Carbohydrate Research, 115 (1983) 234–239
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

A general method for selective silylation of primary hydroxyl groups in carbohydrates and related compounds

KELVIN K. OGILVIE AND GHOLAM H. HAKIMELAHI
Department of Chemistry, McGill University, Montreal H3A 2K6 (Canada)

(Received April 19th, 1982; accepted for publication, July 15th, 1982)

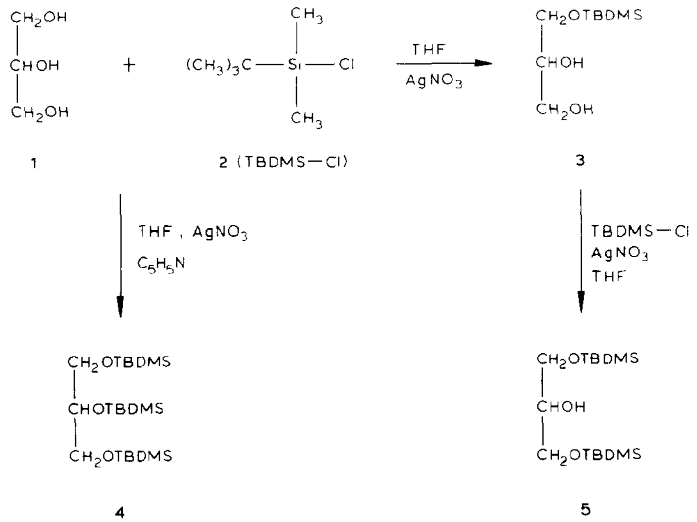
This work shows that primary hydroxyl groups may be selectively silylated with *tert*-butyldimethylsilyl chloride in tetrahydrofuran by using silver nitrate as catalyst. Addition of pyridine to the system causes quantitative silylation of both primary and secondary hydroxyl groups. Silver perchlorate is equally good as a catalyst, whereas tetrabutylammonium nitrate and tetrabutylammonium perchlorate are effective only in the presence of pyridine and do not effect selective reactions.

The selective protection of primary hydroxyl groups in the presence of secondary hydroxyl groups is an important synthetic capability. Numerous protecting groups have been evaluated in this regard, with varying degrees of success[1-3]. In particular, alkylsilyl protecting groups are widely used in synthetic chemistry[4-10]. Specific applications have arisen in the protection of glycerol for the preparation of phospholipids[11,12], in the protection of carbohydrates[13], and in the protection of hydroxyl groups in nucleosides[6-8]. This report describes a general method for the highly selective silylation of primary hydroxyl groups in the presence of secondary hydroxyl groups. Glycerol (**1**), 1,2-*O*-isopropylidene-α-D-glucofuranose (**7**), and 1,2-*O*-isopropylidene-α-D-xylofuranose (**10**) are used as model compounds.

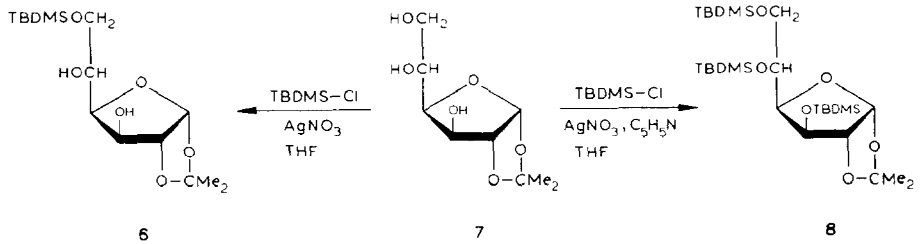
The procedure described arises out of our recently reported procedures for the selective 2′-*O*-silylation[14a] or 3′-*O*-silylation[14b] of ribonucleosides. We described in those reports the pronounced effect of silver nitrate on silylation. Specifically, in the presence of pyridine, silver nitrate catalyzed silylation principally at O-5′ and O-2′ of ribonucleosides. However, silylation occurred exclusively at O-5′ in the absence of pyridine. This has been found to be a general result.

Thus treatment of glycerol (**1**) with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and silver nitrate in oxolane (tetrahydrofuran, THF) gave an 80% isolated yield of the monosilylated glycerol **3**. Separate treatment of **3** with TBDMS-Cl and silver nitrate in THF converted it in 90% yield into the 1,3-di-*O*-(TBDMS)-glycerol (**5**). However, when glycerol is treated with TBDMS-Cl and silver nitrate in THF containing pyridine, a quantitative yield of the triether **4** is obtained.

0008-6215/83/$ 03.00



These conditions were extended to 1,2-*O*-isopropylidene-α-D-glucofuranose (**7**) and 1,2-*O*-isopropylidene-D-xylofuranose (**10**). Compound **7** was selectively silylated at O-6 to give **6** in 94% yield by using TBDMS-Cl and silver nitrate in THF in the absence of pyridine. Under the same conditions, **10** was converted into its 5-TBDMS ether **9** in 96% yield. Both **7** and **10** were fully silylated to **8** and **11**, respectively, in quantitative yields when pyridine was present.



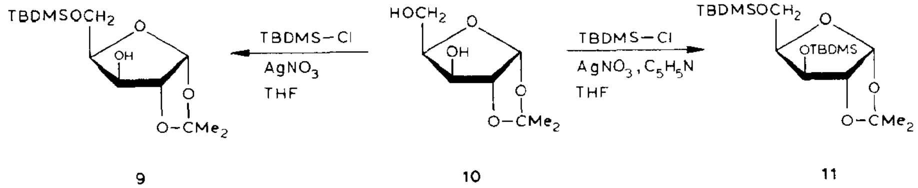


Table I summarizes the results of varying the reaction conditions. It is clear that silver nitrate and silver perchlorate are both very effective catalysts for selective silylation at primary hydroxyl groups. The addition of pyridine causes complete

TABLE I

EFFECTS OF VARIED REACTION CONDITIONS

Compound	*TBDMS-Cl (mmol)*	*Salt (mmol)*	*Base (mmol)*	*Products*[a]
1	3	Bu_4NNO_3 (4)	C_5H_5N (15)	**4** (90%)
1	3	Bu_4NClO_4(4)	C_5H_5N (15)	**4** (90%)
1	3	Bu_4NNO_3 (4)		No reaction
1	3			No reaction
1	3		C_5H_5N (15)	**3** (5%)
1	1.5	$AgClO_4$ (1.5)		**3** (75%)
1	1.5	$AgNO_3$ (2)		**3** (80%)
1[b]	1.2	$AgNO_3$ (1.1)	C_5H_5N (5)	**1**, **3**, **4**, and **5**
7	1.5	$AgClO_4$ (1.5)		**9** (85%)
7	1.5	$AgNO_3$ (2)		**9** (94%)
7[b]	1.2	$AgNO_3$ (1.1)	C_5H_5N (5)	**9**, **10**, and **11**
7	2	Bu_4NO_3 (3)		No reaction

[a] Reaction conditions were the same as those described in detail in the experimental section (THF as solvent, 10-h reaction period). [b] Mixtures of all compounds indicated were obtained in these cases.

silylation and eliminates any selectivity. Silver ion is apparently important in the selective reactions, as tetrabutylammonium nitrate and perchlorate do not cause silylation in the absence of pyridine. However, in the presence of pyridine, these latter reagents permit complete silylation but do not allow selective reaction to occur.

EXPERIMENTAL

General procedures. — All solvents used were freshly distilled. T.l.c. data were recorded from Kieselgel 60F 254 analytical sheets (BDH). Proton n.m.r. spectra were recorded with a Varian T 60A spectrophotometer. ^{13}C Spectra were recorded on Bruker WH90 and WH400 instruments. Column chromatography was performed with silica gel 60 (Merck, 230–400 mesh) in 3-cm diameter columns. Products were obtained on evaporation of the eluting solvent under diminished pressure. Elemental analyses were performed by Canadian Microanalytical Service, Vancouver, B.C. Silver nitrate was used as a fine powder.

1-O-tert-*Butyldimethylsilylglycerol* (**3**). — Glycerol (0.92 g, 10 mmol) was suspended in THF (25 mL) and TBDMS-Cl (3.02 g, 20 mmol) was added, followed by silver nitrate (3.4 g, 20 mmol). The mixture was stirred for 10 h at 25° and then filtered. The filtrate was diluted with water (50 mL) and then extracted with chloroform (50 mL). The chloroform was evaporated and the residue applied to a column of silica gel (20 g), which was eluted successively with dichloromethane (200 mL), chloroform (200 mL), and ethyl acetate. The product was eluted in the first 100 mL of effluent. Evaporation of the solvent left compound **3** as an oil in 80% yield; R_F (t.l.c., iodine stain) 0.41 in ethyl acetate; n.m.r. ($CDCl_3$): δ 0.16 [s, 6H, $Si(CH_3)_2$], 0.99 [s, 9H, $C(CH_3)_3$], 3.11–3.39 (b, 2H, 2OH, exchangeable with D_2O), and 3.61 (b, 5H, $-CH_2CHCH_2-$); ^{13}C-n.m.r. (acetone-d_6, 29.799 p.p.m.): δ 73.065 (CHOH), 65.188 ($CH_2OTBDMS$), 64.056 (CH_2OH), 26.185 (3× CH_3), 18.686 (Si-C), and −5.265 [$Si(CH_3)_2$]; m/z (electron impact) 175 (M^+ $-CH_2OH$), 149 [M^+ $-C(CH_3)_3$], 131 (M^+ −TBDMS); m/z (chemical ionization) 207 (M^+ +H, 100%).

Anal. Calc. for $C_9H_{22}O_3Si$: C, 52.38; H, 10.74. Found: C, 52.03; H, 10.86.

*1,3-Di-*O*-tert-butyldimethylsilylglycerol* (**5**). — Compound **3** (2.06 g, 10 mmol) was dissolved in THF (30 mL). TBDMS-Cl (1.51 g, 10 mmol) was added, followed by silver nitrate (1.7 g, 10 mmol), and the mixture was stirred for 5 h at 25°. The mixture was filtered and the filtrate diluted with 50 mL of water. The aqueous solution was extracted with chloroform, dried (magnesium sulfate), and evaporated. The oily residue was chromatographed on silica gel (30 g) with dichloromethane (100 mL) followed by 9:1 dichloromethane–chloroform, which eluted the product **5** (2.9 g, 90%); R_F (t.l.c., iodine) 0.67 in ethyl acetate; n.m.r. ($CDCl_3$): δ 0.18 [s, 12H, 2 × $Si(CH_3)_2$], 1.01 [s, 18H, 2 × $C(CH_3)_3$], 2.51–2.62 (b, 1H, OH, exchangeable with D_2O), and 3.62–3.73 (m, 5H, $-CH_2CHCH_2-$); ^{13}C-n.m.r.: (acetone-d_6, 29.799 p.p.m.): δ 73.011 (CHOH), 64.757 (2 × $CH_2OTBDMS$), 26.239 (6 × CH_3), 18.794 (2 × Si-C), and −5.211 [2 × $Si(CH_3)_2$]; m/z (electron impact) 263 [M^+ $-C(CH_3)_3$], 189 (M^+ −OTBDMS), 175 (M^+ $-CH_2OTBDMS$), and 131 (OTBDMS); m/z (chemical ionization) 321 (M^+ +H).

*1,2,3-Tri-*O*-tert-butyldimethylsilylglycerol.* — Glycerol (**1** 0.92 g, 1 mmol) was suspended in THF (25 mL). Pyridine (8 g, 0.1 mole), TBDMS-Cl (6.04 g, 40 mmol), and silver nitrate (6.8 g, 40 mmol) were added in that order and the mixture was stirred for 10 h at 25°. The mixture was filtered and the filtrate diluted with 5% aqueous hydrochloric acid (50 mL). The aqueous solution was extracted with chloroform, and the extract dried and evaporated. The residue was applied to a column of silica gel (35 g) that was eluted with dichloromethane. The product **4** (96%) was obtained as a white solid, m.p. 53–54°, R_F (t.l.c. iodine), 0.96 in ethyl acetate; n.m.r. ($CDCl_3$): δ 0.19 [2s, 18H, 3 × $Si(CH_3)_2$], 1.00 [s, 27H, 3 × $C(CH_3)_3$], and 3.52–3.79 (m, 5H, $-CH_2CHCH_2-$); ^{13}C-n.m.r. (acetone-d_6, 29.799 p.p.m.): δ 75.169 (CHOTBDMS), 65.404 (2 × $CH_2OTBDMS$), 26.347 (9 × CH_3), 18.794 (2 × Si-C), 18.633 (Si-C), −4.240 ($Si(CH_3)_2$), and −5.103 [2 × $Si(CH_3)_2$]; m/z (electron impact) 377 [M^+ $-C(CH_3)_3$], and 289 (M^+ $-CH_2OTBDMS$); m/z (chemical ionization) 320 (M^+ +H−TBDMS), and 289 (M^+ $-CH_2OTBDMS$).

Anal. Calc. for $C_{21}H_{50}O_3Si_3$: C, 57.10; H, 11.59. Found: C, 57.22; H, 11.58.

*Silylation of 1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**7**). — A. *Monosilylation.* This reaction was performed as for the preparation of **3**, except that the ratio of silver nitrate:TBDMS-Cl: **7** was 1.4:1.5:1.0. The product was isolated by silica gel chromatography with ethyl acetate. The 6-*O*-monosilyl derivative **6** was obtained in 94% yield: m.p. 62–63°; R_F 0.30 (chloroform); ^{13}C-n.m.r. (acetone-d_6,29.799 p.p.m.): δ 105.7 (C-1), 86.1 (C-2), 75.4 (C-3), 80.6 (C-4), 70.3 (C-5), 65.8 (C-6), 111.5 (C-7), 27.1 (C-8), 26.5 (C-9), 26.2 [$(CH_3)_3$], 18.7 (Si-C), −5.2, and −5.3 [$-Si(CH_3)_2$];

m/z (electron impact) 319 (M^+ $-CH_3$), 219 (M^+ −TBDMS), and 203 (M^+ −OTBDMS).

Anal. Calc. for $C_{15}H_{30}O_6Si$: C, 53.86; H, 9.04. Found: C, 53.45, H, 9.44.

B. *Trisilylation.* This reaction was performed as already described for the preparation of **4**. The ratio of reagents was 15:5:5:11 pyridine:silver nitrate:TBDMS-Cl: **7**. The product was isolated by silica gel chromatography with 1:1 ethyl acetate–chloroform. Compound **8** was obtained as an oil in 95% yield: R_F 0.61 (chloroform); ^{13}C-n.m.r. (acetone-d_6, 29.799 p.p.m.): δ 105.4 (C-1), 85.3 (C-2), 76.3 (C-3), 81.0 (C-4), 72.1 (C-5), 65.7 (C-6), 111.5 (C-7), 27.0 (C-8), 26.5 (C-9), 26.4, 26.3, 26.2 [3 × $(CH_3)_3$], 18.9, 18.8, 18.6 (3 × Si-C), −2.6, −3.0, −3.7, −3.9, −4.2, and −4.9 [3 × $Si(CH_3)_2$].

Silylation of 1,2-O-isopropylidene-α-D-xylofuranose (**10**). — A. *Monosilylation.* The procedure was identical to that for **7**. Compound **9** was obtained as an oil in 96% yield; R_F 0.59 (chloroform); ^{13}C-n.m.r. (acetone-d_6, 29.799 p.p.m.): δ 105.5 (C-1), 85.8 (C-2), 75.0 (C-3), 81.0 (C-4), 61.5 (C-5), 111.5 (C-6), 27.0 (C-7), 26.5 (C-8), 25.95 [$(CH_3)_3$], 18.4 (Si-C), −5.4, and −5.5 [$Si(CH_3)_2$], *m/z* (electron impact) 303 (M^+ −1), 289 (M^+ $-CH_3$), 189 (M^+ −TBDMS), 173 (M^+ −OTBDMS).

Anal. Calc. for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27. Found: C, 55.24; H, 9.52.

B. *Disilylation.* The conditions were identical to those used for preparing **8**. The product **11** was isolated as an oil in 96% yield; R_F 0.67 (chloroform); ^{13}C-n.m.r. (acetone-d_6, 29.799 p.p.m.): δ 105.7 (C-1), 86.2 (C-2), 76.3 (C-3), 82.1 (C-4), 61.4 (C-5), 111.8 (C-6), 27.4 (C-7), 26.9 (C-8), 26.5, 26.3 [2 × $(CH_3)_3$], 18.9, 18.7 (2 × Si-C), −4.4, −4.7, −4.8, and −4.9 [2 × $Si(CH_3)_2$], *m/z* (chemical ionization) 403 (M^+ $-CH_3$), 303 (M^+ −TBDMS), and 207 (M^+ −OTBDMS).

ACKNOWLEDGMENT

We gratefully acknowledge financial assistance from NSERC (Canada) and FCAC (Quebec). We also acknowledge the assistance of Dae-Sil Lee with the ^{13}C-spectral assignments.

REFERENCES

1 J. F. W. McOmie (Ed.), *Protective Groups in Organic Chemistry*, Plenum Press, London, 1973
2 H. Kossel and H. Seliger, *Progr. Chem. Org. Nat. Products*, 32 (1975) 298–508
3 T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1981.
4 G. Stork and P. F. Hurdlik, *J. Am. Chem. Soc.*, 90 (1968) 4462–4464.
5 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94 (1972) 6190–6191.
6 (*a*) K. K. Ogilvie, A. L. Schifman, and C. L. Penney, *Can. J. Chem.*, 57 (1979) 2230–2238; (*b*) K. K. Ogilvie, S. L. Beaucage, A. L. Schifman, N. Y. Theriault, and K. L. Sadana, *ibid.*, 56 (1978) 2768–2780.
7 K. K. Ogilvie, S. L. Beaucage, D. W. Entwistle, E. A. Thompson, M. A. Quilliam, and J. B. Westmore, *J. Carbohydr. Nucleos. Nucleot.*, 3 (1976) 197.
8 S. Hanessian and P. Lavallee, *Can. J. Chem.*, 53 (1975) 2975–2977
9 D. J. Ager and I. Fleming, *J. Chem. Res. (S)*, (1977) 6–7.
10 B. M. Trost and C. G. Caldwell, *Tetrahedron Lett.*, 22 (1981) 4999–5002

11 K. Bruzik and M.-D. Tsai, *J. Am. Chem. Soc.*, 104 (1982) 863–865.

12 C. A. A. van Boeckel, J. J. Oltvoort, and J. H. van Boom, *Tetrahedron*, 37 (1981) 3751–3761.

13 C. Chavis, F. Dumont, R. H. Wightman, J. C. Ziegler, and J. L. Imbach, *J. Org. Chem.*, 47 (1982) 202–206.

14 (*a*) G. H. Hakimelahi, Z. A. Proba, and K. K. Ogilvie, *Tetrahedron Lett.*, 22 (1981) 4775–4778; (*b*) *ibid.*, 22 (1981) 5243–5246; (*c*) *Can. J. Chem.*, 60 (1982) 1106–1113.