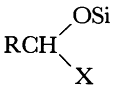
Reactions of Trimethylsilyl Isothiocyanate with Aldehydes and Acetals. Synthesis of Symmetrically and Unsymmetrically Isothiocyanato-Substituted Ethers

Kozaburo NISHIYAMA* and Makoto OBA
Department of Chemistry, Tokyo Metropolitan University, 2-1-1 Fukasawa, Setagaya-ku, Tokyo 158

(Received November 28, 1986)

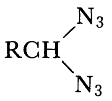
Synopsis. The reactions of trimethylsilyl isothiocyanate (TMSTC) with aldehydes catalyzed by Lewis acid gave α,α′-diisothiocyanato ethers in good to excellent yields. Similarly, unsymmetrical α-isothiocyanato ethers were obtained from the reactions of TMSTC with acetals in appropriate yields.

Silicon compounds carrying a functional group play important roles in organic synthesis.[1] For example, silyl cyanides and silyl azides have been shown to be highly versatile reagents, which converted carbonyl compounds into α-siloxy cyanides (**1a**),[1] α-siloxy azides (**1b**),[2] and *gem*-diazides (**2**).[3,4] As a part of our continuing studies on such silicon compounds, we investigated the synthetic utility of trimethylsilyl isothiocyanate (TMSTC) because there have been a few reports[5] on its reactivity to date. In this paper, we would like to describe $ZnCl_2$-promoted reactions of TMSTC with aldehydes and acetals to give α,α′-diisothiocyanato and α-isothiocyanato ethers, respectively.



$RCH(OSi)X$

1a, X=CN; **1b**, X=N_3



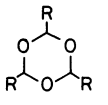
$RCH(N_3)_2$

2

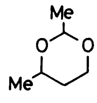
Results and Discussion

The Reaction of TMSTC with Aldehyde. Contrary to the reaction of silyl azide with aldehyde,[4] an 89% of bis(1-isothiocyanato-2-methylpropyl) ether (**4c**) was obtained by a reaction of 2-methylpropanal (**3c**) and TMSTC (2.2 equiv) in the presence of a catalytic amount of $ZnCl_2$ at room temperature for 24 h. Even when the reaction of **3c** with 1.2 equiv of TMSTC was carried out at room temperature for 4 h, the sole product was compound **4c** although the yield became poor. The reaction was also promoted by $SnCl_2$, giving the corresponding ether. By carrying out the reaction for other aldehydes under similar conditions, we obtained some symmetrically disubstituted ethers in good yields. The results and the spectral data of the products are summarized in Table 1. Trichloroethanal and benzaldehyde did not give any products under similar conditions and benzaldehyde was quantitatively recovered after the work-up. Such aldehydes reacted with silyl azide to afford adducts, **1b** and **2**.[4] By using hydrosilanes, several synthetic methods for ethers have been reported under various conditions.[6]

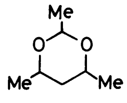
When the reaction of 2-methylpropanal (**3c**) with TMSTC in the presence of $ZnCl_2$ (catalytic amount) was carried out at 90 °C for 0.5 h, 2,4,6-tris(1-methylethyl)-1,3,5-trioxane (**5c**) along with ether **4c** (22%) was isolated in a 36% yield. The trioxane **5c** was also isolated in an 83% yield from the reaction of the aldehyd **3c** with $ZnCl_2$ (0.05 equiv) in the absence of TMSTC at room temperature for 1 h. In addition, a mixture of **5c**, TMSTC, and $SnCl_2$ was stirred for 1.5 h at room temperature, giving a 70% yield of **4c**, and 2,4,6-trimethyl-1,3,5-trioxne (**5f**) was also converted into bis(1-isothiocyanatoethyl) ether (**4f**) in a 73% yield. However, 1,3,5-trioxane (**5e**), 2,4-dimethyl-1,3-dioxane (**6a**), and 2,4,6-trimethyl-1,3-dioxane (**6b**) were recovered quantitatively under similar conditions.



5e, R=H; **f**, R=Me



6a



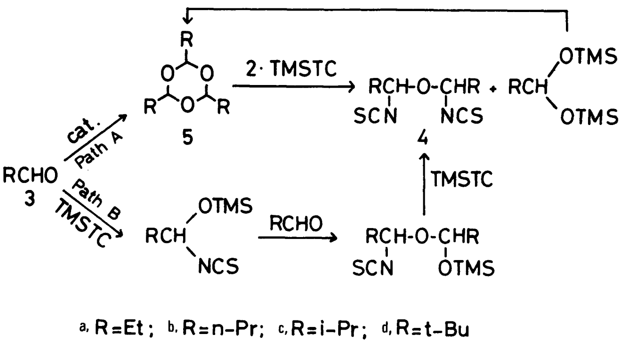
6b

On the basis of these findings, we propose that the reaction of TMSTC with aldehydes takes place as path A rather than path B of the Scheme, i.e. 1,3,5-trioxane **5** initially generated by $ZnCl_2$-catalyzed trimerization of the aldehyde is substituted by TMSTC to form ether **4** and bis(trimethylsilyl) acetal. The latter again trimerizes to trioxane **5** under these conditions. Otherwise, the yield of the product **4** should be at most 67%. As for path B, Mukaiyama et al. considered it a plausible reaction course of ether formation,[6d] i.e. 2:1-addition of aldehyde with silicon compound followed by condensation of the adduct with another silicon compound. That trichloroethanal and benzaldehyde were not converted into ether **4** shows that such aldehydes would not give trioxane **5** under the conditions employed.

Table 1. Yields and Spectral Properties of Ether **4**

Compd	Mp/(θ_m/°C)	Yield/%	FD-MS	IR/cm^{-1}	^{1}H NMR/δ
4a	liq	80[a]	216 (M^+)	2000	1.05 (t, 6H), 1.65—2.10 (m, 4H), 5.09 (t, 2H)
4b	liq	77[a]	244 (M^+)	2000	0.97 (t, 6H), 1.20—2.05 (m, 8H), 5.13 (t, 2H)
4c	liq	89[a]	244 (M^+)	2000	1.06 (d, 12H), 1.80—2.30 (m, 2H), 4.89 (d, 2H)
4d	45—46	84[a]	272 (M^+)	2050	1.03 (s, 18H), 4.72 (s, 2H)
4f	liq	73[b]	188 (M^+)	2000	1.59 (d, 6H), 5.27 (q, 2H)

a) Aldehyde/TMSTC=1/2.2. b) The compound was obtained from 2,4,6-trimethyl-1,3,5-trioxane (**5f**) and TMSTC.

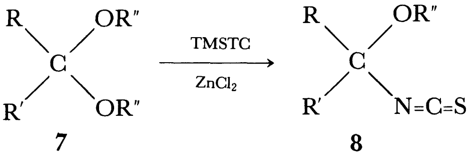


a, R=Et; b, R=n-Pr; c, R=i-Pr; d, R=t-Bu

Scheme 1.

The Reaction of TMSTC with Acetal. As described above, the substitution reaction of trioxane derivatives **5** by TMSTC occurred to give the corresponding ether **4** exclusively. This led us to examine a possibility of unsymmetrical ether formation from acetal with TMSTC.

When a mixture of propanal dimethyl acetal (**7b**), TMSTC, and $ZnCl_2$ was stirred for 4 h at room temperature, the desired ether **8b** was obtained in a 67% yield. This method could be applied to various acetals, and the results are compiled in Table 2. A conversion of acetals **7** into ethers **8** was achieved in good yields, but an isolation of the products depended upon their sensitivity to moisture. Notably, we could not isolate any of the *p*-methoxy derivative **8c** although compound **7c** was quantitatively converted into **8c**, determined by the ^{1}H NMR spectrum.



7 8

a) R=Me, R′=H, R″=Et; b) R=Et, R′=H, R″=Me; c) R=*p*-$MeOC_6H_4$, R′=H, R″=Et; d) R=*p*-MeC_6H_4, R′=H, R″=Et; e) R=C_6H_5, R′=H, R″=Me; f) R=*p*-ClC_6H_4, R′=H, R″=Et; g) R=*p*-$O_2NC_6H_4$, R′=H, R″=Et; h) R=R′=Et, R″=Me; i) R=Me, R′=*i*-Pr, R″=Me; j) R,R′=-$(CH_2)_4$-, R″=Me; k) R,R′=-$(CH_2)_5$-, R″=Me.

In conclusion, the synthesis of α-substituted and α,α′-disubstituted ethers was easily realized by using TMSTC, acetal, and aldehyde. While such ether synthesis is also considered to be achieved by a reaction of halogeno precursor with sodium thiocyanate, the applicability of the method as a general synthetic route to **4** and **8** is limited, due to the inaccessibility of the reagents.

Experimental

Materials. Trimethylsilyl isothiocyanate (TMSTC) was prepared from chlorotrimethylsilane and sodium thiocyanate according to the literature.[7] Acetals, except for commercial products, were synthesized by the reported methods.[8] Commercial products including aldehydes were purified if necessary.

The Reaction of Aldehyde 3 with TMSTC. As an example the reaction of 2-methylpropanal (**3c**) with TMSTC is shown. A mixture of **3c** (3.0 g, 42 mmol), TMSTC (12.0 g, 92 mmol), and $ZnCl_2$ (341 mg, 2.5 mmol) was stirred at room temperature for 24 h. After removal of low-boiling substances, the reaction mixture was triturated with hexane and the resulting precipitates ($ZnCl_2$) were filtered off. The filtrate was stirred with water for an additional 0.5 h. The extract with CH_2Cl_2 was dried over $MgSO_4$, the solvent were evaporated in vacuo, and the residual oil chromatographed on silica gel. Elution with hexane contained 4.6 g (89%) of bis(1-isothiocyanato-2-methylpropyl) ether (**4c**). ^{13}C NMR ($CDCl_3$) δ=17.04, 17.20, 35.10, 89.54, and 138.91. Other spectral data of **4c** and related compounds are shown in Table 1. **4a**: Found: C, 44.21; H, 5.63; N, 12.98%. Calcd for $C_8H_{12}N_2S_2O$: C, 44.41; H, 5.59; N, 12.95%. **4b**: Found: C, 49.00; H, 6.57; N, 11.51%. Calcd for $C_{10}H_{16}N_2S_2O$: C, 49.15; H, 6.60; N, 11.47%. **4c**: Found: C, 49.40; H, 6.75; N, 11.24%. Calcd for $C_{10}H_{16}N_2S_2O$: C, 49.15; H, 6.60; N, 11.47%. **4d**: Found: C, 52.93; H, 7.40; N, 10.23; S, 23.52%. Calcd for $C_{12}H_{20}N_2S_2O$: C, 52.90; H, 7.40; N, 10.29; S, 23.54%. **4f**: Found: C, 38.21; H, 4.26; N, 14.84%. Calcd for $C_6H_8N_2S_2O$: C, 38.28; H, 4.28; N, 34.06%.

Table 2. Yields and Spectral Properties of Ether **8**

Compd	Bp (θ_b/°C)/mmHg$^{a)}$	Yield/%	MS$^{b)}$	IR/cm^{-1}	^{1}H NMR/δ
8a	84—85/60	65	131	2025	1.28 (t, 3H), 1.55 (d, 3H), 3.30—4.15 (m, 2H), 4.98 (q, 1H)
8b	72—73/55	67	131	2050	1.02 (t, 3H), 1.64—2.15 (m, 2H), 3.47 (s, 4H), 4.70 (t, 1H)
8c		0 (100)$^{c)}$		2000	1.24 (t, 3H), 3.68 (q, 2H), 3.78 (s, 3H), 6.84, 7.34 (ABq, 4H)
8d	88/0.5	65 (100)$^{c)}$	162	2000	1.30 (t, 3H), 2.33 (s, 3H), 3.50—4.00 (m, 2H), 7.11, 7.31 (ABq, 4H)
8e	77—78/0.7	65 (100)$^{c)}$	148	2000	3.60 (s, 3H), 5.82 (s, 1H), 7.44 (m, 5H)
8f	83/0.25	76 (100)$^{c)}$	182	2000	1.30 (t, 3H), 3.50—4.05 (m, 2H), 5.85 (s, 1H) 7.38 (s, 4H)
8g	112/0.2	43 (65)$^{c)}$	193	2000	1.35 (t, 3H), 3.50—4.15 (m, 2H), 5.99 (s, 1H), 7.66, 8.27 (ABq, 4H)
8h	52—55/5	61	130	2025	0.97 (t, 6H), 1.87 (q, 4H), 3.32 (s, 3H)
8i	53/5	56	128	2050	0.99 (d, 3H), 1.03 (d, 3H), 1.49 (s, 3H), 1.60—2.20 (m, 1H), 3.37 (s, 3H)
8j	46—47/1.2	50	126	2025	1.50—2.25 (m, 8H), 3.40 (s, 3H)
8k	65/2	70	140	2025	1.40—2.10 (m, 10H), 3.35 (s, 3H)

a) 1 mmHg=133.322 Pa. b) The largest number of the fragment is shown. c) Yields determined by ^{1}H NMR spectrum are indicated in parenthesis.

The Reaction of Acetal 7 with TMSTC. When the boiling points of the products (unsymmetrically substituted ethers) were close to that of TMSTC, the following was representative of the reaction of acetal **7** with TMSTC. A mixture of propanal dimethyl acetal (**7b**, 6.3 g, 60 mmol), TMSTC (3.9 g, 30 mmol), and $ZnCl_2$ (0.4 g, 3 mmol) in dichloromethane (15 cm^3) was stirred at room temperature for 4 h. With aromatic derivatives, the quantities of compound **7** and TMSTC were altered to 30 and 60 mmol, respectively, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) was used as a catalyst in order to avoid a complicated isolation. Work-up was similar to that for **4c** described above. 2.7 g (67%) of 1-isothiocyanatopropyl methyl ether (**8b**) was obtained by distillation at reduced pressure, bp 72—73 °C/55 mmHg. Physical and spectral data of compound **8** are listed in Table 2.

One of us (K. N.) wishes to thank the ministry of Education, Science and Culture for Grant-in-Aid (No 60540338).

References

1) W. P. Weber, "Silicon Reagents for Organic Synthesis," Springer-Verlag, New York (1983).

2) L. Birkofer, F. Müller, and W. Kaiser, *Tetrahedron Lett.*, **1967**, 2781; L. Birkofer and W. Kaiser, *Justus Liebigs Ann. Chem.*, **1975**, 266.

3) K. Nishiyama and A. Watanabe, *Chem. Lett.*, **1984**, 455.

4) K. Nishiyama, M. Oba, and A. Watanabe, *Tetrahedron*, **43**, 693 (1987).

5) For example, A. C. W. Curran and R. G. Shephered, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 983; T. Sasaki, A. Nakanishi, and M. Ohno, *J. Org. Chem.*, **46**, 5445 (1981); R. F. Cunico and L. Bedell, *J. Organomet. Chem.*, **281**, 135 (1985).

6) a) D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, **1974**, 633; b) M. P. Doyle, C. T. West, S. J. Donnelly, and C. C. McOsker, *J. Organomet. Chem.*, **117**, 129 (1976); c) R. Noyori, S. Murata, and M. Suzuki, *Tetrahedron*, **37**, 3899 (1981); d) J. Kato, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, **1985**, 743.

7) British Tomson-Houston Co. Ltd., Brit. Patent 643941 (1950); *Chem. Abstr.*, **45**, 7585 g (1951).

8) T. H. Fifi and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965); S. R. Sandler and W. Karo, "Organic Functional Group Preparations," Academic Press, New York (1972), Vol. 3, Chap. 1, pp. 1—75.