CHEMISTRY LETTERS, pp. 1073-1076, 1992.

Alkoxymethylthiomethylsilanes as a Synthetic Equivalent of Thiocarbonyl Ylides. Synthesis of 1,3-Oxathiolanes and Tetrahydrothiophenes[1)]

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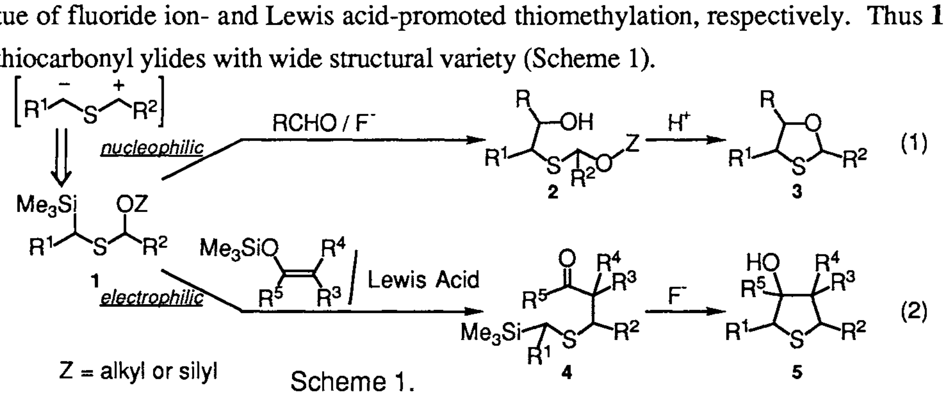
Alkoxymethylthiomethylsilanes, easily prepared, react nucleophilically with aldehydes by the action of fluoride ion and electrophilically with silyl enol ethers in the presence of a Lewis acid. These products can be converted to 1,3-oxathiolanes by acid catalysis and tetrahydrothiophenes by fluoride ion-promoted intramolecular alkylthiomethylation, respectively. By both sequential reactions alkoxymethylthiomethylsilanes serve as substituted thiocarbonyl ylide synthons.

[3+2] Cycloaddition of 1,3-dipolar reagents to components bearing unsaturation is one of the most direct way for the synthesis of five-membered heterocycles, while the generation of well-designed 1,3-dipolar species is generally not so easy and some devices by introduction of stabilizing substituents to such species are required.[2)] From a view point of organic synthesis, these functional groups are not always necessary and the reagents should be designed to possess only desired groups. In such a sense, we have developed a new type of method for the generation of 1,3-heterodipolar reagents, e.g., azomethine ylides and thiocarbonyl ylides, from organosilicon compounds by novel 1,3-elimination reactions. Using this method not only parent azomethine ylide[3a)] and thiocarbonyl ylide[3b)] but also equivalents of novel azomethine ylides bearing alkylidene[3c)] and imino moiety[3d)] are also available at present. In the course of our study, next interest for us is the generation of optionally substituted thiocarbonyl ylides or their equivalents and use of them for the synthesis of substituted tetrahydrothiophene and 1,3-oxathiolanes. In this context we designed alkoxymethylthiomethylsilanes as masked thiocarbonyl ylide synthons with substituents at any position, displaying versatile reactivity.[4)] In this paper we report that alkoxymethylthiomethylsilanes **1** react "nucleophilically" with aldehydes and "electrophilically" with olefins by virtue of fluoride ion- and Lewis acid-promoted thiomethylation, respectively. Thus **1** is a synthetic equivalent of thiocarbonyl ylides with wide structural variety (Scheme 1).

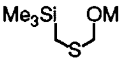
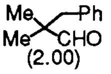
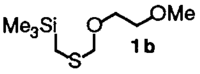
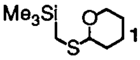
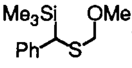


Scheme 1.

First we examined two kinds of method for activation of **1** and reactions with dipolarophiles, such as olefins and carbonyl compounds. One is the method *via* activation of an alkoxy leaving group by a Lewis or

Brϕnsted acid which was effective for the generation of parent azomethine ylide.[3a)] Unfortunately, in this case, any conditions we examined are not effective for reaction of **1** toward dipolarophiles. As another method, we used fluoride ion as an activator for silicon-carbon bond and found that alkoxymethylthiomethylation to an aldehyde occurred (Scheme 1, Eq. 1). Although **2** was not an adduct of expected thiocarbonyl ylide, the present reaction is interesting as a method for generation of an alkylthio carbanion equivalent and some comments are deserved as follows. We realized the use of alkylthiomethylsilanes as an alkylthiomethyl anion equivalent which was difficult hitherto and not so defined, although such a method may be possibly useful for generation of an alkylthiomethyl anion under nearly neutral condition.[5)] Tetrabutylammonium fluoride (TBAF) is the best choice of fluoride ion source under our operation and in this case a catalytic amount of TBAF is sufficient for this reaction (Table 1). This is in marked contrast to the reactivity of methylthiomethylsilane and bis(silylmethyl)-sulfide, though the former was not effective as a methylthiomethyl carbanion equivalent[5a)] and in the latter case a stoichiometric amount of fluoride ion was necessary.[5c)]

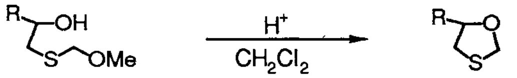
Table 1. Fluoride Ion-Promoted Intermolecular Alkoxymethylthiomethylation[a)]

1 (mmol)		Aldehyde (mmol)	TBAF (mmol)	Conditions Temp.	Time/h	Product 2	Yield / %[b)]
 **1a**	(1.00)	PhCHO (1.98)	0.20+0.20[c)]	rt.	48	**2a**	84
1a	(1.00)	p-$MeOC_6H_4CHO$ (2.00)	0.20	rt.	48	**2b**	72
1a	(1.00)	p-PhC_6H_4CHO (2.00)	0.20+0.20[c)]	rt.	48	**2c**	63
1a	(1.00)	p-ClC_6H_4CHO (2.00)	0.20+0.20[c)]	rt.	72	**2d**	44
1a	(1.00)	Me_3CCHO (2.00)	0.20	rt.	47	**2e**	87
1a	(1.00)	$C_6H_{11}CHO$ (2.00)	0.40	rt.	67	**2f**	64
1a	(1.00)	 (2.00)	0.40+0.20[c)]	rt.	67	**2g**	59
 **1b**	(1.00)	(2.00)	0.20+0.20[c)]	rt.	46	**2h**	60
 **1c**	(1.00)	p-$MeOC_6H_4CHO$ (2.00)	0.20+0.20[c)]	rt.	73	**2i**	68
 **1d**	(1.00)	p-$MeOC_6H_4CHO$ (2.00)	0.20	rt.	22	**2j**	82

a) For a procedure, see text. b) Isolated yield after purification by chromatography on silica gel. c) After several hours, TBAF(0.20 mmol) was added.

Wide structural variety of alkoxymethylthiomethylsilanes **1** and aldehydes are tolerated in this reaction and both aromatic and aliphatic aldehydes are nicely converted to the corresponding adducts **2**.[6)] A general procedure is as follows. A flask containing molecular sieves 4A was flame-dried and purged with nitrogen. To this flask was introduced a solution of tetrabutylammonium fluoride in THF (0.65-0.75 M) *via* a syringe. After stirring for 2h, this well-dried solution was mixed with alkoxymethylthiomethylsilane **1** (1 mmol) and an aldehyde (1.98-2.0 mmol). The mixture was stirred at room temperature and consumption of **1** was monitored by GC and a TBAF solution was added if necessary. The resultant mixture was filtered by celite pad and washed with water followed by conventional work up. A product was purified by chromatography on silica gel.

These adducts **2** can be readily cyclized to 1,3-oxathiolanes **3**[7)] with a catalytic amount of concentrated sulfuric acid in dichloromethane at room temperature (Eq. 3). As a result, alkoxymethylthiomethylsilanes **1** serve as a synthetic equivalent of substituted thiocarbonyl ylides by these sequential "nucleophilic-electrophilic" reactions.



(3)

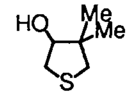
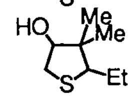
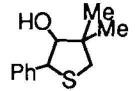
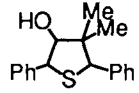
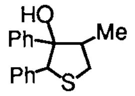
2e, R = *t*-Bu **3e** : 32 %
2g, R = $C(CH_3)_2CH_2Ph$ **3g** : 81 %

Table 2. Reaction of *O,S*-Acetals **1** with Silyl Enol Ether a)

1		Silyl Enol Ether			4	
R^1	R^2	R^3	R^4	R^5	Yield / % b)	
H	H	Me	Me	H	**4a**	70
H	Et	Me	Me	H	**4b**	41
Ph	H	Me	Me	H	**4c**	92
Ph	Ph	Me	Me	H	**4d**	55
Ph	H	Me	H	Ph	**4e**	70

a) $Me_3SiCl-InCl_3$ was used as a Lewis acid. b) Isolated yield by chromatography on silica gel.

Table 3. Fluoride Ion-Promoted Intramolecular Alkylthiomethylation

4 (mmol)	TBAF mmol	Conditions Temp Time/h	5		Yield / % a)
4a (2.0)	0.8	rt, 40		**5a**	69
4b (0.5)	0.4	rt, 72		**5b** b)	53
4c (0.5)	0.2	rt, 23		**5c** b,c)	92
4d (0.35)	0.2	rt, 23		**5d** b,c)	83
4e (0.3)	0.3	rt, 21		**5e** b)	69

a) Isolated yield after purification by chromatography on silica gel. b) A stereoisomeric mixture, unless otherwise noted. c) Ca. 7:3

Tetrahydrothiophenes will be obtained by the sequential "electrophilic-nucleophilic" reactions of **1** with olefins such as silyl enol ethers, if intramolecular alkylthiomethylation can be attained (Eq. 2). Selective cleavage of carbon-oxygen bond of *O,S*-acetals **1** and its reactions with silyl enol ethers were effectively promoted by Lewis acid to afford the corresponding carbonyl compounds **4** in good to excellent yield (Table 2). Final intramolecular alkylthiomethylation seems to be the most difficult class of thiomethylation reactions. Indeed though tetrahydrothiophenes **5** were conveniently obtained by fluoride ion-promoted intramolecular thiomethylation in THF, a stoichiometric amount of TBAF was necessary in some cases (Table 3).[8]

Thus fluoride ion-promoted inter- and intramolecular alkylthiomethylation was effectively achieved and it was found that alkoxymethylthiomethylsilanes reacted with aldehydes and silyl enol ethers as a synthetic equivalent of thiocarbonyl ylides to afford 1,3-oxathiolanes and tetrahydrothiophenes, respectively, though the stereoselectivity was unsatisfied at present. Ease to prepare a variety of precursors with substituents at various positions will also make this method synthetically valuable route to 1,3-oxathiolanes and tetrahydrothiophenes.

Financial support for this work is partly provided by Grants-in-Aid for Sientific Research, Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan, and the Kurata Foundation. We thank Dow Corning Toray Silicone Co. Ltd. and Shin-Etsu Chemical Co. Ltd. for a gift of organosilicon compounds.

References

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2) R. M. Kellog, *Tetrahedron*, **32**, 2165 (1976); "1,3-Cycloaddition Chemistry," ed by A. Padwa, John Wiley & Sons, New York (1984), Vols, 1 and 2; "Advances in Cycloaddition," ed by D. P. Curran, JAI Press Inc., Greenwich, CT (1988), Vol. 1.

3) a) A. Hosomi, Y. Sakata, and H. Sakurai, *Chem. Lett.*, **1984**, 1117; b) A. Hosomi, Y. Matsuyama, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, **1986**, 1073; c) A. Hosomi, Y. Miyashiro, R. Yoshida, Y. Tominaga, T. Yanagi, and M. Hojo, *J. Org. Chem.*, **55**, 5308 (1990); d) Y. Tominaga, K. Ogata, S. Kohra, M. Hojo, and A. Hosomi, *Tetrahedron Lett.*, **32**, 5987 (1991).

4) Alkoxymethylthiomethylsilanes **1a** and **1b** were prepared by the reaction of corresponding trimethylsilylmethylthiolates with methoxymethyl chloride or methoxyethoxymethyl chloride in 84% and 74% yields, respectively. Tetrahydropyranyl derivative **1c** was prepared by the reaction of mercaptomethylsilane and dihydropyran in dichloromethane-benzene mixed solvent with pyridinium *p*-toluenesulfonate catalyst in 65% yield. Phenyl-substituted precursor **1d** was prepared by the reaction of lithiated methyl benzylthiomethyl ether with chlorotrimethylsilane in 83% yield.

5) a) J. Kitteringham and M. B. Mitchell, *Tetrahedron Lett.*, **29**, 3319 (1988); b) A. Hosomi, K. Ogata, K. Hoashi, S. Kohra, and Y. Tominaga, *Chem. Pharm. Bull.*, **36**, 3637 (1988); c) A. Hosomi, K. Ogata, M. Ohkuma, and M. Hojo, *Synlett*, **3**, 557 (1991).

6) All products **2** gave satisfactory ^{1}H NMR, IR,and MS data. E.g., **2a**: R_f=0.30 (hexane/ethyl acetate=5/1); IR(CCl_4) 3450, 2920, 1450, 1310, 1180, 1080, 700 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 2.62 (dd, J=7.8, 13.8 Hz, 1H), 2.82 (dd, J=4.2, 13.8 Hz, 1H), 3.28 (s, 3H), 4.44 (d, J=12.0 Hz, 1H), 4.55 (d, J=12.0 Hz, 1H), 4.61 (dd, J=4.2, 7.8 Hz, 1H), 7.15 (s, 5H); MS: m/z(relative intensity) 180(M^+-H_2O, 0.1), 166(M^+-MeOH, 0.1), 151(1.4), 135(1.5), 120(1.2), 107(17.2), 91(29.1), 79(25.3), 77(20.7), 60(40.0), 45(100). **2g**: R_f=0.41 (hexane/ethyl acetate=5/1); IR (neat) 3450, 2940, 2340, 1490, 1470, 1450, 1180, 1080, 700, 665 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 0.83 (s, 3H), 0.93 (s, 3H), 2.50 (dd, J=9.0, 14.0 Hz, 1H), 2.53 (d, 13.0 Hz, 1H), 2.77 (d, J=13.0 Hz, 1H), 2.93 (dd, J=2.0, 14.0 Hz, 1H), 3.27-3.53 (m, 1H), 3.30 (dd, J=2.0, 9.0 Hz, 1H), 3.35 (s, 3H), 4.47 (d, J=12.0 Hz, 1H), 4.63 (d, J=12.0 Hz, 1H), 7.15 (s, 5H); MS: m/e(relative intensity) 222(M^+-MeOH, 3.8), 195(1.7), 162(11.2), 145(6.9), 133(9.0), 121(8.0), 91(100), 89(24.3), 69(50.7), 65(15.4), 60(30.2), 45(97.8).

7) **3e**: Bp 120 °C/65 mmHg (Kugelrohr); IR(CCl_4) 2950, 2850, 1475, 1460, 1360, 1070, 1050, 980 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 0.98 (s, 9H), 2.69 (dd, J=10.0, 10.2 Hz, 1H), 2.90 (dd, J=6.0, 10.2 Hz, 1H), 3.49(dd, J=6.0, 10.0 Hz, 1H), 4.70 (d, J=5.2 Hz, 1H), 4.91 (d, J=5.2 Hz, 1H); MS m/e(relative intensity) 146(M^+, 32.8), 131(0.9), 103(6.1), 101(7.7), 89(34.7), 60(60.2), 57(100), 41(45.6). **3g**: R_f=0.76 (hexane/ethyl acetate=5/1); IR(neat film) 2975, 2860, 2375, 1600, 1495, 1460, 1390, 1365, 1295, 1220, 1115, 1070, 1030, 700, 665 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 0.87 (s, 3H), 0.97 (s, 3H), 2.33-2.97 (m, 4H), 3.45 (dd, J=6.0, 9.0 Hz, 1H), 4.67 (d, J=5.4 Hz, 1H), 4.93 (d, J=5.4 Hz, 1H), 7.12 (s, 5H); MS m/e(relative intensity) 222(M^+, 21.2), 145(5.3), 130(31.8), 101(25.2), 91(100), 55(27.6), 43(33.4).

8) All products **5** gave satisfactory spectral data. E.g., **5a**: R_f=0.33 (hexane/ethyl acetate=3/1); ^{1}H NMR($CDCl_3$) δ 1.04 (s, 3H), 1.13 (s, 3H), 2.57 (d, J=10.2 Hz, 1H), 2.73 (d, J=10.2 Hz, 1H), 2.76 (dd, J=4.0, 11.2 Hz, 1H), 3.10 (dd, J=4.9, 11.2 Hz, 1H), 3.85 (dd, J=4.0, 4.9 Hz, 1H); ^{13}C NMR($CDCl_3$) δ 20.6, 25.4, 37.1, 40.3, 47.7, 81.5; MS m/e(relative intensity) 132(M^+, 36.4), 99(10.8), 88(27.5), 56(100), 41(50.8). Anal. Found: C;54.30, H;9.25%. Calcd for $C_6H_{12}OS$: C;54.50, H;9.15%.

(Received March 6, 1992)