Substitution Reaction of Organic Halide by Trimethylsilyl Isothiocyanate: Formation of Thiocyanate and Its Rearrangement to Isothiocyanate†

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Synopsis. The reaction of organic halide with trimethylsilyl isothiocyanate (TMSTC) gave thiocyanate **1** and its isomerized isothiocyanate **2**. Details of the substituion and the isomerization reactions were examined.

Recently, the application of silicon reagents has increased regarding organic synthesis. For example, a variety of silyl cyanides and silyl azides have been widely employed as synthetic tools.[1] Although trimethylsilyl isothiocyanate (TMSTC) is one of these silyl pseudo-halides, there have been only a few reports on its reactivity: Our previous report[2] concerning the formation of symmetrically and unsymmetrically isothiocyanato-substituted ethers is one of them. As the substitution reaction by TMSTC, Sasaki et al. explored the reaction of adamantyl chloride in the presence of $TiCl_4$.[3] For introducing NCS group into an organic molecule, the use of metal thiocyanate has been generalized,[4] but no detailed discussion has been given. As one part of our studies on silicon chemistry, we report here on the substitution reaction of organic halide by TMSTC and the rearrangement of thiocyanate into isothiocyanate.

Results and Discussion

When a solution of benzyl bromide and TMSTC in hexamethylphosphoric triamide (HMPA) was stirred at 60 °C for 24 h, a mixture of benzyl thiocyanate **1** and benzyl isothiocyanate **2** was obtained in a ratio of 32 : 68. On the other hand, only *S*-benzylation product **1** was yielded from a reaction which was carried out at room temperature. The effects of the solvent, leaving group, and substituent were examined and the results are summarized in Table 1. The results using sodium thiocyanate are also shown in the parentheses of Table 1. Both isomer ratios of **1** and **2** were very similar. The reaction occured favorably in HMPA or DMF. With benzyl chroride (harder alkylating agent than the bromide), compound **1** resulted as the sole product when the reaction was performed at 60 °C. This result could not be accounted for by "the principle of hard and soft acids and bases" which was often applied to the alkylation of ambident nucleophile.[5] The reactions of other *p*-substituted benzyl bromides, similarly, gave a mixture of **1** and **2**. The *N*-benzylation product was relatively increased by an electron-donating group. Coupled with the result of benzyl chloride, this indicates that *N*-benzylation can be rationalized by the consideration that the carbon-halogen bond breaking is more important than the carbon-nitrogen bond making in a transition state, i.e. the stability of the corresponding benzyl cation.

Table 1. Reaction of Benzyl Bromides and Trimethylsilyl Isothiocyanate

$$R\text{-}X \xrightarrow[24\,h]{TMSTC} \underset{\mathbf{1}}{R\text{-}SCN} + \underset{\mathbf{2}}{R\text{-}NCS}$$

Substrate	Solvent	Temp/ °C	Yield/ %[a]	Ratio 1 : 2
$C_6H_5CH_2Br$	HMPA	RT	89	100 0
			(100)[b]	(100 0)
$C_6H_5CH_2Br$	HAPA	60	83	32 68
			(100)[b]	(23 77)
$C_6H_5CH_2Br$	DMF	60	68	94 6
$C_6H_5CH_2Br$	MeCN	60	0	
$C_6H_5CH_2Cl$	HMPA	60	50	100 0
p-$MeOC_6H_4CH_2Br$	HMPA	60	100	11 89
p-$MeC_6H_4CH_2Br$	HMPA	60	85	25 75
p-$NCC_6H_4CH_2Br$	HMPA	60	92	37 63
p-$O_2NC_6H_4CH_2Br$	HMPA	60	95	46 54

a) Determined by ^1H NMR and no by-product was detected. b) Obtained from NaSCN.

Furthermore, we investigated the substitutent effects on the *S*-benzylation. Plotting the $\log(k_X/k_H)$ values vs. the Hammett's σ constant gave a nonlinear relationship (Fig. 1). Both the electron-attracting and electron-donating substituents accelerated the rate of substitution, suggesting that a gradual change in mechanism occurs. This has been discussed by Swain and Langsdorf[6] in terms of the relative importance of bond-making and bond-breaking in the transition state. This behavior is commonly characteristic for a benzyl-type S_N2 reaction.

For a mechanistic study, the time dependency of the

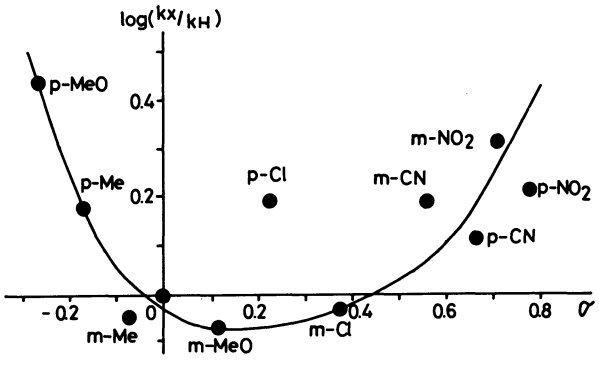

Fig. 1. Hammet's plot for the reaction between benzyl bromides and TMSTC.

† Dedicated to Professor Yoichiro Nagai on the Occasion of his 60th birthday.

product distributions was examined at 60 °C. Compound **1** was predominant during the early stages of the reaction and the molar ratios were gradually changed. After 120 h, the mixture consisted of **1** (9%), **2** (87%), and benzyl bromide (4%). *S*-Benzylation product **1** is the kinetically controlled product and **1** is isomerized to the *N*-benzylation product **2** which is thermodynamically more stable. A treatment of **1** with bromotrimethylsilane gave a mixture of isomerized **2** (55%) and benzyl bromide (16%), and chlorotrimethylsilane converted **1** into only benzyl chloride (51%). In the absence of bromosilane, no isomerization occurred. From these experiments, it is likely that the coexistent bromide ion catalyzes the isomerization of **1** to **2** and *S*-benzylation should be reversible. As shown in the equation, isothiocyanate **2** may be explained as being produced by the competitive *N*-attack of TMSTC on benzyl bromide, not by the direct isomerization of **1** to **2**

$$ArCH_2Br + Me_3SiNCS \rightleftharpoons ArCH_2SCN + Me_3SiBr$$
$$\searrow^{slow} \qquad \mathbf{1}$$
$$ArCH_2NCS + Me_3SiBr$$
$$\mathbf{2}$$

Allyl halide, 1-bromo-3-methyl-2-butene, was also reactive toward TMSTC, giving a mixture of three products. This reaction pathway is supported by the time dependency of the product distribution (Table 2). The intramolecular rearrangement between (A) and (B) was known,[7] and the rearrangement was postulated to take place via a cyclic mechanism:

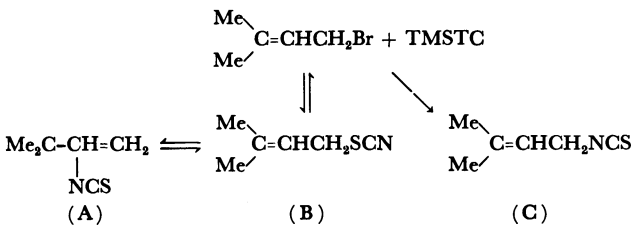

Table 2. Reaction of 1-Bromo-3-methyl-2-butene with TMSTC[a]

Time/h	Product/%		
	(A)	(B)	(C)
24	37	34	29
48	27	25	48
72	23	23	54
120	15	22	63

a) The reaction was carried out in HMPA at room temperature.

These results led us to examine the reactions of vinyl, aryl, and aliphatic halides. As expected, alkyl halide was converted to thiocyanate or isothiocyanate but vinyl and aryl halides were unreactive.

$$PhCH_2CH_2Br + TMSTC \longrightarrow PhCH_2CH_2SCN \quad (56\%)$$
$$Me_2CHCH_2Br + TMSTC \longrightarrow Me_2CHCH_2SCN \quad (12\%)$$
$$EtOCOCH_2Br + TMSTC \longrightarrow EtOCOCH_2NCS \quad (68\%)$$
$$NCCH_2Cl + TMSTC \longrightarrow NCCH_2SCN \quad (39\%)$$

From these results, it has become clear that TMSTC may be a useful reagent for introducing an NCS group under homogeneous and neutral conditions in nonaqueous solvent. Moreover, details concerning *S*- and *N*-benzylation were distinctly observed.

Experimental

Infrared spectra were measured on a Hitachi 260-10 infrared spectrometer. ^{1}H NMR spectra were determined with a Hitachi R-600 or a Varian XL-300 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained using a JEOL DX-300 spectrometer. Trimethylsilyl isothiocyanate (TMSTC) was prepared by the reaction of sodium thiocyanate with chlorotrimethylsilane, bp 144 °C (lit,[8] bp 141.8—142 °C). Organic halides were commercial products and were purified if necessary. Some benzyl bromides were obtained from the corresponding toluenes and *N*-bromosuccinimide in the presence of benzoyl peroxide in CCl_4.

Reaction of Organic Halides with TMSTC. A solution of benzyl bromide (1.71 g, 10 mmol) and TMSTC (1.31 g, 10 mmol) in HMPA (6.7 cm^3) was heated at 60 °C for 24 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed five times with water and dried over $MgSO_4$. After the removal of solvent, fast elution with hexane on silica gel contained benzyl isothiocyanate (0.45 g, 30%), IR (neat) ν 2100 cm^{-1} (NCS); ^{1}H NMR ($CDCl_3$) δ=4.70 (s, 2H) and 7.35 (s, 5H) and benzene eluted benzyl thiocyanate (0.44 g, 30%), mp 42—43 °C, IR (KBr) ν 2150 cm^{-1} (SCN); ^{1}H NMR ($CDCl_3$) δ=4.17 (s, 2H) and 7.38 (s, 5H). The conversion and the ratio were determined by ^{1}H NMR spectra before the chromatographic separation. All the products were identified by a comparison with the authentic samples by at least two of the following methods: Mixed melting point, IR, NMR, and retention time of HPLC.

Kinetic Measurement. A competitive reaction was carried out at −20 °C for 6 min. For example, a solution of benzyl bromide (0.513 g, 3 mmol) and *p*-methoxybenzyl bromide (0.603 g, 3 mmol) in HMPA (4 cm^3) was cooled at −20 °C, and then TMSTC (0.79 g, 6 mmol) was added. The mixture was stirred for 6 min at the temperature. Work-up was similar to that described above. The relative rate of the substitution reaction was determined by ^{1}H NMR spectrum (at 300 MHz) of the products. All competitive reactions were carried out at least twice and the results were obtained from the averaged values.

Rearrangement of Benzyl Thiocyanate to Benzyl Isothiocyanate. An HMPA solution of benzyl thiocyanate (0.22 g, 1.5 mmol) and bromotrimethylsilane (0.31 g, 2 mmol) was stirred at 60 °C for 24 h. Similar work-up gave a mixture of benzyl isothiocyanate (55%), benzyl bromide (16%), and the starting material (29%). The product distribution was determined by ^{1}H NMR spectrum.

Reaction of 1-Bromo-3-methyl-2-butene with TMSTC. A mixture of 1-bromo-3-methyl-2-butene (1.49 g, 10 mmol), TMSTC (1.31 g, 10 mmol), and HMPA was treated at room temperature for 24 h. A similar work-up gave a mixture of 3-isothiocyanato-3-methyl-1-butene (A), 1-thiocyanato- (B), and 1-isothiocyanato-3-methyl-2-butene (C) in a ratio of 37 : 34 : 29, determined by ^{1}H NMR spectrum. An attempt to separate a mixture failed because of the intramolecular rearrangement during the separation on silica gel. Each structure was confirmed by ^{1}H NMR and IR spectra. ^{1}H NMR signals were assigned by their intensities. The time de-

pendency of the product distribution is given in Table 2. 3-Isothiocyanato-3-methyl-1-butene (A), IR (neat) ν 2080 cm^{-1} (NCS); ^1H NMR ($CDCl_3$) δ=1.49 (s, 6H) and 4.99—6.09 (m, 3H). 1-Thiocyanato-3-methyl-2-butene (B), IR (neat) ν 2150 cm^{-1} (SCN); ^1H NMR ($CDCl_3$) δ=1.79 (d, 6H), 3.61 (d, 2H), and 5.32 (t, 1H). 1-Isothiocyanato-3-methyl-2-butene (C), IR (neat) ν 2060 cm^{-1} (NCS); ^1H NMR ($CDCl_3$) δ=1.74 (d, 6H), 4.05 (d, 2H), and 5.30 (t, 1H).

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