Organic Syntheses

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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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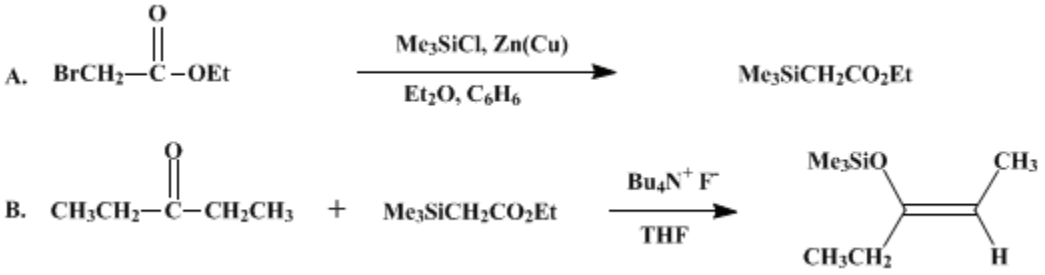
SILYLATION OF KETONES WITH ETHYL TRIMETHYLSILACETATE: (Z)-3-TRIMETHYLSILOXY-2-PENTENE

[Silane, [(1-ethyl-1-propenyl)oxyl]trimethyl-, (Z)-]



Submitted by Isao Kuwajima, Eiichi Nakamura, and Koichi Hashimoto[1].
Checked by Peter J. Card and Richard E. Benson.

1. Procedure

Caution! Ethyl bromoacetate is intensely irritating to eyes and skin. The preparation of this ester should be carried out in an efficient hood. Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Ethyl trimethylsilylacetate* (Note 1). In a 3-L, three-necked flask fitted with a 1-L, pressure-equalizing dropping funnel, mechanical stirrer, and efficient condenser that is connected to a nitrogen source are placed 97.5 g (1.5 mol) of zinc powder (Note 2) and 14.9 g (0.15 mol) of cuprous chloride (Note 3). After the reaction vessel is flushed with nitrogen, a static nitrogen atmosphere is maintained for the remainder of the reaction. A mixture of 150 mL of benzene (Note 5) is added to the flask, and the resulting mixture is refluxed with stirring for 30 min with the aid of an electric heating mantle. Heating is discontinued and a solution of 109 g (128 mL, 1.0 mol) of chlorotrimethylsilane (Note 6) and 184 g (123 mL, 1.1 mol) of ethyl bromoacetate (Note 7) in a mixture of 90 mL of ether and 350 mL of benzene is promptly added through the dropping funnel at such a rate as to maintain the reaction at gentle reflux. The addition takes about 1 hr. After the addition is complete, the mixture is heated at reflux for 1 hr and then cooled in an ice bath. While the mixture is stirred, 300 mL of aqueous 5% hydrochloric acid is added through the dropping funnel over a 10-min period. The liquid layer is decanted into a 3-L separatory funnel and the flask is washed with two 100-mL portions of ether. The ether solutions are added to the separatory funnel, the organic layer is separated, and the aqueous layer is extracted with two 200-mL portions of ether. The organic phases are combined and washed twice with 200-mL portions of saturated aqueous sodium chloride, twice with 200-mL portions of saturated aqueous sodium bicarbonate, and finally with 200 mL of saturated aqueous sodium chloride. The organic layer is dried over anhydrous magnesium sulfate, the mixture is filtered, and the filtrate is concentrated on a rotary evaporator to a volume of about 400 mL. The residual yellow liquid is distilled in a 30-cm vacuum-jacketed Vigreux column at atmospheric pressure until the boiling point is 90°C. The remaining liquid is distilled at reduced pressure to give, after a small forerun, 101–108 g (63–74%, (Note 8)) of ethyl trimethylsilylacetate, bp 93–94°C (104 mm), n_D^{20} 1.4152–1.4154 (Note 9).

B. *(Z)-3-Trimethylsiloxy-2-pentene*. In a dry, 200-mL flask (Note 10) equipped with a Teflon-coated magnetic stirring bar and a three-way stopcock, one exit of which is capped with a small rubber septum, is quickly placed 1.5 g (ca. 6 mmol) of dried tetrabutylammonium fluoride hydrate (Note 11). With the aid of a hypodermic syringe, 50 mL of dry tetrahydrofuran (THF, (Note 12) is added through the septum, and the clear solution is stirred. After 5 min, the reaction vessel is immersed in a hexane/dry ice bath, and 38.4 g (0.240 mol) of ethyl trimethylsilylacetate is added during 10 min through a syringe that

is rinsed with 15 mL of dry THF. After 10 min a solution of 17.2 g (0.200 mol) of 3-pentanone (Note 13) in 15 mL of dry THF is introduced during 10 min to the stirred solution with the aid of a syringe, which is then rinsed with 5 mL of dry THF. The clear solution is stirred for 3 hr, then warmed gradually to 0°C over about 1 hr and finally the temperature is held at 0°C for 2–4 hr (Note 14). Meanwhile, 400 mL of pentane (Note 15) in a dry, nitrogen-filled, 1-L flask equipped with a drying tube and a magnetic stirring bar is cooled with stirring in a hexane/dry ice bath, and the dark-orange reaction mixture is poured into it. The reaction vessel is rinsed with three 50-mL portions of pentane. The pentane rinses are added to the reaction solution and the resulting mixture is filtered through a pad of Hyflo Super Cell on a sintered-glass filter, and the filtrate is washed with 100 mL of saturated aqueous sodium bicarbonate and 100 mL of saturated aqueous sodium chloride. The organic layer is dried over magnesium sulfate, the drying agent is remove by filtration, and the resulting solution is concentrated on a rotary evaporator at room temperature to a volume of 150 mL. The remaining liquid is distilled through a 10-cm Vigreux column. After a very small amount of forerun (< 1 g), 21.9–24.1 g (69–76%) of 3-trimethylsiloxy-2-pentene is obtained, bp 139–142°C; n_D^{20} 1.4133–1.4135 (Note 16).

2. Notes

1. This procedure is based on a report by Fessenden and Fessenden.[2] Cuprous chloride[3] is a more efficient initiator than iodine as specified in the original procedure.
2. The submitters used zinc powder purchased from Koso Chemical (Japan) without any purification. The checkers used product available from Fisher Scientific Company. It is essential to use excess zinc to ensure complete consumption of ethyl bromoacetate, which interrupts the catalytic cycle in Step B of the present silylation reaction.
3. The submitters used cuprous chloride purchased from Koso Chemical Co. Ltd. without purification. The checkers used cuprous chloride available from Fisher Scientific Company.
4. The submitters used diethyl ether, obtained from Showa Ether, after distillation from sodium wire. The checkers distilled the product obtained from Fisher Scientific Company from lithium aluminum hydride.
5. Benzene was distilled over sodium wire before use
6. The submitters used chlorotrimethylsilane obtained from Nakarai Chemical. The material was distilled from calcium hydride or sodium wire before use. The checkers used product available from Aldrich Chemical Company, Inc.
7. The submitters used ethyl bromoacetate (GR grade) obtained from Tokyo Kasei and distilled it before use in an efficient hood. The checkers used product available from Aldrich Chemical Company, Inc.
8. The submitters state that the yield ranged from 68 to 70% for runs made on a 1.5-mol scale.
9. Ethyl trimethylsilylacetate is stable to the usual manipulations, and can be stored in glass containers for years without change of physical and spectral properties. IR (liquid film) cm^{-1}: 1720, characteristic of α-silyl esters. The reported physical constants are bp 76–77°C (40 mm), n_D^{25} 1.4136,[2] n_D^{20} 1.4149.[4] ^1H NMR (CCl_4) δ: 0.17 (s, 9 H, CH_3Si), 1.31 (t, 3 H, $J = 7$, CH_3CH_2), 1.88 (s, 2 H, $SiCH_2$), and 4.14 (q, 2 H, $J = 7$, CH_2O).
10. Tetrabutylammonium fluoride is very hygroscopic. A drybox may be used to avoid rapid manipulation of the fluoride in the atmosphere and exposure of the reagent in the storage vessel to moisture. Alternatively, hydrated tetrabutylammonium fluoride (Note 11) can be dried in the reaction vessel and used directly.
11. Tetrabutylammonium fluoride trihydrate obtained from Fluka AG was dried over phosphorus pentoxide for 48 hr at a pressure of ~0.1 mm. The hygroscopic fluoride was pulverized with the aid of a spatula in a dry atmosphere. The checkers prepared the dry salt by this method using material obtained from Tridom Chemical, Inc.
Alternatively, the fluoride can be prepared as follows: A 10–40% aqueous or alcoholic solution of tetrabutylammonium hydroxide available from several sources is placed in a glass flask fitted with a Teflon-coated magnetic stirring bar and stirred gently. The pH of the solution is adjusted to about 8 by rapid addition of an almost theoretical amount of 48% aqueous hydrofluoric acid with the aid of a plastic pipette. *Caution! Hydrofluoric acid in contact with the skin produces extremely painful burns. Long, acid-resistant gloves should be worn.* Final adjustment of the pH to 7–8, measured with a pH meter, is achieved by addition of 5% aqueous acid. The bulk of the solvent is removed by distillation on a rotary evaporator at ~ 30°C (1 mm). The resulting white paste is further dried as described above to

give the salt as a white mass.
The submitters state that in some cases, probably depending on the source of the hydroxide, the dried salt did not solidify. On such an occasion, the aqueous solution was diluted with deionized water to obtain a ~ 0.5 *M* aqueous solution. The resulting solution was cooled to 5–10°C and allowed to stand to give a white clathrate. The supernatant liquid was removed by a pipette and the clathrate was washed once with cold water. When the clathrate was dried as described above the fluoride was obtained as a solid.[5]
12. Tetrahydrofuran was distilled successively from cuprous chloride and sodium wire,[6] and further purified by distillation from sodium benzophenone ketyl in a recycling still. The checkers used product obtained from Fisher Chemical Company that was distilled from lithium aluminum hydride prior to use.
13. 3-Pentanone obtained form Tokyo Kasei (GR grade) was distilled before use. The checkers used product available from Aldrich Chemical Company, Inc.
14. The reaction is normally complete at −78°C, affording a product of 99.5% isomeric purity. It is advisable, however, to raise the reaction temperature finally to 0°C, since some unknown factors occasionally retard this catalyzed reaction. Development of an orange-to-red color of the mixture usually indicates the progress of the reaction.
15. Pentane was stored over sodium wire. The checkers used product available from Eastman Organic Chemicals.
16. The spectral properties of 3-trimethylsiloxy-2-pentene are as follows: ^{1}H NMR (CCl_4) δ: 0.18 (s, 9 H, SiCH_3), 1.03 (t, 3 H, *J* = 7, CH_3CH_2), 1.48 (d of t, 3 H, CH_3C=CH, *J* = 1 and 6.5), 2.02 (unresolved quartet, 2 H, CH_2CH_3, *J* = 7), 4.47 (q, 1 H, *J* = 7, CH_3CH=C). IR spectrum (liquid film) cm^{-1}: 1678, 1250, and 835. The isomeric purity was 96–99.5% of *Z* isomer as determined by the submitters by GLC comparison with an authentic *E*-[7,8] or *Z*-enriched[8] mixture. The GLC analysis was carried out using the following column and conditions: 3-mm × 6-m stainless steel column, 5% XE-60 on 60–80-mesh Chromosorb P(AW), 80°C, 45 mL of nitrogen per min. The retention times for the *E*-isomer, the *Z*-isomer, 3-pentanone, and ethyl trimethylsilylacetate are 5.2, 5.6, 6.2, and 15.9 min, respectively.

3. Discussion

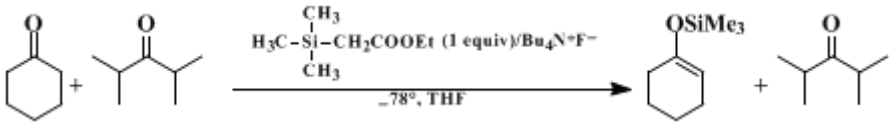
Enol trimethylsilyl ethers belong to a most important class of enol derivatives[9] and serve as good precursors of isomerically pure enolate anions.[8,10] The double bond also resembles that of electron-rich olefins in reactions with electrophiles and sometimes is reactive in electrocyclic reactions.

Among the methods for their preparations, two reactions described by House have been employed widely:[8] a thermodynamically controlled silylation with chlorotrimethylsilane/triethylamine in hot dimethylformamide or a kinetically controlled reaction that involves lithiation with a lithium dialkylamide followed by quenching with the chlorosilane. Each method has its own merits and drawbacks with respect to three important factors: regio-, stereo-, and chemoselectivities.

The present silylation reaction[11] represents a new procedure based on metathetical generation of reactive enolate species,[12] and some characteristic features described below make this reaction complementary to the previous methods.

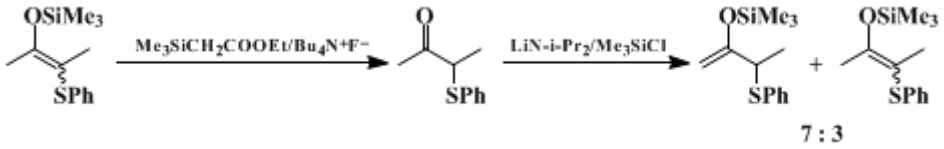
The excellent stereoselectivity as described in the present example is one of the advantages that merits attention.[11] The reaction affords only *Z*-enol silyl ethers when applied to acyclic ketones. For instance, silylation of 5-nonanone and 2-octanone gave (*Z*)-5-trimethylsiloxy-4-nonene and (*Z*)-2-trimethylsiloxy-2-octene (together with 14% of its regio isomer), both in 91% yield.

Chemoselectivity of the reaction constitutes another point of interest. Ketones can be silylated in the presence of functional groups that include oxiranes, esters, nitriles,[11] and even ketones. Thus silylation of one ketone can be performed in the presence of another. The equation shown below illustrates this selectivity.[13]



Alkyl halides[12] and aldehydes[14] are not compatible with the present silylation reaction.

Kinetic selectivity of the silylation reaction is high with methyl isopropyl ketone (99.5% of the less highly substituted isomer),[13] and methyl isobutyl ketone (~ 90%), and fair with 2-methylcyclohexanone (~80%).[11] The nature of the regioselectivity of this reaction appears different from that with lithium dialkylamide for which steric factors may influence the regioselectivity. In fact, silylation of 3-phenylthio-2-butanone with ethyl trimethylsilylacetate at 0°C produced 2-phenylthio-3-trimethylsiloxy-2-butene, whereas treatment with lithium diisopropylamide followed by quenching with chlorortrimethylsilane gave mainly the less highly substituted regioisomer.[13]



Since the only by-product of the reaction is ethyl acetate, the silylated product can be employed for further reactions without purification. Examples include the fluoridecatalyzed aldol reaction[15] and bromination with *N*-bromosuccinimide.[11]

The present reaction can be applied to a variety of ketones including four- to eight-membered and twelve-membered cycloalkanones and acyclic and α,β-unsaturated ketones.[11] It has also been used for primary, secondary, and tertiary alcohols,[16] alkanethiols,[16] phenols,[16] and arylacetylenes.[11]

Ethyl trimethylsilylacetate has also been used for the synthesis of α,β-unsaturated esters.[17] The chemistry of tetrabutylammonium fluoride as a base with mild reactivity has been reviewed.[18]

References and Notes

1. Department of Chemistry, Tokyo Institute of Technology, Tokyo, 152, Japan.
2. Fessenden, R. J.; Fessenden, J. S. *J. Org. Chem*. **1967**, *32*, 3535;
3. Rawson, R. J.; Harrison, I. T. *J. Org. Chem*. **1970**, *35*, 2057.
4. Gold, J. R.; Sommer, L. H.; Whitmore, F. C. *J. Am. Chem. Soc*. **1948**, *70*, 2874.
5. McMullan, R.; Jeffrey, G. A. *J. Chem. Phys*. **1959**, *31*, 1231.
6. See "WARNING," *Org. Synth., Coll. Vol. V* **1973**, 976.
7. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc*. **1976**, *98* 2868.
8. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem*. **1969**, *34*, 2324.
9. Review: Rasmussen, J. K. *Synthesis* **1977**, 91.
10. Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc*. **1968**, *90*, 4462, 4464.
11. Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc*. **1976**, *98*, 2346; Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett*. **1978**, 2079.
12. Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc*. **1975**, *97*, 3257.
13. Kuwajima, I.; Nakamura, E. *Acc. Chem. Res*. **1985**, *18*, 181.
14. Nakamura, E.; Shimizu, M.; Kuwajima, I. *Tetrahedron Lett*. **1976**, 1699.
15. Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc*. **1977**, *99*, 1265.
16. Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Bull. Chem. Soc. Jpn*. **1980**, *54*, 804.
17. Taguchi, H.; Shimoji, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn*. **1974**, *47*, 2529.
18. Review: Kuwajima, I. *J. Synth. Org. Chem. Jpn*. **1976**, *34*, 964; *Chem. Abstr*. **1977**, *86*, 106694v.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium benzophenone ketyl

chlorortrimethylsilane

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether,
diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

hydrofluoric acid (7664-39-3)

iodine (7553-56-2)

zinc,
zinc powder (7440-66-6)

sodium wire (13966-32-0)

cuprous chloride (7758-89-6)

Pentane (109-66-0)

Methyl isobutyl ketone (108-10-1)

2-Octanone (111-13-7)

magnesium sulfate (7487-88-9)

Ethyl bromoacetate (105-36-2)

Methyl isopropyl ketone (563-80-4)

Tetrahydrofuran (109-99-9)

3-pentanone (96-22-0)

lithium aluminum hydride (16853-85-3)

dimethylformamide (68-12-2)

N-bromosuccinimide (128-08-5)

2-methylcyclohexanone (583-60-8)

calcium hydride (7789-78-8)

lithium diisopropylamide (4111-54-0)

CHLOROTRIMETHYLSILANE (75-77-4)

ETHYL TRIMETHYLSILACETATE

(Z)-3-TRIMETHYLSILOXY-2-PENTENE,
Silane, [(1-ethyl-1-propenyl)oxyl]trimethyl-, (Z)- (51425-54-8)

Ethyl trimethylsilylacetate (4071-88-9)

tetrabutylammonium fluoride hydrate (22206-57-1)

3-Trimethylsiloxy-2-pentene

Tetrabutylammonium fluoride (429-41-4)

Tetrabutylammonium fluoride trihydrate (87749-50-6)

tetrabutylammonium hydroxide (2052-49-5)

5-nonanone (502-56-7)

3-phenylthio-2-butanone

2-phenylthio-3-trimethylsiloxy-2-butene

phosphorus pentoxide (1314-56-3)

(Z)-5-trimethylsiloxy-4-nonene