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Note

Synthesis of an aldosyl chloride by the reaction of thionyl chloride with the 1-*O*-thallium(I) salt of an aldose

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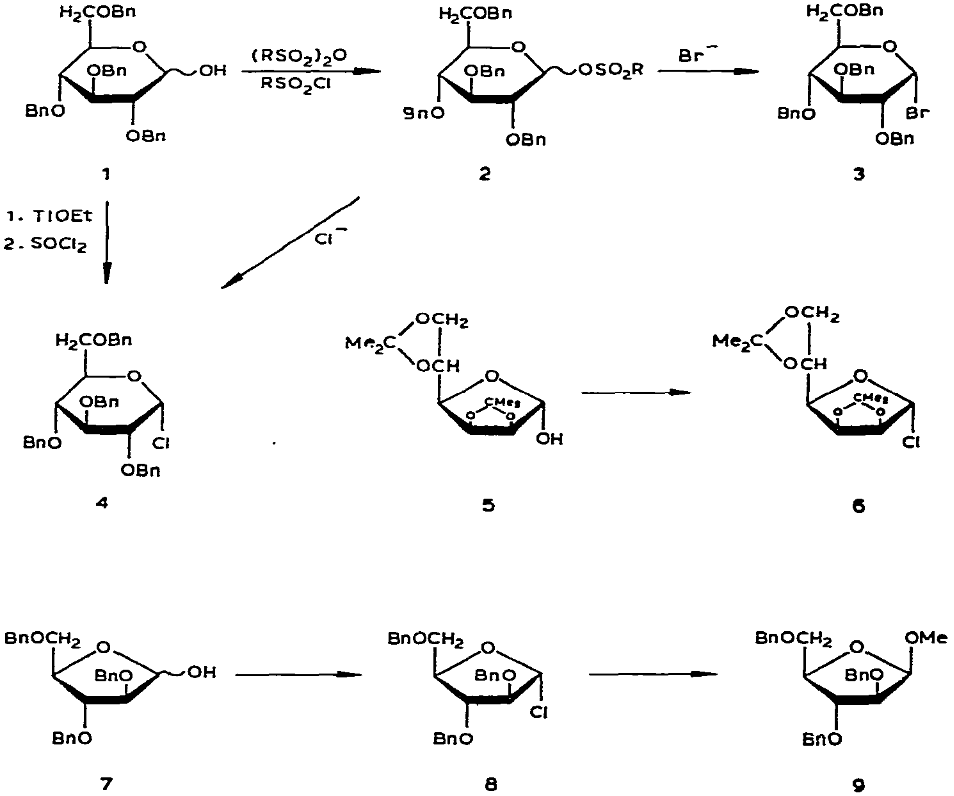
A glycosyl halide may be synthesized[1,2] from a suitable aldose derivative having a free, anomeric hydroxyl group by sulfonylation of this group in the presence of



$$\underset{\mathbf{10}}{R{-}O{-}Tl\,(I)} \xrightarrow{SOCl_2} \underset{\mathbf{11}}{R{-}O{-}SO{-}Cl} + TlCl \longrightarrow \underset{\mathbf{12}}{R{-}Cl} + SO_2$$

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halide ion. For example, the reaction of trifluoromethanesulfonic anhydride with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) in the presence of tetrabutylammonium bromide and *s*-collidine gives[1] the α-bromide (**3**). Analogously, the α-chloride (**4**) is obtained when chloride ion is employed, or, more simply[2], by the base-catalyzed reaction of **1** with methanesulfonyl chloride. These reactions undoubtedly involve a displacement of the sulfonyloxy group of intermediate **2** by halide ion.

A related type of synthesis is described here; *i.e.*, a glycosyl chloride is formed by the action of thionyl chloride on an aldose or, more satisfactorily, on the 1-*O*-thallium(I) salt[3] of the aldose. By use of this procedure, the halide is isolated very conveniently in quantitative yield, paralleling the excellent, quantitative features of many thallium-mediated reactions[4].

Although thionyl chloride is used extensively for the conversion of an alcohol into a chloro derivative, its reaction with 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**5**) was reported[5] to give the α-chloride (**6**) in only 4.5% yield. In the present study, a quantitative yield of **6** was obtained by the following procedure: one molar proportion of thallous ethoxide was added to a solution of **5** in benzene, the solution was evaporated to remove the ethanol liberated, and then one molar proportion of thionyl chloride was introduced. Thallous chloride precipitated rapidly and was centrifuged off, and the solution was evaporated to give an ~100% yield of syrupy **6**, pure according to chromatographic and n.m.r.-spectroscopic evidence.

Employing the same procedure with **1** and with 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**7**) gave quantitative yields of the corresponding α-chlorides (**4** and **8**, respectively). The α-anomeric designation for **8** is based on the small, H-1, H-2 coupling (<1 Hz; ref. 6) observed for the H-1 signal (δ 6.10). Additional evidence was furnished by the reaction of compound **8** with methanol in the presence of silver oxide. This afforded the methyl β-glycoside (**9**) almost exclusively, as shown by a 3-proton singlet at δ 3.45 and a coupling of 4.2 Hz (ref. 6) between H-1 and H-2.

By analogy with the reaction of thionyl chloride with an alcohol, the thallous salt of an aldose (**10**) would be expected[7] to yield a chlorosulfite (**11**). Decomposition of the latter would occur readily, and would be accompanied by an internal, nucleophilic substitution at C-1 by chlorine, to give a glycosyl chloride (**12**). As there is no excess of Cl^- in solution, substitution should take place with retention of configuration[7], although the product that is isolated will be the one favored by equilibration at the anomeric center. Hence, with the D-glucopyranosyl derivative **1**, the α anomer (**4**) is obtained. The D-mannofuranose derivative **5** and the D-arabinofuranose derivative **7** also yield α anomers (**6** and **8**) as products, probably because they are stabilized more than their β anomers by a *quasi*-axial anomeric substituent, as well as by a 1,2-*trans* arrangement. That is, the anomeric effect is operative in the five-membered[8], as well as the six-membered, ring series.

It is worth noting that a quantitative yield of the D-glycosyl chloride **4** was also obtained *without* the use of thallium, *i.e.*, when a solution of aldose **1** and six molar proportions of thionyl chloride in benzene was heated under reflux for five hours, and the solution then evaporated. However, the D-*arabino* derivative (**8**) prepared in this way was contaminated by ~15% of an unidentified product, and the di-*O*-isopropylidene-D-mannose derivative **6** proved to be unstable under the latter reaction-conditions, undoubtedly due to the hydrogen chloride liberated*. Therefore, prior formation of the thallous salt of an aldose is to be recommended when thionyl chloride is used in the synthesis of a glycosyl chloride.

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Solvents were dried over molecular sieves (4A). All glassware was oven-dried. Plates of Silica Gel G were used for t.l.c., and the developing solvent was 1:2 ethyl acetate–petroleum ether. Proton magnetic resonance spectra were recorded with a Varian HA-100 spectrometer, using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported with reference to tetramethylsilane.

2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl chloride (**6**) *from the thallous salt of* **5**. — A solution of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**5**) (0.52 g, 2 mmol) in benzene (20 mL) was dried over molecular sieves (4A; 2 g), and then transferred with a syringe to a flask fitted with a rubber septum. Dry nitrogen was passed through the solution, thallium(I) ethoxide** (Aldrich; 0.53 g, 2.1 mmol) was added, and the solution was stirred for 15 min, and evaporated (to remove ethanol). The yellow-green residue was dissolved by the addition of benzene (20 mL), and thionyl chloride (0.26 g, 2.1 mmol) was introduced, leading to the formation of a white precipitate. The suspension was stirred for 2 h, and then centrifuged; the supernatant solution was filtered through Celite, and the filtrate evaporated, affording a colorless syrup; yield, 0.55 g (100%). According to t.l.c. evidence, the product consisted of a single component, and its ^{1}H-n.m.r. spectrum was indistinguishable from that of **6** prepared[2] by other methods; ^{1}H-n.m.r. data: δ 6.04 (s, 1 H, H-1), 5.1–3.9 (m, 6 H, H-2,3,4,5,6,6′), 1.43 (s, 6 H, 2 CH_3), 1.35 (s, 3 H, CH_3), and 1.30 (s, 3 H, CH_3); $J_{1,2} < 1$ Hz.

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl chloride (**4**). — A solution of **1** (Pfanstiehl; 0.54 g, 1.0 mmol) in chloroform (15 mL) was dried over molecular sieves (4A; 2 g), and then transferred with a syringe to a flask fitted with a rubber septum. Dry nitrogen was passed through the solution, followed, at 0°, by addition of thionyl chloride (0.71 g, 6.0 mmol). The solution was boiled under reflux for 5 h, and then evaporated, affording a colorless syrup; yield, 0.56 g (100%). According to t.l.c. evidence, the product consisted of a single component, and its ^{1}H-n.m.r. spectrum was indistinguishable from that of **4** prepared[2] by other methods; ^{1}H-n.m.r. data: δ 7.6–6.9 (m, 20 H, aryl), 6.1 (d, 1 H, H-1), and 5.0–3.7 (m, 14 H, 4 CH_2, H-2,3,4,5,6,6′); $J_{1,2}$ 4.0 Hz.

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*In the earlier study[5], the reaction was conducted in the presence of pyridine, although the low yield of **6** obtained may have resulted from the use of insufficient thionyl chloride.

**As thallium compounds are extremely toxic[4], rubber gloves should be worn, and operations conducted in a hood.

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