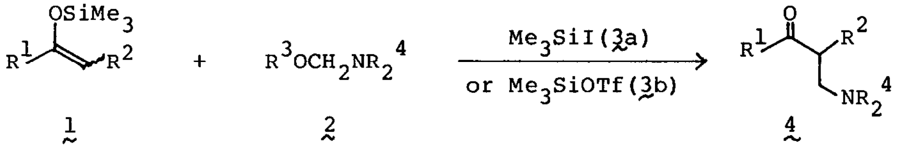
Tetrahedron Letters,Vol.23,No.5,pp 547-550,1982 0040-4039/82/050547-04$03.00/0
Printed in Great Britain

A NOVEL AMINOMETHYLATION OF SILYL ENOL ETHERS WITH AMINOMETHYL ETHERS CATALYZED BY IODOTRIMETHYLSILANE OR TRIMETHYLSILYL TRIFLUOROMETHANESULFONATE[1]

Akira Hosomi, Susumu Iijima and Hideki Sakurai
Department of Chemistry, Tohoku University, Sendai 980, Japan

Summary: The iodotrimethylsilane-catalyzed reaction of silyl enol ethers with aminomethyl ethers in acetonitrile gives aminomethylation products of the corresponding ketones readily. The reaction can also be catalyzed by trimethylsilyl trifluoromethanesulfonate in dichloromethane.

Aminomethylation of ketones is an important reaction for the synthesis of α-methylene ketones.[2] Although preformed Mannich salts are the most representative reagent for the reaction,[3] an elegant but somewhat time-consuming procedure[2b] is required for preparing the reagent and the manipulation is also inconvenient because of the hygroscopic nature of the reagent. Recently, aminomethylation without isolation of the iminium salt has been devised in order to avoid these drawbacks.[4] We now report that *in situ* aminomethylation of ketones can readily be achieved by the reaction of silyl enol ethers(**1**) with aminomethyl ethers(**2**) catalyzed by iodotrimethylsilane(**3a**) or trimethylsilyl trifluoromethanesulfonate(triflate)(**3b**) (eq. 1).

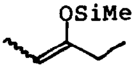
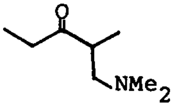
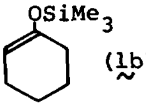
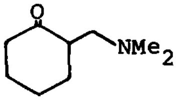
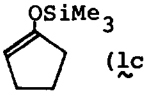
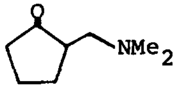
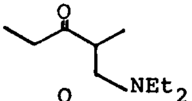
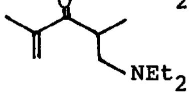
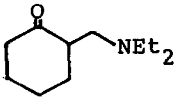
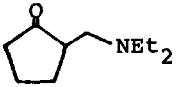
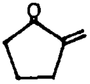
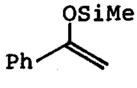
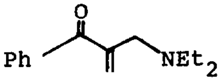


(1)

All reactions proceed very smoothly at room temperature in acetonitrile to give the corresponding β-aminoketones(**4**) in good yield. A catalytic amount (ca. 5 mol%) of iodotrimethylsilane is enough to complete the reaction. The results are listed in Table 1.

n-Butyl dimethylaminomethyl ether(**2a**) gave better results than methyl diethylaminomethyl ether(**2b**), the latter giving, in addition to the expected **4**, by-products(**5**) such as **5a** in entry 4 and **5b** in entry 9 (Table 1) produced by subsequent aminomethylation of **4**.[5] The formation of these by-products, however, could almost be prevented by the addition of a sterically hindered amine such as dicyclohexylmethylamine. With bis(dimethylamino)methane, instead of **2**, the reaction did not proceed smoothly.

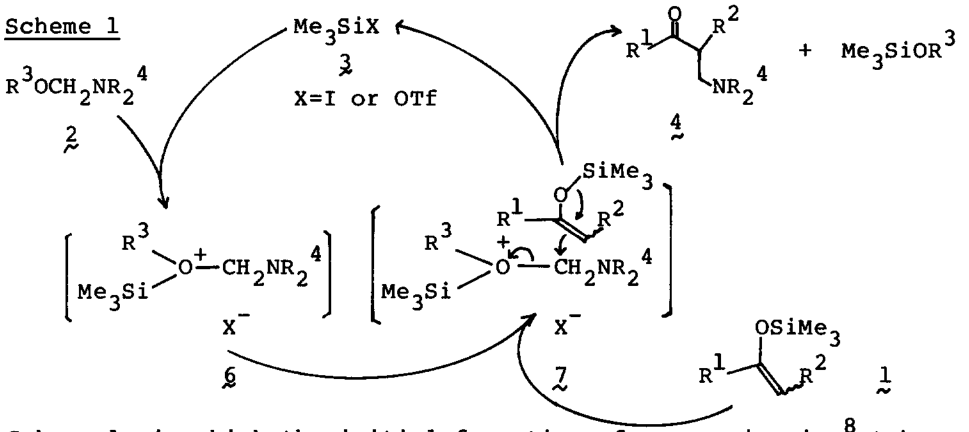
Table 1. Aminomethylation of silyl enol ethers(**1**) with aminomethyl alkyl ethers(**2**) catalyzed by iodotrimethylsilane(**3a**) or trimethylsilyl triflate(**3b**)

Entry	Silyl enol ether (**1**)	Aminomethyl ether (**2**)	Conditions[a]	Products	% Yield[b]
1	 (**1a**)	n-$BuOCH_2NMe_2$ (**2a**)	Me_3SiI(**3a**) CH_3CN, 5h	 (**4a**)	83
2	 (**1b**)	**2a**	**3a** CH_3CN, 8h	 (**4b**)	70
3	 (**1c**)	**2a**	**3a** CH_3CN, 1h		68
4	**1a**	$MeOCH_2NEt_2$ (**2b**)	**3a** CH_3CN, 20h	 (**4c**)  (**5a**)	52^c 11^c
5	**1a**	**2b**	**3a** $(CH_2Cl)_2$, 4.5h[d]	**4c** **5a**	16^c 10^c
6	**1a**	**2b**	**3a**[e] CH_3CN, 9h	**4c**	71
7	**1b**	**2b**	**3a**[e] CH_3CN, 13h		60
8	**1c**	**2b**	**3a**[e] CH_3CN, 4h	 	47 23
9	 (**1d**)	**2b**	**3a** CH_2Cl_2, 20h	 (**5b**)	36^f
10	**1a**	**2a**	Me_3SiOTf(**3b**) CH_2Cl_2, 1.5h	**4a**	68
11	**1b**	**2a**	**3b** CH_2Cl_2, 4h	**4b**	63

[a] All reactions were carried out in the presence of 5 mol% of a catalyst at room temperature unless otherwise stated. [b] Determined by NMR unless otherwise noted. [c] Yields after isolation by GLC. [d] At reflux. [e] Reactions were conducted in the presence of dicyclohexylmethylamine. [f] Yield after isolation by TLC.

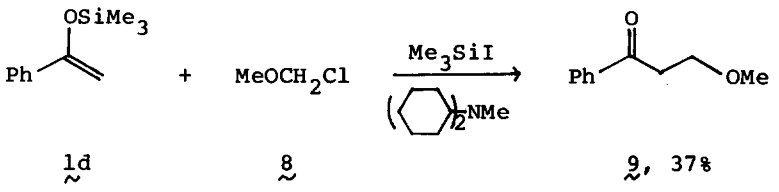
Acetonitrile was the most suitable solvent among examined. Contrary to iodotrimethylsilane-catalyzed allylation of acetals,[6] the reaction in dichloromethane or dichloroethane gave less satisfactory results. In addition, it is interesting to note that trimethylsilyl triflate(3b), which is known as an efficient activator of acetals,[7] can effectively catalyze the reaction in dichloromethane at room temperature.

Scheme 1



Scheme 1, in which the initial formation of an oxonium ion[8] takes place at room temperature, illustrates the mechanistic rationale for the present reaction. Although the mechanism involving the initial formation of an iminium salt[3c] and its subsequent reaction with a silyl enol ether(1)[9] can not necessarily be excluded at present, the fact that generation of the salt could not be observed at all throughout the reaction suggests strongly the formation of an intermediate(6), similar to the intermediates in the reaction of acetals.[6,7] These intermediates must be highly electrophilic and subjected to bimolecular nucleophilic displacement by 1 *via* 7, where 3 is thereby regenerated to complete the catalytic cycle.

Interestingly, during the course of studies on the activation of a heteroatom-substituted methyl ether by iodotrimethylsilane, we have found that the reaction of chloromethyl methyl ether(8) with 1d was catalyzed by 3a to result in the introduction of a methoxymethyl group, instead of an expected chloromethyl group,[10] onto the α-position of the ketone. (eq. 2) This is the first example of activation of a carbon-chlorine bond by 3a. The driving force of activation is presumably due to the formation of the strong silicon-chlorine bond.[11]



(2)

A general procedure is as follows.[12] In a two-necked flask a silyl enol ether (**1**) (1.05 mmol) and an aminomethyl ether (**2**) (1.60 mmol) were placed in acetonitrile (2 ml). Two drops of **3a** (ca. 5 mol%), which had been prepared from hexamethyldisilane and iodine,[13] was added and the resulting mixture was subsequently stirred for 5 hrs at room temperature, disappearance of **1** being best monitored by GLC. After hydrolysis with 2 N hydrochloric acid, non-basic materials are extracted from the aqueous layer with ether. After sodium hydroxide was added to the aqueous solution, the amine was extracted with ether and the extract was worked up as usual.

Acknowledgement: We thank Toshiba Silicone Co., Ltd., and Mitsubishi Chemical Industry Co., Ltd., for their support to the work.

References and Notes

1. Chemistry of Organosilicon Compounds, 153.
2. For a review, see, F.F. Blicke, Org. Reactions, **1**, 303(1942).
3. a) N. Holy, R. Fowler, E. Burnett and R. Lorenz, Tetrahedron, **35**, 613(1979); b) J. Schreiber, H. Maag, N. Hashimoto and A. Eschenmoser, Angew. Chem., Int. Ed. Engl., **10**, 330(1971); c) Y.A. Bryson, G.H. Bonitz, C.J. Reichel, and R.E. Dardis, J. Org. Chem., **45**, 524(1980); d) A. Ahond, A. Cavé, C. Kan-Fan, H.-P. Husson, J. de Rostolan and P. Potier, J. Am. Chem. Soc., **90**, 5622(1968).
4. S. Miyano, H. Hokari, A. Mori and H. Hashimoto, Chem. Lett., 1213(1980).
5. In the presence of **3a**, silyl enol ethers are obtained by the reaction of ketones with bis(trimethylsilyl)amine. See, R.D. Miller and D.R. Mckean, Synthesis, 730(1979).
6. H. Sakurai, K. Sasaki and A. Hosomi, Tetrahedron Lett., **22**, 745(1981).
7. S. Murata, M. Suzuki and R. Noyori, J. Am. Chem. Soc., **102**, 3248(1980), and references cited therein.
8. M.E. Jung and M.A. Lyster, J. Org. Chem., **42**, 3761(1977).
9. a) S. Danishefsky, T. Kitahara, R. McKee and P.F. Schuda, J. Am. Chem. Soc., **98**, 6715(1976); b) S. Danishefsky, M. Prisbylla and B. Liposko, Tetrahedron Lett., **21**, 805(1980); c) N.L. Holy and Y.F. Wang, J. Am. Chem. Soc., **99**, 944(1977).
10. A similar reaction promoted by a Lewis acid has been known. See, I. Paterson, Tetrahedron Lett., 1519(1979).
11. G.G. Hess, F.W. Lampe and L.H. Sommer, J. Am. Chem. Soc., **87**, 5327(1965).
12. All compounds obtained in this work gave satisfactory spectral data and correct elemental analysis.
13. H. Sakurai, A. Shirahata, K. Sasaki and A. Hosomi, Synthesis, 740(1979).

(Received in Japan 23 October 1981)