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An Efficient and Convenient Method for the Preparation of α-Methylenated Ketones from Silyl Enol Ethers

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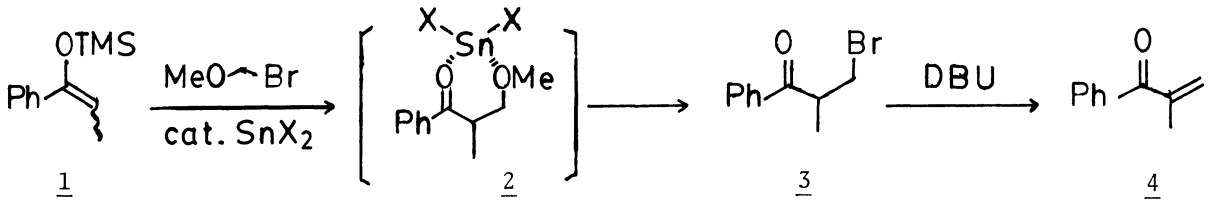
In the presence of a catalytic amount of stannous halide, silyl enol ethers react with bromomethyl methyl ether to give the corresponding α-bromomethyl ketones, which are smoothly converted to α-methylenated ketones on the successive addition of tertiary amine by one-pot procedure. This method is successfully applied to a synthesis of sarkomycin intermediate.

α-Methylenation of ketones is an important reaction for the synthesis of various natural products and generally performed by a two step procedure; for example, a dialkylaminomethyl group or an arylthiomethyl group is firstly introduced to the α-position of a carbonyl function by the application of Mannich base,[1] such as Eschenmoser's salt,[2] or chloromethyl phenyl sulfide[3] to the corresponding silyl enol ethers. Then, the isolated products are converted to the ammonium salts or the sulfoxides, which in turn underwent the elimination to afford the α-methylenated ketones. Now, we wish to report the convenient method for the α-methylenation of ketones *via* α-bromomethylation by one-pot procedure starting from silyl enol ethers and bromomethyl methyl ether in the presence of a catalytic amount of stannous halide. To our knowledge, this is a first general method for the α-bromomethylation of ketone equivalents such as silyl enol ether.

First, the silyl enol ethers (1) of propiophenone was treated with bromomethyl methyl ether (1.2 equiv.) in the presence of a catalytic amount of $SnCl_2$ in CH_2Cl_2 at 0 °C, and it was found that the α-bromomethyl ketone (3) was obtained in 74% yield *via* the formation of the α-methoxymethyl ketone. The α-bromomethyl ketone thus formed was readily converted to the corresponding α-methylenated ketone (4) on the successive treatment with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) by one-pot procedure. After screening the reaction conditions employing the above silyl enol ether (1) as a model substrate, it was found that the reaction proceeded smoothly in CH_2Cl_2 at room temperature in the presence of 5 mol% of $SnBr_2$ to give 4 in an excellent yield (91%) as shown in Table 1.[4]

Although the detailed mechanism is not yet clear, it is assumed that SnX_2 activates bromomethyl methyl ether to generate the oxygen stabilized carbocation ($MeOCH_2^+$) which is attacked by the silyl enol ether to produce the α-methoxymethyl

ketone. This intermediate is also activated by SnX_2 *via* the six-membered chelate complex (2), which is readily attacked by bromide ion to afford the α-bromomethyl ketone as shown in Scheme 1.



1 2 3 4

Scheme 1.

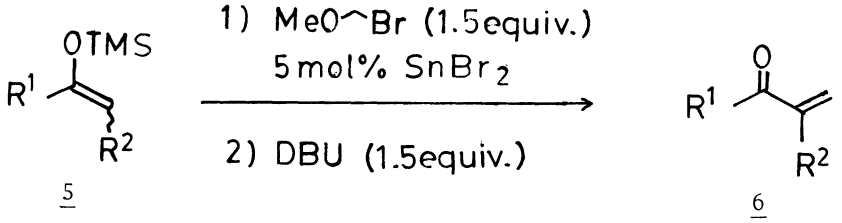
Table 1. The effect of the reaction condition[a)]

Catalyst[b)]	Molar ratio of $BrCH_2OMe$ per 1	Solvent	Temp/°C	Yield of 4/%[c)]
SnF_2	1.5	CH_2Cl_2	r.t.	82
$SnCl_2$	1.2	CH_2Cl_2	0	73
$SnCl_2$	1.5	CH_2Cl_2	r.t.	86
$SnBr_2$	1.2	CH_2Cl_2	0	74
$SnBr_2$	1.2	CH_3CN	0	72
$SnBr_2$	1.2	toluene	0	40
$SnBr_2$	1.2	THF	0	—
$SnBr_2$	1.5	CH_2Cl_2	r.t.	91

a) Silyl enol ether was treated with bromomethyl methyl ether for 1, and then 1 equivalent of DBU to bromomethyl methyl ether was added and the resulting mixture was stirred for 2 h at the same temperature.
b) 5 mol% of catalyst was used.
c) Isolated yields.

Next, the reaction of various silyl enol ethers (5) with bromomethyl methyl ether was tried (see Table 2), and it was found that various silyl enol ethers were successfully employed in the present reaction.

Typical procedure is described for the reaction of 1-phenyl-1-trimethylsilyloxypropene (1): Under an argon atmosphere, to a stirred suspension of $SnBr_2$(0.023 mmol) in CH_2Cl_2(2 ml) were added successively (1)(0.46 mmol) in CH_2Cl_2(2 ml) and bromomethyl methyl ether (0.69 mmol) in CH_2Cl_2 at the room temperature. The reaction mixture was stirred for 1 d at the same temperature, and quenched by the addition of a solution of DBU (0.69 mmol) in CH_2Cl_2(2 ml), stirring was continued for additional 2 h. After the evaporation of the solvent, the residue was purified by preparative TLC to afford 2-methyl-3-oxo-3-phenylpropene (4) (0.42 mmol, 91%).



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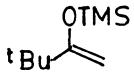
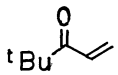
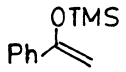
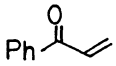
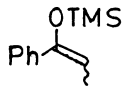
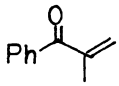
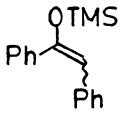
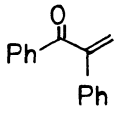
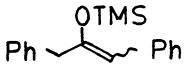
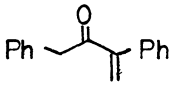
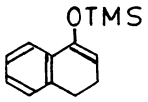
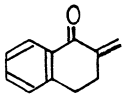
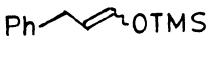
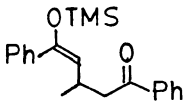
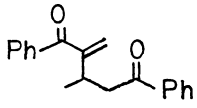
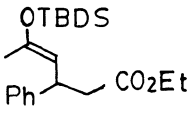
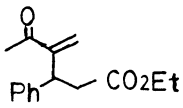
Scheme 2.

Table 2. Synthesis of α-methylenated ketones[a)]

Entry	5	Reaction time/h	Product	Yield/%[b)]
1		3		70
2		1.5		62
3		16		91
4		16		89
5		16		68[c)]
6		16		90[d)]
7		3		48[e)]
8		16		25[f)]
9		40		26[f)]

a) After the α-bromomethylation, the product was treated with DBU for 2 h in the same vessel.

b) Isolated yields. All products gave satisfactory NMR and IR data.

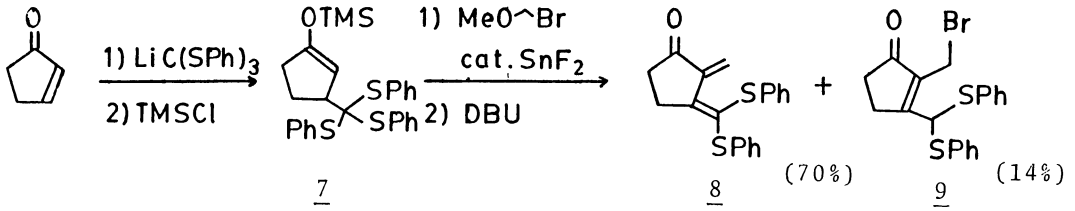
c) SnF_2 was used as a catalyst instead of $SnBr_2$.

d) DBU treatment was not carried out.

e) The reaction was carried out at 0 °C.

f) The parent ketone was recovered (Entry 8: 55%, Entry 9: 36%).

Then, in order to demonstrate the potential utility, the above mentioned reaction was applied to the synthesis of an antitumor antibiotic sarkomycin[6] intermediate. According to Scheme 3, the silyl enol ether (7), derived from 2-cyclopentenone and lithio triphenylthiomethane, was converted to the corresponding α-methylenated ketone (8)[7] in short steps, while the conventional methods[8] required long tedious steps.

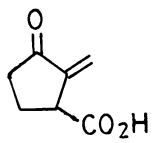


Scheme 3.

It is noted that the α-bromomethylation of silyl enol ethers, one of the important reaction for the synthesis of useful synthetic intermediates as β-functionalized ketone derivatives,[9] is smoothly carried out by using bromomethyl methyl ether in the presence of a catalytic amount of stannous halide, and various α-methylenated ketones are also available easily by one-pot procedure on successive treatment with tertiary amine.

References

1) For a review see: M. Tramontini, Synthesis, 1973, 703.
2) J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, Angew. Chem., Int. Ed. Engl., 10, 330 (1971).
3) I. Fleming, J. Goldhill, and I. Paterson, Tetrahedron Lett., 1979, 3205, 3209.
4) In each case, 10-20% of α-methoxymethyl ketone (2) was isolated, however, the ketone was completely converted into α-bromomethyl ketone (3) by the addition of 0.1-0.2 equivalent of TMSBr to the reaction mixture.
5) This silyl enol ether was obtained by the method of trityl perchlorate catalyzed Michael reaction. S. Kobayashi and T. Mukaiyama, Chem. Lett., 1986, 221.
6) H. Umezawa, Antibiot and Chemoth., 4, 514 (1954).
7) In this case the elimination of thiophenol was accompanied.
8) T. Cohen, Z. Kosarych, K. Suzuki, and L-C. Yu, J. Org. Chem., 50, 2965 (1985) and references cited therein.
9) A. H. Schmidt and M. Russ, Chem. Ber., 114, 1099 (1981).



sarkomycin

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