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Note

A one-flask preparation of methyl 6-azido-6-deoxy-α-D-hexopyranosides*‡

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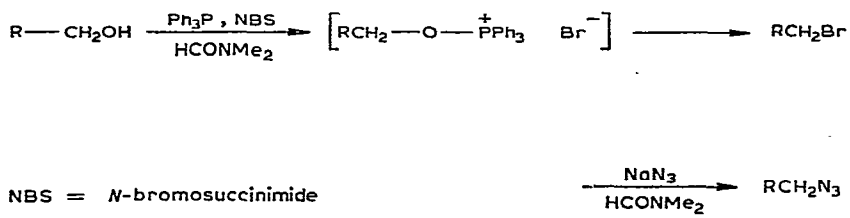
The chemical replacement of a hydroxyl group in an organic compound by a halo, amino, thio, or related function is of great preparative utility. These functional groups may not only be useful as such, particularly in the context of compounds of biological significance, but also as reactive groups that may be engaged in a variety of subsequent transformations.

In connection with a synthetic program in the area of the aminoglycoside antibiotics[1], we had previously developed, and reported[2] on, a halogenation procedure that is selective for primary hydroxyl groups. The reaction involves treatment of a polyhydroxy compound with an *N*-halosuccinimide and triphenylphosphine in *N*,*N*-dimethylformamide under rigorously anhydrous conditions, and it is applicable to a variety of carbohydrate derivatives. We now describe the extension of this reaction to the preparation of primary azides by carrying out the halogenation reaction, and the subsequent conversion of the intermediate halogen derivative into the corresponding azide, in a single flask (see Scheme 1). The reaction is exemplified



Scheme 1

by the preparation of methyl 6-azido-6-deoxy-α-D-glucopyranoside (**1**, isolated as the crystalline triacetate in 75% overall yield) from methyl α-D-glucopyranoside. The

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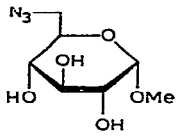
halogenation and azide-displacement reactions were essentially complete in less than 6 h. The product (**1**) had previously been prepared[3] by a procedure involving selective tosylation (2 days at 20°; 55%), isolation of the 6-tosylate, and subsequent displacement with azide ion (in refluxing aq. acetone for 3 days). With the advent of dipolar, aprotic solvents, the azide-displacement step in such reactions has been considerably improved, but the initial, selective sulfonylation reaction is still time-consuming and requires control.

Application of the procedure to methyl 2-(benzyloxycarbonylamino)-2-deoxy-α-D-glucopyranoside[4] gave the corresponding 6-azido derivative **2** in high yield. In the presence of a 3–4-molar excess of the reagent pair, namely, triphenylphosphine–*N*-bromosuccinimide, the bromination reaction could be conducted at room temperature, or lower, to give the crystalline bromo derivative **3**.



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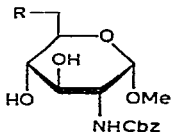
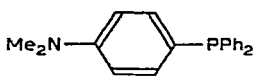


2 R = N_3
3 R = Br



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As the formation of triphenylphosphine oxide in the bromination reaction necessitates, in some cases, purification of the product by chromatography, the possibility of using *p*-(dimethylamino)phenyldiphenylphosphine[5] **4** instead of triphenylphosphine was explored. Indeed, the bromination reaction proceeded as usual in the presence of **4**, and the isolation of the bromo derivative **3** was facilitated by simply extracting the basic, phosphine oxide derivative with aqueous acid. In this way, it was possible to prepare **3** in >70% yield without recourse to chromatographic separation. Sequential azide-displacement was also possible under these conditions.

5′-Azido-5′-deoxynucleosides have been prepared by treatment of certain nucleosides with[6] triphenylphosphine, carbon tetrabromide, and lithium azide in *N*,*N*-dimethylformamide. In our initial studies[2], all attempts to obtain azides directly from alcohols by incorporating lithium or sodium azide in the reaction mixture containing an alcohol, triphenylphosphine, and *N*-bromosuccinimide in *N*,*N*-dimethylformamide resulted in the liberation of nitrogen and the decomposition of the brominating reagent. It appears that azide ion reacts rapidly at the phosphorus atom in the intermediate alkoxyphosphonium salts (see Scheme 1), or with the bromotriphenylphosphonium salt, liberating the alcohol in the first case, and presumably, triphenylphosphine imide, which is ultimately recovered as the corresponding oxide. The same observation was made when lithium azide was added to a solution containing triphenylphosphine and *N*-bromosuccinimide in *N*,*N*-dimethylformamide, but no alcohol.

Castro and co-workers[7] obtained azides from selected alcohols by treatment of the corresponding alkoxytris(dimethylamino)phosphonium salts with sodium azide in refluxing *N*,*N*-dimethylformamide. Thus, by virtue of the presence of the

dimethylamino groups attached to the phosphorus atom, it appears that, in these cases, azide ion preferentially attacks the carbon atom of the alkoxyl group.

The compatibility of various functional groups under the conditions of bromination with triphenylphosphine and *N*-bromosuccinimide[8], coupled with the practical advantages relative to time and simplicity of operation, make the procedure described in this paper a useful method for the incorporation of a primary azide group in simple and in polyfunctional molecules. This group is, of course, readily converted into an amino group by a variety of mild methods[9], including catalytic and chemical reduction. Particularly useful applications* of this procedure can be found[10] in the area of the medicinally important aminoglycoside antibiotics[11], where the replacement of a primary hydroxyl group by an amino group is known to have significant effects on the biological activity of these compounds[12].

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 photoelectric polarimeter. Infrared spectra were recorded with a Beckman model IR-8 spectrometer. N.m.r. spectra were recorded at 100 MHz, for solutions in $CDCl_3$, with a Jeol model JNM-4H-100 instrument, with tetramethylsilane as the internal reference-standard.

Reagents and solvents should be rigorously dried. Solvents were freshly distilled prior to use. To ensure the exclusion of all traces of moisture from the alcohols, each was dissolved in the solvent (*e.g.*, *N,N*-dimethylformamide), a known volume of the solvent was distilled off, and the solution was cooled, and treated with the reagents as described later. T.l.c. was conducted on plates of silica gel G-254 using 10:1 $CHCl_3$–MeOH.

Methyl 2,3,4-tri-O-acetyl-6-azido-6-deoxy-α-D-glucopyranoside. — To a cooled solution of methyl α-D-glucopyranoside (1 g, 5.14 mmoles, predried by azeotropic removal of traces of water), and triphenylphosphine (2.718 g, 10.3 mmoles) in dry *N,N*-dimethylformamide (25 ml) was added *N*-bromosuccinimide (1.844 g, 10.3 mmoles), and the solution was heated for 2 h at 55° with stirring. Methanol (1 ml) was added to the cooled solution to decompose the excess of brominating agent[2], and the solution plus sodium azide (2 g, 30 mmoles) was heated for 4 h** at 80°, with efficient stirring. The solvent was evaporated by codistillation with 1-butanol, the resulting syrup was dissolved in water, and the solution was extracted with 1:1 chloroform–hexane to remove triphenylphosphine oxide. The water phase was evaporated to dryness, the residue was suspended in acetone, the solids were removed by filtration, and the filtrate was evaporated to a syrup that contained methyl 6-azido-6-deoxy-α-D-glucopyranoside (**1**) as the sole reaction-product (to-

*The bromination and azide-displacement reactions can also be conducted in hexamethylphosphoric triamide (HMPT).

**A shorter reaction time is required at higher temperatures.

gether with succinimide and traces of sodium azide). Acetylation with acetic anhydride (2 ml) in pyridine (10 ml) for 24 h, followed by pouring into ice–water, extraction with chloroform, and the usual manipulation, gave the triacetate of **1** as a chromatographically homogeneous, crystalline solid (75%). Trituration with aqueous methanol gave the title compound (1.245 g, 70%), m.p. 102°, which was recrystallized from ethanol; m.p. 103°, $[\alpha]_D^{25}$ +155.4° (*c* 1.3, MeOH); lit.[3] m.p. 103°, $[\alpha]_D^{25}$ +156° (MeOH); n.m.r. data: δ 5.40 (t, H-3, $J_{3,2} = J_{3,4} = 10$ Hz), 5.0 (m, 3 H, H-1,2,4), 3.99 (m, H-5), 3.50 (OCH_3), 3.35 (m, 2 H, H-6,6'), and 2.10 (9 H, CH_3COO).

Methyl 6-azido-2-(benzyloxycarbonylamino)-2,6-dideoxy-α-D-glucopyranoside (**2**). — Triphenylphosphine (1.604 g, 6.11 mmoles) was added to a solution of methyl 2-(benzyloxycarbonylamino)-2-deoxy-α-D-glucopyranoside[4] (1 g, 3.05 mmoles, predried by azeotropic removal of traces of water) in dry *N,N*-dimethylformamide (25 ml), and the solution was cooled. *N*-Bromosuccinimide (1.088 g, 6.11 mmoles) was added in small portions with stirring, the solution was gradually heated to 55°, and stirring was continued for 2 h. Methanol (1 ml) was added, followed by sodium azide (1.90 g, 29.3 mmoles), and the solution was heated for 4 h at 80°, at which time, t.l.c. indicated that the reaction was complete. The solvent was removed by codistillation with 1-butanol, the residue was dissolved in chloroform, and the solution was extracted with water to remove the excess of sodium azide and succinimide. Processing of the organic phase gave a solid residue containing the title compound and triphenylphosphine oxide. Purification was achieved by chromatography on neutral alumina (Fisher, activity 1), first with 1:2 hexane–chloroform, and then with 5:1 chloroform–methanol as developers. The product was obtained as chromatographically homogeneous, pale-yellow crystals (84%). Trituration with cold 2-propanol, followed by recrystallization from the same solvent, gave compound **2**, m.p. 128°, $[\alpha]_D^{25}$ +111.8° (*c* 0.33, MeOH). The material in the mother liquors of crystallization consisted essentially of compound **2**.

Anal. Calc. for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90. Found: 51.11; H, 5.78; N, 15.70.

The bromination and azide-displacement steps could also be performed in dry HMPT, with essentially the same results.

Bromination of methyl 2-(benzyloxycarbonylamino)-2-deoxy-α-D-glucopyranoside. — a. With triphenylphosphine and N-*bromosuccinimide in* N,N-*dimethylformamide at 25°.* To a predried solution of the compound[4] mentioned in the title (0.1 g, 0.3 mmole) in *N,N*-dimethylformamide (5 ml) were added triphenylphosphine (0.24 g, 0.91 mmole) and *N*-bromosuccinimide (0.163 g, 0.91 mmole) at 0°. The solution was stirred for 2 h at room temperature, methanol (1 ml) was added, and the solution was evaporated to dryness in the presence of 1-butanol. The crystalline residue was suspended in water, the product extracted with chloroform, and the extracts processed to give a crystalline residue which was then chromatographed on silica gel by using chloroform, and then 20:3 chloroform–methanol. The fractions containing the product were combined, to give 0.1 g (84%) of crystalline methyl 2-(benzyloxycarbonylamino)-6-bromo-2,6-dideoxy-α-D-glucopyranoside (**3**). Recrystallization

from 95% ethanol gave an analytical sample, m.p. 154°, $[\alpha]_D^{25}$ +111.8° (*c* 0.33, MeOH); mass spectral data: calculated for a fragment $C_{15}H_{18}NO_5$: 292.1184; measured, 292.1180.

Anal. Calc. for $C_{15}H_{20}BrNO_6$: C, 46.16; H, 5.16; Br, 20.49; N, 3.58. Found: C, 46.20; H, 5.31; Br, 20.46; N, 3.55.

b. With p-(*dimethylamino*)*phenyldiphenylphosphine and* N-*bromosuccinimide in* N,N-*dimethylformamide.* The previous experiment was repeated, but using 0.2 g (0.65 mmole) of the reagent[5] **4** instead of triphenylphosphine. The solution was heated, with stirring, for 2 h at 55°. Methanol (1 ml) was added, and the solvents were evaporated by codistillation with 1-butanol. Trituration of the residue with petroleum ether (b.p. 30–60°) removed some of the *p*-(dimethylamino)phenyldiphenylphosphine oxide. The residue was dissolved in ether (80 ml), and the solution was washed with 10% hydrochloric acid (3 × 10 ml), and then with water. Drying and evaporation of the ether layer gave a crystalline residue which was triturated with hexane, to give the desired 6-bromo derivative **3** (0.1 g, 84%), m.p. 149°. Recrystallization from 95% ethanol gave the pure product.

The bromo derivative was also obtained when the reaction was conducted for 18 h at room temperature in the presence of the phosphine derivative **4** (3.5 equiv.) and *N*-bromosuccinimide; yield 69%.

ACKNOWLEDGMENTS

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