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Regioselective Anomeric Deacetylation of Peracetylated Glycopyranoses

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A simple and mild method for regioselective anomeric deacetylation of peracetylated glycopyranoses using copper(II) acetate dihydrate and methanol/water (9 : 1) is described.

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Introduction

In organic synthesis, selective protection and deprotection of polyfunctional molecules are critical problems. In carbohydrate chemistry these problems are more crucial owing to the presence of multiple hydroxyl functions of very similar reactivity. Fully protected sugars, having a free hydroxyl group at the anomeric carbon atom, serve as important domains for the synthesis of oligosaccharides[1] and glycoconjugates, such as glycoproteins[2] and glycolipids, and other such carbohydrate-based biologically active molecules.[3] In addition, the free hydroxyl group at the anomeric carbon can be functionalized so as to provide reactive glycosyl donors,[4] such as glycosyl imidates, fluorides, phosphates, xanthates, and others.

There is a good number of reagents or catalysts reported in the literature for the selective anomeric deacetylation of peracetylated sugars. Some of these methods involve direct hydrolysis using (a) a Lewis acid, mainly BF_3^- etherate,[5] tin(IV) chloride,[6] or AlX_3(Cl,Br);[7] (b) nitrogeneous nucleophiles, such as ammonia,[8a–8c] ammonium carbonate,[8d] benzylamine,[9] ethylene diamine,[10] piperidine,[11] hydrazine,[12] hydrazine hydrate,[13] hydrazine acetate,[14] guanidine, or guanidinium nitrate;[15] (c) other reagent systems like KCN/KOH,[16] HgO/$HgCl_2$,[17] or MgO;[18] or (d) enzymes.[19] This anomeric deacetylation can also be achieved through indirect hydrolysis by converting the anomeric acetate to a more reactive functionality like a glycosyl halide,[20] stannyl ether,[16,21] or *N*-phenylglycopyranosylamine.[22]

The literature procedures sometimes suffer from the cumbersome preparation of, for example, glycosyl halides and the requirement of anhydrous conditions. Most of the procedures require basic conditions and excess reagents, and as the reaction progresses the regioselectivity at C1 decreases. The hazardous nature of mercury(II) salts limits the use of HgO/$HgCl_2$, a relatively mild and neutral system.

Considering all these facts there is an incentive for developing mild, neutral systems for selective anomeric deacetylation of peracetylated sugars. In our research, we have developed a simple and relatively inexpensive method for this goal. The reaction was performed by refluxing the peracetylated sugar for 3–4 h with copper(II) acetate dihydrate and aqueous methanol to effect a smooth, regioselective anomeric deacetylation.

Results and Discussion

Treatment of α-D-glucose pentaacetate, β-D-glucose pentaacetate, α-D-galactose pentaacetate, β-D-rhamnose tetraacetate, β-D-xylose tetraacetate, and α-L-arabinose tetraacetate with copper(II) acetate dihydrate in aqueous methanol at reflux temperature for 3–4 h afforded exclusively the anomeric deacetylated products. The products were isolated by extraction with ethyl acetate, followed by silica-gel column purification. These results are summarized in Table 1, entries 1–6, respectively.

In order to extend the scope of the developed system, the reactions were performed on peracetylated disaccharides, α/β-maltose octaacetate (entry 7) and α/β-lactose octaacetate (entry 8). These octaacetates also underwent anomeric deacetylation smoothly. The physical constants and spectral data of all the compounds were in agreement with those reported in the literature (entries 1–4,[19a] entries 5–6,[8a,14a] and entries 7–8[11,19b,19c]). In all of these cases (entries 1–8), 20–25% of the unreacted starting peracetylated sugar with some amounts of a mixture of other deacetylated products were recovered during column purification. Yields (56–67%) obtained by our method are quite comparable to those of other systems: HgO/$HgCl_2$ (60–74%) and MgO (50–75%). Although nitrogenous nucleophiles give higher yields of anomeric decetylated products, the major drawback in these systems is the higher basicity of the reaction medium.

Under the reaction conditions mentioned, the most common carbohydrate protective groups, such as *O*-benzyl (entry 9) and acetonide (entry 10), remain unaffected.

Certain control experiments were performed while developing the system. In the absence of copper(II) acetate, no

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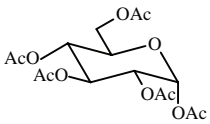
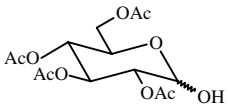
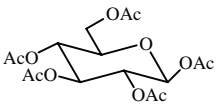
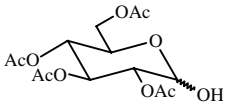
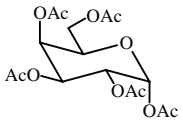
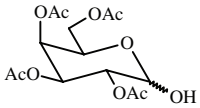
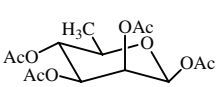
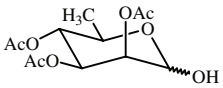
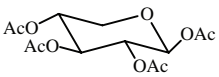
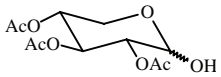
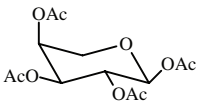
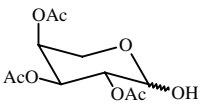
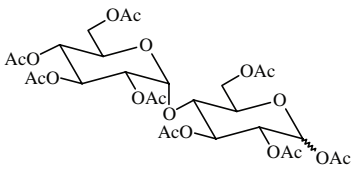
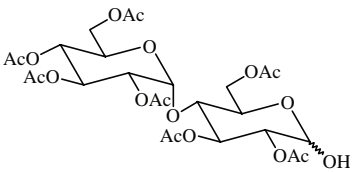
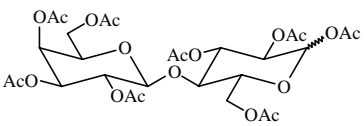
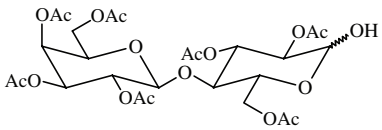
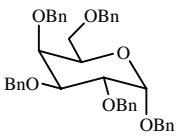
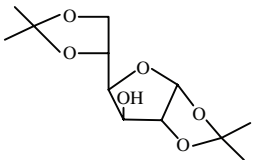
Table 1. Anomeric deacetylation of peracetylated sugars using copper(II) acetate dihydrate and methanol/water (9 : 1)

Entry	Substrate	Product	Isolated yield [%] (α : β ratio)[A]	Time [h]
1			64 (2.3 : 1)	4.0
2			67 (1 : 1)	4.0
3			64 (1.8 : 1)	4.5
4			62 (1.5 : 1)	3.5
5			58 (3.5 : 1)	3.5
6			56 (1 : 1)	3.5
7			61 (1 : 4)	3.0
8			59 (1 : 1)	3.0
9		–	–	6.0
10		–	–	6.0

[A] The α : β ratio was determined by ^{1}H NMR (200 and 500 MHz) spectroscopy.

anomeric deacetylation occurred even after refluxing for 6 h. This study clearly indicated that the Lewis acidity of copper(II) acetate was prerequisite for affecting the deacetylation. The reaction was carried out in anhydrous methanol using anhydrous copper(II) acetate. No significant amount of anomeric-deacetylated product was isolated even after refluxing for 8 h, indicating that the deacetylation may not be occurring by *trans*-esterification but rather by hydrolysis.

The role of methanol could be to act as a co-solvent to solubilize the substrates that otherwise are completely insoluble in water, even in the presence of copper(II) acetate.

In conclusion, a new system for selective anomeric deacetylation has been developed that is simple, mild, and cheap.

Experimental

All the reagents were commercially available and used as received. ^{1}H and ^{13}C NMR spectra were recorded on 200 and 500 MHz instruments.

*Typical Procedure: Anomeric Deacetylation of Penta-*O*-acetyl-β-*D*-glucopyranose (Table 1, entry 2)*

The glucose pentaacetate (0.5 g, 1.28 mmol) was dissolved in 20 mL of methanol/water (9 : 1). Copper(II) acetate dihydrate (0.28 g, 1.28 mmol) was added and the mixture was refluxed for 4 h (monitored by thin layer chromatography). The reaction mixture was cooled to room temperature then filtered, and the filtrate was distilled under reduced pressure to remove methanol. The residue was diluted with 50 mL of water and extracted (2 × 50 mL) with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The viscous residue obtained was purified by dry silica-gel column chromatography using ethyl acetate/hexane (15 : 85) to yield a syrup of the anomeric deacetylated product, 0.28 g (67%). δ_H ($CDCl_3$) 5.44 (0.5 H, d, *J* 4.0, $H_\alpha 1$), 5.26–5.22 (1 H, m, H3), 5.10–5.07 (1 H, m, H4), 4.89–4.85 (1 H, m, H2), 4.73 (0.5 H, d, *J* 8.0, $H_\beta 1$), 4.30–4.08 (1 H, m, H5), 3.90–3.75 (2 H, m, H6 and H6′), 2.08–2.00 (12 H, s, CH_3CO). δ_C ($CDCl_3$) 170.5–168.7 (CH_3CO), 95.0 ($C1_\beta$), 89.0 ($C1_\alpha$), 72.0 (C3), 71.7, 70.9 (C2), 69.7 (C4), 66.5 (C5), 61.7 (C6), 20.11 (CH_3CO).

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