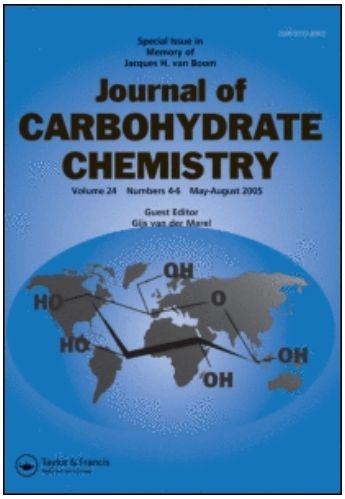

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COMMUNICATION

A SIMPLIFIED, ONE-POT PREPARATION OF ACETOBROMOSUGARS FROM REDUCING SUGARS*

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Acetobromoglycoses continue to be important as glycosyl donors in the synthesis of simple glycosides as well as complex oligosaccharides. From reducing sugars they are usually prepared via their peracetates in two steps. In the first step, sugars are converted to their peracetates using pyridine and acetic anhydride[1,2] and the acetates are then converted in a second step to acetobromosugars using a solution of hydrogen bromide in glacial acetic acid(HBr/HOAc).[2] Although not in use very often Redemann and Niemann[3] as well as Lemieux[4] have described one-pot methods for the preparation of acetobromoglucose wherein the reducing sugar is first treated with acetic anhydride in the presence of sulfuric acid[3] or perchloric acid[4] respectively to afford the peracetate. Direct conversion of the peracetate to its 1-bromo-derivative, in yields ranging from 80-87%, was then achieved by either treating the solution of the peracetate with gaseous HBr[3] or with bromine in the presence of red phosphorus.[4] In another approach to a one-pot method Humoller[5] prepared tri-O-acetyl-β-L-arabinopyranosyl bromide in 40% yield by passing anhydrous HBr gas through a suspension of L-arabinose in acetic anhydride. By an essentially similar method

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Dale[6] obtained acetobromosugars in yields ranging from 26-77% depending upon the sugar. Because acetobromosugars are the compounds most frequently used for synthesizing numerous other sugar derivatives, we thought it would be worthwhile to report our recent observation that acetic anhydride and HBr/HOAc can be used with advantage for the preparation of acetobromosugars.

A typical procedure is described as follows. Acetic anhydride (5 mL/g of sugar) was added at room temperature to a round bottom-flask containing the sample, and while being stirred, a solution of HBr in glacial acetic acid (45% w/v, 1 mL/g of sugar) was added. Stirring was continued until all the solids went into solution (see Table 1). More HBr solution (5 mL/g of sugar) was then introduced, and after stirring for a further period of 2-6 h (see Table 1), the clear solution was concentrated under reduced pressure and repeatedly coevaporated with toluene to a syrup. Addition of dry diethyl ether to the syrup, followed by solvent removal under vacuum, gave fine crystals in almost quantitative yield. They were of such excellent purity (homogeneous by NMR spectroscopy) that they could be used directly in glycosylation reactions. Products from entries 7 and 8 did not crystallize at this stage and their NMR spectra revealed the presence of some furanosyl bromide. The crude product from entry 9, though often crystallized on standing, also contained furanosyl derivative. Therefore products from these reactions were dissolved in dry ether and after diluting with hexane to incipient turbidity and adding ether to make the solution clear were allowed to stand in the cold for crystallization. Crystals were collected by filtration and were obtained in yields of 55-75%.

On dissolution of the sugar, after adding the first aliquot of HBr/HOAc reagent, a clear, colorless/faint yellow solution was obtained indicating completion of acetylation. Removal of volatiles at this stage allows isolation of the peracetylated aldoses as a mixture of their anomers (Table 1). Rhamnose monohydrate (entry 3) went into solution within one min after adding the first portion of the HBr solution. Therefore in such cases addition of the second portion can follow immediately. Interestingly the hydrated disaccharides (entries 1 and 2) also went into solution much faster than some of the anhydrous aldohexoses (entries 4 and 7) listed in Table 1. It is probable that

TABLE 1. Preparation of Acetobromosugars from Reducing Sugars[a]

No.	Reducing sugar	Time required for: Dissolution of sugars[c] (α:β peracetates)	Time required for: Formation of C1-bromide	Product[b]
1.	D-Lactose monohydrate[d] (1)	45 min (1:0.21)	4 h	Acetobromo-α-D-lactose (8)
2.	D-Maltose hydrate (2)	15 min (1:0.37)	2 h	Acetobromo-α-D-maltose (9)
3.	L-Rhamnose monohydrate (3)	1 min (1:0.45)	5 h	Acetobromo-α-L-rhamnopyranose (10)
4.	D-Glucose, anhydrous[d] (4)	5 h (1:0.32)	6 h	Acetobromo-α-D-glucopyranose (11)
5.	4 + 1 mol equiv. H_2O	75 min (1:0.70)	3 h	11
6.	D-Mannose (5)	5 min (1:0.57)	2 h	Acetobromo-α-D-mannopyranose (12)
7.	D-Galactose, anhydrous (6)	3 h (1:0.55)[e]	6 h	Acetobromo-α-D-galactopyranose (13)
8.	6 + 1 mol equiv. H_2O	75 min (1:0.68)[e]	4 h	13
9.	L-Arabinose (7)	30 min (1:1)[e]	2 h	Acetobromo-β-L-arabinopyranose (14)

a. Reactions were carried out on a 1-2 g scale at room temperature.

b. Products were crystalline and their physical properties were consistent with literature data.[7] They gave satisfactory elemental analysis and some of their selected $^{1}H/^{13}C$ nmr data are reported.[8]

c. Following the addition of the first aliquot of HBr/HOAc solution.

d. Reactions were also carried out on 20-40 g scale.

e. Also contained some furanosyl acetate. Better yields of 13 were obtained by the method described by Jeanloz and Stoffyn.[2]

the water of hydration increases the acidity of the reaction mixture thereby catalyzing the acetylation reaction faster. Thus the primary reaction time in the case of these aldoses could be reduced to less than half (entries 5 and 8), without detriment to yield, by carrying out the reaction in presence of the equivalent of water.

When sugars were treated with a mixture of acetic anhydride (5 mL/g of sugar) and the entire amount of HBr/HOAc reagent (5-6 mL/g of sugar) in one step, the formation of the glycosyl bromide was found to be incomplete (TLC) even after stirring for over 24 h at room temperature. The reaction conditions in such cases can be compared with those employed by Humoller[5] and Dale[6] who obtained acetombromosugars in yields ranging from 26-77% depending upon the sugar. In all the above methods the peracetate derivative is formed but is not readily converted to the bromide. This could plausibly be attributed to diminished quantities of free HBr being available in all the above reaction mixtures following the conversion of the free sugar to its peracetate derivative because the addition of a further aliquot of the same HBr/HOAc reagent to the aforementioned incomplete bromination reaction resulted in complete bromination of the intermediate peracetate (TLC).

Similarly, in our two step procedure the HBr of the first aliquot of reagent is probably also depleted during the formation of the peracetate derivative, the second aliquot adding sufficient free HBr to the reaction to complete highly efficient conversions of the glycosyl acetates to their respective glycosyl bromides (Table 1). Although the methods of Redemann and Niemann[3] and Lemieux[4] are also one-pot methods which give good yields of acetobromosugars, our method has the distinct advantage of using one convenient and commercially available reagent to carry out both the acetylation and bromination procedures.

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