Carbohydrate Research, 47 (1976) C8–C10

Preliminary communication

A new synthesis of glycosides. Reactions of trifluoromethanesulfonic anhydride at the anomeric centre

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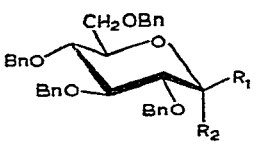
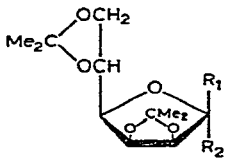
(Received February 11th, 1976; accepted for publication, February 17th, 1976)

Trifluoromethanesulfonates (triflates) undergo vigorous, nucleophilic displacement reactions[1–3], a property that has been utilized in the sugar series in a facile synthesis of 4-deoxy-4-fluoro-D-galactose[4]. This communication describes displacement reactions at the anomeric centre in which triflates act as intermediates, and which furnish a novel procedure for the synthesis of glycosides and higher saccharides.

Our initial attempt[5] to prepare a 1-*O*-triflyl derivative by reaction of triflic anhydride (**1**) with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**2**) in pyridine yielded, instead, the β-pyridinium triflate (**3**) [m.p. 152–153°, $[\alpha]_D$ –20° (*c* 4, chloroform); characterized by elemental analysis, and ^1H and ^{13}C n.m.r. spectroscopy]. This concurs with recent observations by Hall and Miller[6] on the synthesis of pyridinium triflates, and bears an analogy with the formation of pyridinium glycosides from glycosyl halides[7,8]. Because the latter are unreactive towards hindered alkylpyridines[9], 2,4,6-collidine (**4**) was used instead of pyridine; this appeared to promote a rapid formation of the desired 1-triflate (**5**) (chromatographic and n.m.r.-spectral evidence), but, nevertheless, attempts at displacement with ethanol or methanol afforded little glycoside together with as-yet-unidentified products.





2 R_1 = H, R_2 = OH
3 R_1 = $C_5H_5N^+OTf^-$, R_2 = H
5 R_1, R_2 = H, OTf
7 R_1, R_2 = H, Br
8 R_1 = H, R_2 = OCH_3
9 R_1 = OCH_3, R_2 = H
10 R_1 = H, R_2 = D-Glc*p*$(OAc)_4$

11 R_1 = H, R_2 = OH
12 R_1 = H, R_2 = OCH_3
13 R_1 = OCH_3, R_2 = H

By contrast, glycoside formation took place in high yield when the reaction mixture was supplemented by the addition of tetrabutylammonium bromide (**6**), the object being to generate[10] a glycosyl bromide (**7**) *in situ*. Thus, a solution of **2** (1.0 mmole), **4** (3.0 mmoles), and **6** (2.0 mmoles) in dry dichloromethane (5 ml) was added to **1** (1.5 mmoles) at −70°, followed after 1 h at room temperature by methanol (15.0 mmoles), affording, in a reaction time of 1.5 h, a 95% yield of a mixture (isolated by column chromatography on silica gel) consisting of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**8**) (70%; indistinguishable by p.m.r. spectroscopy from the known, syrupy glycoside) and its β anomer (**9**) (25%; syrup, characterized by p.m.r. spectroscopy). When 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (2.0 mmoles) was used as the hydroxylic component, a 60% yield of a disaccharide was obtained in 24 h; according to ^{1}H and ^{13}C n.m.r. spectroscopy, as well as polarimetric data, the product was almost exclusively the α-D-(1→6) compound (**10**).

These findings indicate, therefore, that an aldose derivative such as **2** may be converted into a glycoside (**8**, **9**, or **10**) through the successive intermediacy of a 1-triflate (**5**) and a glycosyl bromide (**7**). In part, this sequence is the converse of that introduced by Kronzer and Schuerch[11], in which silver triflate (or other sulfonate[12]) is used to mediate the reaction between an alcohol and a halide such as **7** (prepared in the conventional way from a 1-*O*-acyl derivative with hydrogen bromide). Although **5** is a presumed intermediate[11] in both sequences, our conditions have been found unfavorable for glycoside formation unless bromide ion is present in the solution. The present procedure also incorporates a halide-exchange step[13,14], which has been shown[10,15,16] to favor the formation of α-D-glucosides from **7**.

A noteworthy feature of the current route to glycosides is that it circumvents the usual practice of employing the reaction of hydrogen halides with 1-*O*-acylaldoses to generate glycosyl halides. As in the formation of **8** or **10** from **2**, this lessens the number of individual steps required in the synthetic sequence. In addition, however, this feature permits the use of such acid-labile protecting groups as acetals which, at present, are not normally employed. To illustrate, when 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**11**) in dichloromethane was treated in succession, as described, with **4**, **6**, **1**, and methanol, a 3:2 mixture of the methyl α- and β-D-glycosides (**12** and **13**) was obtained as the only substantial product (*cf.* ref. 17); these anomers were separated on silica gel in 60% overall yield, and characterized by comparison of their ^{1}H and ^{13}C n.m.r. spectra with those of the known, syrupy glycosides.

ACKNOWLEDGMENTS

The generous support of the Pulp and Paper Research Institute of Canada and the National Research Council is gratefully acknowledged.

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