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Protecting Group Free Glycosidations Using *p*-Toluenesulfonohydrazide Donors

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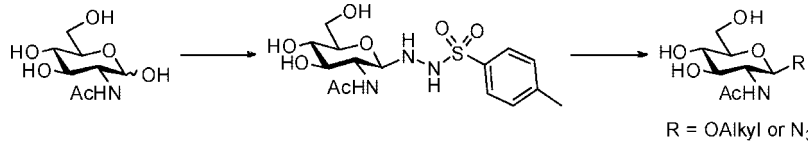
ABSTRACT



***N′*-Glycopyranosylsulfonohydrazides are introduced as glycosyl donors for protecting group free synthesis of *O*-glycosides, glycosyl azides, and oxazolines. Mono- and disaccharides containing a reducing terminal *N*-acetylglucosamine residue were condensed with *p*-toluenesulfonylhydrazide to give the desired *β*-D-pyranose donors. These donors can be activated with NBS and then glycosidated with the desired alcohol or transformed to the oxazoline or glycosyl azide.**

In 1893, Fischer's group reported the acid-catalyzed condensation reaction between glucose and methanol to yield methyl α-D-glucopyranoside in what is now commonly known as the Fischer glycosidation.[1] Since Fischer's report, immense progress has been made in the synthetic methods available to generate complex carbohydrates. These methods have enabled the stereocontrolled synthesis of glycans as large as the recently reported docosanasaccharide.[2] These impressive advances have been facilitated by the development of versatile protecting group strategies and powerful glycosylation conditions.[3]

Despite the advances of modern carbohydrate chemistry, the Fischer glycosidation is still the method of choice for forming simple glycosides because it can be carried out in a single synthetic step and it requires no protecting group manipulations. Many researchers have explored variations on Fischer's initial conditions, but in general, the limitations of the reaction, including the formation of mainly the thermodynamic pyranoside products and the strong acid catalysis required, have not been circumvented.[4] Other excellent examples of efficient protecting group free glycosylations have been reported, but in most cases, the synthesis of the glycosyl donors for these reactions has required protecting group chemistry.[5]

The use of *N′*-glycosyltoluenesulfonohydrazides (GSHs) as glycosyl donors offers numerous advantages: they do not require protecting group chemistry for their synthesis, require only a modest excess of alcohol for glycosidation, and can be activated by readily available reagents. Furthermore, the conditions for glycosyl donor formation and glycosidation are suitably mild that they can be carried out with oligosaccharides. Protected derivatives of GSHs have been investigated by Vasella et al. as precursors of lactone hydrazones.[6] But, GSHs have not previously been investigated as glycosyl donors.

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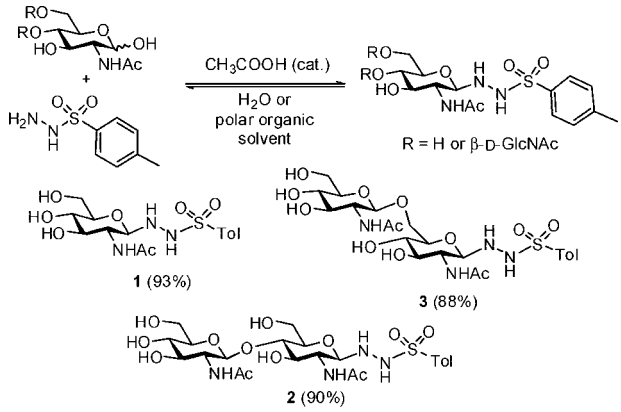
In this report we focus on *N*′-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-*p*-toluenesulfonohydrazide donors, as reducing terminal *N*-acetylglucosamine (GlcNAc) residues are found in a wide variety of biologically important oligosaccharides. The acetamido group at C-2 of GlcNAc is also known to aid in stereochemical control of glycosidation reactions.[7]

The condensation reactions between aldoses and sulfonylhydrazides have been used extensively for the characterization and labeling of mono and oligosaccharides.[8] The crystal structures of a series of *N*′-glycosyl-*p*-toluensulfonohydrazides have been reported.[9]

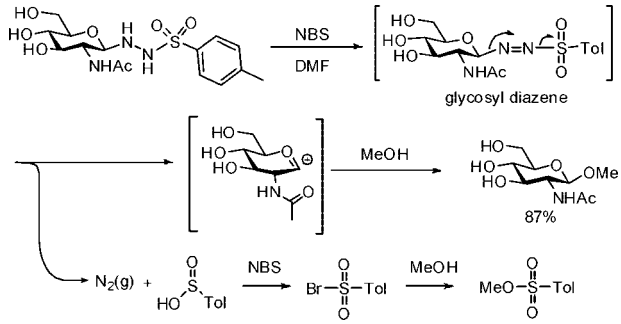
Using ^{1}H NMR, the equilibrium constant for the condensation of *N*-acetylglucosamine and *p*-toluenesulfonylhydrazide to form the *N*′-glycosyl-*p*-toluenesulfonohydrazide (**1**) in aqueous solution was determined to be approximately 30 M^{-1}; thus, concentrated conditions or excess hydrazide is required to drive the reaction to completion.[10] Under nonaqueous conditions, the reaction proceeds to completion in the presence of only a small excess of the desired hydrazide with mild acid catalysis (Scheme 1). Monosaccharide donor **1** was synthesized on a multigram scale in a suspension of DMF with a small excess of hydrazide (1.2 equiv) and a catalytic amount of acetic acid. The product could be easily isolated via precipitation with diethyl ether. The disaccharide donors **2** and **3** were formed on a milligram scale and could be readily purified with reversed-phase chromatography. Under these conditions only the cyclic β-D-pyranosyl donors were observed and the acyclic hydrazones were not present in quantities sufficient to be observed by NMR spectroscopy. The donors (**1**−**3**) are stable under ambient conditions and undergo slow hydrolysis when dissolved in a neutral aqueous solution.

Scheme 1. Formation of Glycosyl Donors



The oxidations of *N*′-alkylsulfonohydrazides have been proposed to proceed through diazene intermediates.[11,12] Acyl hydrazides have been used extensively in peptide chemistry as convenient precursors to carboxylic acids, thioesters, amides, and esters via their oxidization to form acyl diazenes.[13] Following a similar reaction mechanism, oxidation of the glycosyl donors (**1**−**3**) with NBS would lead to a glycosyl diazene (Scheme 2). Elimination of sulfinic acid and nitrogen gas would then give the oxocarbenium ion. The evolution of gas is clearly evident during these glycosidation reactions. The oxocarbenium ion is then trapped by the incoming alcohol wherein the stereochemistry of the attack is biased by the neighboring acetamido group. The sulfinic acid generated in the reaction undergoes further oxidation in situ to generate the sulfonyl halide, and thus, it is necessary to use 2 equiv of oxidizing agent to achieve complete glycosidation. Mass spectral analysis of crude reaction mixtures gave masses consistent with the formation of methyl toluenesulfonate likely resulting from methanol attack on the sulfonyl halide.

Scheme 2. Proposed Mechanism of *N*′-Glycosylsulfonohydrazide Activation



Previously, Vasella et al. have shown that it is possible to form lactone hydrazones from protected *N*′-glycosyl-*p*-toluenesulfonohydrazides under similar oxidation conditions to those used here. The tautomerization of the unprotected diazene to form the lactone hydrazone was only observed with donor **1** when the oxidation was carried out at low temperatures in the presence of a moderately strong base (e.g., DBU, DIPEA).[6]

Activation of the glycosyl donors (**1**−**3**) in the presence of a moderate excess (20 equiv) of the desired alcohol leads to good yields of the β-D-*O*-glycopyranosides (**4**−**15**) (Table 1). Small amounts of the α-glycosides are also formed, despite the neighboring acetamido group. The α-glycoside

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Table 1. Glycosidation Yields and Selectivities[a]

glycosyl donor	alcohol	product	yield (%), (α:β)
1	MeOH [(a)]	**4**	87 (1:10)
1	Cl–OH [(a)]	**5**	72 (1:7)
1	OH [(a)]	**6**	75 (1:8)
1	OH [(b)]	**7**	75 (1:7)
1	OH [(a)]	**8**	74 (1:7)
1	OH [(a)]	**9**	80 (1:7)
1	OH [(a)]	**10**	72 (1:6)
2	MeOH [(a)]	**11**	71 (1:9)
2	Cl–OH [(a)]	**12**	70 (1:7)
3	MeOH [(a)]	**13**	73 (1:9)
3	Cl–OH [(a)]	**14**	71 (1:7)

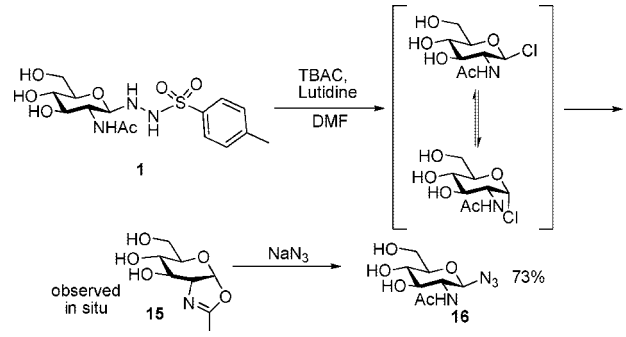
[a] Reaction conditions: (a) NBS (2.4 equiv), alcohol (20 equiv), in DMF at rt; (b) NIS (2.4 equiv), alcohol (20 equiv), in DMF at rt.

is likely the result of participation by the solvent resulting in an alternative ion pair.[14] Other products produced in the reaction included the free hemiacetal, resulting from hydrolysis, and trace amounts of the glycosyl sulfone, resulting from the reaction of the oxocarbenium ion with the generated sulfinic acid. Higher yields of the allyl glycoside (**7**) were obtained using NIS (20% vs 75%), presumably due to competing electrophilic addition to the alkene. The desired glycosides could be readily purified using flash chromatography on silica gel.

When this approach is compared to the facile formation of β-D-2-acetamido-2-deoxyglucopyranosides recently introduced by Cai et al., the current approach gives similar yields but requires a smaller excess of the alcohols.[15] Furthermore, disaccharide donors (**2**, **3**) can be glycosidated with efficiency equal to that of the monosaccharides as was observed with glycosides **11**−**14**.

Although the formation of oxazolines was not observed in the glycosidation reactions, oxazolines could be formed under the conditions shown in Scheme 3. It was essential to have the chloride anion present in the reaction for clean conversion of glycosyl donor **1** to the oxazoline **15**. The requirement for chloride ions suggests the reaction may proceed through an intermediary glycosyl chloride. ^{1}H NMR spectroscopy shows the transient formation of a low-field absorption at 6.3 ppm (Figure 2S, Supporting Information), consistent with the generation of an α-glycopyranosyl chloride. Halide exchange is rapid under these conditions, and the β-glycosyl chloride would then proceed to the oxazoline (Figure 1S, Supporting Information).[16] This oxazoline synthesis may provide a useful route to generate

Scheme 3. Formation of Glycosyl Azide via Oxazoline



reducing terminal oxazolines for use as substrates for endoglucosaminidases to allow the preparation of homogeneous *N*-linked glycoproteins.[17]

The unprotected oxazolines are also considerably more reactive glycosyl donors than their protected counterparts.[15] Acetyl-protected oxazolines generally require a strong lewis acid catalyst (i.e., TMSOTf) for glycoside formation, and thus, they are not used extensively in glycoside synthesis.[18] In contrast, the unprotected oxazoline **15**, formed in situ, can be glycosidated with azide, with only lutidinium hydrochloride present as an acid catalyst, to give **16** in 73% yield. It was not possible to form the glycosyl azide directly in the glycosylation reaction as NaN_3, $TBAN_3$, and $TMSN_3$ were incompatible with the conditions necessary for activation of the glycosyl donors. Thus, this method may provide a useful route to generate glycosyl azides from isolated oligosaccharides for the formation of novel *N*-linked glycoconjugates.[19,20]

In conclusion, GSH glycosyl donors can be formed in high yield under mild conditions and can be readily activated to form a wide range of glycosides without the use of protecting groups. The simplicity of the approach suggests it can be extended to large oligosaccharides isolated from natural sources or those generated by chemoenzymatic synthesis. We are currently exploring the use of this reaction with glycosyl donors other than those based on *N*-acetylglucosamine.

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Supporting Information Available: Figures 1S and 2S, experimental procedures, and ^{1}H and ^{13}C NMR spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

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