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The influence of boric acid on the acetylation of aldoses: 'one-pot' syntheses of penta-*O*-acetyl-β-D-glucofuranose and its crystalline propanoyl analogue

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When glucose and boric acid are heated in acetic acid a soluble compound forms from which, with acetic anhydride and catalytic amounts of sulfuric acid, a mixture consisting of >90% of the glucofuranose per-acetates (α : β ratio 1 : 1.8) is obtained in high yield. In the absence of the sulfuric acid partial acetylation takes place and penta-*O*-acetyl-β-D-glucofuranose (α : β ratio 1 : 52) is obtainable in good yield by removal of boric acid and completion of the esterification by addition of acetic anhydride and pyridine. A new, crystalline glucofuranose, penta-*O*-propanoyl-β-D-glucofuranose, is obtained in 58% yield in a 'one-pot' procedure using boric acid.

The effects of boric acid on the acid-catalysed acetylation of other aldo-hexoses and -pentoses suggest that the synthesis of furanosyl per-esters could be successful with xylose and idose as well as with glucose.

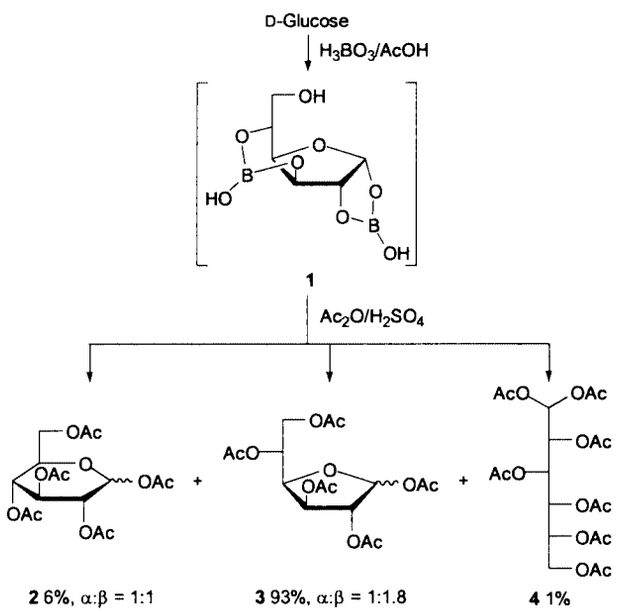
Introduction

While the direct preparations, from glucose, of either penta-*O*-acetyl-α- or β-D-glucopyranose **2** are straightforward,[1] the furanosyl isomers **3**, which have value as starting materials for making glucofuranosides and their *C*-, *N*- and *S*-linked analogues, require several steps. A common method is to constrain the glucose in the furanose form by way of its 1,2-*O*-isopropylidene ketal, and in this way the furanosyl per-esters can be obtained in 41% overall yield after five steps.[2] Otherwise they have been prepared from thiofuranosides made by kinetically controlled cyclizations of glucose dithioacetals using mercury(II) catalysts (five steps from glucose, 31% yield[3]), and recently by the acetolysis of octyl glucofuranosides[4] which were in turn made by the coupling of octan-1-ol with glucose in the presence of $FeCl_3$ (46% overall yield[5]). In some non-specific acetolysis reactions the furanosyl acetates are formed together with the pyranosyl isomers: glucose with acetic anhydride in the presence of Montmorillonite clays gives products containing 7% of the former,[6] whereas the per-acetates formed on acetolysis of methyl β-D-glucopyranoside in the presence of iron(III) chloride comprise 48% of these furanosyl products.[7] We report here that, in the presence of boric acid, glucose can be converted directly and efficiently to its furanosyl per-esters.

Because of the polyfunctionality and isomeric complexity of glucose and the common structural ambiguity of boric acid [$B(OH)_3$, $B(OH)_4^-$], many esters could be formed by their combination, but no specific products appear to have been isolated. Nevertheless, reaction of the sugar with the acid (1 mol equiv.) in acetone in the presence of a strong acid catalyst gives crystalline 1,2-isopropylidene-α-D-glucofuranose 3,5-borate,[8] and ^1H, ^{11}B and ^{13}C NMR[9,10] and thermodynamic[11] evidence is consistent with boric acid and boronic acids [$RB(OH)_2$] reacting by themselves with the sugar in the furanose form to give 1,2 : 3,5-bis-cyclic esters. Phenylboronic acid affords the stable, well known 1,2 : 3,5-bis-ester.[12] With this in mind and with the information that the above mentioned 1,2-ketal can be used to make 6-substituted glucoses,[8] and that the product derived by reaction of glucose with boric acid (2 mol equiv.) in acetone can be converted in three steps to a penta-*O*-benzoylglucofuranose,[13] we have investigated the influence of added boric acid on the acetylation of D-glucose and other aldoses.

Results and discussion

Glucose and boric acid were heated in acetic acid until a solution was obtained (1 h). Acetic anhydride and a catalytic amount of sulfuric acid (conc.) were then added to effect acetolysis of the initial product (expected to be **1**) and give mixtures of the pyranose (**2**) and furanose (**3**) pentaacetates and the acyclic aldehydohydrate heptaacetate **4** (Scheme 1) which



Scheme 1

were quantified by ^1H NMR spectroscopy. Variation in the proportions of boric acid used caused major changes in the ratios of products formed, as illustrated in Fig. 1. In its absence, the pyranoses **2** represented 95% of the pentaacetates formed (α : β ratio 1.8 : 1) whereas, with two or more molar equivalents of boric acid, the products contained 93% of the furanose isomers **3** (α : β ratio 1 : 1.8) (Table 1). The latter observation is consistent with the initial formation of the furanoid borate intermediate **1** and its transesterification without sugar-ring

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Table 1 The effect of boric acid on the proportions of per-acetates formed on acetylation of aldoses[a]

Sugar	Boric acid (mol equiv.)	Per-acetates (%)[b] α-Pyranose	β-Pyranose	α-Furanose	β-Furanose	Aldehydohydrate	Other	α	β
Hexoses[c]									
D-Glucose	0	61	34	2	3	0			
	2.2	3	3	33	60	1			
D-Mannose	0	80	17	2	1	0			
	2.2	9	2	37	12	3	Glucofuranose	12	25
D-Allose[d]	0	25	53	5	16	Trace	Altrofuranose	1	
	2.2	13	24	15	39	3	Altrofuranose	6	
D-Galactose	0	60	15	7	18	Trace			
	2.2	66	16	4	8	6			
L-Idose[d]	0	34	9	26	30	1			
	2.2	3	9	33	54	1			
Pentoses[e]									
D-Ribose	0	12	45	10	27	5	Arabinofuranose	1	
	2.2	11	42	11	29	3	Arabinofuranose	3	1
D-Arabinose	0	12	49	29	8	2			
	2.2	13	55	19	6	7			
D-Xylose	0	62[f]	16	8	10	4			
	2.2	6[f]	2	43	47	2			
D-Lyxose	0	62	11	15	3	6	Xylofuranose	1	2
	2.2	9	2	39	8	3	Xylofuranose	18	21

[a] Conditions are described in the Experimental section. [b] From the integration of the ^{1}H NMR resonances of the 1-H protons. The species listed made up >96% of the resonances in the range δ_H 7.0–5.6 (except for idose with added boric acid, 86%). The values for the α- and β-pyranose esters produced in the absence of boric acid are similar to equilibrium figures.[17] [c] NMR assignments made using data from refs. 4 and 18. [d] Experiments carried out on half the scale. [e] NMR assignments made using data from: 19, 20. [f] NMR assignment made using data from ref. 21.

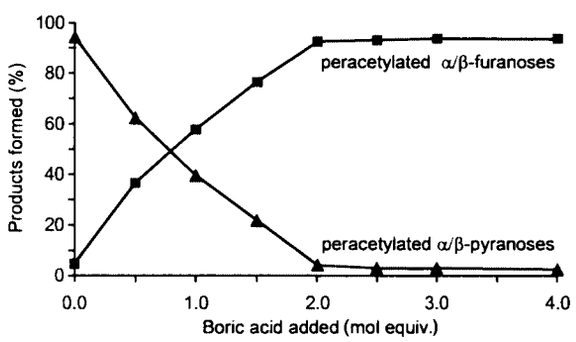


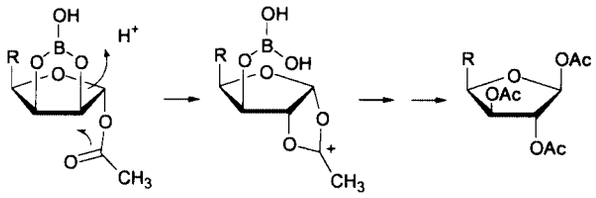
Fig. 1 The effects of varying amounts of boric acid on the products of acid-catalysed acetylation of D-glucose. (Conditions as given in the Experimental section.)

rearrangement. Boric acid also results in the formation of 1% of the acyclic heptaacetate **4**, this compound having also been observed in the products of acetolysis of methyl β-D-gluco-pyranoside in the presence of iron(III) chloride.[7] The identity of the penta-*O*-acetyl-D-glucofuranoses produced *via* ester **1** was confirmed by NMR spectroscopy[2,4] and by their conversion to the known phenyl β-D-glucofuranoside *via* its tetraacetate.[14]

When glucose and boric acid were heated in acetic acid–acetic anhydride without the addition of sulfuric acid, acetylation of the sugar (or more precisely acetolysis of the proposed borate intermediate) still occurred, and this procedure afforded a means of preparing β-D-glucofuranose pentaacetate in high yield (α:β ratio 1:52, by GLC-MS analysis). However, a two-step process was required to achieve this, the first step apparently locking the sugar in the β-furanosyl acetate form by preferential acetolysis at C-1 of the borate **1** with C–O bond fission and inversion of configuration, and the second, a standard acetylation carried out with acetic anhydride in the presence of pyridine after removal of boric acid as the volatile trimethyl borate, completing the esterification. The two anomers could not be separated by chromatography (flash silica column).

With the objective of obtaining a crystalline furanosyl pentaester for use as a more convenient glucofuranosylating reagent, acylation of glucose was repeated in the presence of boric acid but in propanoic acid with propanoic anhydride as acylation agent. With minor modifications to the acetylation procedure to accommodate changes in physical properties of the compounds involved, a solid product was isolated directly, from which pure penta-*O*-propanoyl-β-D-glucofuranose was obtained by recrystallization (58%). Therefore, under the conditions selected, complete acylation occurred without removal of the boric acid. This previously unknown compound is the first readily available, crystalline per-acylated glucofuranose. By comparison, crystalline 1-*O*-acetyl-2,3,5,6-tetra-*O*-benzoyl-β-D-glucofuranose, which can be used as a β-glucofuranosylating agent, can be made in four steps from glucose in an overall yield of 16%.[15]

The effects of boric acid on the acid-catalysed acetylation of other aldo-hexoses and -pentoses are recorded in Table 1 and suggest that this approach to furanosyl derivatives may be synthetically useful with xylose and idose as well as with glucose. In the case of arabinose and galactose, boric acid suppresses slightly the formation of the furanose forms and may be of use for enhancing the yields of their pyranose per-esters. In some cases partial epimerization occurred at C-2 to give some of the isomeric sugars as their acetylated furanoses, and notably in the cases of the structurally related mannose and lyxose, epimerization was enhanced appreciably when boric acid was present. Such isomerization under acetolysis conditions, which is a known characteristic of aldofuranose esters having *cis*-acetoxy groups at C-2 and C-3, has been summarized by Sowa.[16] When pure α-D-mannofuranose pentaacetate was subjected to the boric acid–acetic acid–acetic anhydride–sulfuric acid acetolysing conditions, no epimerization was observed, although there was 22% conversion to the β-anomer. This suggests that the appreciable inversion at C-2 that occurs with mannose itself (Table 1) does so at the borate ester stage as indicated in Scheme 2. The 2,3-borate ester function therefore apparently performs the role played by 2,3-acetoxonium ions during normal direct acetolyses of aldoses containing *cis*-2,3-diols as proposed by Sowa.[16]



Scheme 2

In summary, boric acid has a profound effect on the acetylation and acetolysis of aldoses. By its use, crystalline penta-*O*-propanoyl-β-D-glucofuranose can be made in a simple, inexpensive, 'one-pot' procedure. The suitability of this compound as a glycosylating agent is under investigation.

Experimental

General methods

All non-specialized starting materials were commercially available research-grade chemicals and were used without further purification. Analytical TLC was carried out on pre-coated 0.25 mm thick Merck 60 F_{254} silica gel plates. Visualization was by absorption of UV light, or by thermal development after spraying with ammonium molybdate and cerium(IV) sulfate in dil. sulfuric acid. Mps were measured with a Reichert hotstage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. Microanalyses were carried out at the Campbell Microanalytical Laboratory, University of Otago. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively in $CDCl_3$ solution (unless otherwise indicated) with TMS as internal standard. *J*-Values are given in Hz. The assignments of peaks were made with assistance of DEPT and COSY (^{1}H,^{1}H and ^{1}H,^{13}C) experiments. Mass spectra were recorded by Mr John M. Allen, Horticultural and Food Research Institute of New Zealand in positive mode at 15 keV with caesium as the ionizing agent in an NBA–MeOH or glycerol–MeOH matrix. Petroleum spirit refers to the fraction of distillation range 60–80 °C.

1,2,3,5,6-Penta-*O*-acetyl-β-D-glucofuranose 3β

D-Glucose (5.0 g, 27.8 mmol), boric acid (3.8 g, 60.7 mmol) and acetic acid (100 cm^3) were stirred at 50 °C for 1 h by which time all the sugar had dissolved. Acetic anhydride (100 cm^3) was added and the mixture was heated at 50 °C for 16 h. The boric acid was removed as trimethyl borate by the addition of methanol (20 cm^3) and *in vacuo* concentration of the subsequent mixture to 100 cm^3 and then the addition of methanol (10 cm^3) and concentration *in vacuo* to 50 cm^3 (×2). Acetic anhydride (100 cm^3) and pyridine (100 cm^3) were added and the solution was stirred at 20 °C for 2 h. Following the addition of ice (200 g), the solution was stirred for 1 h and then extracted with $CHCl_3$ (3 × 150 cm^3). The combined extracts were washed successively with water, HCl (2 M) and water, dried ($MgSO_4$), and concentrated *in vacuo* to give the pentaacetates **3** (10.0 g, 92%) as a pale yellow syrup (90% pure, α : β ratio 1 : 52); ^{1}H and ^{13}C NMR data were identical to literature data (refs. 4 and 2, respectively).

1,2,3,5,6-Penta-*O*-propanoyl-β-D-glucofuranose

D-Glucose (5.0 g, 27.8 mmol), boric acid (3.5 g, 56.9 mmol) and propanoic acid (75 cm^3) were stirred at 70 °C for 1 h. Propanoic anhydride (75 cm^3) was added slowly so that precipitation was avoided and the resulting mixture was heated at 70 °C for 48 h. Ice (100 g) and water (750 cm^3) were added and the mixture was stirred vigorously for 1 h. The precipitate was collected, and recrystallized (×2) from EtOH (20 cm^3) to give the *title compound* (7.4 g, 58%) as white prisms, mp 74.5–75.5 °C (from EtOH); $[\alpha]_D^{22}$ −30.8 (*c* 5.0 in $CHCl_3$) (Found: C, 54.8; H, 7.0. Calc. for $C_{21}H_{32}O_{11}$: C, 54.8; H, 7.0%); δ_H 6.14 (1H, s, 1-H), 5.42 (1H, d, *J* 4.8, 3-H), 5.29 (1H, ddd, *J* 9.4, 2.5 and 5.2, 5-H), 5.10 (1H, s, 2-H), 4.63 (1H, dd, *J* 12.3 and 2.5, 6-H^a), 4.55 (1H, dd, *J* 9.4 and 4.7, 4-H), 4.10 (1H, dd, *J* 12.3 and 5.2, 6-H^b), 2.40 (2H, q, *J* 7.6, CH_2), 2.38 (2H, q, *J* 7.6, CH_2), 2.37 (2H, q, *J* 7.6, CH_2), 2.34 (2H, q, *J* 7.6, CH_2), 2.26 (2H, q, *J* 7.6, CH_2), 1.17 (6H, t, *J* 7.6, 2 × CH_3), 1.13 (6H, t, *J* 7.6, 2 × CH_3), 1.09 (3H, t, *J* 7.6, CH_3); δ_C 174.3, 173.4, 173.0, 172.9, 172.9 (5 × C=O), 99.2 (1-C), 80.2 (4-C), 79.9 (2-C), 73.2 (3-C), 68.6 (5-C), 63.3 (6-C), 28.0, 27.7, 27.7, 27.7, 27.6 (5 × CH_2), 9.4, 9.2, 9.2, 9.1, 9.1 (5 × CH_3); *m/z* (FAB) 459.18664 ($M^+ - H$, $C_{21}H_{31}O_{11}$ requires *m/z* 459.18636), 387 ($M^+ - C_3H_5O_2$, 100%), 183 (24), 137 (25), 57 (52).

Phenyl β-D-glucofuranoside

Pentaacetates **3**, made as described in the acetolysis section below and without further purification, were converted *via* the tetraacetyl glycoside to the title compound as previously described[14] (30%), mp 78.5–80.5 °C (from butan-2-one–petroleum spirit) (lit.,[14] 79–80 °C), $[\alpha]_D^{20}$ −143.2 (*c* 2.0 in H_2O) {lit.,[14] $[\alpha]_D^{20}$ −142 (*c* 2.0 in H_2O)} (Found: C, 56.25; H, 6.3. Calc. for $C_{12}H_{16}O_6$: C, 56.25; H, 6.3%); δ_H (d_6-DMSO) 7.29 (2H, t, *J* 7.9, 3′- and 5′-H), 6.99–6.95 (3H, m, 2′-, 4′- and 6′-H), 5.53 (1H, d, *J* 3.8, OH), 5.36 (1H, s, 1-H), 4.93 (1H, d, *J* 4.1, OH), 4.55 (1H, d, *J* 5.4, OH), 4.36 (1H, t, *J* 5.7, OH), 4.11 (1H, d, *J* 3.8, 2-H), 4.06–4.00 (2H, m, 3- and 4-H), 3.77 (1H, dddd, *J* 8.2, 6.2, 5.4 and 3.0, 5-H), 3.55 (1H, ddd, *J* 11.2, 5.7 and 3.0, 6-H^a), 3.36 (1H, dd, *J* 11.2 and 6.2, 6-H^b); δ_C (d_6-DMSO) 157.2 (1′-C), 129.8 (3′- and 5′-C), 121.7 (4′-C), 116.4 (2′- and 6′-C), 107.3 (1-C), 82.9 (4-C), 81.3 (2-C), 75.3 (3-C), 69.8 (5-C), 64.0 (6-C); *m/z* (FAB) 256.09448 (M^+, $C_{12}H_{16}O_6$ requires *M*, 256.09469).

Acetolysis of aldoses in the absence and presence of boric acid

The sugar (0.55 mmol), boric acid (0 or 1.21 mmol) and acetic acid (2 cm^3) were stirred at 50 °C for 1 h. Acetic anhydride (2 cm^3) and sulfuric acid (2 mm^3) were added and heating was continued for a further 3 h. Ice (20 g) was added and the mixture was stirred for 1 h and then extracted with $CHCl_3$ (3 × 20 cm^3). The extracts were washed successively with $NaHCO_3$ (saturated aq.) and water, and dried ($MgSO_4$), and the solvent was removed to give a syrup that was analysed by ^{1}H NMR spectroscopy (see Table 1).

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