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Silylation of Relatively Acidic Compounds with Alkyl Trimethylsilylacetates[1)]

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Silylation of ketones, alcohols, alkanethiols, phenols, and carboxylic acids with alkyl trimethylsilylacetates has been described from synthetic and mechanistic points of view.

In a previous paper we described the reaction of silylated esters with carbonyl compounds.[2,3)] In the presence of tetrabutylammonium fluoride, rather surprisingly, silyl esters underwent desilylation to effect the transfer of the silyl group onto ketones (R-H)[4)] as in Eq. 1. Subsequent studies have shown this

$$RH + Me_3SiCH_2COOR' \xrightarrow{F^-} RSiMe_3 + CH_3COOR' \quad (1)$$

silyl transfer reaction even more versatile; a wide variety of relatively acidic compounds[5)] could also be silylated by this new reaction. The purpose of this paper is to describe the scope of the reaction from synthetic and mechanistic points of view.

The use of trialkylsilyl groups, especially trimethylsilyl group, for protection or activation of some functional groups has become one of the standard tools in organic chemistry,[6)] and a number of silylation methods (replacement of acidic protons with silyl groups) have been reported.[7)] Nonetheless, the number of the basic principles has been rather small. A large body of reactions are based on the equilibrium between a substrate and a silylating reagent with a weak Si–X bond, *e.g.* silylamine or silylamide, as shown in Eq. 2.

$$RH + MeSiX \rightleftharpoons RSiMe_3 + HX \quad (2)$$

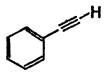
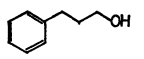
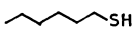
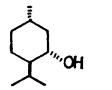
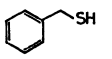
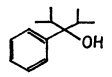
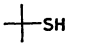
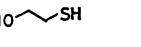
Though this methology allows the use of mild conditions, thermodynamic factors control the selectivities of the reaction.[8)] Further the silylation reactions usually result in the production of nonvolatile by-products such as tertiary amine hydrochloride, amide, *etc.*

Quenching preformed anions with a trialkylchlorosilane constitutes another important methodology, and has a distinctive advantage in enolate chemistry;[9)] this usually allows us to trap the kinetically preffered isomer of enolate anions as its stable silyl derivatives. Rather strong reaction conditions and somewhat laborious procedures, however, generally render this method to be the second choice. As described below, the reaction of an alkyl trimethylsilylacetate, with its characteristic mechanistic pathway and applicability, has proved to provide another useful methodology for silylation of various acidic compounds.

Results and Discussion

The silylation reaction was performed in a very simple manner. Treatment of a mixture of a substrate and ethyl trimethylsilylacetate (ETSA; slight excess) with 2—5 mol% tetrabutylammonium fluoride trihydrate (TBAF) either in a dry aprotic solvent such as tetrahydrofuran (THF) or without a solvent produced the silylated product and ethyl acetate in high yields. Commercially available TBAF was the catalyst of choice because of the ease of handling and the high solubility in organic solvents. Though ETSA was used generally, the methyl ester or its higher homologues could also serve the purpose nicely. The reaction proceeded at room temperature and the product was isolated either after aqueous workup or direct distillation of the reaction mixture. The silylating ability of ETSA–TBAF system is quite high. The reaction with sterically hindered tertiary alcohols and thiols[10)] proceeded exothermically at room temperature. Even such a less acidic substrate as phenylacetylene was silylated in high yield, whereas triphenylmethane remained unchanged after prolonged reaction period. Table 1 shows the examples.

TABLE 1. SILYLATION OF RELATIVELY ACIDIC COMPOUNDS

Compound	% yield	Compound	% yield
	88		83
	92		91
	92		87
	92		82
			83[a)]

a) Bis-silylated product.

Interestingly, simple aliphatic ketones were silylated faster than more acidic compounds like phenols. This aroused our interests to examine the reaction in some detail. Thus, brief studies about the reaction rate with representative substrates were carried out. An equimolar mixture of methyl trimethylsilylacetate (MTSA) and the substrate was treated at 35 °C with a catalytic amount (1.5—3 mol%) of TBAF in an NMR sample tube, and the reaction was monitored mainly by observing the change of the relative intensities of the trimethylsilyl groups; the trimethylsilyl group of MTSA appeared consistently at a slightly higher field than that of the product. Measurements were done for 1-hexanethiol, phenylmethanethiol, *p*-cresol, propionic acid, and benzenethiol, and the results are shown in Fig. 1, where the product yields are plotted against the reaction time. Under these conditions aliphatic ketones and primary alcohols were silylated instantaneously, while triphenylmethane and benzenethiol were not silylated even after 10 d. While 100% conversion of MTSA was observed in

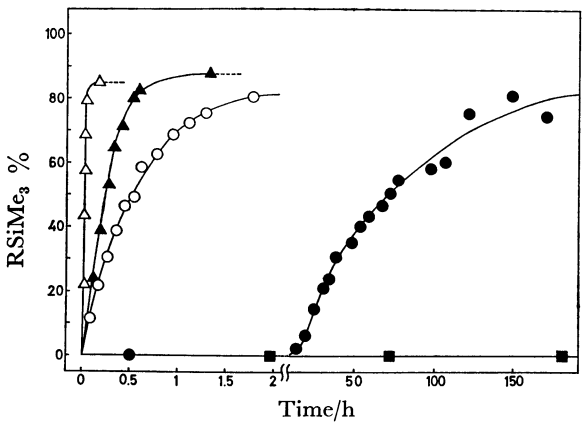


Fig. 1. Silylation of various substrates at 35 °C. △: 1-Hexanethiol (1.9 mol% TBAF), ▲: phenylmethanethiol (2.2), ○: *p*-cresol (2.6), ●: propionic acid (2.3), ■: benzenethiol (1.5).

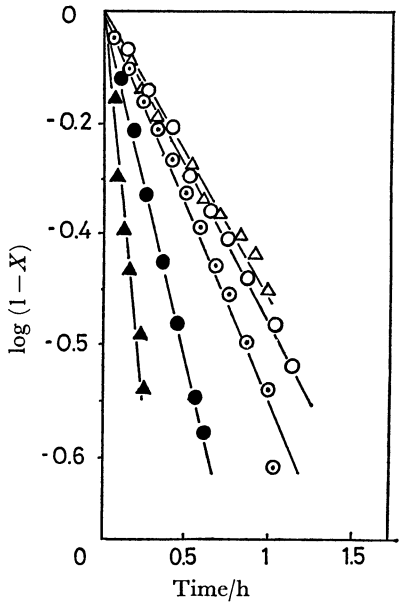
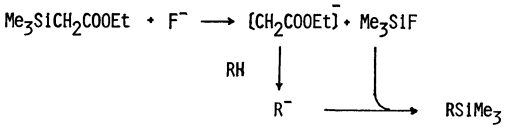


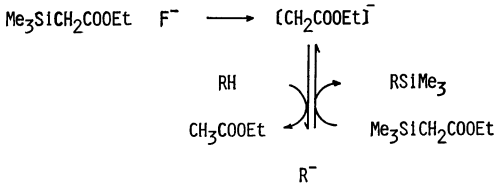
Fig. 2. Silylation of phenylmethanethiol at 35 °C. X=% yield/100, ○: 1.4 mol% TBAF, ⊙: 1.6 mol% TBAF, ●: 2.2 mol% TBAF, ▲: 3 mol% KCN-18-crown-6, △: 2.4 mol% KOMe-18-crown-6.

all runs in Fig. 1 except the case of benzenethiol, 10—15% of the substrate remained unchanged. The content of water in the system, *e.g.* in the catalyst, seems to account for the imcomplete conversion of the substrate. In fact, the substrate underwent 100% conversion when 20—30% excess MTSA was used.

Some efforts to rationalize the reaction rate revealed that the reactions fall into two types. The reaction of cresol followed a first order rate expression, whereas those of thiols and propionic acid (after an induction period) followed second order ones. However, this point was not pursued further because of the experimental difficulties due to the highly sensitive nature of the reaction.[11] Though a specific role of fluoride anion was previously suggested for the present silylation reaction (Scheme 1), the present studies implied another mechanism, namely, an autocatalytic



Scheme 1.



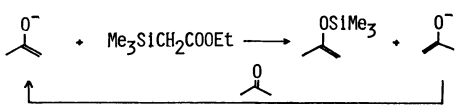
Scheme 2.

one (Scheme 2).

That fluoride is not the only effective catalyst (unlike other similar reactions[3]) was one of those implications. Treatment of a mixture of ETSA and acetophenone with a catalytic amount of KCN/18-crown-6, $KOCH_3$/18-crown-6, or Triton B effected smooth conversion of the ketone into the corresponding enol silyl ether at 0 °C. Silylation of 1-hexanethiol could also be done with those catalysts. The equal efficacy of these catalysts was further proved, in a somewhat quantitative manner, by NMR experiments in which an equimolar mixture of MTSA and phenylmethanethiol was treated with the catalysts (KCN/crown ether, $KOCH_3$/crown ether, or Triton B) as described above (Fig. 2).

In addition to this semiquantitative evidence, a qualitative but direct evidence of the autocatalytic pathway (Scheme 2) was also obtained. Thus, when a mixture of acetophenone and ETSA was treated with 10 mol% of preformed potassium enolate of this ketone solvated by 18-crown-6, quantitative silylation of the ketone occurred within 1 min at 0 °C. Similarly, 10 mol% of potassium 1-hexanethiolate and 18-crown-6 initiated the smooth reaction of 1-hexanethiol with ETSA.

In contrast to the catalytic ability of a potassium enolate/crown ether in the silylation of a ketone, this anion itself could not be silylated by MTSA or ETSA in a stoichiometric reaction. Treatment of the potassium enolate of acetophenone with one equivalent of perhydrodibenzo-18-crown-6 followed by ETSA did not yield any detectable amount of the enol silyl ether, and gave back the starting ketone in high yield. These results fit well with the proposed mechanism, since Eq. 3 involved in the overall reaction pathway does not favor the formation of the enol silyl ether unless the ester enolate on the right side is irreversibly protonated by the neutral ketone to regenerate the ketone enolate.



(3)

The reaction mechanism and the rate profiles described above suggest a certain perspective over the synthetic utility of ETSA as a silylating reagent. One apparent factor that limits the application is the acidity

Table 2. Silylation with ETSA-TBAF[a]

Substrate g (mmol)		ETSA g (mmol)	TBAF mg	Reaction period, h	Yield g (%)	Bp °C/mmHg[b]
3-Phenyl-1-propanol	1.36(10.0)	1.92(12.0)	50	2	1.91(92)	87/4[c]
2,4-Dimethyl-3-phenyl-3-pentanol	1.94(10.2)	1.93(12.1)	63	2.5	2.44(92)	110/7
p-Cresol	1.08(10.0)	1.61(11.0)[d]	83[e]	7	1.49(83)	77/12[f]
1-Hexanethiol	1.77(15.0)	2.40(15.0)	74	5	2.60(91)	62/5[g]
Phenylmethanethiol	3.16(25.5)	4.74(28.0)	228	22	4.42(88)	130/32[h]
2-Mercaptoethanol	0.78(10.0)	3.36(21.0)	87	3	1.85(83)[i]	51/4

a) Reactions were performed by a procedure similar to Method A. b) 1 mmHg=133.322 Pa. c) *Cf.* Ref. 18. d) MTSA was used in place of ETSA. e) BTAF was used in place of TBAF. f) *Cf.* Ref. 19. g) *Cf.* Refs. 16 and 20. h) *Cf.* Ref. 21. i) The product was obtained as a bis-silylated form.

of the substrate relative to that of the alkyl acetate. This, however, does not appear significant for relatively acidic substrates reported here. Among these substrates, on the other hand, the nucleophilicity (toward silicon atom) of the conjugate base of the substrate (R^- in Scheme 1) appears to be important. Prominent decrease of the reaction rate on passing from alcohol to phenol and to acid, or from 1-hexanethiol, phenylmethanethiol, and finally to benzenethiol[12] is in accord with the decrease of the reactivity of their conjugate base. Striking difference of the rate between phenol and benzenethiol is in keeping with the known difference of the affinities of oxygen and sulfur toward silicon.

Thermodynamically controlled silylation reactions are performed under very mild conditions using silylating reagents such as silylamide,[7] whereas kinetically controlled ones have usually been conducted by using strongly basic reagents such as LDA or NaH. In the present reaction, being catalytic with the reactive species, the bulk of the reaction medium remains almost neutral, while the deprotonation takes place in an irreversible manner.

Finally, we draw attention to the absence of any nonvolatile side-products in this reaction, which may allow the use of the unpurified silylation product for further elaboration. Therefore, the present reaction will prove to be complementary to the various existing methodologies of the silylation reactions.

Experimental

All reactions were performed under either argon or nitrogen with magnetic stirring. Tetrahydrofuran (THF) was purified shortly before use by distillation over sodium-benzophenone. TBAF (Fluka AG) was used after overnight evacuation (0.5 mmHg,[13] room temperature) and kept under an inert atmosphere. BTAF was prepared from Triton B methanolic solution (Tokyo Kasei Co.) by the reported method.[3a] Alkyl trimethylsilylacetates were prepared as reported.[14] NMR spectra were taken on a Varian T-60 spectrometer, and chemical shifts are recorded in parts per million downfield from internal tetramethylsilane. IR spectra were taken on a Hitachi EPI G-3 or 260-10 spectrometer, and mass spectra on a Hitachi RMU-7M at 70 eV ionizing irradiation. Gas liquid chromatography (GLC) was performed on a Hitachi 163 instrument equipped with a 0.25 mm×20 m glass capillary tube coated with OV-101. All boiling points are uncorrected.

Silylation of 2-Methyl-2-propanethiol (Method A). To a stirred mixture of 2-methyl-2-propanethiol (1.58 g, 17.6 mmol) and TBAF (992 mg, 0.35 mmol) at room temperature was added ETSA (2.96 g, 18.5 mmol) over a period of 2 min. The reaction was slightly exothermic. After stirring for 2 h, the orange colored reaction mixture was transferred to a distillation apparatus with exclusion of moisture, and distilled under a reduced pressure to give 2.33 g (82%) of (*t*-butylthio)trimethylsilane[15,16] as a colorless oil. Bp 92 °C/88 mmHg[13]; IR(neat): 1364, 1250, 1157, 842, and 754 cm^{-1}; NMR(neat): δ 0.30 (s, 9H) and 1.43 (s, 9H); MS: *m/e* (%) 162 (M^+, 15), 147 (5), 107 (33), 91 (85), 75 (8), 73 (61), 57 (100).

Silylation of l-Menthol (Method B). The reaction was carried out as described above by using *l*-menthol (4.43 g, 28.4 mmol) in 15 ml of THF, TBAF (72 mg, 0.3 mmol), and ETSA (4.77 g, 29.8 mmol). After the reaction was over, the reaction mixture was diluted with 100 ml of hexane, and poured into water. The organic layer was separated and washed once with aq NaCl. Drying over anhydrous $MgSO_4$ and concentration followed by distillation afforded *l*-menthyl trimethylsilyl ether (5.85 g, 92%), which was identical with the authentic sample by NMR and GLC. Bp 135 °C/68 mmHg;[13,17] MS: *m/e* (%) 228 (M^+, 3), 213 (8), 171 (5), 157 (5), 143 (100), 138 (14), 123 (6), 95 (11), 81 (20), 75 (57), 73 (40).

Trimethyl(phenylethynyl)silane. Phenylacetylene (100 mg, 1.0 mmol) and ETSA (192 mg, 1.2 mmol) were added to TBAF (13 mg, 0.05 mmol) in 2 ml of THF. After 26 h, the reaction mixture was diluted with hexane, filtered, and concentrated. Purification of the crude product on preparative TLC gave 151 mg (88%) of the title compound which was identical with the authentic sample by NMR, IR, and GLC.

3-Phenyl-1-(trimethylsiloxy)propane. The product obtained by the present method was identical with the authentic sample[18] by NMR and GLC. MS: *m/e* (%) 208 (M^+, 10), 193 (23), 175 (11), 165 (12), 147 (14), 135 (14), 118 (100), 107 (14), 91 (38), 89 (40), 75 (30), 73 (38).

2,4-Dimethyl-3-phenyl-3-(trimethylsiloxy)pentane. IR (neat): 850, 758, and 705 cm^{-1}; NMR(CCl_4): δ 0.28 (s, 9H), 0.75 (d, J=7 Hz, 3H), 0.80 (d, J=7 Hz, 3H), 1.9—2.7 (m, 2H), 7.17 (s, 5H); MS: *m/e* (%) 249 ($M^+ - 15$, 5), 221 (100), 131 (12), 75 (26), 73 (96).

1-Methyl-4-(trimethylsiloxy)benzene. The product obtained by the present method was identical with the authentic sample[19] by NMR and IR analyses.

(Hexylthio)trimethylsilane.[16,20] IR(neat): 1463, 1253, 1183, 1057, 845, 758 cm^{-1}; NMR(neat): δ 0.25 (s, 9H), 0.7—1.8 (m, 11H), 2.1—2.7 (m, 2H); MS: *m/e* 190 (M^+), 175, 91, 73; Exact mass: 190.1188. Calcd for $C_9H_{22}SSi$: 190.1212.

(Benzylthio)trimethylsilane.[21] Mass spectrum was identical with the reported one.[21] IR(neat): 1250, 840, 755, 700 cm^{-1}; NMR(neat): δ 0.17 (s, 9H), 3.54 (s, 2H), 6.95—7.45 (m, 5H); Exact mass: 196.0731. Calcd for $C_{10}H_{16}SSi$: 196.0742.

[2-(Trimethylsiloxy)ethylthio]trimethylsilane. IR(neat): 1253, 1090, 840 cm^{-1}; NMR(neat): δ 0.07 (s, 9H), 0.26 (s, 9H), 2.48 (t, J=7 Hz, 2H), 3.55 (t, J=7 Hz, 2H); MS: *m/e* (%) 222 (M^+, 1), 207 (19), 149 (100), 119 (35), 103 (31), 75 (40), 73 (47).

Trimethylsilyl Propionate. To a clear solution of BTAF (335 mg, 1.4 mmol) in propionic acid (1.48 g, 20 mmol) was added ETSA (3.84 g, 24 mmol), and the resulting mixture was kept at room temperature for 10 d while crystalline material separated. NMR and IR analyses of the crude reaction mixture indicated nearly complete conversion of the reactants (especially no hydroxylic absorption on IR spectrum). Distillation of the reaction mixture gave 3.08 g of forerun as a 1:1 mixture of ethyl acetate and the title compound, and 1.37 g of the title ester as a fraction boiling at 105—115 °C (lit,[22] bp 122 °C). NMR and GLC analyses of the main fraction indicated the presence of ethyl acetate (11%) and hexamethyldisiloxane (5%) as impurities. The NMR spectrum was identical with the authentic sample except for the impurities, and coinjection on GLC also supported the assignment. Typical retention times of GLC (90 °C) were 3.0, 3.4, and 5.5 min for ethyl acetate, hexamethyldisiloxane, and the title ester, respectively.

Measurement of the Reaction Rates. To preweighed TBAF in an NMR tube under argon kept at −78 °C was added an equimolar mixture of MTSA and the substrate. The tube was sealed and brought to 35 °C and inserted to NMR probe (35 °C). The progress of the reaction was monitored mainly by observing trimethylsilyl groups.

Silylation of Acetophenone in the Presence of Various Catalysts. *a) KCN/18-crown-6 Catalysis*: To a mixture of the title ketone (120 mg, 1.0 mmol) and KCN/perhydrodibenzo-18-crown-6[23] (22 mg, 0.05 mmol) in 2 ml of THF under nitrogen was added ETSA (177 mg, 1.1 mmol) at 0 °C. TLC of the reaction mixture after 10 min showed virtually 100% conversion of the ketone to the corresponding silyl ether. Workup according to Method B gave the crude enol silyl ether (200 mg, 100%) whose NMR spectrum was identical with the authentic one.

b) $KOCH_3$/18-crown-6 Catalysis: The same procedure as described in a) except for the catalyst ($KOCH_3$/perhydrodibenzo-18-crown-6, 22 mg) gave the expected silyl ether in 98% yield (NMR).

c) Triton B Catalysis: To a mixture of acetophenone (2.40 g, 20 mmol) and ETSA (3.84 g, 24 mmol) under nitrogen was added 2 drops of Triton B (40% in methanol) at room temperature. Exothermic reaction occurred, and TLC after 30 min showed complete conversion of the ketone to the enol silyl ether. The crude reaction mixture obtained according to Method B consisted of the enol silyl ether (99%) and the starting ketone (1%).

d) Enolate Catalysis: To a suspension of oil-free KH (1 mmol) and perhydrodibenzo-18-crown-6 (372 mg, 1.0 mmol) in 10 ml of THF was added acetophenone (128 mg, 1.0 mmol) at 20 °C.[24] A Mixture of acetophenone (1.20 g, 10 mmol) and ETSA (1.60 g, 10 mmol) in 2 ml of THF was added to the enolate solution at 0 °C. TLC after 1 min indicated high yield formation of the silyl ether. Workup by Method B gave a mixture of the enol silyl ether (8.1 mmol) and the starting ketone (1.5 mmol) as judged by NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Autocatalytic Silylation of 1-Hexanethiol. 1-Hexanethiol (118 mg, 1.0 mmol) was added to a mixture of oil-free KH (1 mmol) and perhydrodibenzo-18-crown-6 (372 mg, 1.0 mmol) in 8 ml of THF. To the resulting white solution was added a mixture of 1-hexanethiol (1.18 g, 10 mmol) and ETSA (1.60 g, 10 mmol) at −3 °C, and the mixture was stirred for 1 h at 0 °C. NMR of the reaction mixture indicated the formation of the expected silyl sulfide. Workup of the reaction mixture by Method A gave the silyl sulfide in 68% yield (1.30 g) on distillation.

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