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

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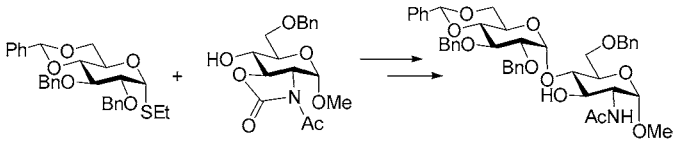
ABSTRACT



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 reactive[4] 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,

(1) (a) Lehman, J. *Carbohydrates: Structure and Biology*; Thieme: Stuttgart, Germany, 1998. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (c) Varki, A. *Glycobiology* **1993**, *3*, 97. (d) *Bioorganic Chemistry: Carbohydrates*; Hecht, S. M., Ed.; OUP: New York, 1999.

(2) Davis, B. G. *Chem. Rev.* **2002**, *102*, 579.

(3) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.

(4) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819.

(5) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787.

(6) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073.

(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.

(8) Wang, Z.-G.; Zhang, Z.; Visser, M.; Live, D.; Zatorski, A.; Iserloh, U.; Lloyd, K. O.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1728. Dudkin, V. Y.; Miller, J. S.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 1791.

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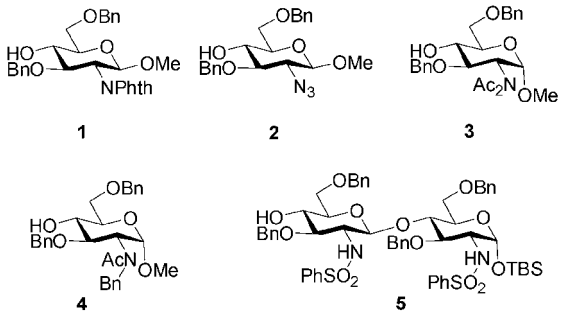
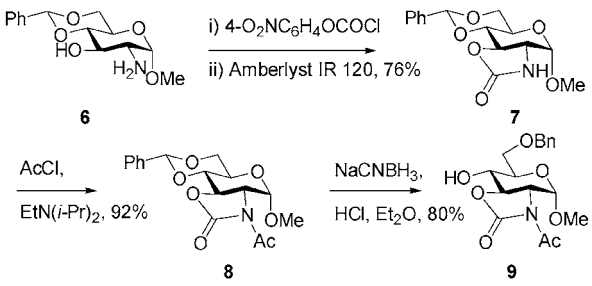
additionally, is converted in a straightforward manner to the target *N*-acetyl protected disaccharides post-glycosylation.[9,10]



A suitable *N*-acetyl oxazolidinone (**9**) was prepared in a straightforward manner from the known[11] glucosamine derivative **6** as shown in Scheme 1. It is of some interest

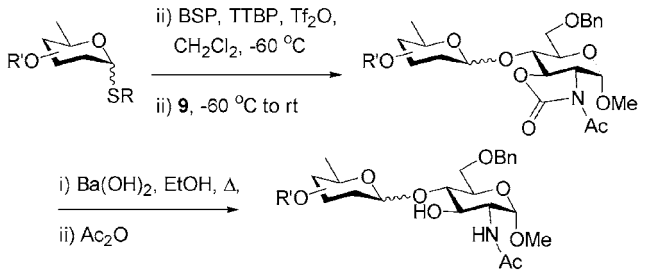
Scheme 1. Preparation of an Oxazolidinone Protected Acceptor



that the acid-mediated, regioselective cleavage of the benzylidene acetal[12] 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 solution[13] and solid phases[14] in this laboratory (Scheme 2). Thus, the various thioglycosides were briefly exposed to the combination of 1-benzenesulfinylpiperidine (**BSP**),[15] 2,4,6-tri-*tert*-butylpyrimidine (**TTBP**),[15,16] and triflic anhydride in dichloromethane at −60 °C before

Scheme 2. Glycosylation of **9** with Thioglycosides and BSP/Tf_2O



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 reinstalled 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**/Tf_2O 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 trichloroacetimidate 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

(9) Oxazolidinone protection of glucosamine affords an α-selective glucosamine donor but its use has not been described in glucosamine acceptors. Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 9461.

(10) 2,3-*O*-Carbonate protection has been applied in glucose acceptors but without any comment on its ability to enhance or diminish nucleophilicity. Zhu, T.; Boons, G.-J. *Org. Lett.* **2001**, *3*, 4201.

(11) Bauer, T.; Tarasiuk, J.; Pasiczek, K. *Tetrahedron: Asymmetry* **2002**, *13*, 77.

(12) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97. Garegg, P. J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; p 53.

(13) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015. Crich, D.; de la Mora, M. A.; Cruz, R. *Tetrahedron* **2002**, *58*, 35. Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640. Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781−784.

(14) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867.

(15) Commercially available from www.lakeviewsynthesis.com.

(16) TTBP is a convenient, crystalline alternative to DTBMP: Crich, D.; Smith, D.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.

(17) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321.

(18) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926.

(19) Sugimura, H.; Watanabe, K. *Synth. Commun.* **2001**, *31*, 2313.

(20) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291.

(21) Note that this selectivity contrasts with that obtained for 2,3-*O*-carbonyl-protected rhamnosyl bromides by the insoluble silver salt method: Bachinovsky, L. V.; Balan, N. F.; Shashkov, A. S.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *84*, 225.

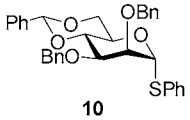
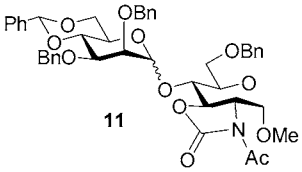
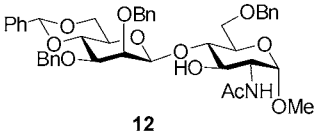
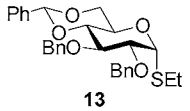
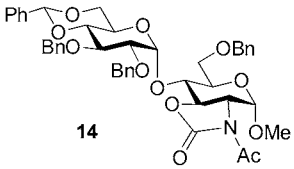
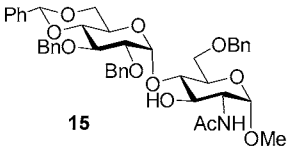
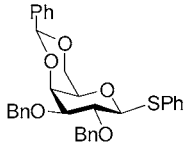
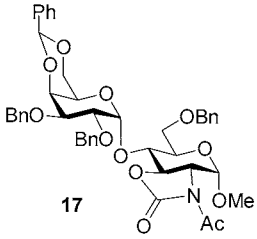
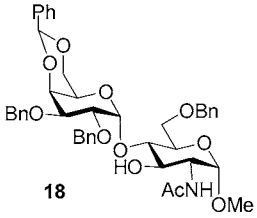
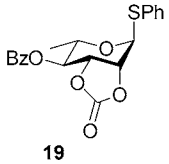
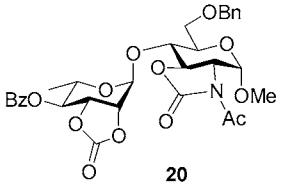
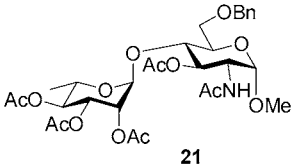
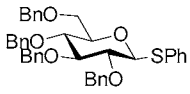
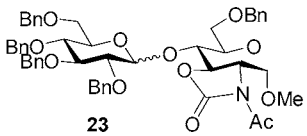
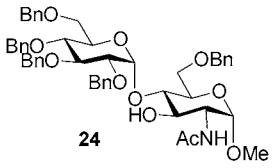
(22) Barresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1995**, *14*, 1043.

(23) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239.

(24) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

(25) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

Table 1. Preparation of 4-*O*-Glycosylated *N*-Acetylglucosamines from Acceptor **9** by the Thioglycoside/BSP/Tf_2O 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 Ac_2O 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 $^4C_1$ 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

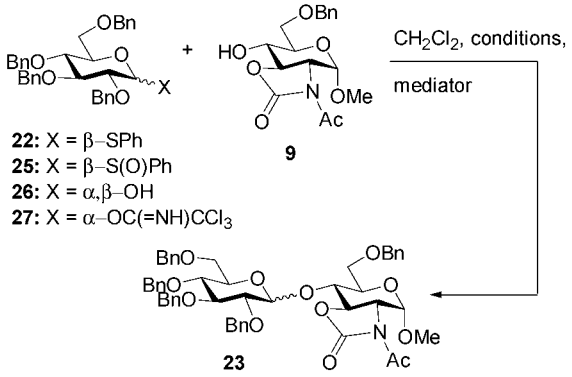
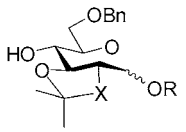


Table 2. Alternative Coupling Methods for the Formation of **23**

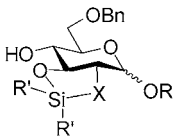
donor	mediator; conditions	anomeric ratio (α/β)	% yield
22[a]	BSP, TTBP, Tf_2O; −60 °C	6.2:1	78
25	TTBP, Tf_2O; −60 °C	α only	63
26	Ph_2SO, Tf_2O, TTBP; −40 °C	α only	59
27	TMSOTf; −30 °C	3.5/1	82

[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

Acknowledgment. We thank the NIH (GM 62160) for support of this work.

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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