

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Abstract: In the reaction of *N*-methylbenzenesulfenamide (**1**) with thioanisole (**4**) in the presence of trifluoroacetic acid (TFA), the initial rate v_0 of total appearance of 2- and 4-(methylthio)phenyl phenyl sulfides (**5**) is first and zero order with respect to the initial concentrations of **1** and **4**, respectively: $v_0 = k_{\text{obs}}[\mathbf{1}]_0$. The pseudo-first order rate constant k_{obs} is evaluated as $5.2 \times 10^{-4} \text{ sec}^{-1}$ with varying concentrations of **4** (0.72 to 5.0 M) in a mixture of **4** and CH_2Cl_2 in the presence of TFA at 10 °C. This data supports the notion that a phenylsulfenium ion intermediate **3** interacting with both the counter ion and the unshared electron-pair of amine is generated by heterolytic *N*-S scission of the protonated sulfenamide **2**, leading to the observed formation of **5**.

Keywords: Phenylsulfenium ion intermediate, Kinetic study, Phenylthiolation, Sulfenamide, Thioanisole.

Introduction

Many researchers have made proposals concerning the generation of sulfenium ion intermediates [1]; this intermediate can only be isolated in the case of coordination with two nitrogen atoms [2], yet several studies [3] have failed to find evidence supporting its existence, as it has too short a lifetime to

exist as the free ion, being converted to sulfonium [4] or thiiranium ions [5] by reaction with sulfides or alkenes, respectively. Thus, the existence of the sulfenium ion has been the subject of controversy for long time. We have proposed that a sulfenium ion with a very short lifetime can exist by interacting with both a counter ion and the unshared electron pair of an amine (i.e. not as a free ion), considering the effects of the counter ion, the amine, solvent nucleophilicity, *etc.* on the reactions of *N*-alkylarenesulfenamides or azides with alkyl aryl sulfides in the presence of trifluoroacetic acid [6].

However, the existence of such an unstable sulfenium ion is still controversial because the product resulting from thiolation of benzene by the sulfenium ion is not detected, the thiolation on toluene rarely occurs [6], and so on. In this paper, we present the first kinetic support for the existence of the ion in the thiolation of a good nucleophilic aromatic compound like thioanisole, and our proposed mechanism [6] for the generation of the sulfenium ion is thus made clear. This work also arouses interest for organic synthesis in view of the observed one-step aromatic thiolation by sulfenium ion.

Results and Discussion

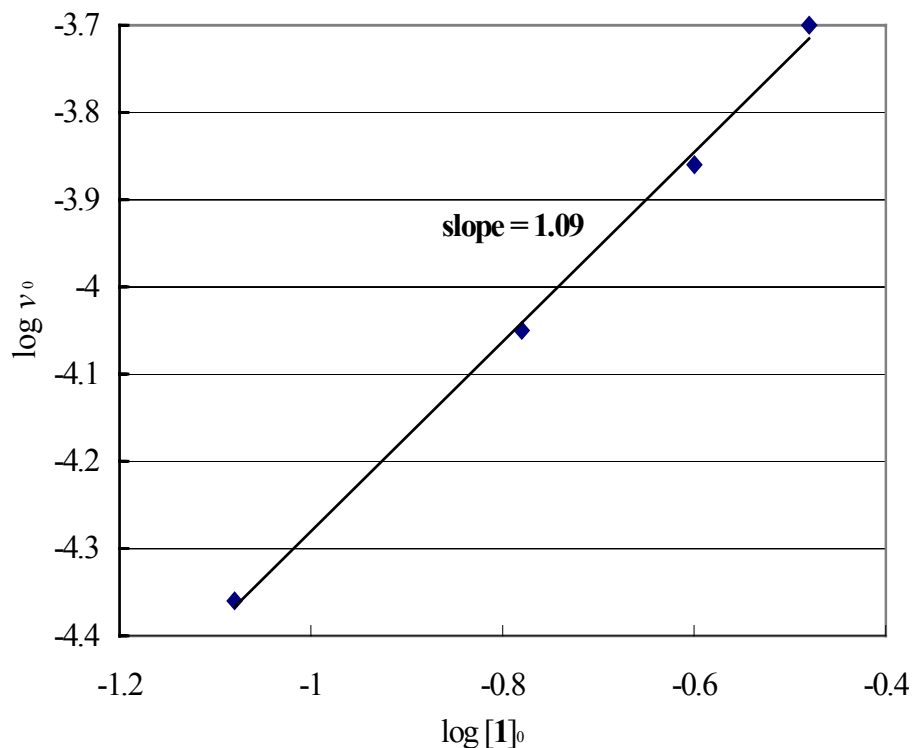
Kinetic study on the reaction of N-methylbenzenesulfenamide (1) with thioanisole (4) in the presence of trifluoroacetic acid (TFA).

The reactions of *N*-methylbenzenesulfenamide (**1**) with thioanisole (**4**) are carried out using both TFA and CH₂Cl₂ at 10 °C, and give 2- and 4-(methylthio)phenyl phenyl sulfides (**5**) (the observed *para/ortho* isomer ratio being *ca.* 10). The reactions producing **5** are quenched by pouring the reaction mixtures into cold triethylamine (see Experimental section). We have already proposed that mechanistically the reactions of *N*-alkylbenzenesulfenamides with **4** in the presence of TFA give 2- and 4-(alkylthio)phenyl phenyl sulfides by phenylthiolation of a phenylsulfenium ion intermediate [6]. In order to establish kinetically the generation of the sulfenium ion, the reaction-orders for the appearance of **5** with respect to **1** and **4** are evaluated by using the differential method as shown below. As for the evaluation, the initial rate technique dealing with the initial rates v_0 for appearance of **5** can avoid possible complications due to the products, and leads to the true order with respect to concentration.

Reaction-order with respect to sulfenamide (1).

The initial rate $v_0 = d[\mathbf{5}]/dt$ at $t=0$ sec for the formation of **5** can be represented by the equation $v_0 = k[\mathbf{1}]_0^m[\mathbf{4}]_0^n$ where $[\mathbf{1}]_0$ and $[\mathbf{4}]_0$ are the initial concentrations of **1** and **4**. Under the reaction conditions, $[\mathbf{4}]_0$ is in excess compared with $[\mathbf{1}]_0$, so that we may write the equation as $v_0 \propto [\mathbf{1}]_0^m$. The initial rates v_0 (see Table 1) at such an excess constant concentration of **4** (*i.e.* 4.3 M) were evaluated for individual initial concentrations of **1**. The details of the determination of v_0 are described in Experimental section. The correlation between the logarithms of v_0 and of $[\mathbf{1}]_0$ gives a linear plot with a slope of 1.09 (Figure 1). The result shows that the production of **5** obeys first order kinetics for **1**.

Figure 1. The logarithms of initial rates ($v_0 = d[5]/dt$ at $t=0$ sec) for the production of 2- and 4-(methylthio)phenyl phenyl sulfides **5** are plotted against the logarithms of the initial concentration $[1]_0$ of sulfenamide **1** in its reaction with thioanisole (**4**) (12.0 mL) in the presence of TFA (8.0 mL) and CH_2Cl_2 (4.0 mL) at 10 °C

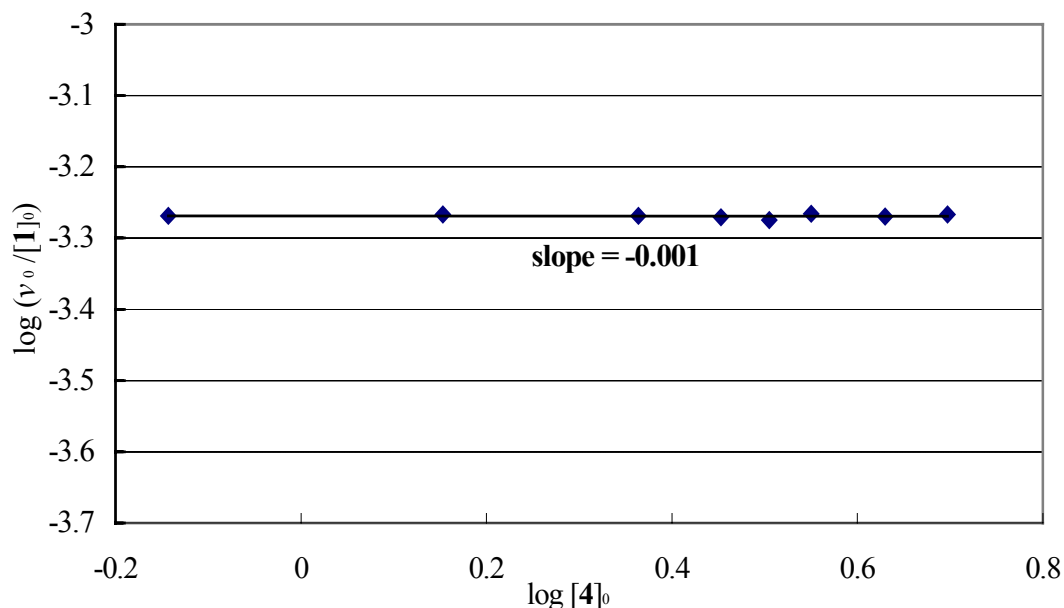


Reaction-order with respect to thioanisole (**4**).

Employing the first order kinetics expression ($v_0 \propto [1]_0 [4]_0^n$) for sulfenamide **1** as described above, the reaction-order n with respect to **4** can be obtained in the similar way, using in this case the equation $v_0/[1]_0 \propto [4]_0^n$. The initial concentration of **4** is varied from 0.72 M to 4.97 M at an initial constant-concentration of **1** (0.17 M). The details for determining the initial rates v_0 (see Table 2) at the individual initial concentrations of **4** are also shown in the Experimental section. The plot of $\log (v_0/[1]_0)$ against $\log [4]_0$ leads to the slope -0.001 representing the reaction-order of **4** (Figure 2). Thus, the production of **5** obeys zero order kinetics for **4**.

With the variation of **4** from 0.72 M to 4.97 M, the amount of CH_2Cl_2 was changed from 58%v/v to 8.3%v/v in the presence of a constant quantity (33%v/v) of TFA. As for the effects on the aromatic thiolation of the sulfenium ion, CH_2Cl_2 is less nucleophilic solvent [6]. The dilution with CH_2Cl_2 in the reactions of sulfenium ions [6] or nitrenium ions [7] with aromatics scarcely affects the yields when TFA is present in at least 30% v/v. The fact that the almost same k_{obs} is obtained from Figures 1 and 2 using different amounts of CH_2Cl_2 as described below indicates that the dilution with CH_2Cl_2 in this reaction system is appropriate.

Figure 2. The logarithms of $v_0/[1]_0$ are plotted against the logarithms of $[4]_0$ in the reaction of sulfenamide **1** (4.0 mmol) with thioanisole **4** in the presence of both TFA (8.0 mL) and CH_2Cl_2 at 10 °C: A mixture (16 mL) of **4** and CH_2Cl_2 is used, and v_0 , $[1]_0$ and $[4]_0$ mean the initial rate for the production of 2- and 4-(methylthio)phenyl phenyl sulfides **5**, the initial concentration of **1** and the initial concentration of **4**, respectively



Evaluation of pseudo-first order rate constant k_{obs} .

Equation 1 can be derived by assuming a steady generation of a phenylsulfenium ion **3** as indicated in Scheme 1; k_1 , k_{-1} and k_2 are the rate constants indicated in Scheme 1.

$$d[3]/dt = k_1[2] - k_{-1}[3] - k_2[3][4] = 0 \quad (1)$$

$$[3] = k_1[2] / (k_{-1} + k_2[4]) \quad (2)$$

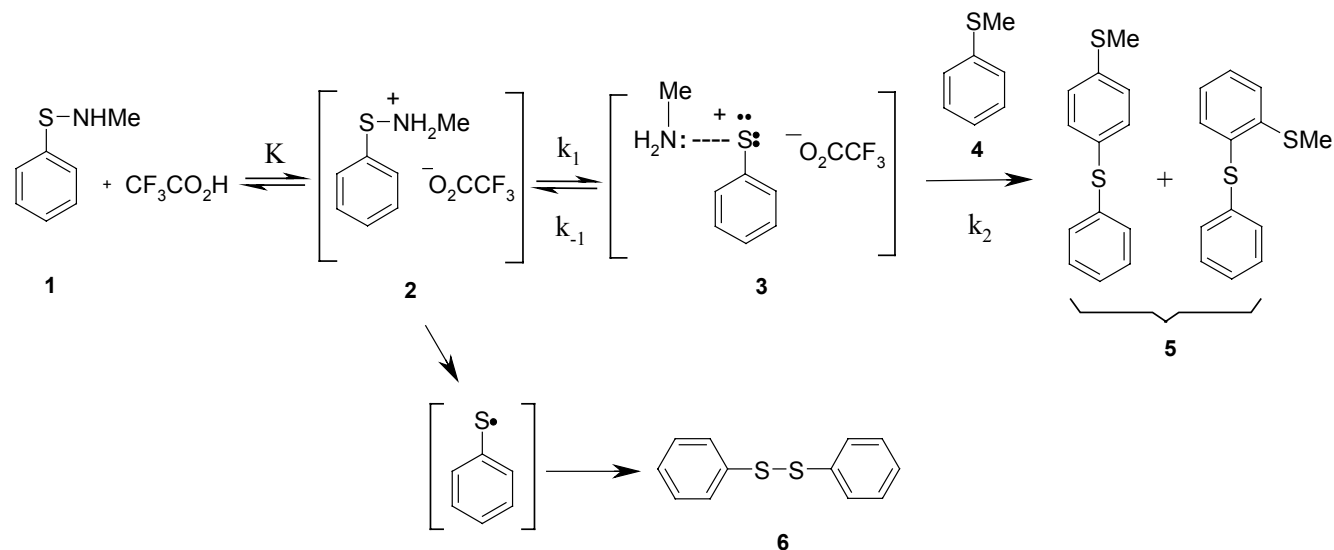
The concentration of **3** is shown in Equation 2, and the rate for appearance of **5** is shown in Equation 3.

$$v = d[5]/dt = k_2[3][4] = k_1 k_2 [2][4] / (k_{-1} + k_2[4]) \quad (3)$$

$$v = k_1[2] \quad (4)$$

When $k_2[4]$ is sufficiently large as compared to k_{-1} , then Equation 4 can be obtained. As shown in Scheme 1, the sulfenium ion interacts with both counter ion and the unshared electron-pair of the amine, and thus **1** may undergo a protonation, not by free protons, but rather by a TFA molecule to produce **2** [6].

Scheme 1



Using the equation $K=[2]/([1][TFA])$ (*i.e.* $[2]=K[TFA][1]$) where K is an equilibrium constant in Scheme 1, then Equation 5 can be derived. The pseudo-first order rate constant k_{obs} is given in Equation 6.

$$v = k_1 K [TFA] [1] \quad (5)$$

$$k_{obs} = k_1 K [TFA] \quad (6)$$

The intercept on the $\log v_0$ axis in Figure 1 corresponds to $\log k_{obs}$ being *ca.* -3.2 because we can represent as $v_0 = k_{obs}[1]_0$ (*i.e.* $\log v_0 = \log k_{obs} + \log [1]_0$). As seen in Figure 2, $\log (v_0/[1]_0)$ becomes constant with varying $[4]_0$ from 0.72 M to 5.0 M. The constant value is -3.28 (as the average) corresponding to $\log k_{obs}$ because of $v_0/[1]_0 = k_{obs}$. Almost the same k_{obs} was obtained from Figures 1 and 2. By adopting the first and zero orders for 1 and 4, respectively, we may evaluate $k_{obs} = 5.2 \times 10^{-4} \text{ sec}^{-1}$ from the average.

Evidence for the generation of phenylsulfenium ion

From Equation 6, the rate constant k_1 for the generation of the sulfenium ion 3 from protonated sulfenamide 2 is equal to $k_{obs}/(K[TFA])$. Regarding the equation $K[TFA]=[2]/[1]$, $K[TFA]$ is sufficiently larger than 1.0. Thus, k_1 must be lower than $5.2 \times 10^{-4} \text{ sec}^{-1}$. The low rate constant k_1 well suggests that the reaction yielding 5 proceeds *via* a very reactive intermediate such as a phenylsulfenium ion. The above-mentioned assumption that $k_2[4]$ is much larger than k_{-1} becomes true when the highly reactive intermediate 3 is generated.

We considered the possibility that the thiolation giving 5 occurs *via* not the sulfenium ion 3 but the protonated sulfenamide 2 as the reactive intermediate. If it were true, the value k_{obs} (equal to $5.2 \times 10^{-4} \text{ sec}^{-1}$) would be identical with $k [TFA]$ by assuming the steady state for 2 in the similar way to that

shown above; k means the rate constant of the formation of **2** from **1** and TFA. But, the rate constant k should not be such a low value as $k_{\text{obs}}/[\text{TFA}]$ because the proton-transfer [8] to amine occurs at the diffusion-controlled rate. Thus, the above possibility can be ruled out. Actually, the formation of **5** by direct reaction of **2** with **4** has been excluded [6].

In a previous paper [6], we have ruled out the possibility that the phenylthiolation giving **5** occurs via a phenylthiyl radical generated by homolytic *N-S* scission of the protonated sulfenamide **2**. Our earlier study [6] also has shown that the reactions of *N*-alkylarenesulfenamides with **4** are influenced by the counter ion, the amine, the aryl substituent of the sulfenamide and the solvent nucleophilicity. This excludes the possibility of a neutral intermediate such as PhSOCOCF_3 .

Therefore, the evidence favors the fact that protonated sulfenamide **2** undergoes a spontaneous *N-S* scission (not induced by **4**) to generate the very reactive sulfenium ion **3**, leading to the production of **5** (Scheme 1). The sulfenium ion does not exist as a free ion, but can be generated by interacting with not only the counter ion but also the unshared electron-pair of the amine (Scheme 1); the interacting amine is not in the solvent, but formed just by heterolytic *S-N* scission of the protonated form **2**. We have already proposed the similar interaction of nitrenium ions with both the counter ion and unshared electron-pair [9].

From the competition between the phenylthiolation giving **5** and the formation of diphenyl disulfide (**6**), we have proposed that the protonated sulfenamide **2** undergoes a homolytic *S-N* scission forming a phenylthiyl radical, producing **6** by its dimerization (Scheme 1) [6]. This type of dimerization is well known [10]. We may consider that the use of the other trapping agents instead of thioanisole **4** provides the different k_{obs} from that in the use of **4** because k_1 depends upon k_2 . In fact, the trapping reaction with anisole or diphenyl sulfide proceeds more rapidly than that with **4**, and we could not observe the thiolation product to benzene [11].

Experimental

General

GLC-MS was recorded with a Shimadzu QP-5000 spectrometer linked to a Shimadzu GLC-17A column (15m \times 0.25 mm) coated with DC-1 (0.25 μm film thickness) made by J & W Scientific. Dichloromethane was purified by standard methods before use, and trifluoroacetic acid (TFA) was purified by distillation. Thioanisole (**4**) and triethylamine were reagent grade (Nacalai Tesque), and used without further purification. *N*-Methylbenzenesulfenamide (**1**) [12] and 2- and 4-(methylthio)phenyl phenyl sulfides **5** were obtained by the method described in the literature [6].

Kinetic study on generation of phenylsulfenium ion **3**

In the reactions of sulfenamide **1** with thioanisole (**4**), the reaction-mixture showed the GLC peaks corresponding to those of **5** (the *ortho*: *para* isomer ratio for **5** was *ca.* 1:10) and diphenyl disulfide (**6**).

Since the total yield of **5** and **6** is less than 100%, some unidentified products must be formed: For example, the reaction of **1** (4.0 mmol) with **4** (12.0 mL) using TFA (8.0 mL) and CH₂Cl₂ (4.0 mL) at 10 °C for 24 h produced **5** (45% yield) and **6** (47% yield). In spite of the formation of other products aside from **5**, the plot of [5] versus reaction time t provides the initial slope v_0 with satisfactory R² during 0-750 sec by using the equation [5] = $(-\alpha \times 10^{-\beta} t^2 + \gamma t)$ (see Tables 1 and 2 below), leading to the good correlation as seen in Figures 1 and 2. This means that the rates of appearance of **5** are not complicated by the presence of the products. At the higher temperature, **5** is formed in higher yields: The reaction of **1** (4.0 mmol) with **4** (3.0 mL) in the presence of TFA (6.0 mL) and CH₂Cl₂ (1.0 mL) at reflux temperature for 5 h gave **5** (70% yield) and **6** (23% yield). But, in this case, the variation of [5] with time could not be obtained accurately because of the fast reaction at high temperature.

Reaction-order with respect to N-methylbenzenesulfenamide **1**.

The reactions of solutions containing varying amounts of **1** (shown below) with **4** (12 mL) were carried out at 10 °C in the presence of both TFA (8.0 mL) and CH₂Cl₂ (4.0 mL); the reactions were started by addition of **1** dissolved in a small amount of CH₂Cl₂ to the mixture of **4**, TFA and CH₂Cl₂. The work-up (*i.e.* the treatment for stopping the reaction) was involved pouring an aliquot (1.0 mL) of the reaction mixture into Et₃N (2.0 mL, an excess with respect to the TFA) cooled at -20°C. After the workup, the amount of **5** was determined by GLC analysis using GLC-MS. The reaction-order of **1** for total appearance of **5** is obtained as follows: at the individual initial concentration [1]₀ (83, 170, 250 or 330 mM), the concentrations [5] at times 150, 300, 450 and 750 sec were determined (Table 1). The concentration [5] was plotted against reaction time t, and the initial slope corresponding to the initial rate ($v_0 = d[5]/dt$ at t=0) for appearance of **5** was evaluated as the γ value by a statistical optimal-method; the optimal values α , β and γ (α or β is a positive integer, and γ is a positive number) as shown in Table 1 are derived by using the equation [5] = $(-\alpha \times 10^{-\beta} t^2 + \gamma t)$ for the each plot above.

Table 1. Kinetic data for obtaining the reaction-order of **1** in the reactions of sulfenamide (**1**) with thioanisole (**4**) (4.3 M) in the presence of TFA (8.0 mL) and CH₂Cl₂ (4.0 mL) at 10 °C

[1] ₀ /10 ⁻³ M	Concentration [5]/10 ⁻³ M					v_0 /10 ⁻⁶ Msec ⁻¹	α	β	R ²
	t=150 sec	t=300 sec	t=450 sec	t=600 sec	t=750 sec				
83	6.2	11	15	16	18	44	3	5	0.997
170	13	24	30	37	42	90	5	5	0.998
250	24	31	45	49	56	137	9	5	0.981
330	31	46	67	77	84	199	1	4	0.993

R² values (*i.e.* the square of the correlation coefficient) in this derivation were satisfactory (Table 1). Then, the plot of log v_0 against log [1]₀ gives a straight line with the slope 1.09 (Figure 1).

Reaction-order with respect to thioanisole(4).

Compound **1** (4.0 mmol) was dissolved at 10 °C in a mixture of **4** (16.0 mL) and CH₂Cl₂ in the presence of TFA (8.0 mL). The work-up of the reaction mixture and the analysis of the products were conducted as indicated above. At individual initial concentrations [4]₀ ranging from 0.72 M to 5.0 M, [5] was plotted against the reaction time (t=150, 300, 450, 600 or 750 sec). The concentration [5] at each time point is shown in Table 2. As described above, the initial rate ($v_0=d[5]/dt$ at t=0) was evaluated as the initial slope (being equal to γ) by employing the equation $[5]=(-\alpha \times 10^{-\beta} t^2 + \gamma t)$. The values v_0 , α , β and R^2 are shown in Table 2. R^2 values were also satisfactory. A double logarithmic plot of $v_0/[1]_0$ against [4]₀ gives a linear line with the slope -0.001 (Figure 2).

Table 2. Kinetic data for obtaining the reaction-order of **4** in the reactions of **1** (0.17 M) with thioanisole (**4**) using a mixture (16.0 mL) of **4** and CH₂Cl₂ in the presence of TFA (8.0 mL) at 10°C

[4] ₀ /M	Concentration [5]/10 ⁻³ M					$v_0 / 10^{-6}$ Msec ⁻¹	α	β	R^2
	t=150 sec	t=300 sec	t=450 sec	t=600 sec	t=750 sec				
0.72	13	22	29	34	38	90	5	5	0.998
1.4	13	22	29	34	37	90	5	5	0.999
2.1	14	24	30	37	43	90	4	5	0.997
2.8	13	23	30	36	41	89	5	5	0.999
3.2	13	23	29	38	41	88	5	5	0.998
3.6	13	23	30	39	42	90	5	5	0.999
4.3	13	24	30	37	42	90	5	5	0.998
5.0	13	23	29	35	39	90	5	5	0.999

References and Notes

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 11. Unpublished data: under similar conditions at 10 °C, the reaction with PhSPh in place of **4** provided the same first and zero orders for **1** and PhSPh, respectively, with $k_{\text{obs}}=1.1 \times 10^{-3} \text{ sec}^{-1}$. The reaction with benzene instead of **4** under similar conditions gave diphenyl disulfide (**6**) selectively in 70-80% yields. This suggests that the phenylthiolation producing **5** competes with the formation of **6**. We assume that the sulfenium ion preferentially reacts with the solvent rather than with benzene, thus leading to undetermined products.
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Sample Availability: Available from the authors.