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## Preliminary communication

# Benzyl trifluoromethanesulfonate. Preparation of tri-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranosyl bromide from 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose*

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Benzyl ether derivatives of carbohydrates are important synthetic intermediates[1]. The success encountered in this laboratory with halide-ion catalysis in the synthesis of α-D-gluco- and α-D-galacto-pyranosides[2,3], utilizing the tetra-*O*-benzylglycopyranosyl bromides, led to an interest in a general method for the preparation of 2-*O*-benzyl derivatives of sugars, particularly of oligosaccharides.

Per-*O*-acetylglycopyranosyl halides having an equatorial 2-acetoxy group generally can be converted in excellent yield into alkyl 1,2-*cis*-orthoacetates by reaction with an alcohol in the presence of quaternary ammonium halide and a suitable buffer such as 2,4,6-trimethylpyridine[4,5]. Particularly when O-2 is equatorial, hydrolysis of the orthoacetates in aqueous acetic acid under kinetic control provides[5] ready access to such compounds as 1,3,4,6-tetra-*O*-acetyl-α-D-gluco-(1) and -galacto-pyranose (2) and to 1,3,4-tri-*O*-acetyl-α-L-fucopyranose. Benzylation of these compounds under conditions wherein neither acetyl-group migration nor loss of acetyl group occurred would therefore provide a convenient route to the desired 2-benzyl ethers.

The commercial availability of trifluoromethanesulfonic acid anhydride (triflic anhydride) has provided ready access to triflate esters that are highly prone to nucleophilic attack[6]. It was considered that benzyl triflate would be a particularly powerful benzylating agent and perhaps allow the benzylation of such compounds as **1** and **2** under adequately mild conditions.

The p.m.r. spectrum for a solution of benzyl alcohol (29 mg, 0.27 mmole) and 2,4,6-trimethylpyridine (37 mg, 0.31 mmole) in 0.2 ml of deuteriochloroform kept at −60° showed signals (p.p.m.) at δ 2.20 (*s*, $CH_3$), 2.38 (*s*, $2CH_3$), 4.59 (*d*, $CH_2$), 6.71 (*s*, 2H), and 7.0–7.7 (*m*, $C_6H_5$ and OH). On the addition of triflic anhydride (78 mg, 0.28 mmole) in

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0.1 ml of the pure solvent, the p.m.r. spectrum changed within 30 min to δ 2.48 (*s*, $CH_3$), 2.67 (*s*, $2CH_3$), 5.46 (*s*, $CH_2$), 7.36 (*s*, 2H), 7.41 (broad *s*, $C_6H_5$). This spectrum remained virtually unchanged when the solution was kept at −60° for 4 days. Thus, benzyl triflate appeared to have been formed and to be usefully stable at this temperature. However, a separation of phases occurred within minutes at room temperature and within a few hours at −20°. That benzyl triflate had in fact been formed was confirmed, and its ability to benzylate an alcohol at −60° was established, by the addition of 2-propanol. After 1 h, a quantitative yield of benzyl isopropyl ether was obtained. Benzyl triflate could also be prepared at −60° in the presence of either pyridine or ethyldiisopropylamine, but 2,4,6-trimethylpyridine proved most useful for the following type of preparation.

A solution of benzyl alcohol (544 mg, 5.04 mmoles) and 2,4,6-trimethylpyridine (610 mg, 5.04 mmoles) in 3.5 ml of dichloromethane was added dropwise to a solution of triflic anhydride (1.42 g, 5.04 mmoles) in 2 ml of dichloromethane. The system was kept anhydrous and maintained at −60°. After 30 min, a solution of 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**2**) (500 mg, 1.44 mmoles) and 2,4,6-trimethylpyridine (285 mg, 2.35 mmoles) in 1 ml of dichloromethane was added dropwise during 60 min. The reaction was monitored by t.l.c. and required 5 days at −60° to go near to completion. As a test for residual triflic anhydride, 2-propanol (5 mmoles) and 2,4,6-trimethylpyridine (5 mmoles) were added, and the solution was maintained for an additional hour at −60° prior to addition to cold water. The crude product, isolated by thorough extraction with dichloromethane, contained ~1.1 mmole of benzyl isopropyl ether. Therefore, benzyl triflate was still present after the 6-day reaction time. The p.m.r. spectrum was consistent with a high yield of 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranose (**3**) contaminated with 2,4,6-trimethylpyridine and benzyl isopropyl ether. Fractionation of the crude product (950 mg) by preparative t.l.c. gave spectroscopically pure **3** (514 mg, 79%), $[\alpha]_D^{25}$ +87° (*c* 0.83, chloroform).

Treatment of **1** under the conditions reported for **2** provided tetra-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranose (**4**, 63%) having physical constants in agreement with those reported by Brennan and Finan[7].

It was reported[7] that the reaction of **4** with hydrogen bromide in acetic acid at 10° for 3 h provides 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl bromide (**5**). The concentration of hydrogen bromide used was not reported and neither was the yield. In our hands, this reaction, using a saturated solution of hydrogen bromide in acetic acid prepared at 0°, caused 80% *O*-debenzylation. With compound **3**, *O*-debenzylation was complete.

Compounds **3** and **4** were added to saturated solutions of hydrogen bromide in dichloromethane prepared at −25°, and the products isolated after a 2-h reaction time at this temperature. P.m.r. analysis of the crude products showed **3** to provide an ~3:1 mixture of 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-galactopyranosyl bromide (**6**) and 3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl bromide, whereas **4** provided an ~2:1 mixture of **5** and 3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl bromide. Compound **6** can be prepared as a nearly pure (p.m.r.) syrup

by reaction of 2 with 3 molecular equivalents of hydrogen bromide (2.7% w/v in dichloromethane) at 0° for 1.5 h.

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