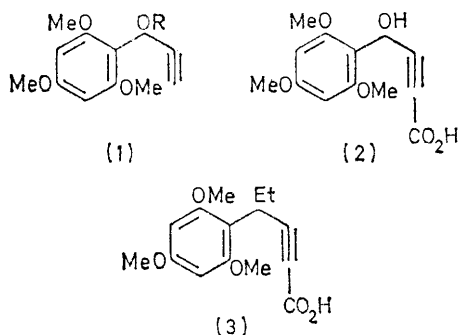


## The Chemistry of Fungi. Part LXXII.<sup>1</sup> The Trimethylsilyloxy-substituent as a Leaving Group

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The trimethylsilyloxy-group formed by trimethylsilylation of various 'activated' alcohols is readily displaced by a variety of nucleophiles, providing *inter alia* new routes to cholest-4-ene and to C-methylated methoxybenzenes.

DURING our investigations concerning a new approach to the grisane system<sup>2</sup> we attempted to improve the solubility parameters in the carboxylation of acetylenes of type (1; R = H) to yield acids, of type (2), by protecting the secondary hydroxylic substituent. Thus, *inter alia*, we readily prepared the trimethylsilyl ether (1; R = SiMe<sub>3</sub>) in high yield. However when subjected to the action of an aliphatic Grignard reagent (to obtain the acetylenic complex), the trimethylsilyloxy-group was



unexpectedly displaced to yield, for example, with ethylmagnesium iodide, and after carboxylation, the acetylene (3). The corresponding displacement does not appear to occur readily with aryl Grignard reagents. Subsequently we have observed that the trimethylsilyloxy-group derived by trimethylsilylation of a variety of 'activated' alcohols is readily displaced by a selection of nucleophiles.

<sup>1</sup> Part LXXI, D. R. Briggs and W. B. Whalley, preceding paper.

<sup>2</sup> M. Ahab, A. D. Borthwick, J. W. Hooper, J. S. Millership, W. B. Whalley, G. Ferguson, and F. C. Marsh, *J.C.S. Perkin I*, 1976, 1369.

Thus reduction with aluminium trichloride-lithium aluminium hydride<sup>3</sup> of the trimethylsilyl ethers of various benzyl alcohols provides an excellent route to the corresponding C-methyl derivatives.

Likewise the allylic alcoholic hydroxy-group of, for example, cholest-4-en-3 $\beta$ -ol is readily displaced, *via* the trimethylsilyl ether, to form cholest-4-ene in high yield; this route is much superior to previous methods.<sup>4</sup>

The silyl ether group may also be displaced by, for example, malonate ion to yield, from benzyl alcohols, the corresponding benzyl malonate (and hence the  $\beta$ -phenylpropionic acid), and by alkyl groups (from alkyl Grignard reagents) to yield alkylbenzenes.

In addition to their implications in synthetic chemistry, our observations constitute a warning about possible complications when the trimethylsilyl ether is used as a protective grouping.

### EXPERIMENTAL

*Method of Silylation.*—This is a modification of that described by Sweeley *et al.*<sup>5</sup> The alcohol (1 g) dissolved in pyridine (5–10 ml) was treated with a mixture of hexamethyldisilazane (4 ml) and chlorotrimethylsilane (2 ml). After 1 h the excess of reagents was removed *in vacuo*. Pyridine (5 ml) was then added to the residue and the resultant suspension was clarified by filtration to remove ammonium chloride. Evaporation furnished the trimethylsilyl ether (usually as a crystalline solid) in almost quantitative yield.

<sup>3</sup> R. B. Brown and A. M. S. White, *J. Chem. Soc.*, 1957, 3755.

<sup>4</sup> H. Hauptmann, *J. Amer. Chem. Soc.*, 1947, **69**, 562; A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1957, 1969.

<sup>5</sup> C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, 1963, **85**, 2497.

1-(2,4,6-Trimethoxyphenyl)prop-2-yn-1-ol.—A solution of 2,4,6-trimethoxybenzaldehyde (6 g) in tetrahydrofuran (200 ml) and ether (200 ml) was added to a suspension of sodium acetylide [from sodium (1.5 g)] in liquid ammonia (250 ml). The mixture was refluxed for 2.5 h, and the ammonia was then allowed to evaporate. Next day, the product was isolated (after acidification of the residue with an excess of 2*N*-sulphuric acid) by extraction with ethyl acetate to yield 1-(2,4,6-trimethoxyphenyl)prop-2-yn-1-ol (6 g), which formed needles, m.p. 122° (from ethyl acetate) (Found: C, 64.9; H, 6.2.  $C_{12}H_{14}O_4$  requires C, 64.9; H, 6.4%),  $\nu_{\max}$  3 450 (OH) and 3 255  $cm^{-1}$  (C:C-H). Prepared quantitatively the trimethylsilyl ether formed a microcrystalline solid, m.p. 83–85° (Found: C, 61.4; H, 7.5.  $C_{15}H_{22}O_4Si$  requires C, 61.2; H, 7.5%),  $\nu_{\max}$  3 310  $cm^{-1}$  (C:C-H),  $\tau$  4.10 (2 H, s, ArH), 4.24br (1 H, s), 6.23 (6 H, s, 2 OMe), 6.40 (3 H, s, OMe), 7.93 (1 H, s), and 9.90 (9 H, s, SiMe<sub>3</sub>).

A solution of this silyl ether (0.3 g) in tetrahydrofuran (30 ml) was added to a solution of ethylmagnesium bromide [from ethyl bromide (2 g) and magnesium (0.6 g)] in ether (20 ml). The solution was refluxed for 0.5 h and cooled, and an excess of crushed solid CO<sub>2</sub> was added. Next day the product was isolated and esterified with diazomethane to yield an oil which was purified by t.l.c. to yield methyl 4-(2,4,6-trimethoxyphenyl)hex-2-ynoate (0.2 g) as an oil (Found: C, 66.3; H, 6.8.  $C_{16}H_{20}O_5$  requires C, 65.8; H, 6.8%),  $\nu_{\max}$  1 715  $cm^{-1}$  (ester),  $\tau$  3.95 (2 H, s, ArH), 4.15 (1 H, t, ArCH), 3.66 (3 H, s, OMe), 3.74 (3 H, s, OMe), 3.70 (6 H, s, 2 OMe), 8.18 (2 H, m, CH<sub>3</sub>·CH<sub>2</sub>), and 9.02 (3 H, t, CH<sub>3</sub>·CH<sub>2</sub>).

Reactions of Trimethylsilyl Ethers of Benzyl Alcohols.—(a) Reduction of the trimethylsilyl ethers listed in the Table

ArCH <sub>2</sub> OH	Benzyl silyl ethers		Formula	Reqd. (%)	
	Found (%)			C H	
Ar = Ph	66.6	9.1	C <sub>10</sub> H <sub>16</sub> OSi	66.7	8.9
2,4,6-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	58.0	8.3	C <sub>13</sub> H <sub>22</sub> O <sub>4</sub> Si	57.7	8.2
3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	60.3	7.7	C <sub>12</sub> H <sub>18</sub> O <sub>3</sub> Si	60.1	7.6
3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	58.6	7.1	C <sub>11</sub> H <sub>16</sub> O <sub>3</sub> Si	58.5	7.2
3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	57.5	8.2	C <sub>12</sub> H <sub>22</sub> O <sub>4</sub> Si	57.7	8.2

with lithium aluminium hydride–aluminium trichloride proceeded rapidly at room temperature to furnish the cor-

<sup>6</sup> K. Aghoramurthy, M. G. Sarngadharan, and T. R. Seshadri, *J. Indian Chem. Soc.*, 1962, **39**, 439.

responding methylbenzenes in quantitative yield, identical with authentic specimens.

(b) A mixture of 2,4,6-trimethoxybenzyl trimethylsilyl ether (1.5 g) and ethylmagnesium bromide [from magnesium (0.2 g) and ethyl bromide (1 g) in ether (90 ml)] was refluxed for 30 min. After purification on silica, 1,3,5-trimethoxy-2-propylbenzene (0.7 g) had m.p. 47° (lit.,<sup>6</sup> 46–47°),  $\tau$  4.09 (2 H, s, ArH), 5.30 (9 H, s, 3 OMe), 7.58 (2 H, t, CH<sub>2</sub>·CH<sub>2</sub>·CH<sub>3</sub>), 8.20 (2 H, m, CH<sub>2</sub>·CH<sub>2</sub>·CH<sub>3</sub>), and 9.18 (3 H, t, CH<sub>2</sub>·CH<sub>2</sub>·CH<sub>3</sub>). Similarly *p*-methoxybenzyl alcohol gave 1-methoxy-4-propylbenzene (50% yield), identical (n.m.r., t.l.c.) with an authentic sample.

(c) A mixture of 2,4,6-trimethoxybenzyl trimethylsilyl ether (1 g), sodium hydride (0.1 g), and diethyl malonate (2 ml) was heated at 100 °C during 12 h, to yield diethyl 2,4,6-trimethoxybenzylmalonate (0.5 g) in needles, m.p. 67° [from light petroleum (b.p. 40–60°)] (Found: C, 59.8; H, 7.3.  $C_{17}H_{24}O_7$  requires C, 60.0; H, 7.1%),  $\tau$  3.90 (2 H, s, Ar), 5.86 (2 H, q, ArCH<sub>2</sub>), 6.22 [1 H, partially obscured, CH(CO<sub>2</sub>·Et)<sub>2</sub>], 6.25 (9 H, s, 3 OMe), 6.80 (4 H, m, 2 CO<sub>2</sub>·CH<sub>2</sub>·CH<sub>3</sub>), and 8.81 (6 H, t, 2 CO<sub>2</sub>·CH<sub>2</sub>·CH<sub>3</sub>).

Similarly 3,4,5-trimethoxybenzyl trimethylsilyl ether gave diethyl 3,4,5-trimethoxybenzylmalonate (40%), m.p. 76° (lit.,<sup>7</sup> 78–79°).

Preparation of Cholest-4-ene.—The trimethylsilyl ether (1.2 g) of cholest-4-en-3 $\beta$ -ol (1.0 g) formed waxy needles, m.p. 83–86° (Found: C, 78.3; H, 11.9.  $C_{30}H_{54}OSi$  requires C, 78.6; H, 11.8%). Reduction of this ether (1.2 g) with lithium aluminium hydride (0.18 g) and aluminium trichloride (1.25 g) in ether (15 ml) during 30 min gave cholest-4-ene (0.8 g) in needles, m.p. 79° (from ethanol–acetone) (lit.,<sup>4</sup> 82–83.5°) (Found: C, 87.6; H, 12.6. Calc. for C<sub>27</sub>H<sub>46</sub>: C, 87.5; H, 12.5%),  $[\alpha]_D^{25} + 71^\circ$  (*c* 10 in CHCl<sub>3</sub>) (lit.,<sup>4</sup> +76°),  $\tau$  4.67 (1 H, m, C-4 proton). The isomeric cholest-5-ene<sup>8</sup> has m.p. 92.5–94°,  $[\alpha]_D - 56^\circ$ .

This work was carried out during the tenure of a Teaching Fellowship (to J. S. M.) at The School of Pharmacy.

[5/2269 Received, 19th November, 1975]

<sup>7</sup> K. I. H. Williams, S. E. Cremer, F. W. Kent, E. J. Sehm, and D. S. Torbell, *J. Amer. Chem. Soc.*, 1960, **82**, 3982.

<sup>8</sup> L. F. Fieser and H. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 253.