Carbohydrate Research, 249 (1993) 91–94
Elsevier Science Publishers B.V., Amsterdam

Facile synthesis of acetylated glycosyl fluorides derived from di- and tri-saccharides

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(Received December 28th, 1992; accepted April 14th, 1993)

ABSTRACT

Peracetylated α-glycopyranosyl fluorides of di- and tri-saccharides are obtained in good yields by treatment of the corresponding peracetylated di- and tri-saccharides with pyridinium poly(hydrogen fluoride). The interglycosidic bonds are not cleaved by the reagent.

INTRODUCTION

During recent years, protected glycosyl fluorides have been increasingly used as glycosyl donors in the synthesis of oligosaccharides because they are readily prepared and behave as stable and efficient glycosylation reagents in reactions catalyzed by Lewis acids[1–4]. Many of the previously described glycosyl fluorides have been prepared by treatment of suitably protected monosaccharides with pyridinium poly(hydrogen fluoride)[5,6]. This reagent is safer and more convenient to handle than the previously used anhydrous hydrogen fluoride[7].

A few acetylated glycosyl fluorides derived from disaccharides have been prepared by treatment of peracetylated disaccharides with anhydrous hydrogen fluoride[7]. This procedure is, however, difficult to use because cleavage of the glycosidic bonds or rearrangements may occur[8]. A number of oligosaccharide fluorides, containing a variety of protecting groups, have been obtained in situ by reaction of the corresponding thioglycosides with *N*-bromosuccinimide–diethylaminesulfur trifluoride[4].

RESULTS

It has now been found that acetylated di- or tri-saccharide glycosyl fluorides may be readily prepared by treatment of the corresponding peracetylated compounds with 3:7 pyridinium poly(hydrogen fluoride) at room temperature. In no

case was cleavage of the interglycosidic bonds observed, even when the reaction with pyridine–hydrogen fluoride was allowed to proceed[9] for 24 h. As found for the reaction of penta-*O*-acetyl-D-glucopyranose with pyridine–hydrogen fluoride, some β-fluoride may be formed initially, but this isomerizes on longer reaction time to the thermodynamically more stable α-fluoride[5]. The optimal reaction time may be found by monitoring the reaction in pyridine–hydrogen fluoride through ^{13}C NMR spectroscopy, observing the signals of the anomeric carbon atoms.

The acetylated fluorides thus obtained may be deacetylated, as already shown in the case of acetofluorolactose[10], and subsequently converted into the perbenzylated fluorides.

EXPERIMENTAL

General methods.—The pyridine–HF reagents was prepared by mixing dry pyridine and anhyd HF at −78°C. Commercial products may be used provided they are kept under anhyd conditions. If the reagent contains water, impure fluorides are obtained, which do not crystallize well. NMR spectra were recorded with a Bruker AM-500 instrument. For spectra obtained in $CDCl_3$ solution the $CHCl_3$ signal at 76.9 ppm was used as internal reference; in D_2O, 1,4-dioxane (67.4 ppm) was used.

Preparation of peracetylated glycosyl fluorides.—To the peracetylated di- or tri-saccharide (5.0 g) in a polyethylene bottle was added 3:7 pyridine–HF (24 mL) and the mixture was stirred for a few min until a homogeneous solution was obtained. It was kept for the appropriate time at room temperature and CH_2Cl_2 (40 mL) was then added. The mixture was washed with water (3 × 40 mL) and with $NaHCO_3$ (40 mL), dried, and evaporated, leaving the crude fluoride.

Hepta-O-acetyl-α-lactosyl fluoride[11] was obtained after 40 min of reaction as a syrup (4.4 g, 94%) which contained traces of the β-fluoride, as seen from NMR spectra. ^{13}C NMR ($CDCl_3$): δ 103.3 (d, C-1, $J_{C\text{-}1,F}$ 229 Hz), 100.4 (C-1′), 74,7 (C-4), 70.0 (d, C-2, $J_{C,2F}$ 24.5), 70.6, 70.4, 70.3, 68.6, 68.5 (C-3,5 and C-2′,3′,4′,5′), 60.9, 60.6 (C-6,6′).

Hepta-O-acetyl-α-maltosyl fluoride was prepared from octa-*O*-acetyl-β-maltose (10 g) using a reaction time of 40 min. The crude product (9.7 g) was crystallized from EtOH to give 6.4 g (68%) of the fluoride; mp 168–170°C. Recrystallization gave a product having mp 171–172°C; $[\alpha]_D^{20}$ + 110.5° (*c* 1.4, $CHCl_3$) (lit.[12] mp 174–175°C, $[\alpha]_D$ + 111.1°). ^{13}C NMR ($CDCl_3$): δ 103.4 (d, C-1, $J_{C\text{-}1,F}$ 230 Hz), 95.4 (C-1′), 70.3 (d, C-2, $J_{C\text{-}2,F}$ 25.2 Hz), 69.9 (d, C-5, $J_{C\text{-}5,F}$ 3.8 Hz), 71.5, 71.4, 69.8, 69.0, 68.3, 67.7 (C-3,4 and C-2′,3′,4′,5′), 61.8, 61.1 (C-6,6′); ^1H NMR: δ 5.64 (dd, H-1, $J_{1,F}$ 50.7, $J_{1,2}$ 2.7 Hz), 5.42 (d, H-1′, $J_{1',2'}$ 4.0 Hz), 4.83 (ddd, H-2, $J_{2,F}$ 23.0, $J_{2,3}$ 10.0 Hz).

Hepta-O-acetyl-α-cellobiosyl fluoride[4e,12,13].—Treatment of octa-*O*-acetyl-α-D-cellobiose (5 g) with pyridine–HF for 4.5 h gave the crude fluoride (4.5 g) which crystallized from EtOH to give 3.0 g (64%); mp 172–174°C. Recrystallization gave

a product having mp 179–180°C; $[\alpha]_D^{20}$ + 30.6° (*c* 1.5, $CHCl_3$); (lit.[12] mp 187°C, $[\alpha]_D$ + 30.6°). ^{13}C NMR ($CDCl_3$): δ 103.4 (d, C-1, $J_{C\text{-}1,F}$ 229 Hz), 100.4 (C-1′), 75.2 (C-4), 70.6 (d, C-5, $J_{C\text{-}5,F}$ 2.5 Hz), 70.3 (d, C-2, $J_{C\text{-}2,F}$, 25.2 Hz), 72.8, 71.9, 71.5, 68.7, 67.8 (C-3, C-2′,3′,4′,5′), 61.5, 61.0 (C-6,6′); ^1H NMR: δ 5.65 (dd, H-1, $J_{1,F}$ 53.0, $J_{1,2}$ 2.7 Hz), 4.87 (ddd, H-2, $J_{2,F}$ 24.2, $J_{2,3}$ 10.1 Hz), 4.53 (d, H-1′, $J_{1',2'}$ 8.0 Hz).

Hepta-O-acetyl-α-gentiobiosyl fluoride.—Reaction of octa-*O*-acetyl-β-gentiobiose (400 mg) with pyridine–HF for 45 min gave 340 mg of a syrup which crystallized from EtOH, yield 280 mg (75%); mp 161–162°C. Further recrystallization gave a product having mp 163–164°C, $[\alpha]_D^{20}$ + 44.5° (*c* 0.6, $CHCl_3$); (lit.[12] mp 168–169°C, $[\alpha]_D^{20}$ 43.8°). ^{13}C NMR ($CDCl_3$): δ 103.5 (d, C-1, $J_{C\text{-}1,F}$ 229 Hz), 100.7 (C-1′), 70.8 (d, C-5, $J_{C\text{-}5,F}$ 5.3 Hz), 70.1 (d, C-2, $J_{C\text{-}2,F}$ 25.2 Hz), 72.6, 71.9, 70.8, 69.3, 68.2, 67.6, 67.0 (C-3,6 and C-2′,3′,4′,5′), 61.8 (C-6′); ^1H NMR: δ 5.75 (dd, H-1, $J_{1,F}$ 53.0, $J_{1,2}$ 2.2 Hz), 4.91 (ddd, H-2, $J_{2,F}$ 24.1, $J_{2,3}$ 10.0 Hz), 4.57 (d, H-1′, $J_{1',2'}$ 8.0 Hz).

Hepta-O-acetyl-α-isomaltosyl fluoride[15].—Reaction of octa-*O*-acetyl-α-isomaltose (0.20 g) with pyridine–HF for 1.2 h gave the crude fluoride (0.17 g) which crystallized from EtOH to give 0.14 g (74%); mp 181°C; $[\alpha]_D^{20}$ + 90.3 (*c* 0.85, CH_2Cl_2); [lit.[15] $[\alpha]_D^{20}$ + 91.2 (*c* 0.8, CH_2Cl_2)]. ^{13}C NMR ($CDCl_3$): δ 103.5 (d, C-1, $J_{C\text{-}1,F}$ 230 Hz), 95.9 (C-1′), 70.1 (d, C-2, $J_{C\text{-}2,F}$ 24.8 Hz), 70.8, 70.4, 69.9, 69.3, 68.3, 68.1, 67.4 (C-3,4,5 and C-2′,3′,4′,5′) 66.2 (C-6), 61.7 (C-6′); ^1H NMR: δ 5.73 (dd, H-1, $J_{1,F}$ 52.5, $J_{1,2}$ 3.8 Hz), 4.90 (ddd, H-2, $J_{2,F}$ 25.2, $J_{2,3}$ 10.5 Hz), 5.15 (d, H-1′, $J_{1',2'}$ 3.4 Hz).

Deca-O-acetyl-α-isomaltotriosyl fluoride was prepared from undeca-*O*-acetyl-isomaltotriose (100 mg), as described already (1 h reaction time). The crude product (92 mg) was purified by filtration over silica gel to give 79 mg (80%) of the fluoride as a colorless syrup; $[\alpha]_D^{20}$ + 80.1 (*c* 0.85, CH_2Cl_2). ^{13}C NMR: δ 103.9 (d, C-1, $J_{C\text{-}1,F}$ 229 Hz), 70.6 (d, C-2, $J_{C\text{-}2,F}$ 24.9 Hz), 72.8, 72.2, 70.2, 70.1, 69.8, 69.5, 69.3, 69.0, 68.7, 68.3, 67.7 (C-3,4,5, C-2′,3′,4′,5′, and C-2″,3″,4″,5″), 66.5, 65.9 (C-6, C-6′), 61.4 (C-6″); ^1H NMR: δ 5.73 (dd, H-1, $J_{1,F}$ 52.5, $J_{1,2}$ 3.8 Hz), 4.89 (ddd, H-2, $J_{2,F}$ 25.3, $J_{2,3}$ 10.5 Hz), 5.11 (d, H-1′, $J_{1',2'}$ 3.4 Hz), 5.15 (d, H-1″, $J_{1'',2''}$ 3.5 Hz).

Deca-O-acetyl-α-maltotriosyl fluoride.—Reaction of undeca-*O*-acetyl-maltotriose (100 mg) with pyridine–HF for 2 h gave the crude fluoride which crystallized from EtOH to give 79 mg (80%); mp 185°C (dec); $[\alpha]_D^{20}$ + 87.9 (*c* 0.7, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 103.6 (d, C-1, $J_{C\text{-}1,F}$ 231 Hz), 95.9, 95.1 (C-1′, C-1″), 70.5 (d, C-2, $J_{C\text{-}2,F}$ 24.7 Hz), 72.4, 72.9, 71.9, 71.3, 71.0, 70.8, 70.1, 69.9, 69.3, 68.3, 67.4 (C-3,4,5, C-2′,3′,4′,5′ and C-2″,3″,4″,5″), 61.0, 60.8, 60.7 (C-6,6′,6″); ^1H NMR: δ 5.68 (dd, H-1, $J_{1,F}$ 50.9, $J_{1.2}$ 3.7 Hz), 4.95 (ddd, H-2, $J_{2,F}$ 24.1, $J_{2,3}$ 10.0 Hz), 5.11 (d, H-1′, $J_{1',2'}$ 3.2 Hz), 5.17 (d, H-1″, $J_{1'',2''}$ 3.5 Hz).

Deca-O-acetyl-α-panosyl fluoride was prepared from undeca-*O*-acetyl-panose (100 mg), as described already (1.5 h reaction time). The crude product (92 mg) was purified by filtration over silica gel to give 84 mg (87%) of the fluoride as a colourless syrup; $[\alpha]_D^{20}$ + 78.7 (*c* 0.4, CH_2Cl_2). ^{13}C NMR: δ 104.5 (d, C-1, $J_{C\text{-}1,F}$ 225 Hz), 70.7 (d, C-2, $J_{C\text{-}2,F}$ 25.4 Hz), 72.7, 72.4, 71.4, 70.2, 70.1, 69.9, 69.7, 69.5, 69.0,

68.3, 67.7, 66.9 (C-3,4,5, C-2′,3′,4′,5′, and C-2″,3″,4″,5″), 66.4 (C-6), 61.4, 61.0 (C-6′, C-6″); ^{1}H NMR: δ 5.68 (dd, H-1, $J_{1,F}$ 51.9, $J_{1,2}$ 3.9 Hz), 4.95 (ddd, H-2, $J_{2,F}$ 24.7, $J_{2,3}$ 10.1 Hz), 5.19 (d, H-1′, $J_{1',2'}$ 3.4 Hz), 5.15 (d, H-1″, $J_{1'',2''}$ 3.5 Hz).

α-Lactosyl fluoride.—The crude hepta-*O*-acetyl-α-lactosyl fluoride described already was treated with methanolic NaOMe to give the deacetylated fluoride, which crystallized from the solution; yield 1.8 g (71%). Recrystallization from water–EtOH gave a product having mp 180–185°C (dec); $[\alpha]_D^{20}$ + 83.9° (*c* 2.5, H_2O); (lit.[14] mp 180–195 (dec), $[\alpha]_D$ + 83.2°. ^{13}C NMR (D_2O): δ 107.9 (d, $J_{C\text{-}1,F}$ 224 Hz, C-1), 106.7 (C-1′), 73.3 (d, C-5, $J_{C\text{-}5,F}$ 3.1 Hz), 71.6 (d, C-2, $J_{C\text{-}2,F}$ 22.9 Hz), 77.8, 76.2, 73.3, 71.9, 71.7, 69.4 (C-3,4 and C-2′-5′), 61.9, 60.3 (C-6, C-6′); ^{1}H NMR: δ 5.50 (dd, H-1, $J_{1,F}$ 53.3, $J_{1,2}$ 2.8 Hz), 3.52 (ddd, H-2, $J_{2,F}$ 26.5, $J_{2,3}$ 10.2 Hz), 4.32 (d, H-1′, $J_{1',2'}$ 7.9 Hz).

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