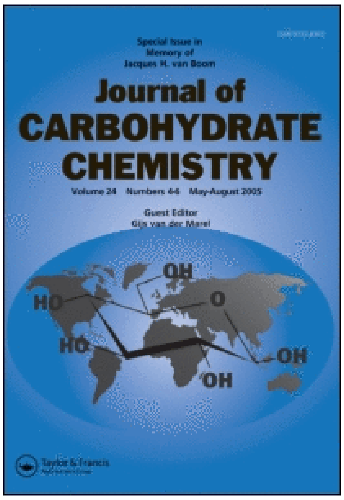

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USE OF FERRIC CHLORIDE IN CARBOHYDRATE REACTIONS.[1]

IV. ACETOLYSIS OF BENZYL ETHERS OF SUGARS

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ABSTRACT

Acetolysis of benzyl ethers of sugars has been carried out with anhydrous ferric chloride in acetic anhydride. By employing this reagent, benzyl ether groups variously placed in sugars or in their glycosides could be removed with ease and replaced by acetyl groups. By controlled acetolysis, preferential removal of certain benzyl groups was possible. The results show that in D-glucose the relative ease of removal of benzyl ether groups by acetolysis follows the order C-6 > C-4 > C-3 > C-2 and that the rate of acetolysis is 6-O-Bn : 3-O-Bn : 2-O-Bn = 125 : 24 : 1. The corresponding methyl ethers were very sluggish towards acetolysis.

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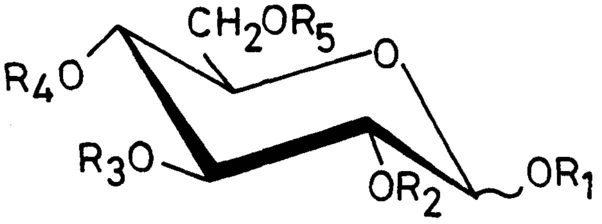
INTRODUCTION

Benzyl ether groups are commonly used as protective groups in carbohydrate synthesis because of their ease of formation and subsequent removal. Often more than one OH group of a sugar is substituted by a benzyl group. If preferential removal of a benzyl group in a per-O-benzyl sugar could be effected, it would be of considerable interest in the synthesis of carbohydrate derivatives. We have earlier shown that anhydrous ferric chloride can be employed as a catalyst for acetalation[2] and acetylation[3] of carbohydrates with many advantages over the traditional catalysts.[4,5] Using a ferric chloride - acetone reagent, glycosides can be directly acetonated to afford the 1,2-O-isopropylidene derivative.[6] The most common amongst the reagents employed for the acetolysis of benzyl ethers of carbohydrates and their derivatives is acetic acid - acetic anhydride - concentrated sulfuric acid.[7-11] In this communication, we describe a convenient method for the partial as well as complete removal of O-benzyl groups in sugars using the reagent ferric chloride - acetic anhydride.

RESULTS AND DISCUSSION

Treatment of O-benzyl sugars with ferric chloride - acetic anhydride resulted in the removal of the O-benzyl group at rates depending upon the



1 : $R_1 = R_3 = R_4 = R_5 = H$, R_2 = Bn*

2 : R_1 (α) = $R_3 = R_4 = R_5$ = Ac, R_2 = Bn

3 : $R_1 = R_2 = R_4 = R_5 = H$, R_3 = Bn

4 : $R_1 = R_2 = R_3 = R_4 = H$, R_5 = Bn

6 : $R_1 = R_2 = R_3 = R_4$ = Ac, R_5 = Bn

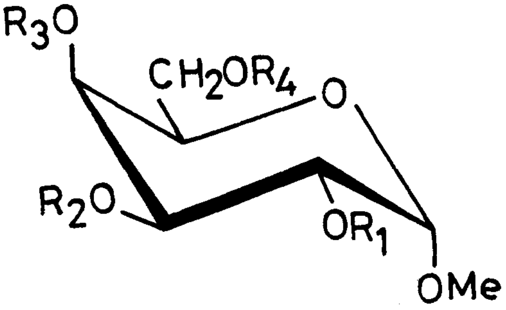
9 : R_1 = Me (α), $R_2 = R_3$ = Bn, $R_4 = R_5 = H$

10 : R_1 = Me (α), R_2 = Bn, $R_3 = R_4 = R_5$ = Ac

11 : $R_1 = H$, $R_2 = R_3 = R_4 = R_5$ = Bn

12 : R_1 (α) = R_5 = Ac, $R_2 = R_3 = R_4$ = Bn

*Bn = $CH_2-C_6H_5$



5 : $R_1 = R_2 = R_3 = H$, R_4 = Bn

7 : $R_1 = R_2 = R_3$ = Ac, R_4 = Bn

8 : $R_1 = R_2 = R_3 = R_4$ = Ac

position of substitution, accompanied by rapid acetylation of any free hydroxyl group present.

The acetolysis of the benzyl ether group in 2-O-benzyl-D-glucopyranose (1)[12] was slow, yielding the peracetylated product which was evident after reaction for 30 min at 30 °C. The O-benzyl cleavage was preceded by the formation of 1,3,4,6-tetra-O-acetyl-2-O-benzyl-α-D-glucopyranose (2),[12] which was complete in less than 15 min, and it was possible to isolate this compound in good yield (75%). While complete acetolysis of 1 required 24 h at room temperature, it required only 12 h at 60 °C. Acetolysis of 3-O-benzyl-D-glucopyranose (3)[13] was faster than its 2-O-analogue (1) by a factor of about 12 at 30 °C and 24 at 60 °C. The benzyl group in 6-O-benzyl-D-glucopyranose (4),[14] as well as in methyl 6-O-benzyl-α-D-galactopyranoside (5),[15] was acetolyzed by ferric chloride - acetic anhydride in 5 min at 60 °C giving glucose pentaacetate[5] and 8,[16] respectively, but the isolation of the acetylated O-benzyl compounds 6 and 7 was not possible under the reaction conditions employed. GC of the acetolysis (2 h, 30 °C) product of methyl 2,3-di-O-benzyl-α-D-glucopyranoside (9)[17] showed the presence of a major component, presumably methyl 3,4,6-tri-O-acetyl-2-O-benzyl-α-D-glucopyranoside (10). However, no attempt was made to isolate this compound. Removal of the aglycon residue in 5 as well as in 9 took place in 3 h at 60 °C. Controlled acetolysis (5 min, 60 °C) of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (11)[18] gave 1,6-di-O-acetyl 2,3,4-tri-O-benzyl-α-D-glucopyranose (12)[7] as a major product as shown by GC.

Thus it is observed with D-glucose that a benzyl ether group attached to a primary carbon is much more labile towards an acetolyzing agent than those attached to secondary carbons. Further, the more distant the secondary carbon to which the O-benzyl group is attached from the anomeric centre, the faster is the acetolysis. The above results show that the cleavage of the C-O-Bn bond in D-glucose by acetolysis follows the order: C-6 > C-4 > C-3 > C-2 and that the rate of acetolysis of 6-O-Bn : 3-O-Bn : 2-O-Bn = 125 : 24 : 1. By employing concentrated sulfuric acid - acetic acid - acetic anhydride, Ponpipom[11] was able to acetolyze 3,4,6-tri-O-benzyl 1,2-O-(1-methoxyethylidene)-β-D-mannopyranose to 1,2,6-tri-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranose and 1,2,4,6-tetra-O-acetyl-3-O-benzyl-α-D-mannopyranose in 71 and 59% yield, respectively. This showed the preferential cleavage of the 6-O-Bn bond over the O-Bn bonds at C-3 and C-4. Furthermore, the cleavage of O-Bn bond at C-4 was more facile than that at C-3. Partial acetolysis[7] of the anhydro ring in 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-glucopyranose to yield 12 also reveals the high susceptibility of the bond involving the primary carbon atom. The results of the present study are thus in conformity with the above as well as with the results of Allerton and Fletcher[8] who acetolyzed benzyl ethers of certain hexitol acetals.

For comparison, a few methyl ethers of D-glucose corresponding to the benzyl ethers mentioned above were acetolyzed with ferric chloride - acetic anhydride. It was observed that demethylation was very sluggish. The relatively facile removal of benzyl groups may be rationalized by the greater stability of the benzyl carbonium ion.

EXPERIMENTAL

Acetolysis was carried out in the following manner. The benzyl ether derivative was added to a solution of anhydrous ferric chloride in acetic anhydride maintained at the required temperature for the desired time period. The solution was then poured into a large excess of ice-cold water and stirred. The product was extracted with chloroform, and the extract was washed successively with aqueous sodium bicarbonate solution (10%, w/v) and water. The dried (sodium sulfate) extract was concentrated to dryness under reduced pressure. For monitoring the reaction, aliquots of the reaction mixture were withdrawn at intervals, processed as above, and analyzed by gas-liquid chromatography (GC). The peaks were identified by comparison with standards which were prepared by the known methods.[5,7,12-18] The final product in all

TABLE 1

Acetolysis of Benzyl Ethers of Sugars Using Ferric Chloride-Acetic Anhydride

Compound No.	Wt. (mg)	$FeCl_3$ (mg)	Ac_2O (mL)	30 °C Time (h)	30 °C Yield[a] (%)	60 °C Time (h)	60 °C Yield[a] (%)
1	65	40	2.0	24	55-60	12	55-60
3	65	40	2.0	2	68-75	0.5	70
4	150	30	2.0	-	-	0.08	75
5	132	26	2.0	-	-	3	65
9	150	60	1.5	24	60	12	63-65
11	150	65	2.0	-	-	12	60

[a] Yield of the corresponding peracetate.

cases was the sugar peracetate, which was crystallized and characterized by its mp, specific optical rotation, IR and NMR. Experimental conditions and results are given in Table 1.

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