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Note

Fluorinated sulphonates*: Ether formation using benzyl and methyl trifluoromethanesulphonate (triflate)

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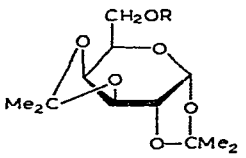
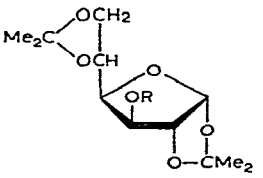
The high susceptibility of fluorinated alkyl and aryl sulphonates to nucleophilic attack[2] has recently attracted interest in carbohydrate chemistry. Kronzer and Schuerch[3] have attempted to use 1-trifluoromethanesulphonates (triflates) as substrates for glycoside formation. Maradufu and Perlin[4], and Hall and Miller[5] have demonstrated the enhanced reactivity of primary and secondary triflates as compared to conventional aryl esters, and Hall and Miller[1] have extended that concept to include 2,2,2-trifluoroethanesulphonates (tresylates) and pentafluorobenzenesulphonates (pentaflates).

Lemieux and Kondo[6] first showed that the hydroxyl groups of sugars could be readily benzylated by reaction with benzyl triflate, and reactions of methyl triflate have been described[7].

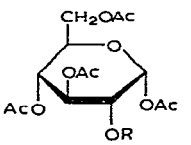
The carbohydrate derivatives **1–3** were treated with benzyl triflate, prepared *in situ* by reaction at low temperature of benzyl alcohol with trifluoromethanesulphonic anhydride (triflic anhydride), using 2,6-di-*tert*-butylpyridine as base. The



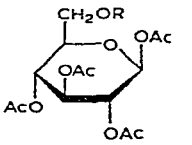
1 R = H
4 R = CH_2Ph
7 R = Me



2 R = H
5 R = CH_2Ph
8 R = Me



3 R = H
6 R = CH_2Ph
9 R = Me



10 R = H
11 R = Me

*Studies of Specifically Fluorinated Carbohydrate Derivatives: Part XVIII. For Part XVII, see Ref. 1.

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reactions were rapid, giving good yields of **4** and **5** and, after column chromatography, 60% of **6**. The work-up procedure was designed to allow for the recovery of the expensive reagent, 2,6-di-*tert*-butylpyridine.

During the development of the above method, a number of alternative procedures were investigated. Attempts to use a large excess of anhydrous potassium carbonate with benzyl triflate derived from triflic anhydride were unsuccessful because the reaction mixture became highly acidic. Anhydrous potassium carbonate could be used with benzyl triflate generated by the reaction of benzyl bromide and silver triflate. This procedure successfully converted **2** into **5**, but 2,6-di-*tert*-butylpyridine was a better base. Other organic bases were also studied. Pyridine and 2,6-dimethylpyridine were *N*-benzylated, hence the use of the more-hindered base, 2,6-di-*tert*-butylpyridine. Lemieux and Kondo[6] used 2,4,6-trimethylpyridine at $\sim -60°$, and Lindberg and co-workers[7] used 2,6-di-*tert*-butyl-4-methylpyridine, which is less-expensive than 2,6-di-*tert*-butylpyridine.

Formation of the methyl ethers **7–9** followed a similar procedure, using commercially available methyl triflate and 2,6-di-*tert*-butylpyridine. Not surprisingly, these reactions were far slower than the benzylation reactions. Heating the reactants under reflux in solution in dichloromethane gave good yields for the conversions **1→7**, **2→8**, and **10→11**. The conversion **3→9** required a substantially longer reaction time and afforded two products, of which the major one was the 2-methyl ether. 2,4,6-Trimethylpyridine was converted into the *N*-methyl triflate salt. Preliminary attempts to benzylate or methylate methyl α-D-glucopyranoside were unsuccessful when CH_2Cl_2 was used as solvent.

EXPERIMENTAL

N.m.r. spectra were measured with a Varian XL-100 (15) instrument fitted with a Varian 620 L (16K) computer for Fourier transform measurements; acetone-d_6 was used as solvent with tetramethylsilane as internal reference for the chemical shifts which are reported on the τ scale. Optical rotations were measured with a Perkin–Elmer 141 Polarimeter at 25 $\pm 1°$. T.l.c. was performed on silica gel G (Stahl), using ethyl ether–toluene (2:1) and detection by charring with H_2SO_4. For short-column (3.5 × 50 cm) chromatography[8], silica gel G was used with a nitrogen pressure of 5–15 p.s.i.; ~120 g of silica gel was used for each gram of material to be separated. All melting points are uncorrected.

The following were purchased from Willow-Brook Laboratories, Waukesha, Wisconsin, and were used without further purification: trifluoromethanesulphonic anhydride, methyl trifluoromethanesulphonate, 2,6-di-*tert*-butylpyridine, and silver trifluoromethanesulphonate.

Benzylations. — (*a*) Trifluoromethanesulphonic anhydride (1 ml, 6 mmol) was added under dry nitrogen to dry CH_2Cl_2 (25 ml) at $\sim -70°$ followed by dropwise addition during 5 min of a solution of benzyl alcohol (0.63 ml, 6 mmol) and 2,6-di-*tert*-butylpyridine (1.5 ml, 6 mmol) in dry CH_2Cl_2 (8 ml). A solution of 1,2:3,4-di-*O*-

isopropylidene-α-D-galactopyranose[9] (0.8 g, 3.1 mmol) and 2,6-di-*tert*-butylpyridine (1.8 ml, 8.1 mmol) in CH_2Cl_2 (10 ml) was then added with stirring (5 min). After stirring for 30 min, the solution was allowed to warm to ambient temperature. Pyridine (1 ml) was then slowly added with stirring and the reaction mixture was washed with water (3 × 15 ml). After drying (Na_2SO_4), filtration, and concentration of the organic layer, a mixture containing **4** and 2,5-di-*tert*-butylpyridine was obtained. The latter was removed at 70°/1 mmHg, leaving 6-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**) as a syrup (1 g, 93%), b.p. 140–145°/0.5 mmHg, $[\alpha]_D$ −59° (*c* 2, chloroform); lit.[10] b.p. 130–160°/0.1 mmHg.

By essentially the above procedure, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[11] (**2**) gave 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**, 89%), b.p. 150–155°/0.5 mmHg, $[\alpha]_D$ −25° (*c* 2, ethanol); lit.[12] $[\alpha]_D$ −26.9° (ethanol).

(*b*) To a suspension of silver trifluoromethanesulphonate(1.6 g, 6 mmol) in cyclohexane (40 ml) at ~ −70° (partial solidification), a solution of benzyl bromide (1.0 ml, 6 mmol) in cyclohexane (5 ml) was added. A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.8 g, 3.1 mmol) and 2,6-di-*tert*-butylpyridine (1.8 ml, 8.1 mmol) in cyclohexane (10 ml) was then added with stirring and cooling. The reaction mixture was allowed to attain room temperature and then stirred for 45 min. Pyridine (1 ml) was added, and **5** (0.89 g, 82%) was extracted and distilled (some degradation occurred) as described for **4**.

Using essentially the above procedure, 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose[13] (**3**) was converted into 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranose (**6**, 60%). The product was not distilled, but when eluted from silica gel, it had $[\alpha]_D$ +80° (*c* 2 chloroform); lit.[14] $[\alpha]_D$ +82° (chloroform).

Deacetylation of **6** with methanolic sodium methoxide gave 2-*O*-benzyl-D-glucopyranose[15], m.p. 176–178°.

Methylations. — (*a*) To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[9] (**1**) (1.1 g, 4.2 mmol) in dry CH_2Cl_2 (20 ml), 2,6-di-*tert*-butylpyridine (2.2 ml, 9.9 mmol), mercuric cyanide (0.025 g), and methyl trifluoromethanesulphonate (1 ml, 9.2 mmol) were added. The mixture was heated under reflux in an atmosphere of nitrogen for 12 h and then cooled, and pyridine (1 ml) was added with stirring. The solution was washed with water (3 × 10 ml), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. 2,6-Di-*tert*-butylpyridine was removed at 60°/0.5 mmHg, and the residue was distilled to give 1,2:3,4-di-*O*-isopropylidene-6-*O*-methyl-α-D-galactopyranose (**7**; 1.1 g, 95%), b.p. 120°/0.5 mmHg, $[\alpha]_D$ −63° (*c* 3 chloroform); lit.[16] $[\alpha]_D$ −63.9°.

By an essentially similar procedure, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) was converted into 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**8**; 1.05 g, 90%), $[\alpha]_D$ −32° (*c* 1, ethanol); lit.[17] $[\alpha]_D$ −34° (ethanol).

Reaction of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose[13] (0.4 g, 1.1 mmol) as described above for **7**, but with a reaction period of 3 days, gave a mixture of two products (t.l.c.). The major product, which was the slower moving (R_F 0.56), was isolated by p.l.c. and recrystallised from ethanol to give 1,3,4,6-tetra-*O*-acetyl-2-*O*-

methyl-α-D-glucopyranose (**9**; 0.15 g, 36%), m.p. 105–107°, $[\alpha]_D$ +139° (*c* 1.6, chloroform); lit.[18] m.p. 107–108°, $[\alpha]_D$ +109.2° (chloroform).

A solution of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose[19] (**10**; 1.08 g, 2.3 mmol), mercuric cyanide (0.025 g), and methyl trifluoromethanesulphonate (0.8 ml, 7.3 mmol) in dry CH_2Cl_2 (20 ml) was heated under reflux for 24 h. Work-up as described for **7** gave a syrup which crystallised on standing. Recrystallisation of the product from ethanol gave 1,2,3,4-tetra-*O*-acetyl-6-*O*-methyl-β-D-glucopyranose (**11**; 0.77 g, 93%), m.p. 91–93°, $[\alpha]_D$ +20° (*c* 2.5, chloroform); lit.[18] m.p. 92–94°, $[\alpha]_D$ +20.5° (chloroform).

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Note added in proof

The use of silver trifluoromethanesulphonate (silver triflate) in the formation of 1,2-orthoesters, and of a disaccharide, has recently been reported [S. Hanessian and J. Banoub, *Carbohyd. Res.*, 44 (1975) C14–C17].