CHEMISTRY LETTERS, pp. 1247-1250, 1989. © 1989 The Chemical Society of Japan

Azilidine-Trimethylsilyl Bromide-Ph_4SbBr System as a Novel Selective Reagent for Synthesis of Silyl Enol Ethers from Cyclic Ketones

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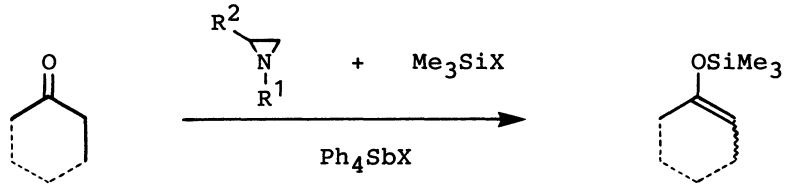
Azilidine-trimethylsilyl bromide-tetraphenylstibonium bromide system is an effective reagent to produce silyl enol ethers from cyclic ketones. This had the specific selectivity to silylate cyclic ketones exclusively even in the case of coexsisting with acyclic ketones.

Silyl enol ethers are valuable intermediates[1] not only as enolate anion equivalents,[2] but also as precursors for 1,2-diols,[3] α-hydroxy ketones,[4] and cyclopropyl alcohols[5] etc. The most standard and simplest method among their preparations which have been extensively studied[6] is the silylation of ketones with silyl halides in the presence of bases.[7] Recently significant improvements have been made in regio-[8,9] and stereoselective silylation.[10] For example, LDA/Me_3SiCl[7,8] and Me_3SiCl/NaI/Et_3N[9] lead to kinetic and thermodynamic regio-isomers selectively from 2-methylcyclohexanone, respectively. Moreover, LiTMP (lithium 2,2,6,6-tetramethylpiperidide)/Me_3SiCl gives (E)-isomers from acyclic ketones and Me_3SiCH_2COOEt/n-Bu_4NF affords (Z)-ones.[10] The chemoselective silylation of polyketones, however, has been remained as an unsolved theme, although the selective generation of carbanion from multifunctional compounds is generally one of the most important synthetic problems. Although there is only one report refered to chemoselective silylation of ketones in the presence of other functional groups such as epoxide,[11] the selectivity between ketones is not investigated so far.



(1)

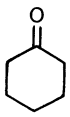
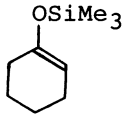
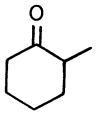
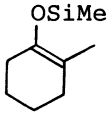
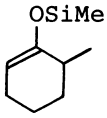
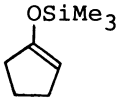
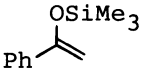
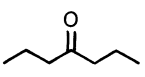
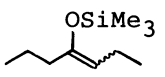
It is well known that oxiranes behave as a base in the presence of halide anions,[12] but the basic ability of azilidines has not been studied. We have already revealed that organoantimony halides have high catalytic activity to the cycloaddition of heterocumulenes to azilidines, where amide anions were assumed to

be intermediates.[13] We here wish to report a novel silylating reagent of ketones; azilidine-trimethylsilyl bromide with catalytic amounts of tetraphenylstibonium bromide (Ph_4SbBr), which achieved the selective silylation in the presence of many enolizable ketones.

Typical experimental procedure was as follows. To a CH_2Cl_2 solution (3 ml) of a ketone (2 mmol) and Ph_4SbBr (0.2 mmol) was added Me_3SiBr (3 mmol) under a nitrogen atomosphere. After stirring at room temperature for 5 min, an azilidine (3 mmol) was added rapidly to the resulting mixture. The reaction was further continued at 40 °C and was monitored by GLC.

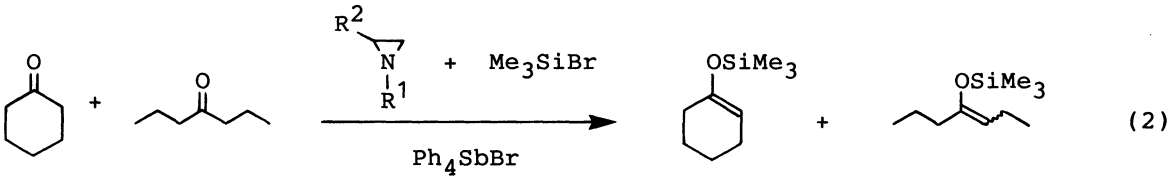
As shown in the Table 1, the combination of N-phenyl-2-methylazilidine, trimethylsilyl bromide and Ph_4SbBr was the most effective and selective silylating reagent. Especially it has high regioselectivity in the reaction of 2-methylcyclohexanone, where the selective formation of thermodynamically controlled product was observed (run 9). The yield and selectivity of enolate were drastically decreased in the absence of Ph_4SbBr (run 8). Moreover, the order of addition of substrates as mentioned in a experimental paragraph was also important, because the addition of ketones into the mixture of azilidines and

Table 1. Silylation of Ketones by Azilidine-Trimethylsilyl Halide-Ph_4SbX System

Run	Ketone	R^1	R^2	X	Time/h	Product (Yield)[b]
1		Ph	H	Br	1	 (89)
2		Ph	H	Cl	15	(0)
3		Ph	Me	Br	2	(100)
4[a]		Ph	Me	Br	2	(63)
5		p-$MeOC_6H_4$	Me	Br	2	(97)
6		n-Bu	Me	Br	2	(22)
7		Ph	H	Br	1	 (82)  (18)
8[a]		Ph	H	Br	1	(19) (6)
9		Ph	Me	Br	2	(91) (7)
10		Ph	H	Br	1	 (76)
11		Ph	H	Br	1	 (18)
12		Ph	H	Br	1	 (39)[c]

Azilidine/ketone/silane/Ph_4SbX = 3/2/3/0.2 mmol, 40 °C, solv. CH_2Cl_2 3 ml.
a) No antimony catalyst. b) GLC yield. c) Ratio of (Z)-isomer and (E)-one was 66 : 34.

silyl bromide gave scarecely desired products. Silyl enol ether of cyclopentanone was likewise prepared in good yield (run 10). In contrast to the cyclic ketones, transformation of acetophenone and di-n-propyl ketone to the corresponding silyl enol ethers did not proceed so well (runs 11,12). Then we attempted the competition reaction of cyclic and acyclic ketones, and achieved selective silylation of cyclohexanone in the presence of di-n-propyl ketone (Eq.2). Such remarkable difference between cyclic and acyclic ketones has not been reported in conventional methods. In addition, the similar chemoselectivity was recognized between cyclohexanone (41%) and acetophenone (8%). On the other hand, the high selectivity like azilidines was not observed in the case using triethylamine as a base. From these results, it was proved that this novel system exhibited characteristic ability to silylate cyclic ketones predominantly.

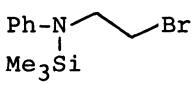


Base

R^1=Ph	R^2=H	rt, 0.5 h	57%	0%
=Ph	=Me	40 °C, 3 h	82%	8%
(Triethylamine)		40 °C, 3 h	76%	26%

We propose a reaction mechanism as follows. As initial addition of ketones to trimethylsilyl bromide is indispensable, the formation of a complex **2** is assumed. The acidic α-proton in cyclic ketones, which is activated by coordination of silyl bromide is abstracted by an azilidines under the catalytic assistance of Ph_4SbBr as shown in Fig. 1, furnishing silyl enol ethers. The recycling use of azilidines might be possible since the yielding 2-bromo amines readily reproduce the starting azilidines by action of a base (Gabriel Synthesis).[14] In the case of acyclic ketones, contrarily, β-bromo silyl amides such as **1** are yielded which have no ability to form silyl enol ethers .[15] This difference may be attributed to lower acidity of α-protones[16] and less stability of the corresponding metal enolate[17] than cyclic ketones.

In conclusion, it was confirmed that this novel system was an effective and selective silylating reagent to cyclic ketones.



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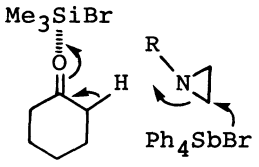

2

Fig. 1.

This study was financially supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science and Culture.

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(Received April 12, 1989)