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TRANSFORMATION OF α-ASSISTED CARBANIONS INTO THE CORRESPONDING TRIMETHYLSILOXY DERIVATIVES USING BIS(TRIMETHYLSILYL) PEROXIDE

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Summary: The reaction of bis(trimethylsilyl)peroxide with lithium derivatives of sulphides and nitriles is reported to give the corresponding O-trimethylsilyl hemithioacetals and cyanohydrins. From these products the carbonyl function can be exposed in acidic media or in the presence of fluoride ions. This methodology provides an attractive route to transform a CH_2-X group (X = PhS, MeS or CN) into the corresponding CHO, allowing the preparation of aldehydes that can be considered difficult to prepare such as, for example, formyltrimethylsilane which was generated and trapped in situ using a Wittig reaction.

In the recent literature, several reports have been focused upon the synthesis of O-trimethylsilyl hemithioacetals and ketals. A possible drawback to the synthetic utility of these compounds, however, stems from the fact that for their preparation, carbonyl derivatives[1,2] are often needed as starting materials. An alternative approach to the synthesis of siloxythioacetals from silylated sulphides uses the sila-Pummerer rearrangement[3-5] as the key step involving the sulphinyl functionality from the oxidation of alkylthio- or phenylthio-trimethylsilylalkanes. This reaction can be sometimes subject to stereo- and electronic effects and therefore, in some cases, vinylsulphides become[6] the main products of the final hydrolytic pathway.

As part of our current interest[7-9] in the synthetic uses of bis(trimethylsilyl)peroxide as an oxysilylating reagent of electron rich systems, we wish to report here a quite general and simple new route to siloxy derivatives **2** bearing groups such as RS (R= Me,Ph) or CN, bonded to the central C atom starting from sulphides and nitriles **1**.

The overall reaction sequence, is shown in the following scheme and the relevant results are summarized in Table 1.

R = Ph, PhS, Me_3Si, t–$BuMe_2Si$

X = PhS, MeS, CN

Table 1. Distribution of the products formed in the reaction of compounds **1a-h** with BuLi followed by bis(trimethylsilyl)peroxide.

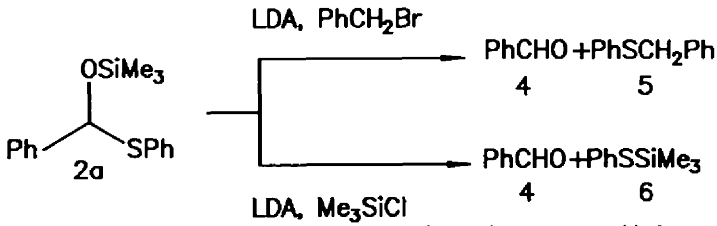
Starting material 1	R	X	Products[a] 2,3 (Yields [b, d])
1a	Ph	SPh	**2a** (70)[b,e] + **3a** (5)[c]
1b	Me_3Si	SPh	**2b** (45)[b]
1c	PhS	SPh	**3c** (20)[b]
1d	*t*-$BuMe_2Si$	SPh	**2d** (45)[d]
1e	Ph	SMe	**2e** (45)[b] + **3e** (30)[c]
1f	Me_3Si	SMe	**2f** (75)[b] + **3f** (5)[c]
1g	Ph	CN	**2g** (35)[b] + **3g** (5)[c]
1h	Me_3Si	CN	**2h** (48)[b] + **3h** (5)[c]

[a] All products gave mass spectra and NMR spectra consistent with the assigned structures (see Experimental section). [b] Yields are of isolated products and are not optimized. [c] GC yields. [d] Yields based on reacted starting material **1**. [e] Traces of PhCHO, were found in the GC/MS analysis of the crude.

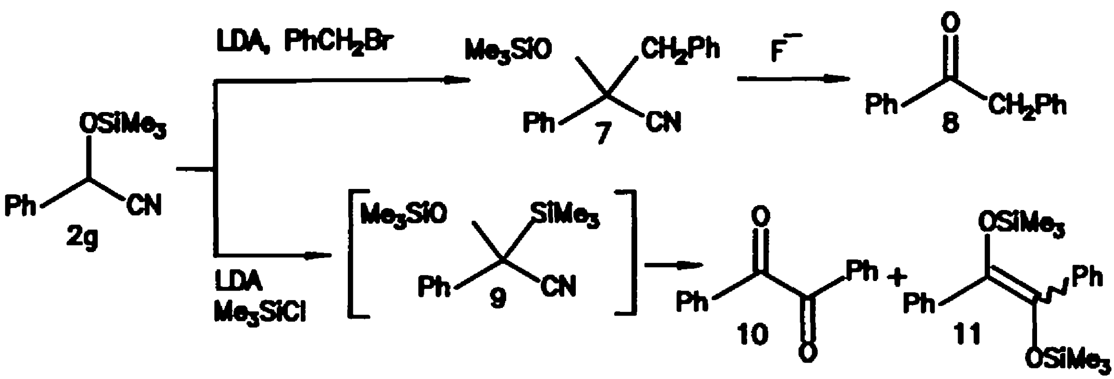
In almost all cases the oxysilylated derivatives **2** were obtained in satisfactory isolated yields; the competing silylation reaction previously noticed[8], has been observed to be, with very few exceptions of very minor importance; only in the case of the bis(phenylthio)methane **1c** the oxysilylation failed completely, and the reaction product recovered, in agreement with previous findings[8], was the silylated derivative **3c**.

The syn α-elimination from organosilanes in which the silicon is bonded to a second row element (O,S,Se) and the carbon atom bears a good leaving group (SPh, CN, Br), known to provide a useful route to the synthesis of carbonyl derivatives, was performed to ascertain the synthetic potential of the O-Si derivatives. An insight into the general reactivity of this class of compounds, shows however that their tendency to undergo α-elimination, appears to be closely related to the nature of the groups X and R bonded to the central carbon atom.

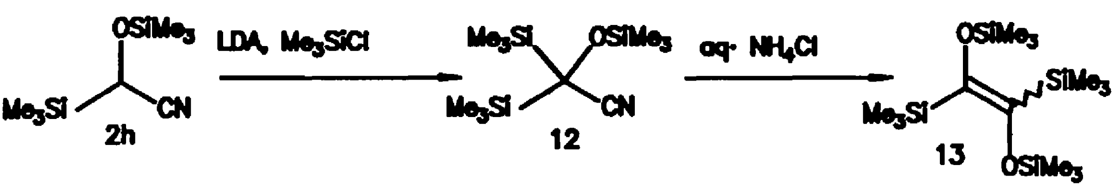
Thus, for example, the exposure of the latent carbonyl functionality in **2a** and **2g** is very easy, the hydrolytic cleavage occurring under very mild conditions on silica and on aqueous NH_4Cl impregnated silica respectively to give PhCHO. Catalytic amounts of HCl (3% ca) are needed, on the other hand, to promote hydrolysis of hemithioacetal **2b** to give the corresponding diphenylthioketal, $(PhS)_2CHSiMe_3$, probably formed via the unstable[10] formyltrimethylsilane intermediate, Me_3SiCHO, whereas treatment of **2h** with 3N HCl, leads to the corresponding cyanohydrine, $Me_3SiCH(OH)CN$, in almost quantitative yield. Again attempts at modifying the structure of the siloxy derivatives by C- functionalisation, upon treatment with LDA, followed by quenching with electrophiles, when performed on **2a**, according to Chan[1], led to



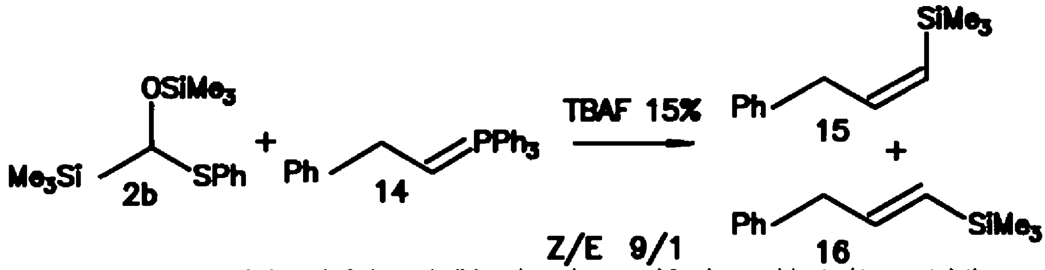
PhCHO as the sole reaction product, whereas the expected reaction occurs with **2g** and **2h** as the starting materials.



Interestingly the C-silylation of these two compounds leads to α-elimination of Me_3SiCN spontaneously (**9**) or in the presence of aqueous NH_4Cl (**12**), the steric crowding most likely providing the driving force for this reaction: the isolation of benzyl **10** and of **11** from **2g** and of **13** from **2h**, provides unambiguous evidence[11] for the formation of benzoyl trimethylsilane and of bis-trimethylsilyl ketone respectively.



Accordingly, when less bulky electrophiles are used, the functionalized product **7** in the nitrile series is stable enough to require fluoride ion treatment in order to expose the latent carbonyl function. To exploit the synthetic equivalency of **2b** to Me_3SiCHO, and in view of the proved low stability[10,12] of this class of compounds under the conditions used for the exposure of the carbonyl function, a key experiment directed to the *in situ* generation and trapping of the α-silylated carbonyl derivative Me_3SiCHO, was performed according to the following scheme.



An equimolar mixture of **2b** and of phenethylidenphosphorane **14**, when subjected to a catalytic amount (15%) of TBAF, led to a Z/E mixture of 1-benzyl-2-trimethylsilyl ethene (**15, 16**) in ca. 50% overall yields, resulting from a Wittig reaction of the ylide with the in situ formed Me_3SiCHO.

The basic concept described in this article, outlines the superiority of this procedure for the introduction of an oxygen functionality starting from sulphides with respect to, for example, the above mentioned Sila-Pummerer reaction, and its uniqueness when nitriles are used as the starting materials. The versatile carbonyl homologation reagents developed from geminally substituted blocks **2** would provide more fruitful synthetic applications which are now being investigated in our laboratory.

EXPERIMENTAL SECTION

^1H nuclear magnetic resonance spectra were measured at 90 MHz on a Varian M-390 spectrometer. Deuterochloroform was used as the solvent. Chemical shifts are reported in ppm (from TMS). Low resolution electron impact (EI) mass spectra, were obtained with a Varian Matt-112S double focusing mass spectrometer operating at 70 eV. The GC analyses were performed using a Varian-3700 gas chromatograph equipped with a 5% phenyl methyl silicone fused silica capillary column.

Flash chromatography was performed on Merck Kieselgel 60 (230-400 mesh).

Solvents were dried and purified by standard methods. All commercial reagents were used without further purification. The bis(trimethylsilyl)peroxide was prepared according to the previously published procedure[7].

General procedure for the preparation of O-trimethylsilylhemithioacetals 2a-f and O- trimethylsilylcyanohydrine 2h. To a sulphide or nitrile solution (15 mmol) in anhydrous diethyl ether (30 ml) at -78° C, a solution of butyllithium (5.3 ml of a 2.5 N solution in hexane, 16 mmol) was added. The mixture turned yellow and lithiation was completed on warming to room temperature and refluxing for 3h. After cooling at -78° C the bis(trimethylsilyl)peroxide (16 mmol in 15 ml of diethyl ether) was added and the reaction was left to reach room temperature overnight. To the crude reaction mixture a saturated aqueous NH_4Cl solution (20 ml) was added, the layers were separated and the organic extracts were washed with water (2 x 20 ml) and dried over sodium sulphate. The solvent was removed in vacuo and the crude products were purified by flash chromatography on silica gel with petroleum ether - benzene (8 - 2) as the eluent and/or by distillation.

Trimethylsiloxy-benzyl-phenylsulphide (2a). This compound was purified by flash chromatography on a silica gel column and distilled (b.p. 125° C/15mmHg);

^{1}H NMR : 0.03 (9H, s, $OSiMe_3$); 6.13 (1H, s, CH); 7.1-7.5 (10H, m, C_6H_5)

MS: 288 (M^+, 12.3); 199 (18.5); 179 (100); 165 (11.2); 149 (14.2); 121 (18.5); 105 (20.0); 91 (50); 77 (31); 75 (73 (96.2).

Trimethylsiloxy-trimethylsilylmethyl-phenylsulphide (2b). This compound was purified by flash chromatography on a silica gel column.

^{1}H NMR : -0.06 (9H, s, $OSiMe_3$); 0.1 (9H, s, $SiMe_3$); 4.93 (1H, s, CH); 7.1- 7.5 (5H, m,C_6H_5)

MS: 284 (M^+, 1.8); 240 (2.8); 224 (4.4); 207 (2.1); 174 (19.5); 167 (5.0); 146 (100); 132 (14.0); 121 (2.4); 109 (3.1); 91 (4.1); 73 (71.2)

Trimethylsiloxy-*tert*-butyldimethylsilylmethyl-phenylsulphide (2d). This compound was purified by flash chromatography on a silica gel column.

^{1}H NMR : -0.06 (9H, s, $OSiMe_3$); 0.05 (3H, s, Me); 0.1 (3H, s, Me); 1.0 (9H, s, tBu); 5.13 (1H, s, CH); 7.1- 7.45 (5H, m, C_6H_5)

MS: 326 (M^+, 1.1); 268 (3.3); 240 (4.6); 225 (7.2); 217 (11.8); 210 (2.7); 180 (3.5); 166 (3.7); 146 (100); 134 (4.2); 109 (2.5); 90 (6.1); 77 (3.6); 75 (6.9); 73 (77.2).

Trimethylsiloxy-benzyl-methylsulphide (2e). This compound was purified by distillation (b.p. 111-112° C/5mmHg)

^{1}H NMR : 0.16 (9H, s, $OSiMe_3$); 1.96 (3H, s, Me); 5.93 (1H, s, CH); 7.16 - 7.46 (5H, m, Ph)

MS: 226 (M^+, 21.3); 211 (16.5); 179 (43.2); 138 (14.9); 108 (18.8); 105 (37.6); 91 (59.7); 77 (29.1); 75 (46.1); 73 (100).

Trimethylsiloxy-trimethylsilylmethyl-methylsulphide (2f). This compound was purified by flash chromatography on a silica gel column.

^{1}H NMR : 0.15 (9H, s, $OSiMe_3$); 0.21 (9H, s, $SiMe_3$); 2.20 (3H, s, Me); 4.45 (1H, s, CH)

MS: 207 (M^+-15, 20.3); 178 (7.1); 163 (16.3); 147 (30.0); 133 (15.3); 105 (6.6); 91 (2.7); 75 (7.6); 73 (100).

Trimethylsilyl(trimethylsiloxy) acetonitril (2h). This compound was purified by distillation (b.p. 81° C/18mmHg).

^{1}H NMR: 0.183 (9H, s, $OSiMe_3$); 0.188 (9H, s, $SiMe_3$); 3.95 (1H, s, CH)

MS: 201 (M^+, 4.15); 186 (20.0); 158 (4.3); 133 (19.5); 131 (5.9); 117 (1.4); 84 (4.1); 75 (6.0); 73 (100).

Procedure for the preparation of phenyl(trimethylsiloxy)acetonitril. (2g). To a solution of LDA (16 mmol in 20 ml of anhydrous diethyl ether) at -78° C, the solution of phenylacetonitrile (16 mmol) in anhydrous ether (10 ml) was added and the lithiation was completed by leaving the reaction mixture to reach room temperature and refluxing for 40 min. After cooling to -78 C, BTMSPO (16 mmol) was added and **2g** was obtained, with the previously reported workup, by distillation. (b.p. 100-103° C /10 mmHg).

^{1}H NMR: 0.23 (9H, s, $OSiMe_3$); 5.43 (1H, s, CH); 7.36 (5H, m, C_6H_5)

MS: 205 (M^+, 12.1); 189 (25.9); 178 (60.3); 149 (10.3); 131 (19.0); 116 (15.5); (46(46.6); 91 (25.9); 77 (46.6); 75 (24.1); 73 (100).

Metallation of 2h followed by functionalisation with trimethylchlorosilane. To a LDA solution (2.5 mmol in 3 ml of anhydrous ether) at -78° C, **2h** (2,5 mmol) in dry ether (10 ml) was added and the reaction mixture was allowed to reach room temperature and left for 2.5 hr. After cooling to -78 C trimethylchlorosilane (2,5 mmol in 5 ml of dry ether) was added and the mixture was left at room temperature for 2 hr. A work-up with NH_4Cl saturated solution followed by ether extraction gave a product with the following mass fragmentation:

MS: 273 (M^+, 1.4); 272 (4.4); 257 (1.5); 243 (0.5); 203 (2.5); 183 (4.0); 171 (13.0); 146 (6.3); 133 (4.2); 130 (3.3); 101 (9.6); 75 (5.0); 73 (100).

Metallation of 2a followed by functionalisation with electrophiles: To a solution of **2a** (1 mmol) in THF (5 ml) cooled at -70° C, n-BuLi (0.4 ml of a 2.5 N solution, 1 mmol) was added and the reaction mixture left to reach room temperature. After cooling to -78° C the electrophilic species was added:

a) **Quench with benzyl bromide**: GC/MS analysis revealed the presence of $PhCH_2SPh$, PhCHO and PhSSPh.

b) **Quench with trimethylchlorosilane**: the GC/MS analysis revealed the presence of PhCHO, PhSPh and PhSSPh.

Metallation of 2g followed by functionalisation with electrophiles: To a LDA solution (2 mmol in 2 ml of anhydrous ether) at -78° C, **2g** (2 mmol) dissolved in the same solvent (4 ml) was added. The reaction was completed by warming for 2 h; after cooling to -78° C, the electrophilic species was added:

a) **Quench with benzylbromide**: the reaction mixture was allowed to reach room temperature and left 2 hr. MS/GC analysis showed the presence of benzyl phenyl trimethylsiloxy acetonitrile **7**:

MS: 295 (M^+, 0.44); 278 (1.0); 253 (1.20); 2.34 (0.81); 203 (23.4); 178 (4.52); 105 (100); 91 (11.6); 77 (19.32); 75 (9.26); 73 (18.53)

The mixture was subsequently treated with TBAF 1N solution in THF and benzyl phenyl ketone was obtained according to Hunig[13].

MS: 196 (M^+, 2.4); 178 (0.24); 165 (1.68); 152 (0.9); 105 (100); 91 (12.5); 77 (73.0); 65 (12.0); 51 (29.3).

b) **Quench with trimethylchlorosilane**: The reaction mixture was left at room temperature for 2h and by GC/MS analysis benzile **10** was detected. Mass spectrometry showed also the presence of a small amount of (E/Z)- $Ph(Me_3SiO)C=C(OSiMe_3)Ph$ (**11**).

MS: 356 (M^+, 4.23); 281 (11.44); 267 (3.45); 203 (5.80); 178 (28.2); 166 (11.76); 146 (8.31); 105 (100); 97 (8.8); 83 (12.85); 81 (34.8); 77 (38.9); 75 (11.91); 73 (98.6); 69 (80.41).

Wittig type reaction of 2b with phenethylidenphosphorane in the presence of fluoride anion. Triphenyl-phenethyl phosphonium bromide (0.16 gr, 0.35 mmol) was mixed with an equimolar amount of bis-trimethylsilyl sodium amide under argon; after addition of THF (10 ml) at 0° C, a rapid formation of the ylid is shown by the appearence of an orange-yellow colour. After cooling to -30° C, a catalytic amount (15 % ca) of TBAF was added followed by addition of **2b** (0.35 mmol) in THF (1 ml). After 15 min at -30° C, the reaction, warmed to room temperature, was stirred for 3 h, hydrolysed with saturated aqueous NH_4Cl, and the aqueous layer extracted with diethyl ether. After removal of the solvent a mixture (35 mg) containing **15** and **16** in a 9/1 approximate ratio was obtained. GC analysis conditions: heating from 60 to 200 C with a temperature increase of 10C /min, respective RT: 15.1 min and 15.7 min. ^1H NMR (300 MHz) analysis clearly established the structure of compounds **15** and **16.**

^1H NMR **15** : 0.50 (s, 9H, $SiMe_3$); 3.40 (m, 2H, CH_2Ph); 5.63 (dt, 1H, $J_A=14$ Hz, $J_B=1.5$ Hz, $CHSiMe_3$); 6.42 (dt, 1H, $J_A=14$ Hz, $J_B=7.1$ Hz, $CHCH_2$); 7.30 (m, 5H, Ph)

16 : 0.53 (s, 9H, $SiMe_3$); 3.46 (m, 2H, CH_2Ph); 5.72 (dt, 1H, $J_A=18$Hz, $J_B=2$Hz, $CHSiMe_3$); 6.14 (dt, 1H, $J_A=18$ Hz, $J_B=9$ Hz, $CHCH_2$); 7.30 (m, 5H, Ph).

MS: 190 (M^+, 19.5); 175 (77.9); 159 (10.55); 145 (10.09); 122 (9.75); 116 (8.25); 99 (10.42); 91 (21.26); 73 (100).

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