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THE SURVIVAL OF TERT-BUTYLDIMETHYLSILYL GROUP OF SILYL ENOL ETHERS IN THE REACTION WITH DIMETHYL(METHYLENE)AMMONIUM IODIDE. REGIOSELECTIVE SYNTHESIS OF TERT-BUTYLDIMETHYLSILYL ENOL ETHERS CONTAINING AN AMINO GROUP.

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Abstract:t-Butyldimethylsilyl enol ethers containing an amino group were obtained in good yields (70~90%) by the reaction of t-butyldimethylsilyl enol ethers with dimethyl(methylene)ammonium iodide (the Eschenmoser salt).

Silyl enol ethers have been recognized as useful reagents for organic synthesis, especially for a regiospecific carbon-carbon bond formation by the direct reaction of the silyl enol ethers with suitable electrophiles.[1)]

In relation to recent considerable efforts for introduction of substituents into 4-position of pyridine regioselectively,[2)] we have encountered that t-butyldimethylsilyl enol ethers (1 or 1') reacted with pyridinium salts to give the corresponding silyl enol ethers of 1,4-dihydropyridine derivatives while 2-oxoalkyl-1,4-dihydropyridines were obtained with trimethylsilyl enol ethers.[3)]

Thus, we have noticed the possibility of survival and re-use of t-butyldimethylsilyl enol ethers. Therefore, in order to simplify the system, we tried the reaction of t-butyldimethylsilyl enol ethers (1 or 1') with dimethyl(methylene)ammonium iodide (2, the Eschenmoser salt) instead of pyridinium salts. As expected, when t-butyldimethylsilyl enol ethers (1 or 1') were allowed to react with 2, the corresponding t-butyldimethylsilyl enol ethers containing an amino group (3 or 3') were obtained in good yields in CH_2Cl_2 at room temperature under nitrogen atmosphere as shown in the scheme. Some of the results are summarized in the Table.

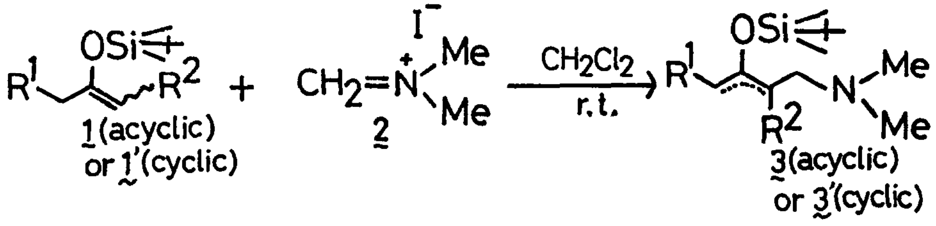
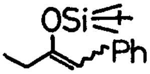
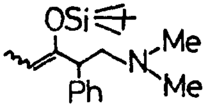
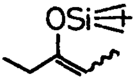
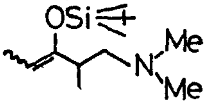
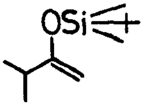
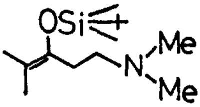
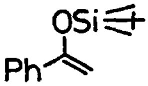
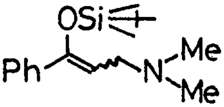
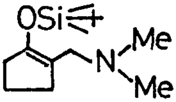
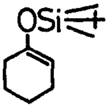
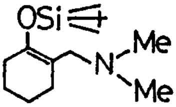


Table Yields of *t*-Butyldimethylsilyl Enol Ethers Containing an Amino Group

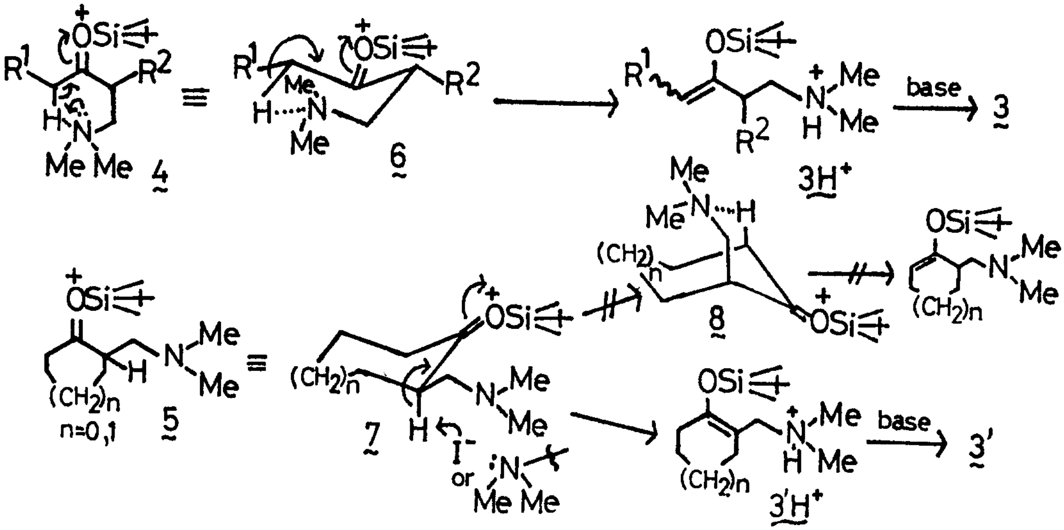
	Silyl Enol Ether (1 or 1')	Reaction Conditions	Product1) (3 or 3')	Yield(%)2)
a		r.t.18h		89
b		r.t.24h		76
c		r.t.16h		58
d		r.t. 5h		92
e		r.t.20h		71
f		r.t.20h		76

1) Satisfactory IR, ^{1}H NMR, and MS data were obtained for 3a, 3b, 3c, 3'e, and 3'f. 3d was identified by IR, ^{1}H NMR, ^{13}C NMR, and high-resolution MS.

2) Isolated yield by TLC (3a, hexane:isopropylamine=100:1), flash column chromatography (3d, hexane:isopropylamine=50:1), and kugelrohr distillation (3b, 3c, 3'e, and 3'f).

As is evident from the Table, when 1a, 1b, and 1c were used, the double bond shifted to the opposite position after the C-C bond formation to afford 3a, 3b, and 3c, respectively, and the presence of any regioisomer could not be detected. However, in the case of 1d, 1'e, and 1'f, the migration of the double bond did not take place. From these results, we rationalize that the oxonium salt (4 or 5) is a possible intermediate, and that the nitrogen atom attacks the proton in a six-membered cyclic transition state (6) to give 3 in the reaction of acyclic silyl enol ethers except 1d, but in the case of cyclic silyl enol ethers (1'e and 1'f), the transition state 7 is more favorable than 8, leading to the preferential formation of 3' (thermodynamic product) via the intermolecular deprotonation by the iodide ion or nitrogen atom.

The literature contains a number of reports on the reactions of alkenes with *N*,*N*-dimethylmethyleneiminium ion to give the unsaturated *t*-amines,4) and it can be assumed that such transformations are examples of the ene reaction.5) Therefore, the concerted process (the ene reaction) might be involved in the present reaction of acyclic silyl enol ethers to give **3** (kinetic product).6)



Danishefsky *et al*. have already reported the reaction of 1-trimethylsilyloxycyclohexene with the Eschenmoser salt,7) and pointed out that hydrogen iodide salt of 1-trimethylsilyloxy-2-*N*,*N*-dimethylaminomethylcyclohexene initially forms *in situ*, and then is hydrolyzed under workup conditions to give 2-*N*,*N*-dimethylaminomethylcyclohexanone, so called Mannich base. Indeed, the ^{1}H NMR spectrum of the reaction between 1-trimethylsilyloxy-1-styrene and the Eschenmoser salt revealed a vinyl proton signal (δ5.38,t,J=7Hz), and workup with aqueous sodium carbonate afforded 2-*N*,*N*-dimethylaminomethylacetophenone in 66% yield. On the other hand, **3d** is obtained when **1d** is used (vide ante). From these results, we believe that hydrogen iodide salts of *t*-butyldimethylsilyl enol ethers (**3H**$^+$ or **3'H**$^+$) are formed *in situ* but not hydrolyzed under weakly basic conditions, on the other hand,the corresponding trimethylsilyl enol ethers are hydrolyzed under the same workup conditions. This rationalization is supported by the literature that hydrolysis of *t*-butyldimethylsilyl enol ethers is slower than that of trimethylsilyl enol ethers.8)

The following procedure for the synthesis of **3d** is representative. To a stirred suspension of the Eschenmoser salt (0.31g, 1.6 mmol) in dry dichloromethane (4 ml) was added *t*-butyldimethylsilyl enol ether of acetophenone (**1d**, 0.35g, 1.5 mmol) at room temperature under nitrogen atmosphere. After stirring for 5 h, the reaction mixture was quenched with 10% aqueous sodium carbonate (10 ml). The product was extracted with dichloromethane (20 ml x 3), and the solvent was evaporated *in vacuo* after being dried over anhydrous magnesium sulfate. The crude product was purified by flash column chromatography with hexane:isopropylamine=50:1 as eluent to afford **3d** (0.40g) in 92% yield. IR (neat): 2930, 2850, 1460, 1250, 1040, 830, 770, and 690 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ -0.10 (s,6H), 0.97 (s,9H), 2.20 (s, 6H), 3.10 (d,J=7Hz,2H), 5.18 (t,J=7Hz,1H),and 7.13~7.60 (m,5H). ^{13}C NMR (CDCl$_3$): δ -4.0 (q), 18.3 (s), 25.9 (q), 45.2 (q), 55.4 (t), 108.3 (d), 126.0 (d),127.6 (d), 127.7 (d), 139.4 (s),and 151.4 (s). High-resolution MS: exact mass calcd for $C_{17}H_{29}NOSi$, 291.2017; found, 291.2049.

Finally,it is noteworthy that **3** and **3'** can be reagents of value for further synthetic transformation and such is now under investigation.

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