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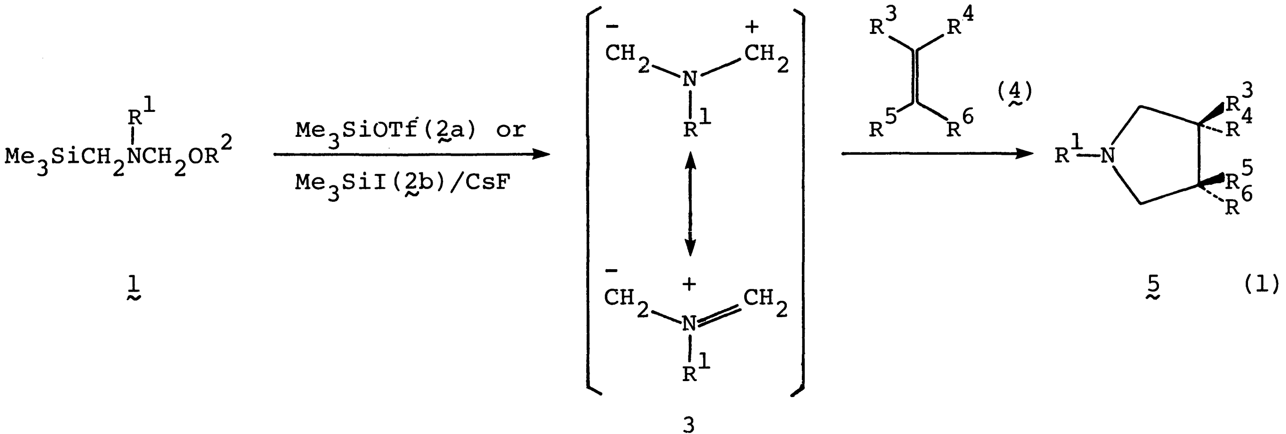
N-(TRIMETHYLSILYLMETHYL)AMINOMETHYL ETHERS AS AZOMETHINE YLIDE SYNTHONS. A NEW AND CONVENIENT ACCESS TO PYRROLIDINE DERIVATIVES[1)]

Akira HOSOMI,* Yasuyuki SAKATA, and Hideki SAKURAI*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980

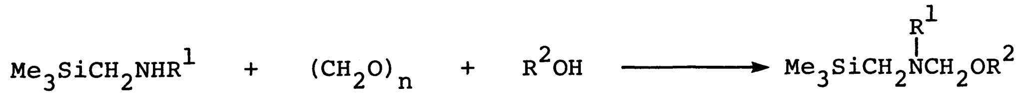
The title compounds, readily prepared from (trimethylsilylmethyl)amines, formaldehyde and an alcohol, react with electron deficient alkenes in the presence of iodosilane or silyl triflate in combination with cesium fluoride to give the corresponding pyrrolidine derivatives stereospecifically in excellent yield.

Azomethine ylides are one of the most important 1,3-dipoles from both synthetic and theoretical point of view.[2)] However, either electron-withdrawing or conjugating substituents are required inevitably for stabilizing the dipoles in the generation of azomethine ylides through thermally induced ring-opening of aziridines.[3)] Therefore, generation of non-stabilized azomethine ylides, especially by fluoride ion-promoted desilylation of immonium salts, has been a current interest.[4)] We have previously demonstrated that α-heteroatom-substituted ethers and related compounds (R^1R^2CXY; X, Y = R_2N, RO, RS and halogen) are activated chemoselectively by iodosilane or silyl triflate to undergo efficient reactions for regiospecific introduction of α-heteroatom-substituted alkyl group to silyl enol ethers and allylsilanes.[5)] In an extension of the study, we report herein that N-(trimethylsilylmethyl)aminomethyl ethers (**1**) activated by trimethylsilyl trifluoromethanesulfonate (**2a**) or iodotrimethylsilane (**2b**) and cesium fluoride readily react with electron deficient alkenes (**4**) to give the corresponding pyrrolidine derivatives (**5**) stereospecifically in good yield. (Eq. 1) This constitutes an unprecedented and expedient route to non-stabilized azomethine ylides (**3**).



3 (1)

The requisite aminomethyl ethers (**1**), unknown up to date, were prepared quite easily from (aminomethyl)silanes (**6**)[6,7)] in good yield.[8)] (Eq. 2)



$$\mathrm{Me_3SiCH_2NHR^1} \quad + \quad \mathrm{(CH_2O)_n} \quad + \quad \mathrm{R^2OH} \longrightarrow \mathrm{Me_3SiCH_2\overset{R^1}{\overset{|}{N}}CH_2OR^2} \qquad (2)$$

6a, R^1=cyclo-C_6H_{11} 7 8a, R^2=Me 1a, R^1=cyclo-C_6H_{11}; R^2=Me
b, R^1=$PhCH_2$ b, R^2=n-Bu b, R^1=$PhCH_2$; R^2=Me
c, R^1=$PhCH_2$; R^2=n-Bu

Aminomethyl ether (1a), catalyzed by 2a, undergoes 1,3-elimination of methoxytrimethylsilane in the presence of electron deficient alkenes (4) to afford the corresponding pyrrolidine derivatives (5, R^1=cyclo-C_6H_{11}) in considerably high yield. Addition of a small amount of cesium fluoride accelerates the reaction and improves the yield of 5 presumably due to desilylation of 1. Nevertheless, it is worth to note that the reaction proceeds sufficiently even without cesium fluoride. The results are listed in Table 1.

Reactions catalyzed by 2a are rather slow at room temperature so that it is necessary to raise the temperature to 50-60 °C for the completion of the reaction. An aprotic polar solvent such as tetrahydrofuran, acetonitrile and hexamethylphosphoric triamide can be used for the reaction, although the reaction proceeds rather slowly in dichloromethane that is usually an efficient solvent for the silyl triflate-catalyzed reaction.5) Iodosilane (2b) also catalyzes the reaction very effectively and the reaction proceeds even at room temperature in this case.

The substituent on the nitrogen atom could be changed widely since 6 can be prepared by the reaction of chloromethyltrimethylsilane and a variety of primary amines.6) For example, as a precursor of the parent azomethine ylide (3, R^1=H), N-benzyl-N-(trimethylsilylmethyl)aminomethyl ethers (1b and 1c) were prepared from benzylamine (6b) in good yield.8) The reactivity of 1b and 1c toward 1,3-dipolarophiles seems to be quite similar to 1a and the corresponding 1-benzylpyrrolidines (5, R^1=$PhCH_2$) that are easily deprotected under mild conditions9) are obtained in good yield.

In conclusion, the in situ generation of azomethine ylides (3) by way of the methods described in this report provides a convenient and versatile alternative to existing procedures4) and opens a novel route to 1,3-elimination reaction of organosilicon compounds.10) The methodology can be presumably applied to the generation of other non-stabilized heteroatom 1,3-dipoles such as carbonyl ylides and thiocarbonyl ylides.11)

As a typical procedure, 2a (80 mg, 0.40 mmol) was added to a solution of 1a (460 mg, 2.0 mmol), dimethyl fumarate (4a) (290 mg, 2.0 mmol) and dried cesium fluoride (62 mg, 0.40 mmol) in THF (5 ml) by using a syringe. After stirring for 18 h at 60 °C, the reaction mixture was cooled to 0 °C and hydrolyzed with 15% aqueous sodium hydroxide. After extractive and drying work-up with ether and potassium carbonate, pyrrolidine (5a) (482 mg, 1.79 mmol) was isolated by TLC (R_f 0.30, ether/hexane = 1/1) in 90% yield.

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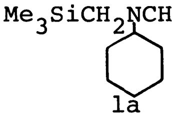
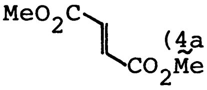
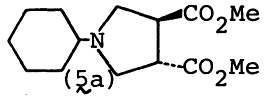
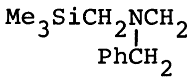
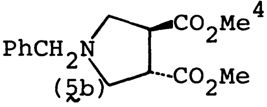
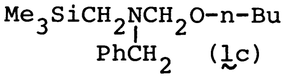
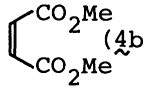
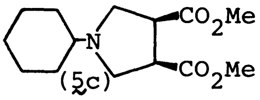
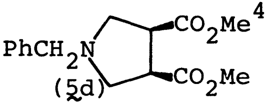
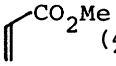
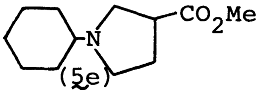
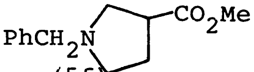
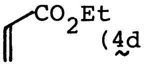
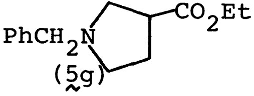
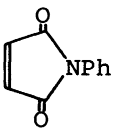
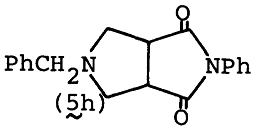
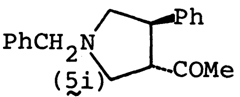
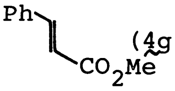
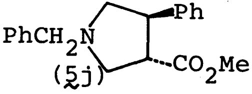
Table 1. Reactions of N-(trimethylsilylmethyl)aminomethyl ethers (**1**) with dipolarophiles (**4**)

Run	Aminomethyl ether (**1**)	Dipolarophile (**4**)	Conditions[a)]	Product (**5**)	% Yield[b)]
1	 (**1a**)	 (**4a**)	Me_3SiOTf (**2a**) 60 °C, 26 h, THF	 (**5a**)	58
2	**1a**	**4a**	**2a**, CH_3CN 60 °C, 24 h	**5a**	57
3	**1a**	**4a**	**2a**, CsF, THF 60 °C, 18 h	**5a**	90
4	**1a**	**4a**	**2a**, CsF, HMPA 70 °C, 24 h	**5a**	83
5	**1a**	**4a**	Me_3SiI (**2b**) CH_3CN, rt, 24 h	**5a**	47
6	 $Me_3SiCH_2N(CH_2Ph)CH_2OMe$ (**1b**)	**4a**	**2a**, CH_3CN 60 °C, 15 h	 (**5b**) 4g)	74
7	**1b**	**4a**	**2a**, CsF, THF 60 °C, 25 h	**5b**	83
8	 $Me_3SiCH_2N(CH_2Ph)CH_2O\text{-}n\text{-}Bu$ (**1c**)	**4a**	**2b**, CsF, CH_3CN 50 °C, 10 h	**5b**	75
9	**1a**	 (**4b**)	**2a**, CsF, THF 60 °C, 36 h	 (**5c**)	72
10	**1b**	**4b**	**2a**, CsF, THF 60 °C, 25 h	 (**5d**) 4g)	83
11	**1a**	 (**4c**)	**2a**, CsF, THF 60 °C, 18 h	 (**5e**)	80
12	**1c**	**4c**[c)]	**2b**, CsF, CH_3CN 60 °C, 15 h	 (**5f**)	91
13	**1b**	 (**4d**)[c)]	**2a**, CsF, THF 60 °C, 25 h	 (**5g**)	85
14	**1c**	**4d**[c)]	**2b**, CsF, CH_3CN 50 °C, 24 h	**5g**	80
15	**1c**	 (**4e**)	**2b**, CsF, CH_3CN 50 °C, 20 h	 (**5h**)	81
16	**1c**	 (**4f**)	**2b**, CsF, CH_3CN 50 °C, 24 h	 (**5i**)	68
17	**1c**	 (**4g**)	**2b**, CsF, CH_3CN 60 °C, 15 h	 (**5j**)	56

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a) 5-20 mol% of **2a** or **2b** and/or CsF were employed. 1:1-1.05 Molar ratio of **1** to **4** was used unless otherwise noted. b) Yield after isolation by TLC. c) Two equivalents of **4** to **1** were used.

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2) Reviews and pertinent articles of azomethine ylides: R. M. Kellog, Tetrahedron, 32, 2165 (1976); J. W. Lown, Rec. Chem. Prog., 32, 51 (1971); C. G. Stuckwisch, Synthesis, 1973, 469; I. Fleming, "Frontier Orbitals and Organic Chemicl Reactions," John Wiley & Sons, London (1976), Chap. 4; R. Huisgen, J. Org. Chem., 41, 404 (1976).

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6) J. E. Noll, J. L. Speier, and B. F. Daubert, J. Am. Chem. Soc., 73, 3867 (1951).

7) G. M. Robinson and R. Robinson, J. Chem. Soc., 123, 532 (1923); T. D. Stewart and W. E. Bradley, J. Am. Chem. Soc., 54, 4172 (1932).

8) Preparation of **1** is as follows: To a solution of formalin and an alcohol (1.2 equivalent) was added an appropriate **6** over 0.5 h under ice-cooling. After stirring for additional 1-3 h, potassium carbonate (K_2CO_3) was added to separate the organic materials. The oily layer was separated and the residue was washed with ether and the combined solution was dried over K_2CO_3. After the solvent and excess alcohol were removed under vacuum, **1** was isolated by distillation. **1a**: 51%; bp 55-57 °C (1.5 mmHg); ^1H NMR (CCl_4) δ 0.10 (s, 9H), 0.97-2.10 (m, 10H), 2.24 (s, 2H), 2.30-2.70 (m, 1H), 3.17 (s, 3H), 4.04 (s, 2H); ^{13}C NMR ($CDCl_3$) δ -1.83 (q, 3C), 26.05 (t, 3C), 30.61 (t, 2C), 38.77 (t, 1C), 53.92 (q, 1C), 62.34 (d, 1C), 86.75 (t, 1C). **1b**: 76%; bp 77-78 °C (0.6 mmHg); **1c**: 85%; bp 99 °C (0.6 mmHg). All new compounds obtained in this work gave satisfactory spectral data and elemental analyses.

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11) Indeed, we have found that chloromethyl trimethylsilylmethyl sulfide is a precursor of the parent thiocarbonyl ylide under analogous conditions.

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