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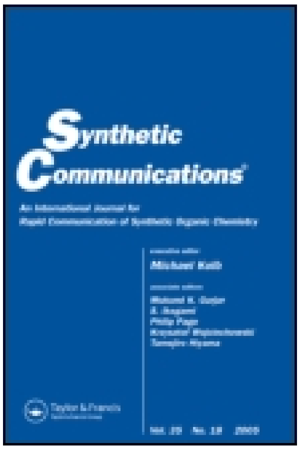

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
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An Efficient and Regioselective Deprotection Method for Acetylated Glycosides

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Published online: 18 Oct 2011.

To cite this article: Jubiao Li & Yanguang Wang (2004) An Efficient and Regioselective Deprotection Method for Acetylated Glycosides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:2, 211-217, DOI: 10.1081/SCC-120027255

To link to this article: http://dx.doi.org/10.1081/SCC-120027255

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SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 2, pp. 211–217, 2004

An Efficient and Regioselective Deprotection Method for Acetylated Glycosides

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ABSTRACT

A new regioselective 2-*O*-deacetylation methodology of acetylated glycosides using 85% hydrazine hydrate in THF is described. Using this method, acetylated 1-thio-glycoside could also be selectively deprotected to give 3-*O*-deprotected compound.

Key Words: Acetylated glycosides; Regioselective deprotection; Phenylthioglycosides; Hydrazine hydrate.

It is well-known that carbohydrates play important roles in many biological processes,[1] such as cell-to-cell recognition and interaction, signal transduction, and attachment of pathogen to host cells. To elucidate the factors

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DOI: 10.1081/SCC-120027255
0039-7911 (Print); 1532-2432 (Online)

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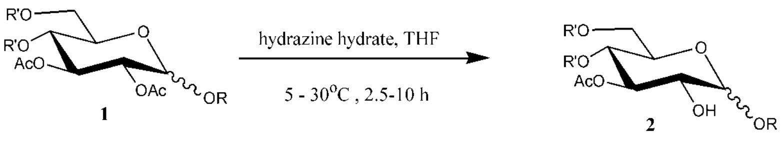
controlling these interactions at the molecular level, it is of the utmost importance to have sufficient amounts of pure and well-defined oligosaccharides with different sizes. So far, great efforts have been paid to the development of new, easy, and effective methods for regio- and stereoselective synthesis of oligosaccharides. Most of the reported methods involve the use of diverse selective protecting groups and multiple protection–deprotection steps, whereupon problems are encountered in achieving high yielding and stereoselective couplings for multifunctional carbohydrate donors and acceptors.[2] In this context, new regioselective protection–deprotection methods will play an important role in carbohydrate chemistry.

On the other hand, monosaccharides containing only one free hydroxyl group on C-2 are useful intermediates for a variety of purposes such as the synthesis of oligosaccharides and the inversion of configuration of the hydroxyl group, but most published routes suffer either excessive length of reaction process and poor yields, or harsh reaction conditions.[3]

Since acetyl group has been widely used as a protecting group for hydroxyl groups in carbohydrate chemistry, regioselective 1-*O*-deacetylations of acetylated glycoside derivatives is indispensable on the synthesis of oligosaccharides. During our efforts of establishing carbohydrate-based libraries, we developed a new regioselective 2-*O*-deacetylation method of glycosides.

At first, methyl 2,3,4,6-tetra-*O*-acetyl-*α*-D-glycopyranoside (**1a**) was treated with 1.0 equiv of 85% hydrazine hydrate at 5°C in THF, and the reaction selectively gave a 2-*O*-deacetyl-product, methyl 3,4,6-tri-*O*-acetyl-*α*-D-glycopyranoside (**2a**), in 48.8% yield (Sch. 1). The unreacted **1a** was recovered in 50.5% yield through column chromatography. The prolongation of reaction time resulted in the decrease of regioselectivities and yields. These results promoted us to investigate the regioselective deacetylation of other acetyl-protected glycosides **1b**–**h**, and the results are summarized in Table 1.

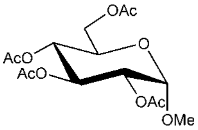
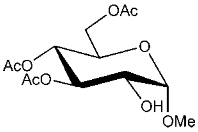
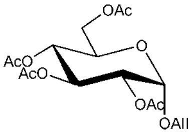
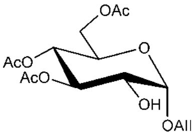
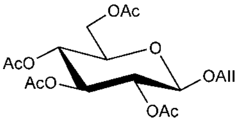
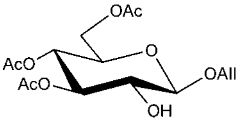
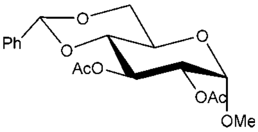
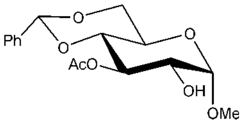
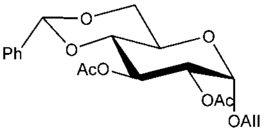
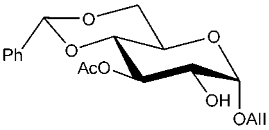
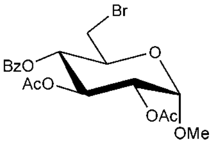
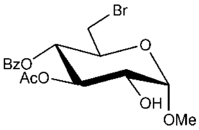
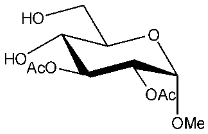
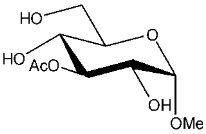
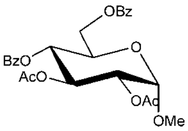
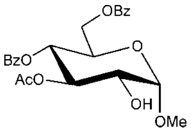
As shown in Table 1, peracetylated glycosides **1b** and **1c** reacted with 85% hydrazine hydrate at 5°C in THF to give 2-deprotected compounds **2b** and **1c** in 46.5% and 45.7%, respectively (entry b and c). At similar conditions, 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-*α*-D-glycopyranosides **1d** and **1e** also



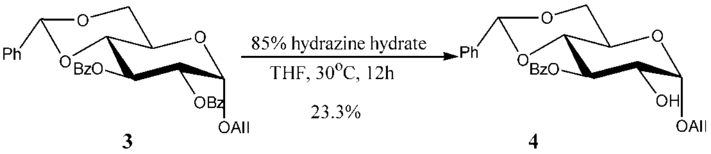
R= CH_3 or All R'= protecting group or bromo

Scheme 1.

Table 1. Regioselective deacetylation at the C-2 position of glycosides.

Entry	Substrate	Product	Time (h)	T (°C)	Yield[a] (%)
a			10	5	48.8
b			10	5	46.5
c			10	5	45.7
d			2.5	30	59.8
e			2.5	30	58.6
f			4	5	80.3
g			5	30	60.4
h			4	30	73.7

[a] Isolated yield based on the substrate.

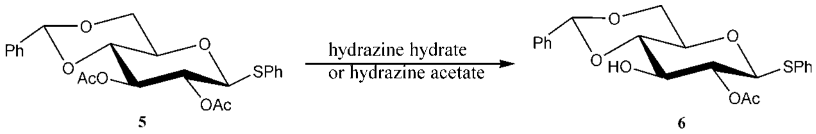


Scheme 2.

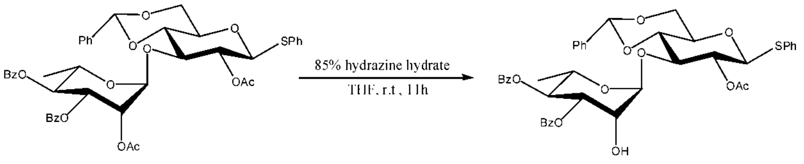
afforded 2-*O*-deprotected products **2d** and **2e** in 59.8% and 58.6% yields, respectively (entry d and e). Methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glycopyranoside (**1f**) (entry f), methyl 2,3-di-*O*-acetyl-α-D-glycopyranoside (**1g**) (entry g) and methyl 2,3-di-*O*-acetyl-4,6-di-*O*-benzoyl-α-D-glycopyranoside (**1h**) (entry h) gave the corresponding 2-deprotected products in higher yields (60.4–80.3%). This results indicated that the acetyl group at the C-3, 4 as well as C-6 position of glucosides were stable under the conditions of regioselective deprotection. In a summary, the regioselective deacetylation of acetyl-protected glycosides **1a–h** could be achieved in only two or three steps in mild conditions with moderate yield, and the unreacted substrates, which without any doubt could be reused, would be easily recovered through column chromatography. Thus a better method of preparing free 2-OH glycoside with less reaction steps was obtained in comparision with the reported methods.[3c,3g]

To further illustrate the usefulness of this methodology, we also examined benzoyl-protected glycopyranoside (**3**) and selectively obtained a 2-*O*-debenzoylated compound **4** in lower yield (23.3%) (Sch. 2).

Phenylthioglycosides have been widely used in glycosidation and related reactions due to their ease of formation, relative stability to various reaction conditions, and convenient activation with electrophilic reagent or oxidizing agents.[4] Therefore, we examined the regioselective deacetylation of thioglycoside. It was found that treatment of phenyl 2,3-di-*O*-acetyl-4,6-benzylidene-1-thio-β-D-glycopyranoside **5** with 1.0 equiv of 85% hydrazine hydrate at 5°C in THF for 7 h resulted in 3-*O*-deacetylated compound **6** in 22.7% yield and 2, 3-*O*-bisdeacylated compound in 15.6% yield (Sch. 3). We also tested the selectivity of hydrazine acetate[5] and found that **5** reacted with hydrazine acetate in the 30°C in THF/CH_2Cl_2 for 4 h to give the



Scheme 3.



7

8

Scheme 4.

corresponding 3-*O*-deprotected product **6** in good yield (64.4%) with a recovery of unreacted **5** in 33.1%. These results showed a different selectivity with both position 2 and 3 being cleaved, which may be due to the strong anomeric and stereoelectronic effects associated with phenylthioglycoside.

Disaccharide **7** is a significant building block to synthesis of many sugar cores of natural products, such as Incanoside,[6] Ballotetroside,[7] and two new phenylpropanoid glycosides from Lamiophlomis rotata[8] and from Fernandoa adenophylla.[9] In our procedure to synthesis of the Incanoside, it is important to get the free 2′-OH of disaccharide. The chemoselective deacetylation between benzoyl and acetyl groups was usually conducted in acid conditions,[10] resulting in the undesired removing of 4,6-protecting group. Based on our regioselective and chemoselective deacetylation method, compound **8** was obtained from **7** in the basic condition by treatment with 3.0 equiv of 85% hydrazine hydrate in THF at room temperature for 11 h in good yield (73.8%) (Sch. 4).

In conclusion, we have developed a new regioselective 2-*O*-deacetylation of acetylated glycosides using 85% hydrazine hydrate at 5–30°C in THF. As compared with the published methods, this one is simple and efficient, and can be run in mild conditions with moderate yields. The regioselective 3-*O*-deprotection was also achieved for the phenylthioglycosides under similar conditions. The free 2-OH of disaccharid was obtained by regioselective and chemoselective deacetylation in the basic condition. This regioselective deacetylation would find general use in carbohydrate chemistry. Further studies on the mechanism and applications of the reaction are in progress in our laboratory.

EXPERIMENTAL

General Procedure

To a solution of pure allyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glycopyranoside (**1e**) (2.4 g, 6.11 mmol) in THF (30 ml) was added 1.0 equiv of 85% hydrazine hydrate (0.38 mL, 6.11 mmol). The mixture was stirred at

30°C for 2.5 h, and then the reaction mixture was quenched by the addition of H_2O (20 ml) and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was subject to column chromatography on silica gel with petroleum ether/EtOAc (5 : 1) as the eluent to give (**2e**) (1.32 g, 58.6%) as a white solid and 0.89 g (**1e**) was recovered. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26–7.46 (m, 5H, Ph), 5.88–5.95 (m, 1H, $CH_2{=}C\mathit{H}{-}CH_2$), 5.49 (s, 1H, CHPh), 5.24–5.37 (m, 3H, H-3, and $C\mathit{H_2}{=}CH{-}CH_2$), 4.95–4.96 (d, 1H, H-1, $J = 3.86$ Hz), 4.24–4.30 (m, 2H, H-6a, and one proton of $CH_2{=}CH{-}C\mathit{H_2}$), 4.04–4.08 (dd, 1H, one proton of $CH_2 = CH{-}C\mathit{H_2}$), 3.89–3.94 (ddd, 1H, H-6b), 3.72–3.76 (t, 1H, H-4), 3.66–3.67 (m, 1H, H-2), 3.57–3.59 (t, 1H, H-5), 2.21 (s, 3H, $C\mathit{H_3}CO$) ppm.

ACKNOWLEDGMENTS

The work was supported by The National Natural Science Foundation of China (No. 20272051) and by The Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, P.R.C.

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