

Oxazolidinone Protection of *N*-Acetylglucosamine Confers High Reactivity on the 4-Hydroxy Group in Glycosylation

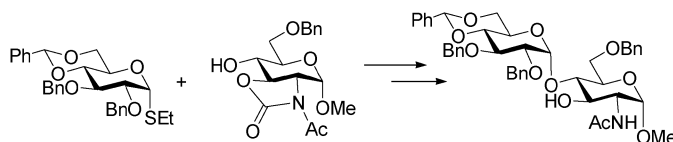
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ABSTRACT



The preparation of a convenient oxazolidinone protected *N*-acetyl glucosamine 4-OH derivative is reported. This substance exhibits enhanced reactivity as a glycosyl acceptor in a variety of coupling methods, the products of which are converted to the target *N*-acetylglucosaminyl saccharides under very mild conditions.

Glycosylation of the 4-hydroxyl group of selectively protected *N*-acetyl glucosamine derivatives is both extremely important and notoriously difficult. The importance stems from the widespread nature of glycosidic bonds to this hydroxyl group in biologically important polymers in general,¹ but especially in the common core pentasaccharide of the *N*-linked glycoproteins.² The difficulty arises from the well-known lack of reactivity of this particular alcohol, which is due to a combination of steric hindrance, common to most pyranose 4-OH's,³ and the involvement of the *N*-acetyl group in a hydrogen-bonded network.⁴ Typically, the problem is addressed through the use of *N*-phthalimido glucosamine or 2-azido-2-deoxy glucose derivatives, as exemplified by **1** or **2**. *N,N*-Diacetyl and *N*-acetyl-*N*-benzyl protected glucosamine derivatives, e.g. **3** and **4**, also show enhanced reactivity as glycosyl acceptors. Among these four the azide (**2**) is the most reactive⁴ and has proven its value in a

synthesis of the common core trisaccharide of the *N*-linked glycans,⁵ but the most convenient preparation employs triflyl azide and is inconvenient on a large scale.⁶ Substances **1**, **3**, and **4** suffer from the relatively harsh conditions required to cleave the phthalimide,⁷ the instability of **3** toward premature hydrolysis, and the complex NMR spectra engendered by the fully substituted amide in **4**.⁴ Interestingly, sulfonamide protected glucosamine derivatives (**5**) have proven to be serviceable glycosyl acceptors whose deprotection may be conveniently achieved in parallel to benzyl ethers by means of sodium in liquid ammonia.⁸ We now show that oxazolidinone protection of *N*-acetylglucosamine affords a very convenient and highly reactive glycosyl acceptor that,

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(7) The tetrachlorophthalimides are easier to cleave but are not considered as their more crystalline nature renders them insufficiently soluble at the low temperatures (≤ 60 °C) used for glycosylation in this laboratory. Debenham, J. S.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 3302.

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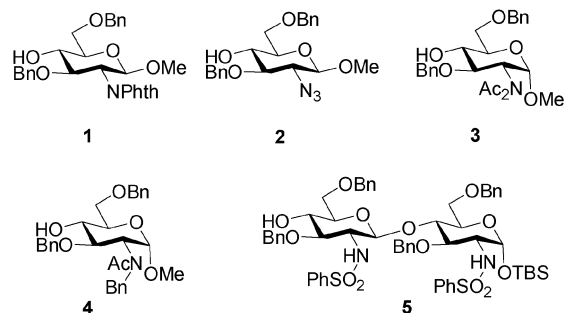
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additionally, is converted in a straightforward manner to the target *N*-acetyl protected disaccharides post-glycosylation.^{9,10}

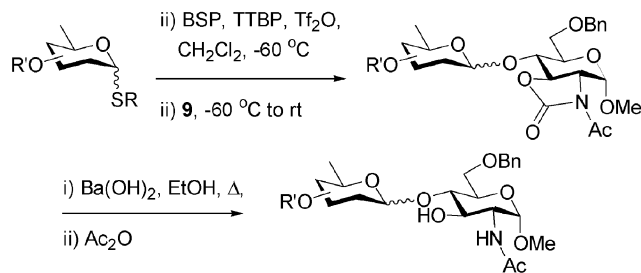


Scheme 1. Preparation of an Oxazolidinone Protected Acceptor

that the acid-mediated, regioselective cleavage of the benzylidene acetal¹² is fully compatible with the *N*-acetyl oxazolidinone group in **8**.

Acceptor **9** was then subjected to coupling with a range of thioglycosides under the standardized activation conditions employed in both the solution¹³ and solid phases¹⁴ in this laboratory (Scheme 2). Thus, the various thioglycosides were briefly exposed to the combination of 1-benzenesulfinylpyridine (**BSP**),¹⁵ 2,4,6-tri-*tert*-butylpyrimidine (**TTBP**),^{15,16} and triflic anhydride in dichloromethane at $-60\text{ }^{\circ}\text{C}$ before

Scheme 2. Glycosylation of **9** with Thioglycosides and BSP/Tf₂O



addition of the acceptor and warming to room temperature (Table 1). After isolation of the disaccharides, the *N*-acetyl oxazolidinone moiety was removed with barium hydroxide in ethanol and the acetamide reinstated by brief treatment with acetic anhydride (Scheme 1 and Table 1).

All of the couplings presented in Table 1 proceeded without event, leaving only the stereoselectivities in need of comment. Coupling to the mannosyl donor **10** was β -selective as anticipated,^{13,17} but less so than might have been expected. Nevertheless, the two anomers were readily separated thereby providing an entry into the key linkage of the *N*-linked glycans. The 4,6-*O*-benzylidene protected donor **13** afforded a highly α -selective coupling, again in line with precedent,^{13,18} thereby providing a convenient entry into the repeating unit of heparin.¹ Interestingly, the 4,6-*O*-benzylidene protected galactosyl donor **16**,¹⁹ like its glucose counterpart but in contrast to the mannose series, was also highly α -selective and affords the linkage at the core of the keratin sulfate repeating unit.¹ The rhamnosyl donor **19** was highly α -selective, again in line with precedent,^{13,20,21} whereas lower selectivity was obtained with the less rigid tetra-*O*-benzyl glucose donor **22**.

Although the broad, general **BSP**/Tf₂O protocol is the coupling method of choice in our laboratory for glycosidic bond formation, it is by no means the only method available.²² We have glycosylated acceptor **9** by three other methods to test its generality as an improved acceptor alcohol (Scheme 3, Table 2).

In the event, as is evident from Table 2, acceptor **9** performs well in Kahne's sulfoxide method,²³ Gin's dehydrative coupling sequence,²⁴ and Schmidt's trichloroacetimide protocol.²⁵

Finally, the question of the reasons underlying the enhanced reactivity of acceptor **9** obviously arises, aside from the obvious elimination of the NH bond. The possibility that

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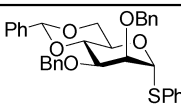
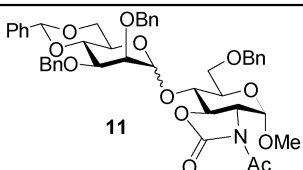
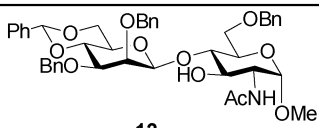
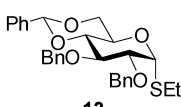
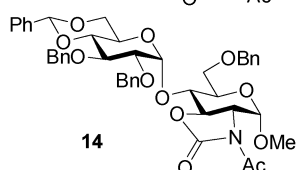
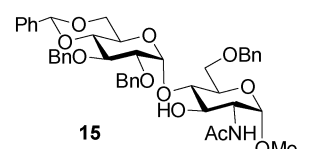
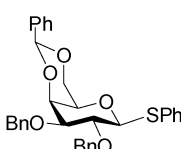
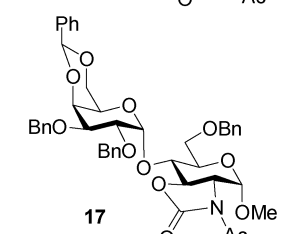
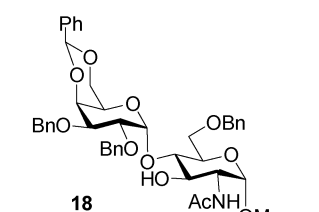
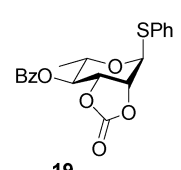
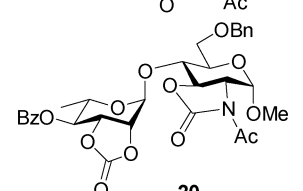
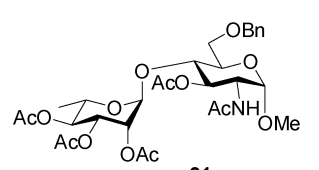
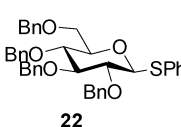
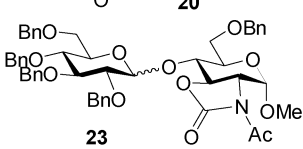
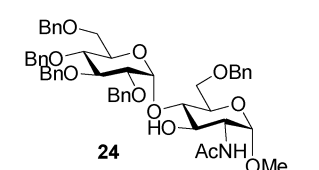
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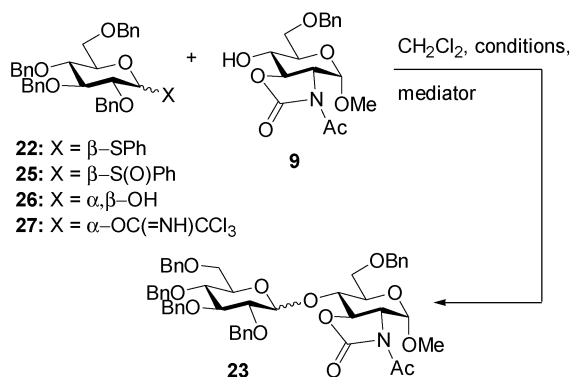
Table 1. Preparation of 4-*O*-Glycosylated *N*-Acetylglucosamines from Acceptor **9** by the Thioglycoside/BSP/Tf₂O Method

donor	coupled product	anomeric ratio (α/β)	% yield	deprotected product	%yield
 10	 11	1:2.7	82	 12	80 ^a
 13	 14	α only	87	 15	76
 16	 17	α only	85	 18	81
 19	 20	α only	66	 21	48 ^b
 22	 23	6.2:1	78	 24	62 ^c

^a Only the β -anomer was deprotected. ^b In this case the esterification was conducted with Ac₂O in pyridine. ^c Only the α -anomer was deprotected.

the oxazolidinone ring confers a twist, or even an inversion of conformation, of the pyranose ring thereby exposing the 4-OH more is ruled out by the scalar couplings around the ring which clearly indicate a standard ⁴C₁ chair. It seems most likely, therefore, that the enhanced reactivity of **9**

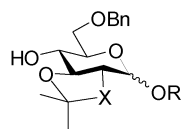
simply arises from the tied back nature of the protection on O-3, which minimizes steric hindrance about the 4-OH. This being the case, it is likely that cyclic carbonates spanning O-2 and O-3 will enhance the reactivity of the 4-OH in other donors. Indeed, although no formal comparisons were made, the work of Boons suggests that this may well be the case.¹⁰ Similarly, it is likely that 2,3-acetonide (**28**) and even silylene

Scheme 3. Glycosylation of **9** by Alternative Methods**Table 2.** Alternative Coupling Methods for the Formation of **23**

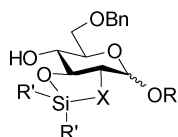
donor	mediator; conditions	anomeric ratio (α/β)	% yield
22 ^a	BSP, TTBP, Tf ₂ O; -60 °C	6.2:1	78
25	TTBP, Tf ₂ O; -60 °C	α only	63
26	Ph ₂ SO, Tf ₂ O, TTBP; -40 °C	α only	59
27	TMSOTf; -30 °C	3.5/1	82

^a The last entry of Table 1 is reproduced here for convenient comparison.

(**29**) protected acceptors will show enhanced reactivity, although this remains to be tested.



28: X = O or NAc



29: X = O or NAc

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Supporting Information Available: Synthetic details and characterization for all new molecules. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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