Pergamon

Tetrahedron Letters, Vol. 35, No. 24, pp. 4247-4250, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0761-L

Chemical Regioselective Hydrolysis of Peracetylated Reducing Disaccharides, Specifically at the Anomeric Centre: Intermediates for the Synthesis of Oligosaccharides.

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Abstract: Reaction of reducing disaccharide peracetates **1**, **5**, **9** and **13** with hydrazine hydrate in acetonitrile gave predominantly the corresponding heptaacetates **2**, **6**, **10** and **14**, with the free hydroxyl group at C-1 or the hexaacetates **3**, **7**, **11** and **12**, with the hydroxyl groups at C-1,2 or C-1,3 and the pentaacetates **4** and **8** with the hydroxyl groups at C-1,2,3, depending on the quantity of reagent used.

The oligosaccharide moieties of glycoproteins and glycolipids are components of biological membranes and are known to be involved in biological processes such as cell-cell interaction and cell-virus recognition. This has stimulated considerable interest in the synthesis of a variety of oligosaccharides. The major challenges in oligosaccharide syntheses remain in the methodologies to generate glycosidic linkages with the desired configurations, and in devising a suitable protective-group strategy for the hydroxyl groups.[1]

We have described the use of enzymes for selective acetylation and deacetylation reactions of carbohydrates and their derivatives[2-5]. In this communication we now report a simple and relatively inexpensive method for selective deacetylation of reducing disaccharide peracetates to give the corresponding heptaacetates with the OH group at the anomeric position (C-1), the hexaacetates with the OH groups at C-1,2 and C-1,3,and the pentaacetates with the OH groups at C-1,2,3 positions.

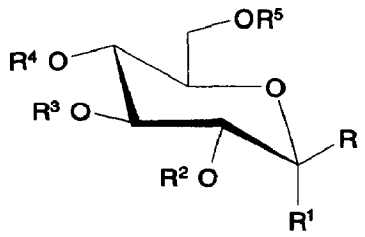
Selective deesterification of fully acetylated glycosides and 1,2-*O*-isopropylidene-aldofuranose derivatives using hydrazine hydrate in combination with pyridine-acetic acid or pyridine has been described[6]. Piperidine[7] and hydrazine acetate[8] have been used to prepare the heptaacetates **2** and **10** from their corresponding octaacetate derivatives. However, piperidine on prolonged treatment leads to the corresponding 1-piperidyl-2-hydroxy-hexaacetate derivative and hydrazine acetate is considerably more expensive than hydrazine hydrate.

Treatment of ß-cellobiose octaacetate (**1**), ß-lactose octaacetate (**5**), ß-maltose octaacetate (**9**) and α/β-melibiose octaacetate (**13**) with 1.2 mol. equiv. of hydrazine hydrate (24% hydrazine content) in acetonitrile afforded predominantly the heptaacetates **2**, **6**, **10** and **14**, respectively. When the reaction of **1** and **5** was performed with 2.5 mol. equiv. of the reagent, hydrolysis of the C-2 and C-3 ester groups also occurred to give, in addition to the expected heptaacetates, the corresponding hexaacetates **3** and **7**, and the pentaacetates **4** and **8**, respectively. Under similar reaction conditions compound **9** gave a mixture of the heptaacetate **10** and the hexaacetates **11** and **12** (see Table). Compound **13** when treated with 2.5 mol. equiv. of hydrazine

hydrate gave a complex mixture of deesterified products.

The physical constants of the heptaacetates **2**, **6** and **10** were in agreement to those reported in the literature[5,7] The structures of the hepta-, hexa-, and the penta-acetates were confirmed by 2D n.m.r. experiments. The fact that the resonances due to H-1 in **2**, **6**, **10** and **14**; the H-1,2 resonances in **3**, **7** and **12**; the H-1,3 signals in **11**; and H-1,2,3 signals in **4** and **8** were shifted upfield on deacetylation, indicated that the free hydroxyl groups were located at C-1 in the heptaacetates; C-1,2 and C-1,3 in the hexaacetates and C-1,2,3 in the penta-acetates.

It is of interest to note that the pattern of hydrolysis of the second and third ester groups in the β-1,4 linked disaccharides **1** and **5** is different from those of the α-1,4 and α-1,6 linked disaccharides **9** and **13**.



1 R = OAc; R^1 = H; R^2 = R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

2 R = R^1 = H, OH; R^2 = R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

3 R = R^1 = H, OH; R^2 = H; R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

4 R = R^1 = H,OH; R^2 = R^3 = H; R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

5 R = OAc; R^1 = H; R^2 = R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl

6 R = R^1 = H,OH; R^2 = R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl

7 R = R^1 = H,OH; R^2 = H; R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl

8 R = R^1 = H,OH; R^2 = R^3 = H; R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl

9 R = OAc; R^1 = H; R^2 = R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl

10 R = R^1 = H, OH; R^2 = R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl

11 R = R^1 = H, OH; R^3 = H, R^2 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl

12 R = R^1 = H, OH; R^2 = H; R^3 = R^5 = Ac; R^4 = 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl

13 R = R^1 = H,OAc; R^2 = R^3 = R^4 = Ac; R^5 = 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl

14 R = R^1 = H,OH; R^2 = R^3 = R^4 = Ac; R^5 = 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl

A typical procedure for the selective deesterification of reducing disaccharide peracetates is as follows: a solution of, for example cellobiose octaacetate (**1**, 5 g) in acetonitrile (50 ml) was treated with hydrazine hydrate (1.2 mol. equiv., 1.85 ml) at 5°C for 16 h. The reaction mixture was then neutralized with IRA 120 ion exchange resin (H^+), filtered, concentrated and crystallised or purified by silica gel column chromatography to give the corresponding heptaacetate. In order to prepare the hexa- and penta-acetates the reaction was performed with 2.5 mol. equiv. of hydrazine hydrate and the reaction worked up as above to give, after silica gel column chromatography, the desired products (see Table).

Table: Regioselective Hydrolysis of Peracetylated Reducing Disaccharides using Hydrazine Hydrate.

Substrate	Hydrazine hydrate (mol.eqiv.)	Time (h)	Product (acetates) hepta- hexa- penta-	Yield (%) h.p.l.c. [9]	Isolated yield (%) unoptimised	optimised
Cellobiose octaacetate (**1**)	1.2	16[a]	**2**			90
1	2.5	2.5	**2** **3** **4**	43 45 7	20 4	
Lactose octaacetate (**5**)	1.2	16[a]	**6**			88
5	2.5	2.5	**6** **7** **8**	40 41 13	20 8	
Maltose octaacetate (**9**)	1.2	16[a]	**10**			86
9	2.5	2.5	**10** **11** **12**	48 23 29	11 16	
Melibiose octaacetate (**13**)	1.2	16[a]	**14**			82

[a] The duration of the deacylation reaction represents an unoptimised time

Acknowledgement
We thank EC for a fellowship (to RK) under the framework of the BRIDGE programme.

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9. H.p.l.c. analysis performed on a Novapak ® C18 reverse phase column (Waters). Mobile phase: solution A: water-trifluoroacetic acid (0.1%, TFA), solution B: water-acetonitrile (2:3)-TFA (0.1%); gradient A: from 80 to 60%, 15 min.; flow rate 1.2mL/min; uv detection at 215nm.

(*Received in UK* 7 *April* 1994; *accepted* 15 *April* 1994)