Generation of a Lewis Acid Activated Formaldimine and Its Reaction with Enol Silyl Ethers. N-Unsubstituted Aminomethylation

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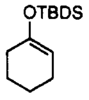
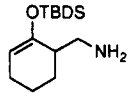
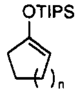
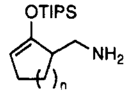
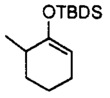
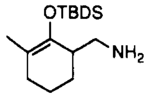
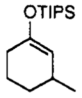
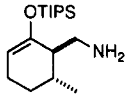
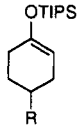
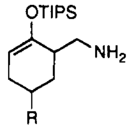
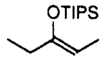
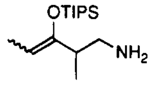
Summary: *N*-(Trimethylsilyl)formaldimine–$AlCl_3$ complex **2b** was generated by treating (trimethylsilyl)methyl azide with $AlCl_3$. The reaction of **2b** with various kinds of enol triisopropylsilyl ethers afforded α'-aminomethylated enol silyl ethers in good yields.

Although the Mannich-type aminomethylation reaction[1] has proven itself as a useful methodology for the preparation of nitrogen-containing compounds, the procedure is usually limited to the introduction of tertiary amino groups, with only a few papers reporting a synthetic equivalent containing the primary amino group.[2,3]

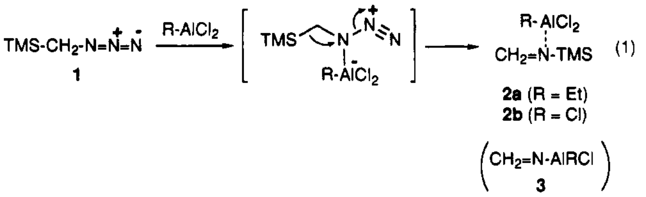
Lewis acid mediated reactions of imines with various nucleophiles have also been studied extensively,[4] but, due to its high lability, generating synthetically useful unsubstituted formaldimine, $CH_2{=}NH$ has been notoriously difficult.[5]

In order to develop a useful procedure for the introduction of the N-unsubstituted aminomethyl group, we investigated the reactions of (trimethylsilyl)methylazide **1**[6] with several Lewis acids. The reactions with $BF_3{\cdot}OEt_2$, $TiCl_4$, or $SnCl_4$ gave rather complicated results, but use of $EtAlCl_2$ or $AlCl_3$ generated the N-silylated formaldimines[7] **2a,b**, which were identified as follows: On treating **1** with ca. 1.1 equiv of $EtAlCl_2$ in $CDCl_3$ at 0 °C or at room temperature, the ^1H NMR spectrum of the resulting clear solution of **2a** exhibited characteristic absorptions at δ 8.30 (d, 1 H, J = 16 Hz) and 8.70 (d, 1 H, J = 16 Hz) attributable to the $CH_2{=}N$ group of formaldimine[8] and 0.60 (s, 9 H) accompanied by the disappearance of the signals due to **1** [δ 0.10 (s, 9 H) and 2.75 (s, 2 H)]. The absence of a signal due to TMS-Cl supports formation of **2a**, rather than **3**. In the presence of $AlCl_3$, **1** gave **2b**, which, although it did not appear as sharp absorptions [δ 8.2–8.6 (br, 1 H) and 8.7–9.0 (br, 1 H)], gave much more satisfactory results in the reactions with nucleophiles.

Table I. Reaction of 2b with Enol Silyl Ethers

entry	enol silyl ether	product	yield (%) of 4
1			56
2			n = 1 66 (76[a]) = 2 93 (64[a]) = 3 71 (73[a,d])
3			73 (85[a])
4			94 (94 : 6[b])
5			R = Me 87 (73 : 27[c]) = ^{t}Bu 98 (74 : 26[c])
6			79 (65[a])

[a] Yield of **5**. [b] Ratio of trans:cis isomers. [c] Ratio of diastereomers. The stereochemistry is not determined. [d] The major (90%) product was the ammonium salt of **4′**.



1 (1)

2a (R = Et)
2b (R = Cl)

$(CH_2{=}N{\text -}AlRCl)$ **3**

The aldimine **2b** reacted with enol trimethylsilyl ethers to afford the corresponding aminomethylated products. The resulting β-amino ketones were usually labile under the basic workup conditions, and we failed to isolate them. The products were isolable following N-benzoylation.[9] However, on using *tert*-butydimethylsilyl or triisopropylsilyl ethers, the reaction proceeded through aminomethylation followed by selective abstraction of an α'-hydrogen[10] to give the aminomethylated enol silyl ethers **4** in good yields (eq 2).[11] The regioisomeric product **4′**

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(1) For reviews on the Mannich reaction, see: (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 893–951. (b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791. (c) Tramontini, M. *Synthesis* **1973**, 703.

(2) Mannich reaction including the synthetic equivalent of $^+CH_2NH_2$: Becker, H. G. O.; Fanghanel, E.; Ecknig, W. *Angew. Chem.* **1960**, *72*, 633.

(3) Reactions including the synthetic equivalent of $^+CH_2NH_2$: (a) Bestmann, H. J.; Wolfel, G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 53. (b) Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G. *Synlett* **1990**, *10*, 621. (c) Morimoto, T.; Takahashi, T.; Sekiya, M. *J. Chem. Soc., Chem. Commun.* **1984**, 794. (d) Okano, K.; Morimoto, T.; Sekiya, M. *J. Chem. Soc., Chem. Commun.* **1984**, 883. (e) Katritzky, A. R.; Jiang, J.; Urogdi, L. *Tetrahedron Lett.* **1989**, *30*, 3303.

(4) (a) Pilli, R. A.; Russowsky, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1053. (b) Gennari, C.; Schimperna, G.; Venturini, I. *Tetrahedron* **1988**, *44*, 4221. (c) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4335. (d) Brandstadter, S. M.; Ojima, I.; Hirai, K. *Ibid.* **1987**, *28*, 613. (e) Colvin, E. W.; McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539 and references cited therein.

(5) Although $[CH_2{=}NH_2]SbCl_6$ was prepared as a stable solid by treating methyl azide with $SbCl_5$ and HCl, its acidic property seems to preclude its functioning as a synthetically useful electrophile: Goubeau, J.; Allenstein, E.; Schmidt, A. *Chem. Ber.* **1964**, *97*, 884.

(6) (a) Nishiyama, K.; Tanaka, N. *J. Chem. Soc., Chem. Commun.* **1983**, 1322. (b) Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett.* **1983**, 1131.

(7) It has been reported that *N*-(trimethylsilyl)formaldimine itself was generated from α-[*N*-(trimethylsilyl)amino]acetonitrile but underwent oligomerization at −10 °C: Guillemin, J.-C.; Ammi, L.; Denis, J.-M. *Tetrahedron Lett.* **1988**, *29*, 1287.

(8) For ^1H NMR of this type of methylene hydrogens, see: Shapiro, B. L.; Ebersole, S. J.; Karabatsos, G. J.; Vane, F. M.; Manatt, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 4041.

(9) A β-amino ketone can be isolated as a benzamide in moderate yield by treatment of the reaction mixture with aqueous sodium hydroxide and benzoyl chloride.

(10) For enelike reactions of enol silyl ethers with electrophiles see: (a) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 3323. (b) Magnus, P.; Mugrage, B. *J. Am. Chem. Soc.* **1990**, *112*, 462. (c) Magnus, P.; Coldham, I. *J. Am. Chem. Soc.* **1991**, *113*, 672.

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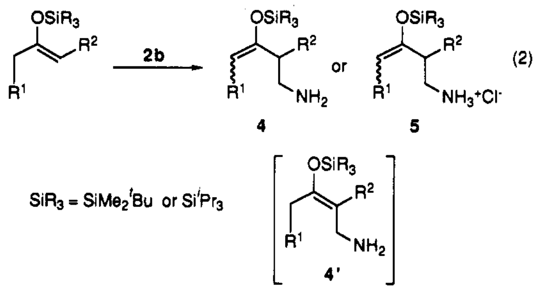

could not be detected, even in the reactions of enol ethers with no α′-hydrogen. For example, the reaction with the enol ether of acetophenone gave a rather complex mixture, from which β-(N-benzoylamino)propiophenone alone was isolated in moderate yield following treatment with benzoyl chloride.[9] These features contrast nicely with those of reactions with $Me_2N{=}CH_2I$.[12] The stereochemical outcome has also been examined using 3- or 4-substituted cyclohexanone derivatives. The former preferentially produced trans adduct (entry 4),[13] whereas selectivity was lower with the latter (entry 5, Table I).

Interestingly, workup with a buffer solution (pH = 7.4) rather than aqueous sodium hydroxide gave the corresponding hydrochloride **5** as white crystalline compounds. No isomerization of the double bond was observed except in the case of the cycloheptanone derivative (entry 2, Table I).

The stereoselectivity exhibited in entry 5 of Table I provides information concerning the reaction mechanism. A concerted ene reaction of 4-alkyl-1-siloxycyclohexene should give the trans product via axial attack of **2b**, because the cyclic transition-state structure[14] of the ene reaction requires abstraction of an axial α′-hydrogen. Judging from the stereoselectivity in entry 5, which is as low as that of the reaction of the 4-substituted enol ether with a Lewis acid activated electrophile,[15] the stepwise reaction mechanism seems more plausible.

The products **4** containing the enol silyl ether moiety as well as the primary amino group show promise for use in the construction of heterocycles via regioselective C–N and C–C bond formation.

We are currently studying synthetic applications of **4** and the reactions of **2a,b** with various kinds of nucleophiles.

Acknowledgment. This work was partially supported by Grants from the Ministry of Education, Science, and Culture of the Japanese Government.

Supplementary Material Available: Experimental procedures and spectral data of **4** and **5** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) Typical procedure is as follows: To a suspension of $AlCl_3$ (73 mg, 0.55 mmol) in CH_2Cl_2 (1.5 mL) was added (trimethylsilyl)methyl azide (82 μL, 0.55 mmol) at −45 °C, and the mixture was stirred at this temperature for 1 h and then at 0 °C for 0.5 h and finally at room temperature for 0.5 h. The resulting solution was cooled to −10 °C, and to this was added 0.50 mmol of enol silyl ether. After 10–40 h at −10 °C, aqueous sodium hydroxide was added. Usual workup followed by silica gel chromatography gave the enol silyl ether of β-amino ketone.

(12) The reaction of $Me_2N{=}CH_2I$ with 1-(*tert*-butyldimethylsiloxy)cyclohexene gave 2-(aminomethyl)-1-siloxycyclohexene as a sole product: Wada, M.; Nishihara, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 5405. See also: Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715.

(13) In contrast to the high regioselectivity observed in the reaction with **2b**, $Me_2N{=}CH_2I$ seems to induce the isomerization of the double bond of 3-methyl-1-(triisopropylsiloxy)cyclohexene under the reaction conditions to afford a mixture of two regioisomers.

(14) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947.

(15) For example, treatment of 4-*tert*-butyl-1-(trimethylsiloxy)cyclohexene with chloromethyl phenyl sulfide under the influence of $TiCl_4$[16] afforded 4-*tert*-butyl-2-[(phenylthio)methyl]cyclohexanone as a mixture (63:37) of diastereoisomers.

(16) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 993.

Cyclizations of Functionalized Acylsilanes To Form 2-Silyldihydropyrans and 2-Silyldihydrofurans

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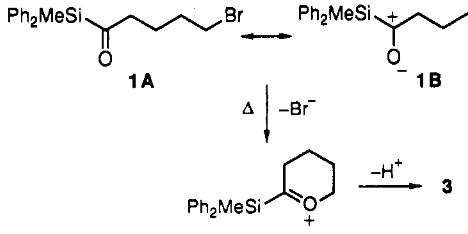
Summary: Cyclizations of (δ-haloacyl)- and (γ-haloacyl)silanes in a polar aprotic solvent gave 2-silyldihydropyrans and 2-silyldihydrofurans in good yields. This new type of cyclization could also be initiated by a carbocation and an olefin.

Acylsilanes are a useful class of compounds in organic synthesis.[1,2] Much of the attention paid to the chemistry of acylsilanes has been focused on the electrophilic reaction of the carbonyl carbon. In this report, we wish to address the previously ignored nucleophilic nature of the carbonyl oxygen.

In a project exploring the radical chemistry of acylsilanes, we prepared (bromoacyl)silane **1**[3] via silylation of 1,3-dithiane[4,5] followed by alkylation with 1,4-dibromobutane and hydrolysis.[6] Although bromide **1** is stable in refluxing benzene overnight, we found that heating **1** in

Scheme I



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(1) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647.

(2) Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147.

(3) Tsai, Y.-M.; Cherng, C.-D. *Tetrahedron Lett.* **1991**, *32*, 3515.

(4) Brook, A. G.; Duff, J. M.; Jones, P. F.; Davis, N. R. *J. Am. Chem. Soc.* **1967**, *89*, 431.

(5) Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434.

(6) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.