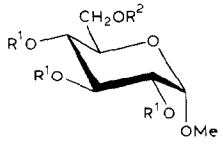
Carbohydrate Research, 138 (1985) 143–147
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Selective acylation of methyl α-D-glucopyranoside at O-6 by reaction with hexachloroacetone and pentachloroacetone

ALAN H. HAINES* AND E. JOHN SUTCLIFFE
School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ (Great Britain)
(Received August 8th, 1984; accepted for publication, September 17th, 1984)

The selective protection of carbohydrates and their derivatives is a subject of continuing interest[1,2] and it has recently assumed increased importance as a result of the current widespread use of carbohydrates as a source of chiral building blocks for the synthesis of natural products[3–5]. Therefore, the report[6] that trichloroacetylation of alcohols by hexachloroacetone, in the presence of strong hydrogen-bond acceptors, is a stereoselective process, which allows, for example, the acylation of 1-propanol in the presence of 2-propanol with 94% selectivity, led us to examine the applicability of this type of reaction in carbohydrate chemistry. We now report on the reaction of methyl α-D-glucopyranoside (**1**) with hexachloroacetone and pentachloroacetone.



1 $R^1 = R^2 = H$
2 $R^1 = R^2 = Ac$
3 $R^1 = Ac, R^2 = COCCl_3$
4 $R^1 = Ac, R^2 = COCHCl_2$
5 $R^1 = Ac, R^2 = H$

Treatment of **1** with 1 mol of hexachloroacetone in *N,N*-dimethylformamide at room temperature for three days, followed by acetylation of the crude product, gave (t.l.c.) two products of similar chromatographic mobility in addition to a considerable proportion of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (**2**). Column chromatography of this mixture afforded methyl 2,3,4-tri-*O*-acetyl-6-*O*-trichloroacetyl-α-D-glucopyranoside (**3**) and methyl 2,3,4-tri-*O*-acetyl-6-*O*-dichloroacetyl-α-D-glucopyranoside (**4**) in a combined molar yield of 43%, and in the

*To whom enquiries should be addressed.

0008-6215/85/$ 03.30

molar ratio 1.7:1. The ^{1}H-n.m.r. spectrum of **4** contained a sharp singlet at δ 5.98 for the dichloroacetyl group, and a signal at 164.1 p.p.m. in the ^{13}C-n.m.r. spectrum is assigned to the carbonyl carbon atom of the dichloroacetyl group. The ^{13}C signal for the related carbon atom in **3** was at 161.1 p.p.m. For methanol, ethanol, 1-propanol, and 2-propanol, resonances of the carbonyl carbon atoms of the chloroacetates, dichloroacetates, and trichloroacetates lie in the ranges 166.7–168.1, 163.8–165.3, and 161.7–162.5 p.p.m., respectively. The identity of **3** and **4** was confirmed through unequivocal synthesis by acylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[7] (**5**) with the appropriate acid chloride or acid anhydride.

Formation of the 6-dichloroacetate **4** in addition to the 6-trichloroacetate **3** was not unexpected in view of the observation[6] that methyl dichloroacetate was a minor product in the reaction of methanol with hexachloroacetone under similar conditions, but the relatively large proportion of **4** formed was surprising. The formation of methyl dichloroacetate was rationalised[6] by the suggestion that the trichloromethyl anion formed in step *1* of the reaction can abstract a positively charged chlorine atom from a hexachloroacetone molecule, affording carbon tetrachloride and a pentachloroacetonide anion (step *2*). Protonation of the latter species then affords pentachloroacetone (step *3*) which, because of the superior leaving-group ability of $^-CCl_3$ compared to that of $^-CHCl_2$, will act as a dichloroacetylating reagent on reaction with an alcohol, through a haloform-type cleavage reaction (step *4*).

$$ROH + Cl_3CCOCCl_3 \rightarrow H^+ + ROCOCCl_3 + {}^-CCl_3 \quad 1$$
$$^-CCl_3 + Cl_3CCOCCl_3 \rightarrow CCl_4 + Cl_2{}^-CCOCCl_3 \quad 2$$
$$Cl_2{}^-CCOCCl_3 + H^+ \rightarrow Cl_2CHCOCCl_3 \quad 3$$
$$ROH + Cl_2CHCOCCl_3 \rightarrow H^+ + ROCOCHCl_2 + {}^-CCl_3 \quad 4$$

In order to avoid the formation of mixed esters, and to take advantage of the seemingly high reactivity and selectivity of pentachloroacetone towards **1**, the latter compound was treated with 2 mol of pentachloroacetone in *N,N*-dimethylformamide. Chromatography of the acetylated product gave 59% of the 6-dichloroacetate **4**.

For the temporary and selective protection of primary alcohol groups in carbohydrates, the trityl group has been used most often, and this group may be selectively removed under acidic conditions or by hydrogenolysis[8,9]. More recently, sterically demanding trialkylsilyl groups have assumed importance for this type of selective protection[9]. Generally, these groups can be removed under acidic or basic conditions, and, more usefully, by fluoride-induced cleavage. The utility of such derivatives as **4** in synthesis requires that the dichloroacetyl group be removed selectively, without concomitant acyl migration. The selective removal of one acyl group in the presence of other acyl groups is a challenging problem[2], although a classic example exists in the selective cleavage of the 2-*O*-acyl group in 3,4,6-tri-*O*-

acetyl-2-*O*-trichloroacetyl-β-D-glucopyranosyl chloride by treatment with ethereal ammonia[10]. Also, the chloroacetyl group has found considerable use in the synthesis of partially acylated sugars, since it can be removed selectively under mild, neutral conditions on treatment with thiourea[2]. However, there are few reports of dichloroacetyl derivatives of carbohydrates[11].

Attempted removal of the dichloroacetyl group in **4** by treatment with thiourea in ethanol or aqueous 70% acetic acid failed. The knowledge that methyl dichloroacetate is hydrolysed under alkaline conditions 16,000 times faster than methyl acetate[12], coupled with a report[13] on the use of the dichloroacetyl group as a protecting group in oligoester synthesis, suggested that hydrolysis with dilute, aqueous base might achieve selective deacylation at O-6 in ester **4**. Treatment of **4** with dilute aqueous ammonia gave methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**5**) in only very low yield, but with ammonia in dry diethyl ether, a reagent which has found application for the selective removal of 2-*O*-trichloroacetyl groups in mono-[10], di-[14,15], and tri-saccharide[16] derivatives, **4** was converted into **5** in 86% yield.

Use of the dichloroacetyl group for the selective protection of primary hydroxyl groups clearly extends the range of options for synthesis. The lability of dichloroacetates towards basic reagents complements the properties of trityl derivatives, which are stable in basic media.

EXPERIMENTAL

N.m.r. spectra were recorded usually for solutions in $CDCl_3$ (internal Me_4Si) with JEOL PMX60SI (^1H, 60 MHz) and FX-100 (^{13}C, 25.05 MHz) spectrometers. Optical rotations were measured at ambient temperature with a Perkin–Elmer 141 polarimeter. Column chromatography was performed on Merck Kieselgel (70–230 mesh), using ethyl acetate–toluene (1:5) as eluent unless stated otherwise. *N,N*-Dimethylformamide was stored over molecular sieves before use and diethyl ether was refluxed over, and distilled from, calcium hydride, and then stored over sodium wire. Routine identifications of compounds were made by comparison of i.r., ^1H-n.m.r., and ^{13}C-n.m.r. spectra, and by determination of m.p.

Reaction of methyl α-D-glucopyranoside (**1**) *with hexachloroacetone in* N,N-*dimethylformamide.* — To a solution of **1** (2 g, 10.3 mmol) in *N,N*-dimethylformamide (50 mL) was added hexachloroacetone (1.56 mL, 2.719 g, 10.3 mmol), and the mixture was stored for 3 days at room temperature and then concentrated under reduced pressure. The residue was treated with acetic anhydride (5 mL) in pyridine (35 mL) for 12 h. The crude product, obtained by concentration of the reaction mixture, contained (t.l.c.) methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (**2**), and two faster running components. Column chromatography of the mixture gave, first, methyl 2,3,4-tri-*O*-acetyl-6-*O*-trichloroacetyl-α-D-glucopyranoside (**3**; 1.3 g, 27%) and, subsequently, methyl 2,3,4-tri-*O*-acetyl-6-*O*-

dichloroacetyl-α-D-glucopyranoside (**4**; 0.71 g, 16%), the physical constants of which were identical with those of the authentic compounds described below.

*Methyl 2,3,4-tri-*O*-acetyl-6-*O*-trichloroacetyl-α-*D*-glucopyranoside* (**3**). — To a solution of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[7] (**5**; 0.35 g, 1.1 mmol) in toluene (10 mL) was added trichloroacetyl chloride (0.198 g, 1.1 mmol) and then pyridine (2 mL). The mixture was stored at room temperature for 2.5 h, poured into water, and extracted with several portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated, and the crude product was purified by column chromatography and crystallised from ethyl acetate–light petroleum to give **3** (0.3 g, 59%), m.p. 97–98°, $[\alpha]_D$ +88° (*c* 0.1, ethanol). N.m.r. data: ^1H, δ 2.02 (s, 3 H, AcO), 2.08 (s, 6 H, 2 AcO), 3.44 (s, 3 H, MeO), 3.84–5.20 (cm, 6 H, H-1,2,4,5,6,6'), 5.52 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3); ^{13}C, δ 20.6, 55.5, 66.8, 67.0, 68.8, 69.9, 70.6, 89.4 (Cl_3C), 96.7 (C-1), 161.6 (Cl_3CCO), 169.4 (CH_3CO), 169.9 (2 CH_3CO).

Anal. Calc. for $C_{15}H_{19}Cl_3O_{10}$: C, 38.7; H, 4.1; Cl, 22.8. Found: C, 38.4; H, 4.1; Cl, 23.0.

*Methyl 2,3,4-tri-*O*-acetyl-6-*O*-dichloroacetyl-α-*D*-glucopyranoside* (**4**). — A solution of **5** (0.3 g, 0.94 mmol) in toluene (10 mL) was treated with dichloroacetic anhydride (0.22 g, 0.92 mmol) and pyridine (2 mL). The mixture was stored for 21 h at room temperature, and then concentrated under reduced pressure. Residual pyridine was removed by co-evaporation with toluene, and the crude product was purified by column chromatography and crystallised from ether–light petroleum to give **4** (0.35 g, 87%), m.p. 65–67°, $[\alpha]_D$ +134° (*c* 0.1, ethanol). N.m.r. data: ^1H, δ 2.00, 2.04, 2.08 (3 s, 9 H, 3 AcO), 3.44 (s, 3 H, MeO), 3.80–5.24 (cm, 6 H, H-1,2,4,5,6,6'), 5.50 (t, 1 H, $J_{2,3} = J_{3,4} = 9$ Hz, H-3), 5.98 (s, 1 H, Cl_2CHCO); ^{13}C, δ 20.6, 55.5, 63.9, 64.9, (Cl_2CHCO), 66.9, 68.7, 69.8, 70.6, 96.7 (C-1), 164.1 (Cl_2CHCO), 169.5 (CH_3CO), 170.0 (2 CH_3CO).

Anal. Calc. for $C_{15}H_{20}Cl_2O_{10}$: C, 41.8; H, 4.7; Cl, 16.4. Found: C, 41.7; H, 4.6; Cl, 16.6.

Reaction of **1** *with pentachloroacetone in* N,N-*dimethylformamide*. — A solution containing **1** (2 g, 10.3 mmol) and pentachloroacetone (2.8 mL, 4.73 g, 20.5 mmol) in *N*,*N*-dimethylformamide was stored at room temperature for 3 days and then concentrated under reduced pressure. The residual syrup was treated with acetic anhydride (5 mL) in pyridine (35 mL) for 3 h, the mixture was concentrated, and the syrupy residue was subjected to column chromatography. The major component was crystallised from ether–light petroleum to give **4** (2.6 g, 59%), m.p. 65–67°.

Selective deacylation of **4**. — Anhydrous ammonia was passed for 5 min through a solution of **4** in dry ether (15 mL) cooled in an ice–salt bath. The solvent was then removed under reduced pressure and the resulting syrup was purified by column chromatography (ethyl acetate–toluene, 2:5). Recrystallisation of the product from ether–light petroleum gave methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**5**; 0.32 g, 86%), m.p. 108–110° (lit.[7] m.p. 108–110°), which had

i.r. and ^{1}H-n.m.r. spectra indistinguishable from those of an authentic sample.

^{13}C-N.m.r. data on chloro-, dichloro-, and trichloro-acetates of methanol, ethanol, 1-propanol, and 2-propanol in $CDCl_3$ solution. — (*a*) *Chloroacetates.* $ClCH_2CO_2Me$ 40.9 (CH_2Cl), 53.2 (CH_3), 168.1 p.p.m. (CO); $ClCH_2CO_2Et$ 14.0 (CH_3), 41.0 (CH_2Cl), 62.3 (CH_2O), 167.5 p.p.m. (CO); $ClCH_2CO_2Pr$ 10.3 (CH_3), 21.9 (CCH_2C), 40.9 (CH_2Cl), 67.7 (CH_2O), 167.3 p.p.m. (CO); $ClCH_2CO_2iPr$ 21.7 (CH_3), 41.2 (CH_2Cl), 70.0 (CH), 166.7 p.p.m. (CO).

(*b*) *Dichloroacetates.* Cl_2CHCO_2Me 54.3 (CH_3), 64.2 ($CHCl_2$), 165.3 p.p.m. (CO); Cl_2CHCO_2Et 13.8 (CH_3), 63.8 (CH_2O), 64.5 ($CHCl_2$), 164.8 p.p.m. (CO); Cl_2CHCO_2Pr 10.1 (CH_3), 21.8 (CCH_2C), 64.4 ($CHCl_2$), 69.0 (CH_2O), 164.6 p.p.m. (CO); Cl_2CHCO_2iPr 21.3 (CH_3), 64.6 ($CHCl_2$), 71.9 (CH), 163.8 p.p.m. (CO).

(*c*) *Trichloroacetates.* Cl_3CCO_2Me 65.6 (CH_3), 89.6 (CCl_3), 162.5 p.p.m. (CO); Cl_3CCO_2Et 13.7 (CH_3), 65.5 (CH_2), 89.9 (CCl_3), 161.8 p.p.m. (CO); Cl_3CCO_2Pr 10.1 (CH_3), 21.7 (CCH_2C), 70.9 (CH_2O), 90.0 (CCl_3), 161.9 p.p.m. (CO); Cl_3CCO_2iPr 21.5 (CH_3), 74.5 (CH), 90.1 (CCl_3), 161.7 p.p.m. (CO).

REFERENCES

1 A. H. HAINES, *Adv. Carbohydr. Chem. Biochem.*, 33 (1976) 11–109.
2 A. H. HAINES, *Adv. Carbohydr. Chem. Biochem.*, 39 (1981) 13–70.
3 A. VASELLA, in R. SCHEFFOLD (Ed.), *Modern Synthetic Methods*, Vol. 2, Salle and Sauerländer, Frankfurt, 1980, pp. 173–267.
4 S. HANESSIAN, *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon, Oxford, 1983.
5 B. FRASER-REID AND R. C. ANDERSON, *Prog. Chem. Org. Nat. Prod.*, 39 (1980) 1–61.
6 R. S. FREEDLANDER, T. A. BRYSON, R. B. DUNLAP, E. M. SCHULMAN, AND C. A. LEWIS, JR., *J. Org. Chem.*, 46 (1981) 3519–3521.
7 D. HORTON AND J. H. LAUTERBACH, *J. Org. Chem.*, 34 (1969) 86–92.
8 B. HELFERICH, *Adv. Carbohydr. Chem.*, 3 (1948) 79–111.
9 T. W. GREENE, *Protective Groups in Organic Synthesis*, Wiley, New York, 1981, ch. 2.
10 P. BRIGL, *Hoppe-Seyler's Z. Physiol. Chem.*, 116 (1921) 1.
11 R. U. LEMIEUX AND G. HUBER, *Can. J. Chem.*, 31 (1953) 1040–1047.
12 E. S. GOULD, *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart, and Winston, New York, 1959, p. 317.
13 Y. IWAKURA, K. HAYASHI, K. IWATA, AND S. MATSUO, *Makromol. Chem.*, 108 (1967) 300–303.
14 B. H. KOEPPEN, *Carbohydr. Res.*, 13 (1970) 193–198.
15 K. TAKEO, *Carbohydr. Res.*, 48 (1976) 290–293.
16 K. TAKEO, K. MINE, AND T. KUGE, *Carbohydr. Res.*, 48 (1976) 197–208.