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Facile Approach to 2-Acetamido-2-deoxy-β-D-Glucopyranosides via a Furanosyl Oxazoline

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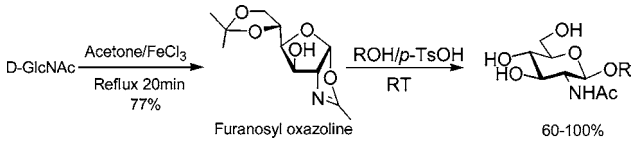
ABSTRACT



A concise and convenient route that may be easily scaled is reported for the preparation of unprotected β-glucopyranosides of *N*-acetyl-D-glucosamine. Reaction of a wide variety of alcohols with a reactive, readily prepared furanosyl oxazoline under acidic conditions affords the corresponding β-D-glucopyranosides in good to high yields. Primary alcohols gave only β-D-glucopyranosides. A mechanism is proposed for this transformation.

N-Acetyl-D-glucosamine (GlcNAc) is one of the most frequently encountered hexosamines in biologically important glycolipids, polysaccharides, and glycoproteins. It exists mainly in the pyranose form, and in the majority of cases it is found as either N- or O-linked β-pyranosides.[1] However, because the 2-acetamido group is a poor participating group, the chemical synthesis of O-linked GlcNAc β-glycosides is not straightforward,[2] especially when the acceptor is a complex sugar. Indirect routes to such β-glucopyranosides are most often employed using a temporary protecting group for the 2-amino functionality such as phthalimido,[3] tetrachlorophthalimido,[4] troc-amido,[5] chloroacetamido,[6] trichloroacetamido,[7] or azido[8] groups. The acetamido group is generated after removing the protecting group followed by an acetylation step. The direct synthesis of O-linked GlcNAc β-glucopyranosides using the acetamido group is more straightforward but less common and restricted to the preparation of glycosides with simple aglycones.[9] Typically, the synthesis (Scheme 1) involves glycosylation of simple alcohols by reaction with peracetylated *N*-acetylglucopyranosyl chloride (**2**) under Koenigs−Knorr conditions[10] that employ poisonous heavy metal salts such as mercury cyanide or mercury chloride as a promoter. Another route involves reaction of peracetylated glucopyranosyl oxazoline (**5**) with alcohols to afford the desired 2-acetamido-2-deoxy-β-D-glucopyranosides.[11] The pyranose oxazoline (**5**) is generally considered as the intermediate[12] that leads to β-glycosides (**4**) when the glycosyl chloride (**2**) reacts with an alcohol.

(1) Kennedy, J. F.; White, C. A. *Bioactive Carbohydrates: In Chemistry, Biochemistry and Biology*; Ellis Horwood Publishing, Ltd.: Chichester, 1983.
(2) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167−1195.
(3) Lemieux, R. U.; Takeda, T.; Chung, B. Y. In *Synthetic Methods for Carbohydrates*; El Khadem, H. S., Ed.; ACS Symposium Series 39; American Chemical Society: Washinton, DC, 1976; pp 90−115.
(4) Debenham, J.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 3302−3303.
(5) Dullenkopf, W.; Castro-Palomino, J. C.; Manzoni, L.; Schmidt, R. R. *Carbohydr. Res.* **1996**, *296*, 135−148.
(6) Kiso, M.; Anderson, L. *Carbohydr. Res.* **1985**, *136*, 309−323.
(7) Blatter, G.; Beau, J.-M.; Jacquinet, J.-C. *Carbohydr. Res.* **1994**, *260*, 189−202.
(8) Greilich, U.; Brescello, R.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Org. Bioorg. Chem.* **1996**, 663−672.
(9) (a) For a review, see: Debenham, J. S.; Rodebaugh, R.; Fraser-reid, B. *Liebigs Ann. Recl.* **1997**, 791−802. (b) Horton, D. *Methods Carbohydr. Chem.* **1972**, *6*, 282−285. (c). Wong, T. C.; Townsend, R. R.; Lee, Y. C. *Carbohydr. Res.* **1987**, *170*, 27−46.
(10) Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957.
(11) (a) Zurabyan, S. E.; Volosyuk, T. P.; Khorlin, A. Y. *Carbohydr. Res.* **1969**, *9*, 215−220. (b) Urabyan, S. E.; Antonenko, T. S.; Khorlin, A. Y. *Carbohydr. Res.* **1970**, *15*, 21−27.
(12) Lubineau, A.; Gallic, J. L.; Malleron, A. *Tetrahedron Lett.* **1987**, *28*, 5041−5044.

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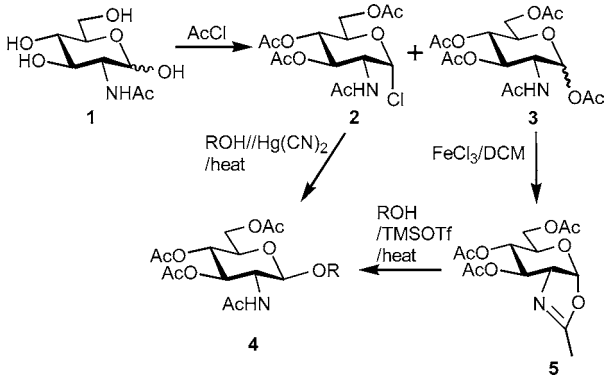
Due to its low reactivity as a donor, harsh reaction conditions[2,11] using strong Lewis acids (such as TMSOTf) or strong Brønsted acids (such as *p*-TsOH) as well as elevated temperature are required for glycosylations. Although some improvements were achieved using 1,2-dichloroethane as a solvent[13] and $FeCl_3$,[14] $CuCl_2$,[15] or $Yb(OTf)_3$[16] as catalysts, elevated temperature is still required. Recently, Boysen et al.[17] designed a bicyclic thioglycoside as a versatile GlcNAc donor, and Mohan et al.[18] employed microwave as an efficient way of heating to convert a pyranose oxazoline derivative to some *N*-acetyllactosamine glycosides.

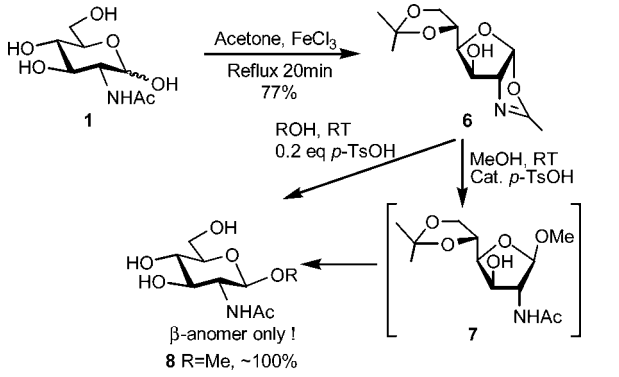
Scheme 1. Conventional Routes to GlcNAc β-Glycosides **4**



The chloride (**2**) is prepared by reacting *N*-acetylglucosamine (**1**) with neat acetyl chloride[19] (Scheme 1). Although this reaction works reasonably well, it is not a clean reaction.[20] Together with the desired chloride (**2**), frequently pentaacetate (**3**) remains, and recrystallization does not remove this side-product. Consequently, the impurity (**3**) has to be removed by chromatography; alternatively, the crude chloride (**2**) is used for glycosylation, and the impurity (**3**) has to be removed at the next step. However, chromatography of polar acetamido intermediates is troublesome, because they have poor solubility in common organic solvents and streak badly. Consequently, the preparation of β-glucopyranosides of GlcNAc with simple aglycones by conventional routes that start from *N*-acetylglucosamine is not a straightforward task. In this study, we report a simple and general method for the preparation of 2-acetamido-2-deoxy-D-glucopyranosides from a furanose oxazoline derivative.

When planning the synthesis of a bioactive phytosphingosine and glycosylceramide derivatives, we envisioned the use of a furanose oxazoline (**6**) as a key intermediate (Scheme 2). Compound **6** can be conveniently prepared on a large scale in good yield (77%) from *N*-acetylglucosamine with dry acetone using anhydrous $FeCl_3$ as a catalyst.[21] The crude furanose oxazoline **6** is pure enough for use in the next step without the need for chromatography. The literature reports that the furanose oxazoline **6** can be converted to the methyl β-furanoside **7** when reacted with dry methanol (as a solvent) for 3 h at pH 3∼4 using *p*-TsOH as a catalyst.[22] However, our experience indicates that under the reported conditions, the furanoside **7** forms initially and then slowly converts to a new spot on TLC identified as the pure methyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**8**). The rate for conversion of **7** into **8** accelerates if the amount of *p*-TsOH is increased. For example, if 0.5 equiv of *p*-TsOH is used, compound **6** can be converted to compound **8** within 1 h. The 5,6-*O*-isopropylidene group is apparently transacetalized in-situ with methanol. To stop the transformation at the stage of furanoside **7**, the acidity of the reaction has to be carefully controlled.

Scheme 2. New Route for Synthesis of β-Glycosides **8**

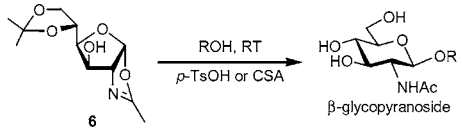


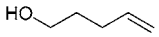
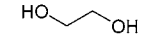
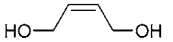
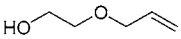
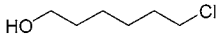
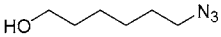
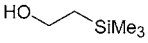
The direct transformation of the furanose **6** to pyranoside **8** proceeds equally well on a small or large scale. When performed on a 20 gram scale, compound **8** was obtained in quantitative yield by simply evaporating the reaction mixture after neutralization with Et_3N, followed by multiple washing of the residue with CH_2Cl_2 in order to remove *p*-TsOH salts. Furthermore, compound **6** could be prepared from **1** on a large scale without the need for chromatography. This now provides a viable two-step procedure to prepare compound **8** that is otherwise troublesome to make using conventional approaches. A literature search revealed that there are no other instances of the direct conversion of a furanosyl oxazoline to 2-acetamido-2-deoxy-β-D-glucopyranosides. However, Gigg's group have reported a similar transformation using a furanose phenyloxazoline derivative to prepare, in a one-pot reaction, the 4,6-*O*-benylidene acetal of two β-glycosides of GlcNBz.[23]

(13) Warren, C. D.; Jeanloz, R. W. *Carbohydr. Res.* **1977**, *53*, 67−84.
(14) (a) Kiso, M.; Anderson, L. *Carbohydr. Res.* **1979**, *72*, C12−C14. (b) Kiso, M.; Anderson, L. *Carbohydr. Res.* **1979**, *72*, C15−C17.
(15) Wittmann, V.; Lennartz, D. *Eur. J. Org. Chem.* **2002**, 1363−1367.
(16) Crasto, C. F.; Jones, G. B. *Tetrahedron Lett.* **2004**, *45*, 4891−4894.
(17) Boysen, M.; Gemma, E.; Lahmann, M.; Oscarson, S. *Chem. Commun.* **2005**, 3044.
(18) Mohan, H.; Gemma, E.; Ruda, K.; Oscarson, S. *Synlett* **2003**, 1255−1256.
(19) Horton, D. *Methods Carbohydr. Chem.* **1972**, *6*, 282−285.
(20) (a) Heidlas, J. E.; Lees, W. J.; Pale, P.; Whitesides, G. M. *J. Org. Chem.* **1992**, *57*, 146−151. (b) Macmillan, D.; Daines, A. M.; Bayrhuber, M.; Flitsch, S. *Org. Lett.* **2002**, *4*, 1467−1470. (c) Bamford, M. J.; Pichel, J. C.; Husman, W.; Patel, B.; Storer, R.; Weir, N. G.; *J. Chem. Soc., Perkin Trans. 1* **1995**, 1181−1187.
(21) Mack, H.; Basabe, J. V.; Brossmer, R. *Carbohydr. Res.* **1988**, *175*, 311−316.
(22) Furneaux, R. H.; Gainsford, G. J.; Lynch, G. P.; Yorke, S. C.; *Tetrahedron* **1993**, *42*, 9605−9612.

Compared to the traditional methods that require at least three transformations as well as multiple chromatographic steps, the new route requires only two steps without chromatography to prepare unprotected 2-acetamido-2-deoxy-β-D-glucopyranosides from *N*-acetylglucosamine. The concise method, its convenience, and its high stereoselectivity prompted us to explore the scope of this reaction. We first investigated the reaction of furanose oxazoline **6** with commercially available primary alcohols (Table 1, entries 1−12). In general, oxazoline **6** reacted smoothly with all the primary alcohols to afford exclusively β-glucopyranosides. With smaller and more reactive alcohols such as allyl, benzyl, glycol, we used 0.5 equiv of anhydrous *p*-TsOH or CSA (camphor sulfonic acid) as a catalyst, while for larger and less reactive alcohols, we increased the amount of *p*-TsOH or CSA to 1 equiv in order to accelerate the reactions. Normally, the reactions were carried out in neat alcohol solution. However, for more expensive alcohols (entries 11 and 12), the reaction was performed using CH_2Cl_2 as a cosolvent without a decrease in stereoselectivity. For glycosides with aglycones of smaller size (entries 1, 2, 4, 13, and 14), the corresponding alcohols are more volatile, and consequently unreacted alcohol was removed by evaporation; the glycosides were obtained after multiple washings with CH_2Cl_2. However, as the size of the aglycones increases, the corresponding alcohols tend to be less volatile, and the glycosides have better solubility in CH_2Cl_2; therefore, these glycosides were isolated by chromatography.

Table 1. Glycosylations of Alcohols with Compound **6**



Entry	Glycosyl accceptor	Solvent ratio[a]	Yield[b]	α:β Ratio
1	Allyl alcohol	1:0	82%[c]	0:1
2	Benzyl alcohol	1:0	73%[c]	0:1
3	1-Octanol	1:0	69%	0:1
4		1:0	76%[c]	0:1
5		1:0	78%[d]	0:1
6		1:0	77%[d]	0:1
7		1:0	74%	0:1
8		1:0	65%	0:1
9		1:0	63%	0:1
10		1:0	72%	0:1
11		1:2	70%	0:1
12		1:2	61%	0:1
13		1:0	73%	0:1
14	Isopropyl alcohol	1:0	77%[c]	1:6
15	*t*-Butyl alcohol	1:0	51%	1:4

[a] ROH/CH_2Cl_2. [b] Yields are reported after chromatography. [c] Glycosides could also be obtained without chromatography; yields are ~10% lower. [d] No dimers were detected.

The glycosylation conditions are compatible with many functional groups. Alkenes are well-tolerated, while the halides, the trimethylsilylethyl group, as well as the azido group are also unaffected.

The furanose oxazoline **6** can also glucosylate secondary and tertiary alcohols. For example, when cyclohexanol was used, the corresponding cyclohexyl β-glucopyranoside was obtained as the only product in 73% yield without the need for chromatography. However, small amounts of α-isomers were observed with *i*-propyl or *tert*-butyl alcohols. The reaction with *tert*-butyl alcohol was sluggish. Remarkably, despite steric hindrance, the yield of the *tert*-butyl glucoside was moderate.

The reaction of a furanose derivative to form a pyranoside[24] requires opening of the anomeric acetal of the furanoside and formation of a new acetal linkage with the 5-hydroxyl group. Logically, this should lead to the formation of an open-chain GlcNAc intermediate. The ring reclosure from a linear intermediate should afford, in principle, a mixture of anomeric glycosides; in the case of pyranosides, the α-anomers are usually the predominant products due to the anomeric effect as seen, for example, in Fisher glycosidation of GlcNAc.[25] However, the reaction of furanose oxazoline **6** with alcohol occurs with high stereoselectivity. During the reaction of **6** with methanol, two intermediates were observed by TLC; methyl β-D-furanoside **7** ($R_f = 0.72$) appeared first. Before the complete disappearance of **7**, another product ($R_f = 0.30$) appeared, which was converted to the pyranosides **8** ($R_f = 0.16$). We were able to halt the reaction by treating the reaction mixture with Dowex-2 (OH^-) resin to remove the acid catalyst, and the lower spot ($R_f = 0.30$) was isolated and identified as the triol **9**. Clearly, the furanose oxazoline ring was first opened by the attack of methanol under acidic conditions to yield **7**, and subsequently the acetonide undergoes transacetalation with methanol to afford **9**, which then rearranged to **8** through a faster process. Unfortunately, no intermediates could be observed during the transformation of **9** to **8**.

The transformations of methyl furanoside **7** as well as **9** to **8** were first reported by Jacquinet et al.[26] They discovered that these methyl furanosides could rearrange quantitatively to pyranoside **8** by treatment with 60% acetic acid−water at 100 °C for 10 min. Although very efficient, this method has not found widespread use.

To explain the β-selectivity of glucopyranoside formation, we speculate that there is an assisted ring opening of the furanoside from the *N*-acetyl group (Scheme 3). Thus, under

(23) (a) Gigg, R.; Conant, R.; *J. Chem. Soc., Perkin Trans. 1* **1977**, 2006−2014. (b) Gent, P. A.; Gigg, R.; Conant, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1858−1863.

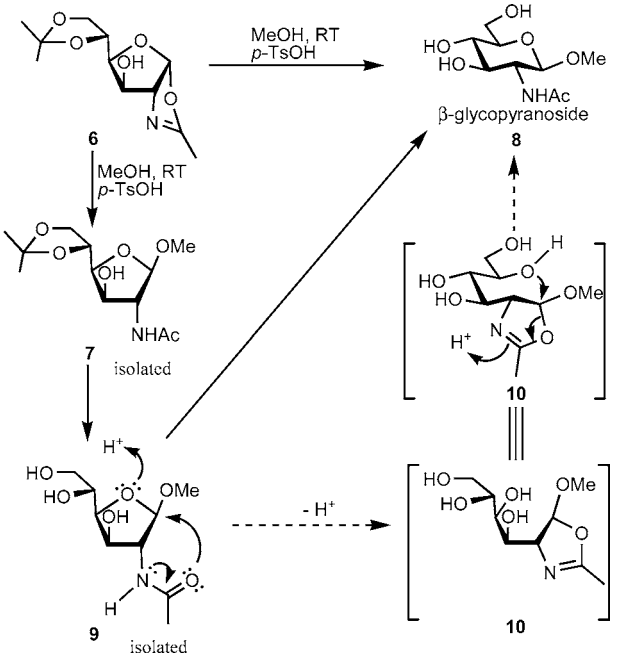
(24) Garegg, P. J.; Johansson, K.-J.; Konradsson, P.; Lindberg, B. *J. Carbohydr. Chem.* **1999**, *18*, 31−40.

(25) (a) Galemmo, R. A., Jr.; Horton, D. *Carbohydr. Res.* **1983**, *119*, 231−240. (b). Hecker, S. J.; Minich, M. L.; *J. Org. Chem.* **1990**, *55*, 6051−6054.

(26) Jaquinet, J.-C.; Sinaÿ, P. *Carbohydr. Res.* **1974**, *32*, 101−114.

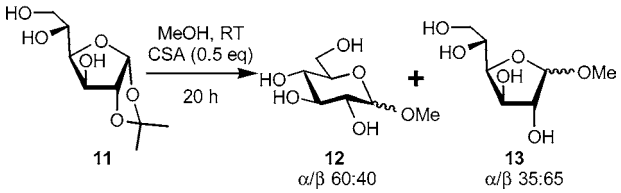
p-TsOH catalysis, the ring oxygen of **9** is first protonated and undergoes an *N*-acetyl-assisted ring opening; the carbonyl oxygen attacks the anomeric center from the opposite side of the ring and inverts the anomeric configuration to form an open-chain oxazoline intermediate **10**, which quickly undergoes another ring closure with 5-OH to regenerate the NAc group; since the attack by 5-OH on the anomeric center is also from the opposite direction, a double inversion restores the anomeric center to the original β-configuration. The partial formation of small amounts of α-glucopyranosides in the cases of some secondary and tertiary alcohols can be attributed to the in situ acid-catalyzed anomerization of the initially formed β-glucopyranosides. When the reaction mixtures of **6** with primary alcohols were left at room temperature for a prolonged time (several nights), we observed the formation of small amounts of α-pyranosides.

Scheme 3. Proposed Mechanism



To confirm the above hypothesis, we reacted 1,2-*O*-isopropylidene-α-D-glucofuranose (**11**), a furanose that does not have an *N*-acetyl group to participate during the reaction (Scheme 4), with MeOH under anhydrous camphor sulfonic acid (CSA, 0.5 equiv) catalysis. The glycosylation proceeded much more slowly (20 h), and the reaction gave an α/β mixture of methyl furanosides and methyl pyranosides. These results are rationalized in terms of the absence in **11** of a neighboring *N*-acetyl participating group, and the accompanying NAc assisted ring opening. For this reason, the reaction proceeds more slowly, and since 2-OH is not a participating group, there is no possibility to form cyclic intermediates to control the anomeric configuration of the glycosides formed. We also found support of this proposed mechanism from Jacquinet et al.'s original publication,[26] where the authors treated two free amino derivatives related to de-*N*-acetylated compound **7** or **9** with acid. It was observed that the transformations to the corresponding pyranoside were more difficult than with the N-acetylated derivatives **7** and **9**. This could be attributed primarily to the protonation of the amino groups; however, in our opinion, the absence of an acetamido group at the C-2 position to assist the opening of the furanoside is also a contributing factor. In addition, these authors used 60% acetic acid−water as solvents to transform compounds **7** and **9** to **8** in quantitative yields. Consistent with our hypothesis, no other hydrolyzed or acetylated products were obtained, indicating that under these conditions water and acetate were not involved in the reaction.

Scheme 4. Reaction of Compound **11** with MeOH



In summary, we have discovered a new route to unprotected 2-acetamido-2-deoxy-β-D-glucopyranosides from *N*-acetyl-D-glucosamine, which proceeds via a furanose oxazoline intermediate. The method is well suited to large-scale work, and for simple glycosides no chromatography steps are required. Glycosides with larger aglycones require a single chromatographic step. Since the product is a 2-acetamido-2-deoxy-β-D-glucopyranoside, these unprotected derivatives are directly available for subsequent steps. The new methodology is mild and compatible with a range of functional groups and has become the method of choice for 2-acetamido-2-deoxy-β-D-glucopyranoside synthesis in our group.

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Supporting Information Available: Experimental procedures and ^{1}H NMR and other spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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