Stereoselective Synthesis of α-*C*-Glucosamines via Anomeric Organosamarium Reagents

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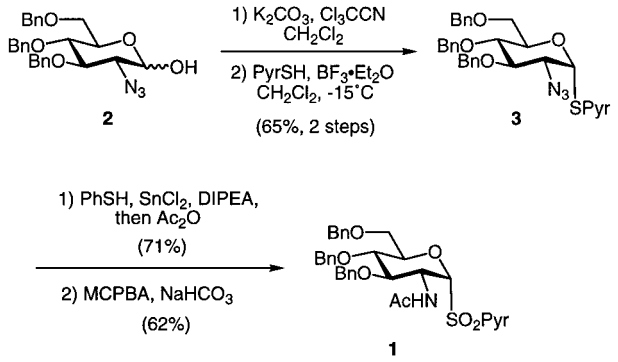
Abstract: The direct coupling of the pyridyl sulfone of *N*-acetylglucosamine with aldehydes or ketones is promoted by samarium diiodide affording the corresponding α-*C*-glycosides preferentially. A *C*-disaccharide has been synthesized using this approach.

In the past few years *C*-disaccharides and *C*-trisaccharides have become important biological tools for the study of carbohydrate-protein interactions in lectins and glycosidases.[1] Despite the tremendous work carried out in the development of synthetic techniques to obtain *C*-disaccharides and higher *C*-oligomers, none have been applied to 2-acetamido-2-deoxy sugars at the nonreducing position. In this paper, we present an extremely mild approach for the synthesis of α-*C*-glycoside analogues of *N*-acetylglucosamine by a simple titration of a THF solution of 2-acetamido-2-deoxyglucosyl 2-pyridyl sulfone and a carbonyl compound with samarium diiodide. These results contribute to our overall study on anomeric organosamarium reagents for the stereoselective synthesis of *C*-glycosides.[2,3] We show that this approach may be applicable for the synthesis of a *C*-disaccharide containing *N*-acetylglucosamine in the non-reducing end which is the first of its kind.

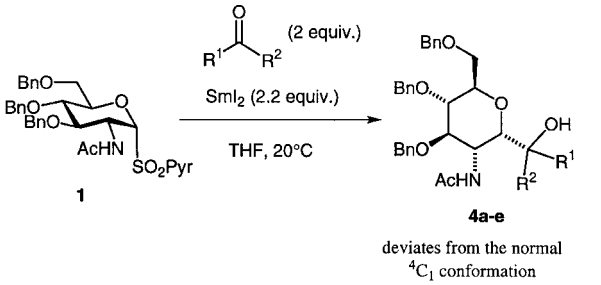
The synthesis of the 2-pyridyl sulfone of *N*-acetylglucosamine **1**, as illustrated in Scheme 1, began with the hemiacetal **2** easily prepared from the azidonitration of 3,4,6-tri-*O*-benzylglucal.[4] Hence transformation of **2** to the α-oriented 2-pyridyl sulfide **3** was made possible via a two-step procedure involving formation of the β-trichloroimidate followed by its treatment with 2-mercaptopyridine and $BF_3{\cdot}Et_2O$. Subsequent reduction of the azide using the Bartra procedure[5] and acetylation, and then oxidation of the sulfide with MCPBA led to the glycosyl 2-pyridyl sulfone **1**.

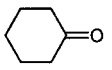
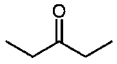
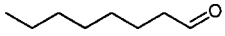
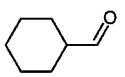
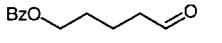


Scheme 1

Subjecting a THF solution of the pyridyl sulfone **1** and cyclohexanone to SmI_2 led to an instantaneous consumption of the one-electron reducing agent with the production of a *C*-glycoside mixture in 77% yield after chromatography (Table 1, entry 1). As was observed earlier with *N*-acetylgalactosamine,[2c,f,g] the use of **1** led to the predominant formation of the α-*C*-glycoside **4a** with an α:β ratio of 3.6:1.[7] We note again the efficiency of this coupling reaction considering the availability of a potentially acidic proton of the acetamide group. The coupling of **1** with other carbonyl compounds was also α-selective as shown in Table 1 (entries 2-5). In the case of aldehydes (entries 3-5), a stereoselectivity of 4.3-10:1 was observed at the newly created exocyclic stereocenter of **4c-e**[8] implying that the anomeric samarium species is more selective than that noted for the corresponding C1-lithium reagent.[9] We tentatively assign the major isomers of entries 3-5 to possess the (*S*)-configuration at the exocyclic stereocenter based on earlier results both in SmI_2-induced α-*C*-glycosylations[2c-f] as well as those performed under reductive lithiation conditions.[10] In all these cases the same stereoisomer was obtained as the major product. The *C*-glycosides **4a-e** also possess abnormal ring conformations as seen from the small coupling constants $J_{H2,H3}$, $J_{H3,H4}$ and $J_{H4,H5}$ of less than 2 Hz.[8] The expected $^4C_1$ conformation with *trans*-diaxial orientations of the H2, H3, H4 and H5 protons would require coupling constants of approx. 9 Hz. This deviation has been observed before with other α-*C*-glycosides and is probably due to some $A^{1,3}$ strain.[2f,11]

Table 1. SmI_2-promoted *C*-glycosylations with pyridylsulfone **1**[a]



Entry	Carbonyl comp.	*C*-glycoside (isolated yields)[b]		α:β	Stereoselect.[c]
1		**4a**	77%	3.6:1	-
2		**4b**	51%	3.3:1	-
3		**4c**	63%	3.6:1	4.7:1
4		**4d**[8]	48%	3.6:1	>10:1
5		**4e**	64%	3.0:1	4.3:1

[a]See ref. 6 for experimental details. [b]Based on isolated, chromatographically pure material. [c]Stereoselectivities refer to the new exocyclic stereogenic center of the α-*C*-glycoside

The α-selectivity observed is explained by the strong complexation between the *N*-acetamide group and the metal ion in the initially formed α-organosamarium **5**. A conformational change to an inverted chair or skew boat conformation could then occur placing the C1-Sm bond in an

energetically more favorable equatorial position (see Figure 1).[12] A configurational change may competitively occur to give the β-organosamarium species. However, this anomerization process is sufficiently retarded because of the strong complexation between the metal ion and the acetamide group, such that coupling of the carbonyl compound with the α-anomer is favored. It is interesting to note that pyridyl sulfone **1** affords reduced α:β-selectivities compared with the *N*-acetylgalactosamine case (approx. 3.5:1 compared to 4-20:1 for the latter). It is expected that the conformational change should be more advantageous for **6** than for **5** as the placement of an axially oriented C4-OBn group in a pseudo-equatorial position would lead to a greater stability of this conformer and hence higher α-selectivity for **6**.

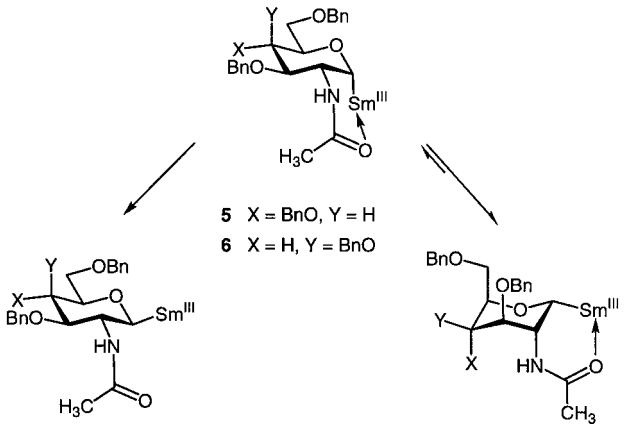
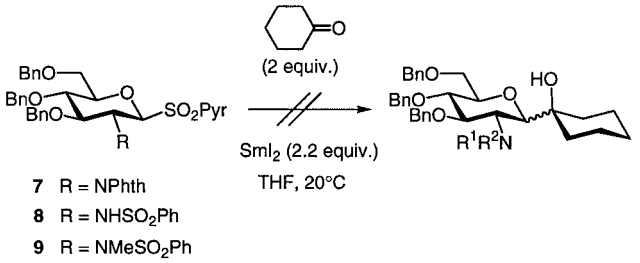


Figure 1

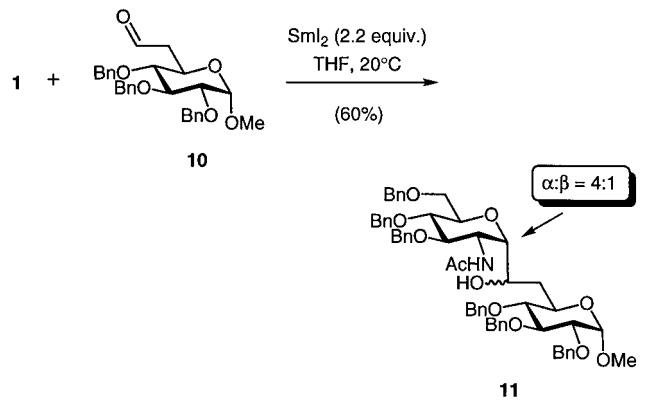
Other *N*-protecting groups such as the phthalimide in **7**, and the sulfonamides in **8** and **9** (Scheme 2) were also tested in order to examine their influence on the stereoselectivity of the coupling at the anomeric center. Surprisingly, in all cases these proved to be unrewarding in that considerable degradation was observed with no sign of any coupling products. Competitive reduction of these protecting groups by SmI_2 may take place.



Scheme 2

Finally, we show that the pyridyl sulfone **1** can be used for the facile synthesis of a *C*-disaccharide. Treatment of a THF solution of **1** and **10**[13] with SmI_2 afforded the *C*-disaccharide **11**[14] in a 60% yield with an α:β-selectivity of 4:1 (Scheme 3). This represents the first *C*-disaccharide containing an *N*-acetylglucosamine unit at the nonreducing position.

In conclusion, the anionic approach to the synthesis of *C*-glycosides including a *C*-disaccharide employing samarium diiodide has now been expanded to the *N*-acetylglucosamine case which displays a preference for the α-anomer. Further work is in progress to investigate whether a change in the nitrogen substituent to a non-coordinating group could lead to the formation of the corresponding β-*C*-glycosides.



Scheme 3

Aknowledgements

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(3) For a recent use of glycosyl pyridyl sulfones and phenylsulfones for the preparation of *C*-glycosides of *N*-acetylneuraminic acid and KDN, see: Vlahov, I.R.; Vlahova, P.I., Linhardt, R.J. *J. Am. Chem. Soc.* **1997**, *119*, 1480; Du, Y. T.; Linhardt, R.J. *Carbohydr. Res.* **1998**, *308*, 161; Du, Y; Polat, T.; Linhardt, R.J. *Tetrahedron Lett.* **1998**, *39*, 5007.

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(6) *Typical procedure:* A 0.1 M THF solution of SmI_2 (2.2 equiv.) was added quickly to a well degassed solution of pyridyl sulfone **1** (1 equiv.) and the carbonyl substrate (2.0 equiv.) in THF (5 ml /

mmol of **1**). The reaction mixture was treated with saturated NH_4Cl, extracted twice with CH_2Cl_2, and the organic phase was dried and evaporated to dryness. The crude product was purified by flash chromatography.

(7) In an earlier paper (ref. 2f) we reported that coupling of **1** with cyclohexanone led only to the product of desulfonylation. As the pyridyl sulfone **1** in this case was prepared from **2** via the reduction of the azide group with Ph_3P and subsequent hydrolysis and acetylation, it is possible that **1** was contaminated with Ph_3PO. We have previously observed that contamination of the corresponding pyridyl sulfone of *N*-acetylgalactosamine with Ph_3PO does not lead to the formation of *C*-glycosides, but rather the 1-deoxy derivative (ref. 2f).

(8) Selected ^1H NMR (200 MHz, $CDCl_3$) data for the major isomer of **4d**: δ 6.58 (1H, d, *J* = 9.2 Hz, NH), 4.33 (1H, bdd, *J* = 7.8, 6.2 Hz, H5), 4.24 (1H, bd, *J* = 9.2 Hz, H2), 3.93 (1H, bd, *J* = 7.1 Hz, H1), 3.90 (1H, dd, *J* = 10.1, 7.8 Hz, H6a), 3.74 (1H, bs, H3), 3.60 (1H, dd, *J* = 10.1, 6.2 Hz, H6b), 3.44 (1H, bs, H4), 3.39 (1H, dd, *J* = 7.1, 2.2 Hz, H7), 1.84 (3H, s, $COCH_3$). MS (electrospray) *m/z* 610.3 (M + Na), 588.3 (M + 1), 570.3 (M – H_2O); HRMS *m/e* calcd for $C_{36}H_{45}NNaO_6$ (M +Na) 410.3145, found 410.3133.

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(14) Selected ^1H NMR (200 MHz, $CDCl_3$) data for the major isomer of **11**: δ 6.31 (1H, d, *J* = 9.4 Hz, NH), 4.31 (1H, d, *J* = 3.6 Hz, H1), 4.30 (1H, bd, *J* = 9.4 Hz, H2'), 4.33 (1H, bdd, *J* = 7.8, 6.2 Hz, H5'), 3.86 (1H, dd, *J* = 10.0, 8.0 Hz, H6a'), 3.83-3.58 (5H, m, H1', H3, H3', H5, H6a', H6b'), 3.50 (1H, bs, H4'), 3.39 (1H, dd, *J* = 9.5, 3.6 Hz, H2), 3.21 (1H, m, H7), 3.18 (3H, s, OCH_3), 3.16 (1H, dd, *J* = 9.5, 9.5 Hz, H4), 2.01 (1H, m, H6a), 1.78 (1H, m, H6b), 1.68 (3H, s, $COCH_3$).