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An improved procedure for the synthesis of sugar chloroacetates and some substitution reactions thereof

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Abstract. An improved and simplified procedure for the preparation of some sugar chloroacetates is described. Nucleophilic substitution of the chlorine atom in some of the products yields the corresponding α-substituted acetate esters.

Introduction

The chloroacetyl group has been useful in the synthesis of partially acylated sugars and oligosaccharides[1–7], the particular advantage being its ease[1,2,8–10] of removal under mild and essentially neutral conditions, thus avoiding the problems of acyl migration. The usual procedure[1–5] for the introduction of these groups is the reaction of a dilute solution or suspension of the appropriate substrate with chloroacetyl chloride (**1**) in the presence of an exact equivalent of pyridine, under carefully controlled conditions. The described yields are quite variable.

Attempts to utilize this protective function during selective acylation studies[11] on some disaccharide aldonic acids were unsuccessful. Prolonged reaction times, in excess of 24 h, were required, and it was observed that during this period reaction took place between chloroacetyl groups already introduced with the pyridine still remaining in the reaction mixture. Prolonged contact between **1** and pyridine can result in quaternisation, thereby causing problems[1,2]. The quaternisation of *N*-(chloroacetyl)sphingosine by pyridine has been noted[1], although no similar problems with chloroacetates have so far been recorded. The interference could be minimised by the replacement of pyridine with 2,6-lutidine. In the above study this base was ineffective, as was the use of chloroacetic anhydride (**2**)/pyridine. The synthesis of some mono(chloroacetates) of partially acetylated derivatives of D-glucose using this reagent combination has been described[12], and without complications. The current problem was resolved eventually by use of the anhydride **2** under non-quaternising conditions. The results of a study on a number of model compounds and some reactions of the products are now described. The reactions are easy to perform, without special precautions, to give the products in high yield. In all cases anhydride **2** of technical quality could be used without causing problems. The procedure is an improvement on the pre-existing methods.

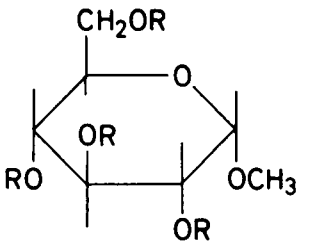
Results and discussion

Attention was directed initially to the preparation of a fully chloroacetylated aldoside. Methyl α-D-glucoside (**3**) in *N*,*N*-dimethylformamide solution was treated with the anhydride **2** in the presence of sodium hydrogen carbonate at room temperature to give the known crystalline tetra-ester **4** in 88% yield. Treatment of **3** with **1** in the presence of pyridine had been shown[1,2] previously to furnish **4**, but in low yield (19%). When a solution of **4** in pyridine was stirred for 1 h at room temperature none of the ester could then be detected (TLC). The water-soluble product, insoluble in ether or dichloromethane, was apparently a quaternised derivative of **4**. This facile quaternisation could account for the poor yield of **4** reported[1,2] previously.

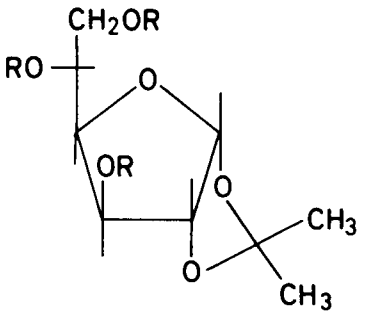
The derivatisation procedure was then applied successfully to the triol **5**, the diols **6** and **7**, and the monohydroxy derivatives **8** to **12** to give the corresponding chloroacetates **13** to **20** in good to excellent yields. The yields of compounds **16** and **17** indicated that insignificant acyl migration had occurred under the reaction conditions.

Attempts to chloroacetylate the diol **6** selectively, with one equivalent of anhydride **2** at 0° were unsuccessful. The reaction product was shown (TLC) to be composed of a mixture of unreacted **6**, the diester **14**, and two closely separated components, assumed to be the two mono-ester of the diol **6**. No attempt was made to separate this mixture. During the preliminary studies to develop the reaction conditions attempts were made to utilize sodium acetate as the base component. In all cases mixed products were obtained. The ^{1}H NMR spectra of these showed the additional presence of acetoxy functions, arising presumably through nucleophilic substitution of chlorine in the ester groups by acetate ions. Treatment of the diester **14** in *N*,*N*-dimethylformamide solution with excess sodium benzoate or excess sodium azide afforded the novel α-substituted acetates **21** and **22** which were characterised by ^{1}H-NMR spectroscopy. Catalytic de-esterification of **21** yielded the original diol **6**, as the only product, confirming thus the unlikelihood of inversion during the substitution reaction. The results showed furthermore that the halogen in sugar chloroacetates can be replaced without causing significant hydrolysis. Simple aliphatic haloacetates can undergo similar displacement reactions[13,14].

formulae 3-9



(3) R = H
(4) R = $ClCH_2-C(=O)-$



(5) R = H
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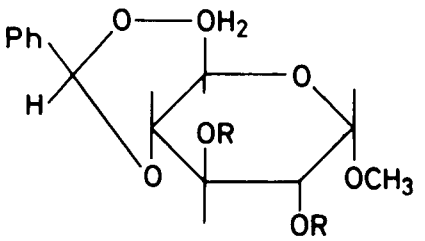
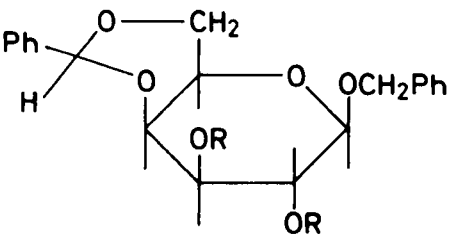
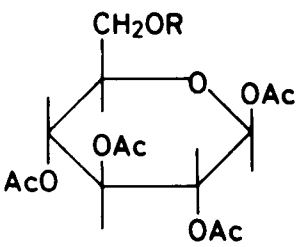


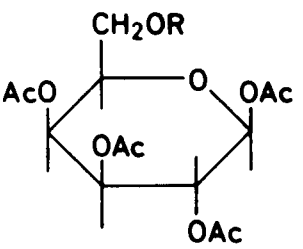
(6) R = H
(14) R = $ClCH_2-C(=O)-$
(21) R = $PhC(=O)-O-CH_2-C(=O)-$
(22) R = $N_3CH_2C(=O)-$



(7) R = H
(15) R = $ClCH_2-C(=O)-$



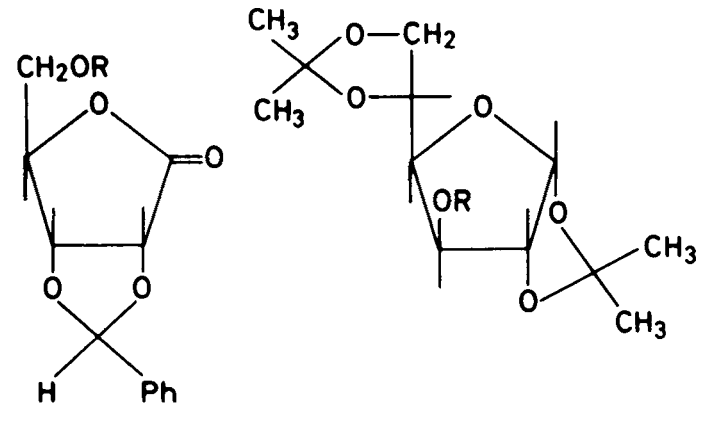
(8) R = H
(16) R = $ClCH_2-C(=O)-$
(23) R = $BrCH_2-C(=O)-$



(9) R = H
(17) R = $ClCH_2-C(=O)-$
(24) R = $BrCH_2-C(=O)-$

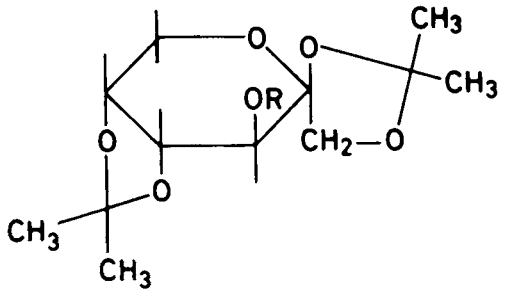
The use of bromoacetyl esters has been recommended[7] recently for the preparation of the corresponding glycosyl bromides, useful as intermediates in oligosaccharide syntheses. The main advantage of this protecting group over chloroacetates lies in the milder[10] manner of its removal. Its introduction, however, requires the use of bromoacetyl bromide as reagent. Treatment of the tetraacetate **9** with bromoacetyl chloride has led[7] to mixtures of the bromoacetate **24** and the chloroacetate **17** due to concomitant halogen interchange. Treatment of **9** with the acid bromide

formulae 10-25



(10) R = H
(18) R = $ClCH_2-C(=O)-$

(11) R = H
(19) R = $ClCH_2-C(=O)-$



(12) R = H
(20) R = $ClCH_2-C(=O)-$
(25) R = $ICH_2-C(=O)-$

gave **24** in moderate yield, but chromatographic purification was necessary.

In view of the observed facile displacement of halogen in chloroacetates *(vide supra)* it was decided to explore a simple exchange procedure for the synthesis of bromoacetates. Treatment of the monochloroacetates **16** and **17** in *N,N*-dimethylformamide solution with excess dry sodium bromide gave the corresponding bromoacetates **23** and **24** in good yield, providing thus a useful alternative to the direct esterification procedure. Attempted bromide exchange on the diester **14**, in a similar manner, was unsuccessful. The product was a mixture of bromo- and chloroacetyl esters and no attempt was made to resolve it. When the diacetal monochloroacetate **20** was treated with excess sodium iodide the corresponding iodoacetate **25** was obtained. The method appears to be most suited to monoesters.

Experimental

General methods

Optical rotations were determined with a Perkin Elmer automatic polarimeter, Model 241 MC on 1% chloroform solution at 20°C. Thin-layer chromatography on pre-coated plates of silica gel (Merck) was performed with ethyl acetate/hexane (1/1 v/v). Detection was effected by charring with 5% (v/v) sulfuric acid 140°C. Solutions in organic solvents were dried with anhydrous sodium sulphate and concentrated at 40° *in vacuo*. ^{1}H-NMR, spectra were routinely recorded at room temperature for solutions in $CDCl_3$ (internal standard Me_4Si) with a Varian EM 3940 spectrometer operating at 90 MHz. Petroleum ether refers to the fraction of b.p. 60–80°C.

Methyl 2,3,4,6-tetrakis-O-(chloroacetyl)-α-D-glucoside (**4**)

A solution of the anhydride (**2**, 5.30 g) in *N,N*-dimethylformamide (10 ml) was treated with methyl α-D-glucoside (**3**, 1.0 g) and sodium hydrogen carbonate (0.5 g). The mixture was stirred at room temperature for 4 h, and then poured with stirring into ice water (100 ml). The white precipitate was collected by filtration, washed with water and dried (P_4O_{10}) *in vacuo*. Recrystallisation of the crude product (2.82 g, 100%) from chloroform/light petroleum gave the tetra-ester **4** (2.46 g, 88%), m.p. 96–97°C, $[\alpha]_D$ + 107.4°. Lit.[1,2] m.p. 95–97°C; $[\alpha]_D$ + 106°.

1,2-O-Isopropylidene-3,5,6-tris-O-(chloroacetyl)-α-Dglucofuranose

Compound **5**[15] (1.0 g), the anhydride **2** (2.4 g) and sodium hydrogen carbonate (0.5 g) in *N,N*-dimethylformamide (5 ml) were stirred at room temperature for 3½ h. Isolation of the crude product (1.99 g, 97.5%) in the same manner as described above, followed by recrystallization from ether/light petroleum yielded compound **13** (1.6 g, 64%), m.p. 85–86°C, $[\alpha]_D$ + 10.7°. $C_{13}H_{19}Cl_3O_8$ calcd.: C 40.1, H 4.3; found: C 40.2, H 4.3%.

Methyl 4,6-O-benzylidene-2,3-bis-O-(chloroacetyl)-α-D--glucopyranoside (**14**)

A mixture of the diol **6** (1.0 g), the anhydride **2** (2.4 g) and sodium hydrogen carbonate (0.5 g) in *N,N*-dimethylformamide (5 ml) was stirred at room temperatuire for 2 h and then subjected to the same work-up procedure. Recrystallization of the crude product (1.54 g, 96.5%) from dichloromethane/light petroleum gave the title compound **14** (1.35 g, 84.6%), m.p. 146–147.5°C, $[\alpha]_D$ + 63°. Lit.[1] m.p. 147–148°C; $[\alpha]_D$ + 65.4°.

Benzyl 4,6-O-benzylidene-2,3-bis-O-(chloroacetyl)-β-D--galactopyranoside (**15**)

Diol **7**[17] (1.0 g), anhydride **2** (1.84 g) and sodium hydrogen carbonate (0.2 g) in *N,N*-dimethylformamide (5 ml) were stirred at room temperature for 18 h. Recrystallisation of the crude product (1.28 g, 90%), obtained in the above manner, from 2-propanol gave di-ester **15** (0.81 g, 72%), m.p. 143–145.5°C, $[\alpha]_D$ + 39.2°. $C_{24}H_{24}Cl_2O_8$ calcd.: C 56.4, H 4.7; found: C 56.2, H 4.7%.

6-O-(Chloroacetyl)-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (**16**)

The tetra-acetate **8**[18] (1.0 g), the anhydride **2** (1.0 g) and sodium hydrogen carbonate (0.4 g) in *N,N*-dimethylformamide (6 ml) were stirred at room temperature for 2½ h. The crtude product (1.15 g, 94.5%) obtained in the usual manner was recrystallised from ethanol to give compound **16** (0.95 g, 78%), m.p. 142.5–144°C, $[\alpha]_D$ + 7.0°. Lit.[3] m.p. 138–140°C.

6-O-(Chloroacetyl)-1,2,3,4-tetra-O-acetyl-β-D-galactopyranose (**17**)

Treatment of the tetra-ester **9**[7] (1.0 g), in the same way as described for compound **8** and recrystallisation of the crude product (1.12 g, 92%) from 2-propanol gave the title compound **17** (0.93 g, 76.5%), m.p. 130–132°C, $[\alpha]_D$ + 22°. Lit.[5] m.p. 129–131°C; $[\alpha]_D$ + 20°.

2,3-O-(R)-Benzylidene-5-O-(chloroacetyl)-D-ribono-1,4-lactone (**18**)

The lactone **10**[19] (1.03 g), the anhydride **2** (1.5 g) and sodium hydrogen carbonate (0.15 g) in *N,N*-dimethylformamide (5 ml) were stirred at room temperature for 5 h and processed in the described manner. Recrystallisation of the product (1.34 g, 98%) from aqueous acetone gave compound **18** (1.01 g, 74%), m.p. 146–148°C, $[\alpha]_D$ − 66°. $C_{14}H_{13}O_6Cl$ calcd.: C 53.8, H 4.2; found: C 53.6, H 4.1%.

3-O-(Chloroacetyl)-1,2; 5,6-di-O-isopropylidene-α-D-glucofuranose (**19**)

The diacetal **11**[15] (0.68 g) in *N,N*-dimethylformamide (3 ml) was treated with the anhydride **2** (0.90 g) and sodium hydrogen carbonate (0.1 g) and after $3\frac{1}{2}$ h at room temperature was processed to give the crude product (0.6 g, 67.2%). This was recrystallised, with some difficulty, from aqueous ethanol to give pure compound **19** (0.295 g, 33.2%), m.p. 60.5–62°C, $[\alpha]_D$ −33°. $C_{14}H_{21}O_7Cl$ calcd.: C 49.9, H 6.3; found C 49.5, H 6.2%.

3-O-(Chloroacetyl)-1,2; 4,5-di-O-isopropylidene-β-D-fructopyranose (**20**)

Compound **12**[20] (1.41 g) in *N,N*-dimethylformamide (7 ml) was treated with the anhydride **2** (1.87 g) and sodium hydrogen carbonate (0.21 g) in the above manner. Recrystallisation of the crude product (1.54 g, 84%) from light petroleum gave the title compound **20** (1.26 g, 69%), m.p. 84.5–85°C, $[\alpha]_D$ −162.5°. $C_{14}H_{21}O_7Cl$ calcd.: C 49.9, H 6.3; found: C 50.1, H 6.2%.

Methyl 4,6-O-benzylidéne-2,3-di-O-(benzoyloxyacetyl)-α-D--glucopyranoside **21**)

A solution of compound **14** (0.2 g) in *N,N*-dimethylformamide (15 ml) was treated with the anhydrous sodium benzoate (2.0 g) and the mixture was heated with stirring for 24 h at 80°C. The reaction mixture was then diluted with ice-water (30 ml) and poured with stirring into ice-water (120 ml). The white precipitated material was collected by filtration, washed with ice-water and dried *in vacuo* (P_4O_{10}). Recrystallisation of the crude product (0.255 g, 91.5%) from ethanol or 2-propanol gave the title compound **21** (0.14 g, 51%), m.p. 152–154°C, $[\alpha]_D$ +23°. $C_{28}H_{26}O_8Cl$ calcd.: C 63.4, H 5.0; found: C 62.9, H 4.95%.

Methyl 4,6-O-benzylidene-2,3-bis-O-(azidoacetyl)-α-D-glucopyranoside (**22**)

A solution of compound **14** (1.134 g) in *N,N*-dimethylformamide (10 ml) was treated with sodium azide (0.51 g) and the mixture was allowed to stir at room temperature for 48 h. Pouring the reaction mixture into ice-water (200 ml) precipitated a pale yellow solid which was collected by filtration, washed with ice-water and dried *in vacuo* (P_4O_{10}). Recrystallisation of the crude product (1.05 g, 90%) from ethanol gave compound **22** (0.89 g, 76.5%), m.p. 84.5–87.5°C, $[\alpha]_D$ +59.6°. $C_{18}H_{20}N_6O_8Cl$ calcd.: C 48.2, H 4.5%, N 18.75; found: C 48.1, H 4.5, N 18.75%.

6-O-(Bromoacetyl)-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (**23**)

A mixture of compound **16** (0.2 g) and sodium bromide (1.53 g) in *N,N*-dimethylformamide (2 ml) was allowed to stir at room temperature for 48 h. The mixture was poured into ice-water (20 ml) and the precipitated material was collected by filtration, washed with water and air dried. Recrystallisation of the crude product (0.192 g, 87%) from ethanol gave the bromoacetate **23** (0.146 g, 66%), m.p. 123–125°C, $[\alpha]_D$ +8.2°. $C_{16}H_{21}O_{11}Br$ calcd.: C 41.0, H 4.5; found: C 41.6, H 4.6%.

6-O-(Bromoacetyl)-1,2,3,4-tetra-O-acetyl-β-D-galactopyranose (**24**)

Compound **17** (0.4 g) in *N,N*-dimethylformamide (5 ml) was treated with sodium bromide (3.2 g) in the same manner as described for compound **16**. Recrystallisation of the crude product (0.37 g, 84%) from ethanol gave the bromoacetate **24** (0.275 g, 62.5%), m.p. 113–115°C, $[\alpha]_D$ +19.5°. Lit.[5] m.p. 112–115°C, $[\alpha]_D$ +18.7°.

1,2; 4,5-Di-O-isopropylidene-3-O-(iodoacetyl)-β-D-fructopyranose (**25**)

A solution of the chloroacetate **20** (0.5 g) in acetone (5 ml) was treated with sodium iodide (0.33 g) and allowed to stir at room temperature for 24 h. Pouring the mixture into ice water (50 ml) gave a white precipitate, which was collected by filtration, washed with water and dried *in vacuo* (P_4O_{10}). Recrystallisation of the crude product (0.6 g, 94%) from ether/light petroleum gave the iodoacetate **25** (0.45 g, 71%), m.p. 118.5–120.5°C, $[\alpha]_D$ −128°. $C_{14}H_{21}IO_7$ calcd.: C 39.3, H 4.95; found: C 39.5, H 5.0%.

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