Regioselective 1-*O*-Acyl Hydrolysis of Peracylated Glycopyranoses by Mercuric Chloride and Mercuric Oxide

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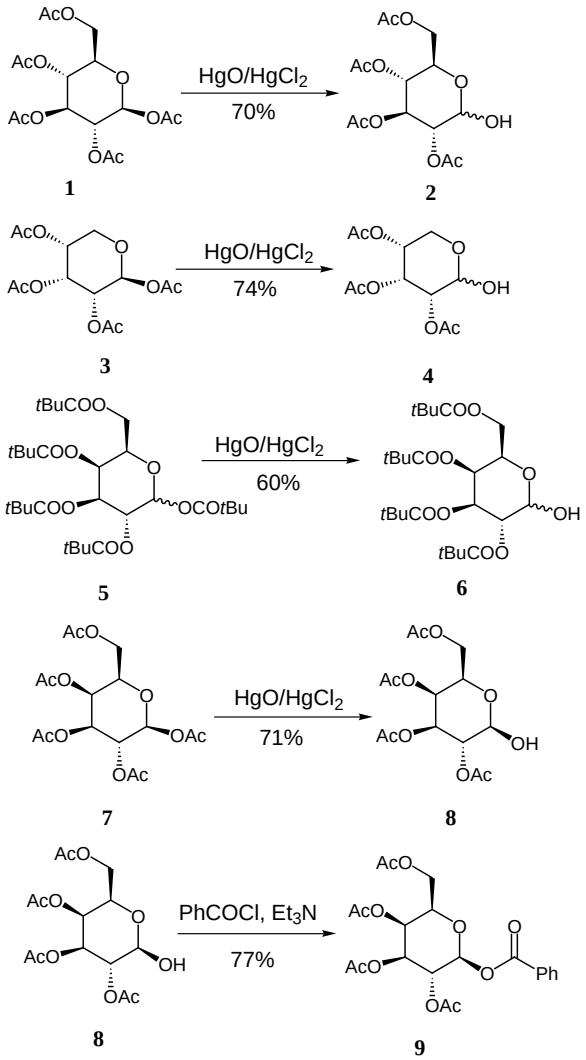
Abstract: A convenient synthetic method for regioselective 1-*O*-acyl hydrolysis of peracylated glycopyranoses into tetra-*O*-acylglycopyranoses using mercuric chloride and mercuric oxide in aqueous acetone is described.

Key words: glycopyranoses, oligosaccharides, regioselectivity, stereoselectivity, mercuric chloride

Fully protected sugars having one free hydroxyl group at the anomeric carbon are versatile building blocks for the synthesis of oligosaccharides and glycoconjugates.[1] Several methods for selective deprotection of C-1 acetates of glycopyranoses are known in the literature. Some of them involve a two-step reaction sequence in which in the first step, D-glycopyranose pentaacetates are converted to unstable glycosyl halides, and in the second step, the halides are hydrolyzed in the presence of expensive reagents like silver carbonate or nitrate.[2] Other methods involve regioselective deacetylation at the anomeric position by using bis(tributyltin)oxide,[3] ammonia,[4] butylamine,[5] hydrazine,[6] hydrazine acetate,[7] piperidine,[8] KCN/KOH,[3] and enzymes.[9] Some of these procedures involve either highly basic conditions[3–8] or expensive reagents.[2] Several of the available methods also have severe drawbacks such as side product formation[8] and unstable intermediates such as glycosyl halides.[2] We now report a convenient method for regioselective 1-*O*-acyl hydrolysis of peracylated glycopyranoses that is inexpensive, mild, and occurs at neutral pH. The reaction is unprecedented, and was discovered unexpectedly during our work on the use of HgO and $HgCl_2$ for hydrolysis of dithioacetals in carbohydrates.

β-D-Glucose pentaacetate (**1**) was reacted with yellow HgO and $HgCl_2$ in refluxing aqueous acetone for two days. After purification, 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**2**) was obtained in 70% yield (α:β ratio 1:3.9) (Scheme). To define the scope of this new hydrolysis reaction, other sugars such as β-D-ribopyranose-1,2,3,4-tetraacetate (**3**) and D-galactose pentapivalate (**5**) were also reacted with HgO and $HgCl_2$ to provide the corresponding products **4** (α:β ratio 5.3:1) and **6** (α:β ratio 1:1) in 74% and 60% yields, respectively. Under similar reaction conditions, β-D-galactose pentaacetate (**7**) also reacted with HgO and $HgCl_2$ to afford regio- and stereoselectively 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose (**8**) in 71% yield (Scheme). In this case, the other epimer was not detected in the crude reaction mixture neither by ^1H NMR nor by TLC analysis. The structures of compounds **2**, **4**, **6** and **8** were determined on the basis of earlier reported data.[4a,10,11] In all cases, 15–20% of the starting material was recovered from the reaction mixture, indicating that the deacylation reactions were indeed regioselective.



Scheme

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As outlined above, a variety of methods are available for the regioselective 1-*O*-deacylation of peracetylated glycopyranoses.[2–9] The yields reported for these methods range from 30–100% and depend on the particular substrate, reagent, and conditions employed. The presently described method does not offer a clear advantage in yield over the reported procedures, but it does provide a method that is carried out under neutral conditions, which may offer advantages in situations in which non-basic conditions would be desirable.

The epimers of **2**, **4**, and **6** were extremely difficult to separate and configuration assignments at the C-1 anomeric position were established by ^{1}H NMR spectroscopy. The stereochemistry at the anomeric carbon of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose (**8**) was unambiguously confirmed by single-crystal X-ray structure analysis (Figure) of its benzoyl derivative **9** (Scheme). The α and β ratios of **2**, **4**, and **6** were determined by ^{1}H NMR integration of the C-1 protons.

In conclusion, we have demonstrated regioselective C-1 deacylation of fully acetylated glycopyranoses in good yield by mercuric chloride and mercuric oxide. Our method is very mild, occurs under neutral conditions, utilizes inexpensive reagents, and does not require anhydrous conditions.

Melting points are uncorrected and were determined on Thomas Hoover Melting Point Apparatus. The ^{1}H NMR spectra were recorded on Gemini (300 MHz) and Bruker (500 MHz) spectrometers with $CDCl_3$ as solvent and TMS as internal standard. Microanalyses were performed at the Purdue Microanalysis Laboratory and all values were within the ±0.13–0.05 range of the calculated compositions.

1-*O*-Acyl Hydrolysis of Peracylated Glycopyranoses 1, 3, 5 and 7; General Procedure

Peracylated glycopyranose **1**, **3**, **5** or **7** (4.34 mmol) in acetone and H_2O (40:10 mL) was stirred at r.t. with yellow HgO (4.88 g, 22.52 mmol) while a solution of $HgCl_2$ (4.40 g, 16.20 mmol) in acetone (20 mL) was added dropwise. The reaction mixture was heated at reflux for 2 d, cooled to r.t., filtered through Celite, and concentrated in vacuo. The residue was extracted with $CHCl_3$ (3 × 100 mL), the $CHCl_3$ layers were washed with sat. aq KI solution (2 × 60 mL) and then H_2O (50 mL), dried (Na_2SO_4), and concentrated. The resulting residues were purified by flash chromatography (25 g, 3 × 40 cm column of silica gel, 230–400 mesh) eluting with hexanes–EtOAc (60:40) to furnish the desired compounds **2**, **4**, **6** or **8** in 60–74% yields. The structures of compounds **2**,[4a,10] **4**,[4a] **6**[11] and **8**[12] were determined by comparing their spectral data with those reported earlier.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-benzoyl-β-D-galactopyranose (9)

Benzoyl chloride (0.069 mL, 0.49 mmol) was added dropwise to a well-stirred solution of **8** (0.17 g, 0.49 mmol) in Et_3N (1.0 mL) and anhyd CH_2Cl_2 (10 mL) at 0 ° C under nitrogen. The reaction mixture was stirred at r.t. for 4 h, washed with H_2O (2 × 10 mL), brine (2 × 10 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by using flash chromatography (20 g, 2 × 40 cm column of silica gel, 230–400 mesh), eluting with hexane–EtOAc (80:20), to furnish the desired compound **9** as a white crystalline solid (0.17 g, 77%); mp 104–106°C.

IR (KBr): ν = 2962, 1750, 1223 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, 2 H, *J* = 7.39 Hz), 7.58 (t, 1 H, *J* = 7.46 Hz), 7.44 (t, 2 H, *J* = 7.74 Hz), 5.88 (d, 1 H, *J* = 8.32 Hz), 5.52 (dd, 1 H, *J* = 8.39 Hz, 10.41 Hz), 5.46 (d, 1 H, *J* = 3.26 Hz), 5.16 (dd, 1 H, *J* = 3.37 Hz, 10.47 Hz), 4.14 (m, 3 H), 2.17 (s, 3 H), 2.03 (s, 3 H), 2.00 (s, 3 H), 1.97(s, 3 H).

ESMS: *m/z* = 475 (MNa^+).

Anal. Calcd for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 55.62; H, 5.35.

Crystallographic Data for Compound 9[13]

Crystals of compound **9** suitable for X-ray structure analysis were obtained by crystallization from CH_2Cl_2 and hexane solution.

Data for **9**: $C_{21}H_{24}O_{11}$ (452.42), colorless; orthorhombic; space group $P2_12_12_1$: a = 9.3116 (3), b = 10.9783 (3), c = 21.7691 (7) Å; V = 2225.4 (2) Å^3, Z = 4; D_c = 1.350 g cm^{-3}. Preliminary examination and data collection were performed with Mo K_α radiation (λ = 0.71073 Å) on a Nonius KappaCCD at 150 K. 14143 reflections were collected, of which 5026 were unique. Data were collected to a maximum 2θ of 54.9°. The structure was solved by direct methods using SIR.[14] All remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least-squares where the function minimized was $\Sigma w(|Fo|^2 - |Fc|^2)^2$ and the weight w is defined as $w = 1/[\sigma^2(Fo^2) + (0.0378P)^2 + 0.4390P]$ where

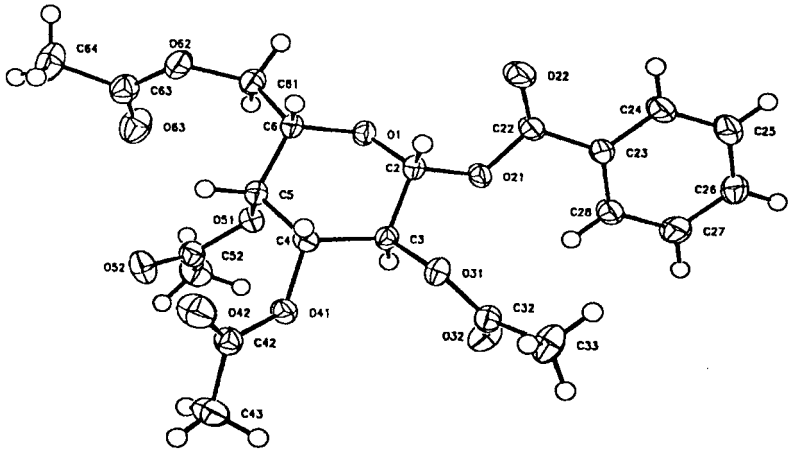

Figure ORTEP diagram of **9**

$P = (Fo^2 + 2Fc^2)/3$. $R1 = 0.039$, $wR2 = 0.089$, goodness of fit = 1.028. The highest peak in the final difference Fourier had a height of 0.20 e/A^3. The minimum negative peak had a height of –0.22 e/A^3. The factor for the determination of the absolute structure[15] refined to 0.00. Refinement was performed on a Alpha Server 2100 using SHELX-97.[16] Crystallographic drawings were done using programs ORTEP[17] and PLUTON.[18]

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References

(1) Sweeley, C. C.; Siddiqui, B. In *The Glycoconjugates*; Horowitz, M. I.; Pigman, W., Eds.; Academic Press: New York, **1977**.
(2) (a) Schmidt, V. O. T.; Herok, J. *Liebigs Ann. Chem.* **1954**, *587*, 63. (b) Georg, A. *Helv. Chim. Acta* **1932**, *15*, 924. (c) Schlubach, H. H.; Wolf, I. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 1507. (d) Nef, J. U. *Liebigs Ann. Chem.* **1914**, *403*, 333. (e) Bonner, W. A. *J. Am. Chem. Soc.* **1958**, *80*, 3372.
(3) Watanabe, K.; Itoh, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *154*, 165.
(4) (a) Fiandor, J.; Garcia-Lopez, M. T.; De Las Heras, F. G.; Mendez-Castrillon, P. P. *Synthesis* **1985**, 1121. (b) Knerr, L.; Pannecoucke, X.; Luu, B. *Tetrahedron Lett.* **1998**, *39*, 273. (c) Redoules, D.; Perie, J. *Tetrahedron Lett.* **1999**, *40*, 4811.
(5) (a) Sim, M. M.; Kondo, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 2260. (b) Boger, D. L.; Teramoto, S.; Zhou, J. *J. Am. Chem. Soc.* **1995**, *117*, 7344.
(6) (a) Khan, R.; Konowicz, P. A.; Gardossi, L.; Matulova, M. *Aust. J. Chem.* **1996**, *49*, 293. (b) Kolb, H. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2629. (c) Ren, T.; Liu, D. *Tetrahedron Lett.* **1999**, *40*, 7621.
(7) Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 369.
(8) Rowell, R. M.; Feather, M. S. *Carbohydr. Res.* **1967**, *4*, 486.
(9) (a) Hennen, W. J.; Sweers, H. M.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 4939. (b) Bastida, A.; Fernandez-Lafuente, R.; Fernandez-Lorente, G.; Guisan, J. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 633.
(10) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3171.
(11) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883.
(12) Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 369.
(13) Selected bond lengths (Å) and angles (°) of **9**: O(1)–C(2) 1.409(2), O(21)–C(2) 1.420(2), O(31)–C(3) 1.444(2), O(41)–C(4) 1.442(2), O(51)–C(5) 1.441(2), C(6)–C(61) 1.521(3), O(21)–C(22) 1.363(2), C(3)–C(2) 1.515(2), O(1)–C(2)–O(21) 107.36(14), O(1)–C(2)–C(3) 105.04(14), O(1)–C(6)–C(5) 110.38(14), O(41)–C(4)–C(5) 110.35(14), C(3)–C(4)–C(5) 110.70(14), C(22)–O(21)–C(2) 118.03(13), C(32)–O(31)–C(3) 117.58(13), C(42)–O(41)–C(4) 118.69(13), C(2)–O(1)–C(6) 111.21(13).
(14) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Cascarano, G. L.; Moliterni, A. G. G.; Burla, M. C.; Polidori, G.; Camalli, M.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
(15) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.
(16) Sheldrick, G. M. *SHELEX97, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, **1997**.
(17) Johnson, C. K. *OrtepII Report ORNL-5138*; Oak Ridge National Laboratory: Tennessee, **1976**.
(18) Spek, A. L. *PLUTON. Molecular Graphics Program*; University of Utrecht: The Netherlands, **1991**.