Carbohydrate Research, 210 (1991) 333–337
Elsevier Science Publishers B.V., Amsterdam

Note

A short synthesis of 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranose and the corresponding α-glucosyl chloride from D-mannose*

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(Received June 8th, 1990; accepted for publication August 6th, 1990)

2-Acetamido-2-deoxy-D-glucopyranose is a constituent of many biologically important glycoconjugates. Chemical syntheses of model compounds related to these substances require glycosyl donors which favor the formation of either 1,2-*cis* or 1,2-*trans* glycosidic linkages. Glycosyl donors derived from 2-amino-2-deoxy-D-glucose that show a β-directing effect in the glycosylation reaction are relatively easily accessible[1]; more difficult to obtain are their α-directing counterparts.

The 2-azido glycosyl halide approach is the most useful means for the stereoselective synthesis of the α-glycosidic linkage in the aminosugar series. According to this strategy[2], the nonparticipating azido group is positioned at C-2 of the requisite monosaccharide, which is then converted into a glycosyl halide. After glycosylation, the azido group can be readily converted into a 2-amino or 2-acylamino function. According to the existing methods[3–5], however, the preparation of the precursors of glycosyl halide derivatives of 2-azido-2-deoxy-D-glucose is a tedious, multistep process. This, to a considerable extent, is because logical precursors such as the C-2 sulfonate derivatives of methyl α-D-mannopyranoside do not undergo S_N2 displacement reactions easily[6,7], and therefore cannot be used as intermediates to efficiently synthesize the corresponding 2-azido-2-deoxy-D-glucose derivatives. If an efficient inversion of the D-*manno* to D-*gluco* configuration is to be achieved by the S_N2 displacement of a suitable leaving group, then the reaction should be carried out with a (usually less accessible) derivative of β-D-mannose[7]. Recent critical evaluation[8] of the available routes to the precursors of glycosyl halides of 2-azido-2-deoxyhexoses found the azidonitration method[5] most advantageous. That procedure, however, requires resolution of a complex mixture of products by chromatography.

This laboratory has recently reported[9] that treatment of 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose (**1**) with diethylaminosulfur trifluoride (DAST) afforded the corre-

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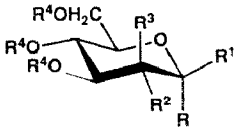
0008-6215/91/$03.50

sponding derivative of 2-deoxy-2-fluoro-D-glucose in high yield. The reaction of alcohols with dialkylaminosulfur trifluorides, to give the corresponding deoxyfluoro derivatives, has been referred to[10] as a "direct replacement of a hydroxyl group by fluorine". This reaction, however, is based on the displacement of the dialkylaminodifluorosulfonyl group (in the intermediate formed from the starting sugar and the reagent) with a fluoride ion. Thus, S_N2 displacement with the azide ion of a suitable sulfonyl derivative of **1** appeared to be a viable alternative to the existing preparations of 2-azido-2-deoxy-D-glucose tetra-acetates. An analogous reaction on a derivative of methyl β-D-mannopyranoside has been described[5]. The present Note describes the conversion of the known[11] 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethylsulfonyl-β-D-mannopyranose (**2**) to the title glucosyl chloride **7**, *via* the 2-azido-D-glucose derivative (**3**), in the overall yield of ~67%. The described synthesis of **7** is experimentally less demanding than procedures developed previously, and the conversion of D-mannose to **3** can be performed without isolation of intermediates by chromatography. The preparation of **2** in the yield of 92% (*cf.* 60%, ref. 11) from **1** by a slight modification of the original procedure is also described.



	R	R1	R2	R3	R4
1	H	OAc	H	OH	Ac
2	H	OAc	H	OTf	Ac
3	H	OAc	N_3	H	Ac
4	H,OH		H	OMs	H
5	H	N_3	OAc	H	OAc
6	H	N_3	OH	H	H
7	Cl	H	N_3	H	Ac
8	H	Cl	N_3	H	Ac

Reactions of **2** with sodium azide in ethanol, acetonitrile, or 2-methoxyethanol at room temperature (not described in the Experimental) were very slow. Only traces of products, both more and less polar than the starting material (t.l.c.), were formed during 18 h. Similar treatment, but at 100°, resulted in virtually complete conversion of **2** into polar products. Acetylation of each of these crude products in pyridine with acetic anhydride gave the same major product, showing marginally faster t.l.c. mobility than **2**. The material was isolated by chromatography and identified by n.m.r. spectroscopy as 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**5**). Compound **5** was previously obtained[12] (87%) by acetylation of the product of attempted displacement with azide ion of the 2-methanesulfonyloxy (mesyloxy) group in 2-*O*-mesyl-D-mannopyranose (**4**). The plausible mechanism suggested[12] for the conversion of **4** into β-D-glucopyranosyl azide (**6**), involving neighboring group participation of the axial 1-OH group in the

displacement of the mesyloxy group, is analogous to the one operating[13] in the reaction of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside with DAST, to form 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-α- and -β-D-glucopyranosyl fluorides, and in similar systems[14,15]. The formation of an anomeric azide from **2** in the present case can be rationalized in a similar way by assuming anomerization, with or without concomitant deacetylation at O-1, before the displacement of the triflyloxy group by the azide ion could take place at C-2.

The reaction of **2** with lithium azide in acetone (not described in the Experimental) was more encouraging. Although the reaction at room temperature was slow, after 40 h of reaction time t.l.c. showed that the conversion of **2** was almost complete. Only traces of products more polar than the starting material were formed. The mixture contained a small proportion of **5** (t.l.c.), and the major product, having higher chromatographic mobility than **5**, was identified as the desired title compound **3**. When **2** was treated with either lithium or sodium azide in *N,N*-dimethylformamide (DMF) at room temperature for 40–45 min virtually pure **3** was formed. Most of the product could be isolated by direct crystallization from the crude reaction mixture. A further amount of **3** was obtained by chromatography of the material in the mother liquor, affording a total yield of 85%. Compound **3** was smoothly converted into 3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl chloride (**7**) by treatment with dichloromethyl methyl ether (DCMME) in the presence of a catalytic amount of zinc chloride. The ^{1}H-n.m.r. spectral data observed for **7** were identical with those reported[16], but the observed $[\alpha]_D$ value was more positive by ~63° (+133° *vs.* +70.1°) than that reported. A small portion of the β-anomeric chloride **8** was formed in this reaction.

EXPERIMENTAL

General methods. — Optical rotations were measured at 25° with a Perkin–Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (t.l.c.) on precoated slides of Silica Gel G F254 (Analtech) was performed with solvent mixtures of appropriately adjusted polarity: *A*, carbon tetrachloride–acetone; and *B*, toluene–acetone. Detection was effected by charring with 5% sulfuric acid in ethanol and, when applicable, with u.v. light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, No. 9385). To chromatograph the glucosyl chloride **7**, the silica gel was dried at 160° for 16 h. Unless indicated otherwise, n.m.r. data were extracted from spectra measured at 25° on solutions in $CDCl_3$ with a Varian XL 300 spectrometer. The proton signal assignments were made by first-order analysis of the spectra, and were supported by homonuclear decoupling experiments. Of two magnetically nonequivalent geminal protons, the one resonating at lower field is denoted Ha and the one at higher field Hb. Carbon signal assignments were made by mutual comparison of the spectra, and by comparison with spectra of related substances. All chemical shifts are reported relative to that of tetramethylsilane. Ammonia c.i. mass spectra were obtained with a Vacuumetrics d.c.i. probe using an Extrel ELQ-400-3 mass spectrometer. Unless stated otherwise, solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 2 kPa/40°.

1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethylsulfonyl-β-D-mannopyranose (**2**). — Trifluoromethanesulfonic anhydride (7.35 mL, 45 mmol) was added dropwise *during 1 h*, at −10 to −20°, to a stirred solution of **1** (refs. 9 and 12) (7.94 g, 22.8 mmol) and pyridine (4.3 mL) in dry dichloromethane (220 mL). T.l.c. (solvent *A*) showed shortly that the reaction was complete, and the mixture was worked up as described[11]. Crystallization from ethanol gave 9.8 g (90%) of **2**, and chromatography of the material in the mother liquor raised the total yield of the desired material to 93%, m.p. 119–120°; lit.[8] yield 60%, m.p. 120°; ^{1}H-n.m.r.: δ 5.92 (s, 1 H, H-1), 5.30 (t, 1 H, $J_{4,5} = J_{3,4}$ 9.9 Hz, H-4), 5.18 (m, 2 H, H-2,3), 4.25 (dd, 1 H, $J_{5,6a}$ 5.13, $J_{6a,6b}$ 12.5 Hz, H-6a), 3.84 (m, 1 H, H-5), 4.18 (dd, 1 H, $J_{5,6b}$ 2.57 Hz, H-6b), 2.17, 2.12, 2.10, and 2.07 (4 s, 12 H, 4 CH_3CO); ^{13}C-n.m.r.: δ 89.1 (C-1), 81.2 (C-2), 73.6 (C-5), 69.7 (C-3), 64.7 (C-4), and 61.7 (C-6).

1,3,4,6-Tetra-O-acetyl-2-azido-2-deoxy-β-D-glucopyranose (**3**). — A solution of **2** (10.5 g, 21.8 mmol) and sodium or lithium azide (100% molar excess) in DMF (210 mL) was stirred at room temperature for 45 min, when t.l.c. (solvent *B*) showed that the reaction was complete. One major product, moving faster than the starting material, was formed. The mixture was concentrated at 133 Pa/40°, and the residue was partitioned between dichloromethane and water. The organic phase was dried and concentrated, then crystallization of the residue from isopropyl ether gave **3** (6.43 g), m.p. 96–97°; lit.[4] m.p. 97°. Chromatography of the material that remained in the mother liquor gave a further crop (0.58 g) of the product, bringing the total yield to 86%; c.i.m.s.: *m/z* 391 ($M + 18$)$^+$. The ^{1}H-n.m.r. data were identical with those reported[4]; the ^{13}C-n.m.r. spectrum showed δ 92.6 (C-1), 72.8 (C-3,5), 68.0 (C-4), 62.7 (C-2), and 61.5 (C-6).

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl azide (**5**). — A solution of **2** (0.48 g, 1 mmol) and sodium azide (0.13 g, 2 mmol) in 2-methoxyethanol (10 mL) was stirred overnight at 100°. After concentration of the reaction mixture by coevaporation with toluene, the dark residue was treated with pyridine (5 mL) and acetic anhydride (1 mL) for 2 h. Conventional processing and chromatography (solvent *B*) of the crude product gave **5** (50–75 mg, 13–23%), m.p. 120–122°, lit.[13] m.p. 129°; c.i.m.s.: *m/z* 391 ($M + 18$)$^+$; ^{1}H n.m.r.: δ 5.32 (t, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 5.21 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 5.06 (t, 1 H, $J_{1,2}$ 9.2 Hz, H-2), 4.76 (d, 1 H, $J_{1,2}$ 8.8 Hz, H-1), 4.38 (dd, 1 H, $J_{5,6a}$ 4.8, $J_{6a,6b}$ 12.5 Hz, H-6a), 3.90 (ddd, 1 H, $J_{5,6b}$ 2.2 Hz, H-5), 4.27 (dd, 1 H, H-6b), 2.20, 2.18, 2.13, and 2.11 (4 s, 12 H, 4 CH_3CO); ^{13}C-n.m.r.: δ 88.0 (C-1), 74.1 (C-5), 72.7 (C-3), 70.8 (C-2), 68.0 (C-4), and 61.7 (C-6).

3,4,6-Tri-O-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl chloride (**7**). — A mixture of **3** (3.73 g, 10 mmol) and freshly fused zinc chloride (~300 mg) in alcohol-free chloroform (15 mL) containing DCMME (15 mL) was stirred for 2 h at 60°, when t.l.c. (solvent *B*) showed that the conversion of **7** into a major and a very minor, faster moving product was complete. After concentration of the mixture, and coevaporation with toluene, the residue was chromatographed (solvent *A*) to give first amorphous **7** (3.14 g, 85%), $[\alpha]_D$ +133° (*c* 1, MeCN); lit.[16] $[\alpha]_D$ +70°; c.i.m.s.: *m/z* 367 ($M + 18$)$^+$; ^{1}H-n.m.r. data identical with those reported[16]; ^{13}C-n.m.r.: δ 91.7 (C-1), 70.8, 70.7 (C-3,5), 67.7 (C-4), 62.3 (C-2), and 61.2 (C-6).

Anal. Calc. for $C_{12}H_{16}ClN_3O_7$: C, 41.21; H, 4.61; Cl, 10.14; N, 12.02. Found: C, 41.30; H, 4.63; Cl, 10.21; N, 11.95.

Eluted next was a small amount of byproduct showing in its c.i.m.s. a peak at *m/z* 367 $(M + 18)^+$; ^{1}H-n.m.r. (C_6D_6): δ 5.03 (t, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 4.90 (t, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 4.43 (d, 1 H, $J_{1,2}$ 9.0 Hz, H-1), 4.18 (dd, 1 H, $J_{5,6a}$ 4.4, $J_{6a,6b}$ 12.6 Hz, H-6a), 3.86 (dd, 1 H, $J_{5,6b}$ 2.1 Hz, H-6b), 3.02 (t, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 2.93 (ddd, 1 H, H-5), 1.70, 1.68, and 1.65 (3 s, 9 H, 3 CH_3CO). These data are virtually identical with those published[16] for 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranosyl chloride (**8**), except for the chemical shift for H-3 (given as δ 4.53, presumably a misprint). The ^{13}C-n.m.r. showed δ 89.1 (C-1), 75.7 (C-5), 73.1 (C-3), 67.7, 67.2 (C-2,4), and 61.6 (C-6).

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