Note

Nucleophilic substitution-reactions at C-2 of methyl 3-0-benzoyl-4,6-0-benzylidene-2-0-(trifluoromethylsulfonyl)- α -D-glucopyranoside*

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Ali and Richardson², and Miljkovic *et al.*³ reported that methyl α -D-glucopyranoside species functionalized with a methylsulfonyl group at O-2 are much less reactive than the corresponding β anomers under bimolecular, nucleophilic-substitution reaction-conditions. Recently, on the other hand, trifluoromethanesulfonates (triflates) have been shown to be useful as synthetic, intermediary substrates for reactions in the field of carbohydrate chemistry; Binkley and Hehemann⁴ demonstrated their utility for the reaction with iodide, Umezawa *et al.*⁵ for deoxygenation of sugar derivatives, and Ranganathan and Larwood⁶ for conversion of adenosine into the corresponding product bearing a sugar moiety having the D-arabino configuration (*i.e.*, inversion at C-2'), where SN2 reactions have been reported to be difficult due to the steric effect of the heterocyclic moiety.

We have recently established¹ novel procedures for the regioselective 2'-Odeacylation of fully acylated purine and pyrimidine ribonucleosides⁷, and the method has also proved useful for fully acylated glycosyl compounds¹; *e.g.*, methyl 3-Obenzoyl-4,6-O-benzylidene- α -D-glucopyranoside (65% yield) could be readily prepared from the corresponding 2,3-dibenzoate; the product was converted into the corresponding 2-triflate (1) (88% yield) by treating with trifluoromethanesulfonic anhydride (2 equiv.) in pyridine in the usual way. The triflate chemistry⁴⁻⁶ mentioned prompted us to investigate the nucleophilic-substitution reactions of 1 by use of a series of nucleophiles, and the results thus obtained are described herein.

The reactions of 1 performed by use of sodium benzoate (2), sodium azide (3), sodium methanethioxide (4), sodium benzenethioxide (5), and sodium methoxide (6) in N,N-dimethylformamide (HCONMe₂) were effectively induced as expected. The conditions used and the results obtained are summarized in Table I. All of the reactions were found to proceed in >80% yield, and all of the products were assigned the α -D-manno configuration from their ¹H-n.m.r. data; *i.e.*, the 2-O-benzoyl- (7),

^{*}Partial Protection of Carbohydrate Derivatives. Part 7. For Part 6, see ref. 1.

X of nucleophile (NaX)	Formula	Temp. (°C)	Reaction time (h)	Yield (%) of the α-D-mannopyranoside derivative
-OBz	2	80	5	82
-N ₃	3	80	2	86
-SMe	4	0	1	89
-SPh	5	50	6	83
-OMe	6	room temp.	overnight	85

NUCLEOPHILIC SUBSTITUTION OF METHYL 3-O-BENZOYL-4,6-O-BENZYLIDENE-2-O-(TRIFLUOROMETHYL-SULFONYL)- α -D-GLUCOPYRANOSIDE (1)^{α}

^aAll of the reactions were performed by use of 1 (0.52 g, 1 mmol).



2-azido-2-deoxy- (8), 2-deoxy-2-(methylthio)- (9), 2-deoxy-2-(phenylthio)- (10), and 2,3-anhydro- α -D-mannopyranoside derivative (11), respectively. Among the products, 8 was *O*-debenzoylated with sodium methoxide in methanol, and the product was converted into 2-amino-2-deoxy-D-mannose (12) (55% yield) by reduction with hydrogen in the presence of palladium black. In addition, 10 was desulfurized by treating with Raney nickel W-2 in ethanol under reflux, to give methyl 3-*O*-benzoyl-2-deoxy- α -D-arabino-hexopyranoside (13) in 89% yield.

Nucleophilic substitution of the SN2 type was thus proved to be effectively induced at C-2 of a methyl α -D-glucopyranoside 2-triflate derivative.

EXPERIMENTAL

General methods. — Melting points were determined with a micro meltingpoint apparatus (Yanagimoto Co., Inc.) and are uncorrected. Specific rotations were determined with a JASCO DIP-4 apparatus (Nippon Bunko Co., Inc.) for solutions in HCONMe₂ unless otherwise noted. ¹H-N.m.r. spectra were recorded with a Varian T-60 instrument, for solutions in chloroform-d, with tetramethylsilane as the internal standard. I.r. spectra were recorded with a Hitachi 285 instrument, and elementary

TABLE I

analyses were made with a Perkin–Elmer 240-002 apparatus. T.l.c. was performed with Merck silica gel $60F_{254}$ (thickness 0.25 mm) by use of 19:1 benzene–acetone, and 9:1 benzene–isopropyl ether (by which all of the reactions were monitored). Column chromatography was performed on Wakogel C-300.

Methyl 3-O-benzoyl-4,6-O-benzylidene-2-O-(trifluoromethylsulfonyl)- α -D-glucopyranoside (1). — To a solution of methyl 3-O-benzoyl-4,6-O-benzylidene- α -D-glucopyranoside¹ (0.80 g, 2.2 mmol) in pyridine (10 mL) was added trifluoromethylsulfonic anhydride⁸ (0.83 mL), the temperature being kept at -10° , and the mixture was stirred for 1 h at 0°. Crushed ice (20 g) was then added, and the crystals that were precipitated were filtered off, and subjected to chromatography on a column of silica gel by use of 50:50:1 benzene-cyclohexane-acetone as the eluant. Fractions containing the product were combined, and evaporated to dryness; the residue crystallized, to give 1 (0.99 g, 88% yield); m.p. 125-126° (from methanol), $[\alpha]_D^{23} + 39^{\circ}$ (c 1, chloroform).

Anal. Calc. for C₂₂H₂₁F₃O₉S: C, 50.96; H, 4.08; S, 6.18. Found: C, 51.42; H, 4:10; S, 6.49.

Methyl 2,3-di-O-benzoyl-4,6-O-benzylidene- α -D-mannopyranoside (7). — A mixture of **1** (0.52 g, 1 mmol) and sodium benzoate (**2**) (0.26 g, 2 mmol) in HCONMe₂ (2 mL) was stirred for 5 h at 80°, cooled, and evaporated to a syrup; this was chromatographed on a column of silica gel by use of 1:1 benzene-cyclohexane with a gradient increase of acetone from 0 to 2%, to give 7 (0.40 g, 82% yield); syrup, $[\alpha]_D^{23} - 145^\circ$ (c 1.0, chloroform) {lit.⁹ $[\alpha]_D - 141^\circ$ (c 1.62, chloroform)}; 7 was identified with an authentic specimen⁹ by ¹H-n.m.r. spectroscopy.

Methyl 2-azido-3-O-benzoyl-4,6-O-benzylidene-2-deoxy- α -D-mannopyranoside (8). — A mixture of 1 (0.52 g, 1 mmol) and sodium azide (3) (130 mg, 2 mmol) was stirred for 2 h at 80°, cooled, and evaporated to a syrup, which was chromatographed on a column of silica gel by use of 100:100:1 benzene-cyclohexane-acetone as the eluant, to give syrupy 8 (0.35 g, 86% yield); $[\alpha]_D^{23} + 60^\circ$ (c 0.5, chloroform); v_{max}^{NaCl} 2100 cm⁻¹; ¹H-n.m.r. (chloroform-d, with Varian T-60 instrument): δ 3.37 (s, 3 H, OCH₃), 4.73 (d, 1 H, J_{1,2} 1.5 Hz, H-1), and 5.70 (dd, 1 H, J_{2,3} 4.0, J_{3,4} 9.0 Hz, H-3).

Anal. Calc. for $C_{21}H_{21}N_3O_6$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.34; H, 5.20; N, 9.76.

Methyl 3-O-benzoyl-4,6-O-benzylidene-2-deoxy-2-(methylthio)- α -D-mannopyranoside (9). — To a solution of 1 (0.52 g, 1 mmol) in HCONMe₂ (3 mL) was added sodium methanethioxide (4) (0.08 g, 1.1 mmol), the temperature being kept at 0° by ice-cooling (because of the exothermic nature of this reaction), and the mixture was stirred for 1 h. It was then dissolved in chloroform (50 mL), and the solution was successively washed with M hydrochloric acid, aqueous sodium hydrogencarbonate solution (saturated), and water, dried (anhydrous magnesium sulfate), and evaporated to a syrup which was chromatographed on a column of silica gel by use of 1:1 benzene-cyclohexane with a gradient increase of acetone from 0 to 1%, to give 9 (0.37 g, 89% yield); syrup, $[\alpha]_D^{23} + 74^\circ$ (c 0.5, chloroform); ¹H-n.m.r. (chloroform-d): δ 2.10 (s, 3 H, S-CH₃), 3.40 (s, 3 H, OCH₃), 3.58 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 4.5 Hz, H-2), 4.93 (d, 1 H, H-1), and 5.75 (dd, 1 H, $J_{3,4}$ 9.0 Hz, H-3).

Anal. Calc. for C₂₂H₂₄O₆S: C, 63.44; H, 5.81; S, 7.70. Found: C, 63.75; H, 6.02; S, 7.43.

Methyl 3-O-benzoyl-4,6-O-benzylidene-2-deoxy-2-(phenylthio)- α -D-mannopyranoside (10). — To a solution of benzenethiol (0.25 mL) in HCONMe₂ (1 mL) was added 2M sodium methoxide (0.5 mL), and the mixture was stirred for 30 min at room temperature. Compound 1 (0.52 g, 1 mmol) was then added, and the mixture was stirred for 6 h at 50–55°, cooled, dissolved in chloroform (50 mL), and the solution successively washed with M aqueous sodium hydroxide solution, M hydrochloric acid, aqueous sodium hydrogencarbonate solution (saturated), and water, dried (anhydrous magnesium sulfate), and evaporated to dryness; the residue crystallized, to give 10 (0.50 g, 83% yield); m.p. 124–125° (from ethanol), $[\alpha]_D^{23}$ +65° (c 1, chloroform); ¹H-n.m.r. (chloroform-d): δ 3.36 (s, 3 H, OCH₃), 4.92 (s, 1 H, H-1), 5.50 (s, 1 H, CH-Ph), and 5.80 (dd, 1 H, J_{2,3} 5.0, J_{3,4} 9.0 Hz, H-3).

Anal. Calc. for C₂₇H₂₆O₆S: C, 67.76; H, 5.48; S, 6.70. Found: C, 67.65; H, 5.55; S, 6.90.

Methyl 2,3-anhydro-4,6-O-benzylidene- α -D-mannopyranoside (11). — To a solution of 1 (0.52 g, 1 mmol) in 1:2 HCONMe₂-anhydrous methanol (1.5 mL) was added 2M sodium methoxide solution in methanol (1 mL), and the mixture was kept overnight at room temperature. Addition of water (20 mL) precipitated crystals that were filtered off, and recrystallized, to give 11 (0.22 g, 85% yield); m.p. 143–145° (from methanol), $[\alpha]_D^{23} + 112°$ (c0.8, chloroform) {lit.¹⁰ m.p. 143–145°, $[\alpha]_D^{15} + 107°$ (c 1.6, chloroform)}.

2-Amino-2-deoxy-D-mannose hydrochloride (12). — To a solution of 8 (0.39 g, 1 mmol) in anhydrous methanol (3 mL) was added 2m sodium methoxide solution in methanol (10 drops), and the mixture was stirred overnight at room temperature, and evaporated to a syrup; this was dissolved in 2:2:1 1,4-dioxane-acetic acid-water, palladium black (50 mg) was added, and the suspension was stirred overnight under hydrogen. The catalyst was filtered off, the filtrate was evaporated to dryness, and the residue was dissolved in 6m hydrochloric acid. The solution was boiled under reflux for 6 h, and evaporated, the residue was dissolved in ethanol, and the solution evaporated; this procedure was repeated, to afford white, crystalline 12 (0.12 g, 55% yield); m.p. 177-178°, $[\alpha]_D^{23} - 0.8°$ (c 1, water) {lit.¹¹ m.p. 178-180°, $[\alpha]_D - 3°$ }.

Methyl 3-O-benzoyl-2-deoxy- α -D-arabino-hexopyranoside (13). — A solution of 10 (0.3 g, 0.5 mmol) in ethanol was boiled under reflux, in the presence of Raney nickel W-2 (~1 g), for 2 h, cooled, the catalyst filtered off, and the filtrate evaporated to dryness. The residue was chromatographed on a column of silica gel by use of 1:1 benzene-cyclohexane with a gradient increase of acetone from 1 to 2%. The fractions containing 13 were combined, evaporated to dryness, and the residue crystallized, to give 13 (0.13 g, 89% yield), m.p. 172–174° (from ethanol), $[\alpha]_D^{23} + 47°$ (c 0.6, chloroform); ¹H-n.m.r. (chloroform-d, with the Varian T-60 apparatus): δ 1.8–2.5 (m, 2 H, H-2,2'), 3.35 (s, 3 H, OCH₃), 4.80 (br d, 1 H, $J_{1,2} \sim 4$ Hz, H-1), 5.2–5.6 (m, 1 H, H-3), and 7.2–8.2 (m, 5 H, OCOC₆H₅). *Anal.* Calc. for C₁₄H₁₈O₆: C, 59.56; H, 6.43. Found: C, 59.27; H, 6.35.

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