Silyl Derivatives in the Synthesis of *trans*-β-Trimethylsilyl-α,β-unsaturated Ketones

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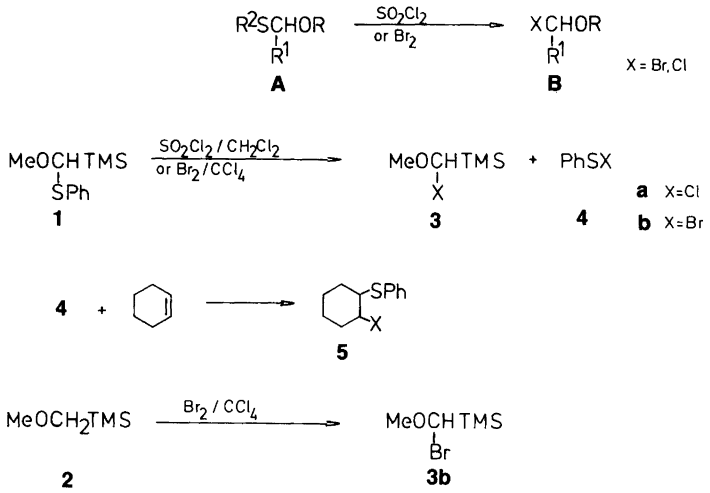
Methods for the preparation of α-halo-α-(trimethylsilyl)methyl ethers are described. These substances react with (trimethylsilyl)methyl ketones to yield β-methoxy-β-(trimethylsilyl)ethyl ketones. Sodium trimethylsilanoate in dichloromethane solution has been found to be an efficient base for methanol elimination from the latter, whereby *trans*-β-trimethylsilyl-α,β-unsaturated ketones are formed.

Vinylsilanes are generally useful intermediates in organic synthesis.[1] We are engaged in chemistry requiring such intermediates and now report a new method for the synthesis of the vinyl silanes *trans*-β-trimethylsilyl-α,β-unsaturated ketones.

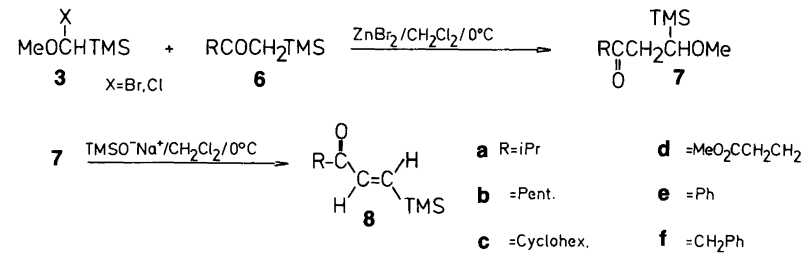
The starting material was the halo(trimethylsilyl)methyl ether **3**, which was prepared by a procedure analogous to the methods we developed recently for the synthesis of αhalo ethers; the latter were obtained by the treatment of *O,S*-acetals with sulfuryl chloride or bromine (Scheme 1; **A** → **B**).[2] Selective cleavage of the C–S bond in the trimethylsilyl (TMS) derivative **1**[3] proceeded readily to furnish the α-halo ether **3** on treatment of compound **1** with the halogenating agent in the cold. The co-product, the phenylsulfenyl halide **4**, was trapped by addition of cyclohexene, which resulted in the formation of the adduct **5**. The α-halo ether was isolated by distillation of the product mixture.

The α-bromo ether **3b** can also be prepared by direct bromination of the simple trimethylsilylmethyl ether **2**, by analogy with the bromination of the triphenylsilyl homologue reported very recently.[4] Chlorination of the simple ether **2** with sulfuryl chloride, however, was unsatisfactory.

α-Halo ethers are highly reactive towards a variety of nucleophiles.[5] The synthon **3** is simi-



Scheme 1.



Scheme 2.

larly useful for the introduction of the alkoxy-TMS methyl group into organic molecules.

Another silyl derivative, the trimethylsilylmethyl ketone **6**, was used in the synthesis of the β-TMS ketone **7** (Scheme 2). We have reported recently that the former is a useful intermediate in selective synthesis of halomethyl ketones.[6] Studies on the preparation of α-substituted ketones by cleavage of the C–Si bond in α-TMS ketones with electrophiles have been few.[6,7] On the other hand, the isomeric silyl enol ethers are well known to undergo α-substitution when treated with electrophiles.[1,8]

In the reaction between compounds **3** and **6** a small amount of zinc bromide was found to catalyze the reaction, which was run in dichloromethane at 0 °C. The resultant β-silyl ketone **7** could be isolated and purified. The subsequent methanol elimination reaction, however, proceeded equally well without isolation of the intermediate **7**.

Two molar equivalents of the trimethylsilylmethyl ketone **6** were required for optimum yield of the product **7**. In the presence of equimolar amounts of compounds **3** and **6** very little of the silane **7** was seen in the product (GLC), presumably because of methanol elimination from the latter. Subsequently, acid may be generated by reaction of methanol with the $ZnBr_2$ or the TMS halide. The acid is trapped by reaction with the TMS-ketone **6** to give the corresponding methyl ketone. Both methyl cyclohexyl ketone and the vinylsilane **8c** were identified as reaction products in the reaction of one equivalent of **6c** with **3**.

In the elimination of methanol from compound **7** to give the vinyl derivative **8**, potassium *tert*-butoxide in THF at 0 °C was an unsatisfactory reagent, and compound **7** was resistant to triethylamine in dichloromethane. We had observed, however, that rapid elimination of methanol occurred occasionally during the extraction of the organic solution containing compound **7**, giving the vinylsilane **8**. This observation was rationalized as being due to hydrolysis of the TMS halide and formation of the base sodium trimethylsilanoate, which is soluble in the organic layer. The literature appears to contain little information on the use of sodium trimethylsilanoate as a base except for polymerization reactions and ester cleavage.[9]

The high solubility of sodium trimethylsilanoate in an organic solvent such as dichloromethane may have useful applications. In the methanol elimination from compound **7**, a solution of sodium trimethylsilanoate (0.3 equiv.) in dichloromethane was added dropwise to a cold solution of **7**. The smooth elimination reaction required <1 h for completion and gave exclusively the *trans* derivative **8**. When less base was used (0.1 equiv.) the elimination was considerably slower (48 h).

Experimental

The ^1H–NMR spectra were recorded at 300 MHz and the ^{13}C–NMR spectra at 75 MHz. The mass spectra under electron impact conditions were recorded at 70 eV ionizing energy. Isobutane was used for chemical ionizing mass spectrometry (CI); the spectra are presented as *m/z* (% rel. int.).

Chloro(methoxy)methyltrimethylsilane (**3a**). Sulfuryl chloride (0.68 ml, 8.6 mmol) in dry dichloromethane (5 ml) was added dropwise with stirring to a solution of phenylsulfenyl(methoxy)-methyltrimethylsilane[3] (1.95 g, 8.6 mmol) in dry dichloromethane (10 ml) under N_2 at 0 °C. The resultant solution was stirred at 0 °C for 30 min before a solution of cyclohexene (1.06 ml, 10.6

mmol) in dry dichloromethane (3 ml) was added dropwise. The mixture was stirred for 30 min, the solvent distilled off and the residue distilled at reduced pressure; yield 0.95 g (81 %), b.p. 62 °C/70 mmHg. ^{1}H–NMR ($CDCl_3$): δ 0.15 (TMS), 3.55 (OMe), 5.32 (CH).

Bromo(methoxy)methyltrimethylsilane (**3b**). *Method A:* Bromine (2.0 g, 12.7 mmol) in dry tetrachloromethane (10 ml) was added dropwise with stirring under N_2 to a solution of methoxymethyltrimethylsilane[10] (1.5 g, 12.7 mmol) in dry tetrachloromethane (15 ml) at ambient temperature. The stirring was continued for 4 h before the mixture was evaporated at reduced pressure and the residue distilled; yield 1.24 g (55 %), b.p.40 °C/10 mmHg. ^{1}H–NMR ($CDCl_3$): δ 0.15 (TMS), 3.49 (OMe), 5.69 (CH). Analysis by GLC (SP 2100, 70 °C isotherm.) > 97 % pure.

Method B: Bromine (0.16 ml, 3.1 mmol) in dry dichloromethane (2 ml) was added dropwise with stirring under N_2 to a solution of phenylsulfenyl (methoxy)methyltrimethylsilane[3] (707 mg, 3.1 mmol) in dry dichloromethane (5 ml). The mixture was stirred at 0 °C for 30 min before a solution of cyclohexene (0.38 ml, 0.38 mmol) in dry dichloromethane (2 ml) was added dropwise. After stirring for 30 min the solvent was removed and the residue distilled; yield 340 mg (56 %).

General procedure for the preparation of 2-methoxy-2-trimethylsilylethyl ketones (**7**). TMSmethyl ketone (3.0 mmol), zinc bromide (0.15 mmol) and the bromo- or chloro(methoxy)methyltrimethylsilane (**3**) (1.5 mmol) were dissolved in dry dichloromethane (7 ml) under N_2 at 0 °C. The resultant solution was allowed to reach ambient temperature, stirred for 1–24 h (**7a–7f** for 4, 24, 5, 1.5 and 1 h, respectively), diluted with diethyl ether and shaken with aqueous saturated $NaHCO_3$. The dried ($MgSO_4$) solution was evaporated and the residual material subjected to flash chromatography on silica gel using hexane/EtOAc (6:1*v/v*).

1-Methoxy-4-methyl-1-trimethylsilyl-3-pentanone (**7a**). Compound **7a** was obtained in 61 % yield as an oily material. Anal. $C_{10}H_{22}O_2Si$: C, H. ^{1}H–NMR ($CDCl_3$): δ 0.00 (TMS), 1.07 (2×CH_3, d, *J* Hz), 2.37 (1H, CH_2CH, dd, *J* 16.5, 3.5 Hz) and 2.73 (1H, CH_2CH, dd, *J* 16.5, 3.5 Hz), 2.62 (m, *CH*CO), 3.26 (OMe), 3.43 (*CH*CH_2, dd, *J* 9.5, 3.5 Hz). ^{13}C–NMR($CDCl_3$): δ 3.4 (TMS), 24.8 (2×CH_3), 48.2 (*CH*CO), 48.8 (CH_2CH), 67.0 (OMe), 78.1 (CH_2*CH*), 220.7 (CO). MS: 170(8, *M*), 155(16), 127(100), 99(24), 73(99).

1-Methoxy-1-trimethylsilyl-3-octanone (**7b**). Compound **7b** was obtained in 52 % yield as an oily material. Anal. $C_{12}H_{26}O_2Si$: C, H. ^{1}H–NMR ($CDCl_3$): δ 0.00 (TMS), 0.85 and 1.2–1.6 (Bu), 2.42 (CH_2CO, t), 2.33 (1H, CH_2CH, dd, *J* 16.5, 3.5 Hz) and 2.65 (1H, CH_2–CH, dd. *J* 9.0, 3.5 Hz), 3.41 (CH_2–*CH*, dd, *J* 9.0, 3.5 Hz), 3.28 (OMe). ^{13}C–NMR ($CDCl_3$): δ 3.6 (TMS), 21.0 (Me), 29.5, 30.4, 38.4 (3×CH_2), 50.8 and 51.3 (CH_2COCH_2), 67.3 (OMe), 78.6 (CH), 218.0 (CO). MS(CI): 213(100, *M*+1), 215(62), 199(14), 159(45), 99(35).

Methyl 6-methoxy-4-oxo-6-trimethylsilylhexanoate (**7d**). Compound **7d** was obtained in 63 % yield as an oily substance. Anal. $C_{11}H_{22}O_4Si$: C, H. ^{1}H–NMR ($CDCl_3$): δ 0.00 (TMS), 2.41 (1H, CH_2CH, dd, *J* 16.5, 3.5 Hz), 2.5–2.8 (2×CH_2; 1H, CH_2CH), 3.27 (OMe), 3.40 (CH_2*CH*, dd, *J* 9.0, 3.5 Hz), 3.63 (CO_2Me). ^{13}C–NMR ($CDCl_3$): δ 3.6 (TMS), 34.8, 45.2, 51.4 (3×CH_2), 58.8, 67.2 (2×OMe), 78.6 (CH), 180.2 (CO_2Me), 215.7 (CO). MS(CI): 247(10, *M*+1), 215(21), 159(40), 117(100), 115(57).

3-Methoxy-1-phenyl-3-trimethylsilyl-1-propanone (**7e**). Compound **7e** was obtained in 62 % yield as an oily substance. Anal. $C_{13}H_{26}O_2Si$: C, H. ^{1}H–NMR ($CDCl_3$): δ 0.00 (TMS), 2.80 (1H, CH_2CH, dd, *J* 16.5, 3.5 Hz) and 3.24 (1H, CH_2CH, dd, *J* 16.5, 9.5 Hz), 3.21 (OMe), 3.54 (*CH*CH_2, dd, *J* 9.5, 3.5 Hz), 7.3–7.9 (Ph). ^{13}C–NMR ($CDCl_3$): δ 3.6 (TMS), 47.3 (CH_2), 67.3 (OMe), 79.1 (CH), 135.2, 135.5, 139.9, 144.4 (Ph), 207.1 (CO). MS: 336(1,*M*), 193(39), 177(16), 105(100), 77(47), 73(88).

4-Methoxy-4-trimethylsilyl-1-phenyl-2-butanone (**7f**). Compound **7f** was obtained in 66 % yield as an oily substance. ^{1}H–NMR ($CDCl_3$): δ 0.00 (TMS), 2.44 (1H, CH_2CH, dd, *J* 16.5, 3.5 Hz) and 2.74 (1H, CH_2CH, dd, *J* 16.5, 9.5 Hz) (CH_2CH), 3.28 (OMe), 3.42 (*CH*CH_2, dd, *J* 9.5, 3.5 Hz), 3.75 (CH_2Ph), 7.2–7.3 (Ph). ^{13}C–NMR ($CDCl_3$): δ 3.8 (TMS), 51.0 (CH_2CH), 58.3 (CH_2Ph), 67.6 (Me), 79.0 (CH), 134.4, 136.1,

136.9, 141.6 (Ph), 215.4 (CO). MS(CI): 251(100, $M+1$), 235(56), 219(61), 131(4), 119(16).

General procedure for the preparation of ethenylsilanes (**8**). A solution of sodium trimethylsilanoate (0.4 mmol) in dry dichloromethane (5 ml) was added dropwise with stirring under N_2 to a solution of the 2-methoxy-2-trimethylsilylethyl ketone **7** (1.3 mmol) in dry dichloromethane (5 ml) at 0 °C. The solution was stirred for 1 h at 0 °C and then washed with water; the dried ($MgSO_4$) solution was evaporated at reduced pressure and the residual material subjected to flash chromatography on silica gel using hexane/EtOAc (6:1 *v/v*).

(E)-*4-Methyl-3-oxo-1-trimethylsilyl-1-pentene* (**8a**). Compound **8a** was obtained in 77 % yield as an oily substance. Found: C 62.86; H 10.60. Calc. for $C_9H_{18}OSi$: C 63.47; H 10.65. ^{1}H–NMR ($CDCl_3$): δ 0.07 (TMS), 1.04 (2×CH_3, d, J 7 Hz), 2.87 (m, CHC=O), 6.47 and 7.04 (CH=CH, d, J 20 Hz). ^{13}C–NMR ($CDCl_3$): δ 1.8 (TMS), 22.0 (2×CH3), 41.2 (CH), 143.8 and 149.7 (CH=CH), 206.6 (C=O). MS(CI): 171(27, $M+1$); 155(34); 127(21); 75(100); 73(41).

(E)-*1-Trimethylsilyl-3-oxo-1-octene* (**8b**).[11] Compound **8b** was obtained in 93 % yield as an oily substance. Anal. $C_{11}H_{22}OSi$: C,H. ^{1}H–NMR ($CDCl_3$): δ0.09 (TMS), 0.84 and 1.2–1.6 (Bu), 2.54 (CH_2CO), 6.42 and 7.00 (CH=CH, d, J 20 Hz). ^{13}C–NMR ($CDCl_3$): δ 2.0 (TMS), 17.7, 26.3, 27.7, 35.3 (Bu), 43.3 (CH_2CO), 146.2 and 150.1 (CH=CH), 204.5 (CO). MS: 198(1,M), 183(15), 127(78), 99(32), 73(100).

(E)-*3-Oxo-3-phenyl-1-trimethylsilyl-1-propene* (**8e**).[8] Compound **8e** was obtained in 76 % yield as an oily substance. ^{1}H–NMR ($CDCl_3$): δ 0.09 (TMS), 7.18 and 7.20 (CH=CH, d, J 19 Hz), 7.3–7.9 (Ph). ^{13}C–NMR ($CDCl_3$): δ 1.9 (TMS), 132.2 (CH), 132.4 (CH), 136.4 (CH), 141.2 (C), 141.7 (CH), 153.3 (CH), 194.1 (CO).

(E)-*3-oxo-4-phenyl-1-trimethylsilyl-1-butene* (**8f**).[12] Compound **8f** was obtained in 60 % yield as an oily substance. ^{1}H–NMR ($CDCl_3$): δ 0.09 (TMS), 3.94 (CH_2), 6.64 and 7.30 (CH=CH, d, J 20 Hz), 7.3–7.5 (Ph). ^{13}C–NMR ($CDCl_3$): δ 2.0 (TMS), 50.5 (CH_2), 130.7 (CH), 132.5 (CH), 133.3 (CH), 138.2 (C), 145.3 (CH), 151.7 (CH), 201.0 (CO).

Preparation of methyl (E)-*4-oxo-6-trimethylsilyl-5-hexenoate* (**8d**) *without isolation of the intermediate* **7d**. Methyl 4-oxo-5-trimethylsilylpentanoate[6] (291 mg, 1.44 mmol), zinc bromide (14 mg, 0.06 mmol) and chloro(methoxy)methyltrimethylsilane (106 mg, 0.72 mmol) were dissolved in dry dichloromethane (3 ml) under N_2 at 0 °C. The mixture was allowed to reach ambient temperature and stirred for 20 h. The solution was diluted with ether and shaken wih aqueous saturated $NaHCO_3$, and the dried ($MgSO_4$) solution evaporated. The residue, which was the crude compound **7d**, was dissolved in dichloromethane (5 ml) and sodium trimethylsilanoate (24 mg, 0.21 mmol) was added with stirring under N_2 at 0 °C. The stirring at 0 °C was continued for 2 h, and the solution was diluted with diethyl ether and washed with brine. The dried ($MgSO_4$) solution was evaporated and the product purified by flash chromatography on silica gel using hexane/EtOAc (200:35 *v/v*); yield 85 mg (55 %) of an oily substance. Analysis by GLC (SP2100, 160 °C isotherm.) > 97 % pure. ^{1}H–NMR ($CDCl_3$): δ 0.10 (TMS), 2.5–3.1 (2×CH2), 3.59 (OMe), 6.38 and 7.07 (CH=CH, d, J 19 Hz). MS(CI): 215(100, $M+1$), 199(15), 184(10), 183(68).

(E)-*1-Cyclohexyl-3-trimethylsilyl-2-propen-1-one* (**8c**). Compound **8c** was obtained as above from cyclohexyl trimethylsilylmethyl ketone and compound **3a**, without isolation of the intermediate **7c**. The product was purified by flash chromatography on silica gel using hexane/EtOAc (30:1 (*v/v*); yield 68 % of an oily substance. Anal. $C_{12}H_{22}OSi$: C,H. ^{1}H–NMR ($CDCl_3$): δ 0.11 (TMS), 0.8–2.4 (cyclohex.), 6.46 and 7.08 (CH=CH, d, J 19 Hz). MS: 210(1,M), 183(3), 137(4), 127(54), 99(19), 73(100).

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