SmI_2-Promoted Deprotection of *N*-(Arylsulfonyl)glucosamines

Daniel C. Hill, Lisa A. Flugge, and Peter A. Petillo*

Department of Chemistry, School of Chemical Sciences, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801

Received February 26, 1997

The synthesis of glycosaminoglycans and other nitrogen-containing oligosaccharides requires the installation of a 2-deoxy-2-amino functionality.[1] While traditional synthetic strategies often employ starting materials with the amino group in place (e.g., **1**),[2] other approaches have been suggested, most notably the iodo sulfonamidation method pioneered by Danishefsky and co-workers.[3,4] In our hands, the Danishefsky methodology is a powerful method for effecting glycosidic bond formation. Unfortunately, subsequent deprotection of the aromatic sulfonamides under strongly reducing conditions has been shown to be incompatible with the other functionality found in the glycosaminoglycan backbone.[4] Danishefsky and co-workers have investigated sulfonamides that can be deprotected under nonreducing conditions,[5] although we have found that the *N*-tosyl- and *N*-phenylsulfonamides give the best yields of the key glycosidic bond-forming steps required for glycosaminoglycan synthesis.

We now report the SmI_2-mediated deprotection of *N*-tosyl-2-deoxy-2-amino- and *N*-sulfonyl-2-deoxy-2-aminoglycosides after purification results in superior yields of the free amines (Table 1).[6] This approach obviates the need for harsh Na^0/NH_3 reductions and is compatible with a wide variety of protecting groups often employed in oligosaccharide syntheses. Vedejs and Lin have reported that the SmI_2-promoted deprotection of arenesulfonamides occurs in excellent yields without epimerization.[7] Using a modified version of their protocol, we established that **1** and **3** (Table 1, entries 1 and 2) can be deprotected with SmI_2 in yields of 85% and 73% after purification.[8] The reductions typically take longer to complete than those reported by Vedejs and Lin (2−3 days vs 24 h), and in general, the phenylsulfonamides reduce more quickly than the tosylamides.

Deprotection of *N*-tosylglucosamine derivatives **5** and **6** (Table 1, entries 3 and 4) proved problematic, as all reduction attempts resulted in cleavage of the C6 esters followed by cleavage of the C4 esters and other undetermined side reactions. In all attempts, the tosylsulfonamides remained intact, even when up to 15 equiv of SmI_2 and extended reaction conditions were employed. Reports on the reduction of aromatic carboxylic acid derivatives, including esters, by SmI_2 have been summarized.[9] These reductions typically require the addition of either an acid or base catalyst, and in general, it is believed that simple esters should survive SmI_2 conditions. We discount the possibility that the starting materials were contaminated, as they were rigorously purified prior to use. The possibility exists that our reaction conditions (10−15 equiv of SmI_2 in refluxing THF for extended periods of time) may promote the ester reductions. It remains to be determined if selective ester reduction in the absence of exogenous acid or base catalyst would prove synthetically useful for the preparation of deprotected carbohydrates.

The SmI_2-promoted deprotection of a range of glucosamine dimers (Table 1, entries 5−9) proceeded smoothly to yield the corresponding amines in yields ranging from 43 to 70% after purification.[10] This represents a 3−5-fold increase in yield compared to those typically observed for the corresponding Na^0/NH_3 reductions.[8] The bulk of the mass balance in most cases was unreacted starting material. All glycosidic linkages remained intact, and no monomers were detected. Furthermore, we see no evidence to suggest that cleavage of the (*p*-methoxyphenyl)methyl (MPM, Table 1, entries 5 and 6), benzyl (Table 1, entries 5−9), benzylidene (Table 1, entries 7−9), or acetamido groups (Table 1, entry 9) occurs. This is in stark contrast with the results from Na^0/NH_3 reductions where decomposition to monomer fragments always occurs and removal of these protecting groups is often observed. Thus, the SmI_2-deprotection offers a strategy for further nitrogen functionalization while keeping the hydroxyl protecting groups intact.

These observations suggest that the selective deprotection of glucosamine polymers such as the glycosaminoglycans and chitin and chitosan fragments may be possible. Furthermore, the observation that SmI_2 cleaves simple esters may allow, in some instances, for the complete deprotection of oligosaccharides in a single, relatively mild step if a large excess of SmI_2 is employed.

In conclusion, the SmI_2-promoted reduction of (arenesulfonyl)glucosamine derivatives proceeded in good yield with retention of the carbohydrate backbone and without loss of common hydroxyl protecting groups.

* To whom correspondence should be addressed.

(1) For reviews of glycosaminoglycan structure and function see: (a) Hascall, V. C.; Kimura, J. H. *Methods Enzymol.* **1982**, *82*, 769. (b) Kjellen, L.; Lindahl, U. *Ann. Rev. Biochem.* **1991**, *60*, 443. (c) Toole, B. P. *Curr. Opin. Cell Biol.* **1990**, *2*, 839.

(2) For example see: (a) Takanashi, S.; Hirasaka, Y.; Kawada, M. *J. Am. Chem. Soc.* **1962**, *84*, 3029. (b) Jeanloz, R. W.; Flowers, H. M. *J. Am. Chem. Soc.* **1962**, *84*, 3030. (c) Flowers, H. M.; Jeanloz, R. W. *Biochemistry* **1963**, *3*, 123. (d) Walker-Nasir, E.; Jeanloz, R. W. *Carbohydr. Res.* **1979**, *68*, 343. (e) Slaghek, T.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1992**, *33*, 4971. (f) Klaffke, W.; Warren, C. D.; Jeanloz, R. W. *Carbohydr. Res.* **1993**, *244*, 171.

(3) The Danishefsky glycosylation methods have been reviewed. See: Danishefsky, S. J.; Randolp, J. T.; Roberge, J. Y.; McClure, K. F.; Ruggeri, R. B. *Recent Applications of the Glycal Assembly Method: Solid-Phase Synthesis of Oligosaccharides and Glycoconjugates*; E. Schering Research Foundation Lecture; Springer Verlag: New York, 1995; Vol. 26 and references therein.

(4) Carter, M. B.; Petillo, P. A.; Anderson, L. A.; Lerner, L. E. *Carbohydr. Res.* **1994**, *258*, 299.

(5) (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863. (c) Danishefsky, S. J.; Koseki, K.; Griffith, D. A.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Oriyama, T. *J. Am. Chem. Soc.* **1992**, *114*, 8331. (d) Roberge, J. Y.; Beebe, X.; Danishefsky, S. J. *Science* **1995**, *269*, 202.

(6) SmI_2-mediated C-glycosylations have been reported: Jarreton, O.; Skrydstrup, T.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 1661.

(7) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.

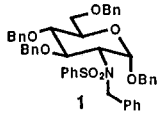
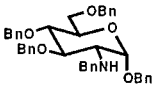
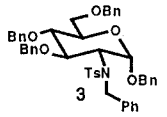
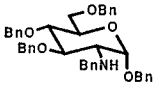
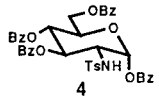
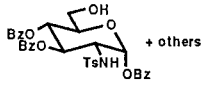
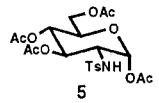
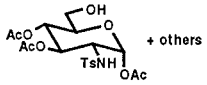
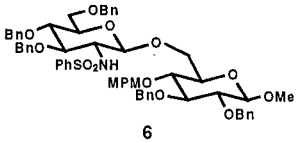
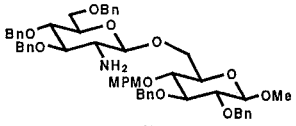
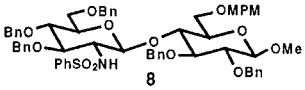
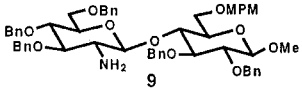
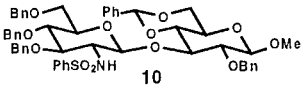
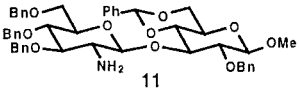
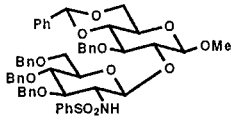
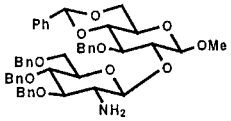
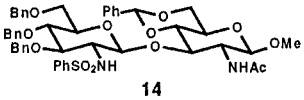
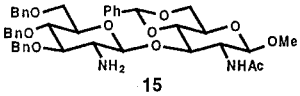
(8) The syntheses of *N*-tosylglucosamine and *N*-sulfonylglucosamine and their derivatives have been reported. See: (a) Takiura, K.; Koizumi, K.; Takeuchi, A. *Nippon Kagaku Kaishi* **1965**, *85*, 399. (b) Micheel, F.; Michaelis, E. *Chem. Ber.* **1958**, *91*, 188.

(9) See, for example: (a) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660. (b) Molander, G. A. Reductions with Samarium(II) Iodide. *Org. React.* **1994**, *46*, 211.

(10) Glucosamine dimers **7**, **9**, **11**, **13**, and **15** were synthesized by the iodo sulfonamidation methodology in purified yields ranging from 30 to 82% (unoptimized). Complete experimental details are included as Supporting Information. The syntheses of the glycosyl acceptor precursors have been published. See: (a) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371. (b) Garegg, P. E.; Iverson, T.; Ascarson, S. *Carbohydr. Res.* **1976**, *50*, c12−c14.

S0022-3263(97)00367-8 CCC: $14.00

Table 1. Conversion of *N*-(Arylsulfonyl)glucosamines to Glucosamines

Entry	N-Arylsulfonylglucosamine Substrate	Glucosamine: Yield	
1	 1	 2	85%
2	 3	 2	73%
3	 4	 + others	
4	 5	 + others	
5	 6	 7	56%
6	 8	 9	48%
7	 10	 11	46%
8	 12	 13	43%
9	 14	 15	70%

Experimental Section

Preparation of Methyl 2-Deoxy-2-amino-3,4,6-tri-*O*-benzyl-D-glucopyranosyl-*β*-(1→4)-2,3-di-*O*-benzyl-6-*O*-[(*p*-methoxyphenyl)methyl]-*β*-D-O-glucopyranoside (10). Phenylsulfonamide **9** (52.1 mg, 0.05 mmol) was dried by azeotropic distillation with anhydrous benzene (4 × 5 mL), transferred to a one-piece reflux apparatus with the aid of 4 mL of anhydrous THF, and concentrated *in vacuo*. The vessel was charged with fresh THF (4 mL) and DMPU (0.75 mL), degassed (three freeze-pump-thaw cycles), and placed under argon. SmI_2 (1 mmol, 10 mL of a 0.1 M solution in THF, Aldrich) was added via gastight syringe and the solution refluxed for 72 h until all SmI_2 was consumed (as judged by the solution color). The solution was concentrated *in vacuo*, dissolved in 15 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (2 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a solution of **10** in DMPU. DMPU was removed *in vacuo* using a Hickman still (80 °C water bath) and the residue purified by flash column chromatography (SiO_2, 2:3 EtOAc:CH_2Cl_2) to yield 21.2 mg (48%) of **10** as a thick oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (br s, 2H), 2.78 (dd, J = 9.9, 8.1 Hz, 1H), 3.24 (ddd, J = 9.8, 4.2, 2.0 Hz, 1H), 3.25 (t, J = 9.3 Hz, 1H), 3.40 (dd, J = 9.0, 7.8 Hz, 1H), 3.43 (ddd, J = 9.7, 3.7, 2.0 Hz, 1H), 3.52−3.65 (m, 4H), 3.56 (s, 3H), 3.73 (s, 3H), 3.78 (dd, J = 10.9, 1.8 Hz, 1H), 3.90 (dd, J = 11.0, 3.8 Hz, 1H), 4.04 (dd, J = 9.6, 8.8 Hz, 1H), 4.29 (d, J = 7.6 Hz, 1H), 4.36 (d, J = 7.8 Hz, 1H), 4.43 (s, 2H), 4.55 (ABq, J_{ab} = 12.2 Hz, $\delta\nu_a$ = 4.63, $\delta\nu_b$ = 4.47, 2H), 4.66 (ABq, $\delta\nu_a$ = 4.75, $\delta\nu_b$ = 4.57, J_{ab} = 10.9 Hz, 2H), 4.75 (ABq, $\delta\nu_a$ = 4.84, $\delta\nu_b$ = 4.66, J_{ab} = 11.0 Hz, 2H), 4.81 (ABq, $\delta\nu_a$ = 4.93, $\delta\nu_b$ = 4.68, J_{ab} = 11.3 Hz, 2H), 4.90 (ABq, $\delta\nu_a$ = 5.01, $\delta\nu_b$ = 4.78, J_{ab} = 11.6 Hz, 2H), 6.86−7.37 (m, 29H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.05, 56.89, 57.69, 67.99, 68.57, 72.90, 73.17, 74.49, 74.55, 75.06, 75.18, 75.53, 75.82, 78.42, 81.79, 82.77, 84.97, 104.51, 107.85, 113.64, 126.80, 126.85, 127.25, 127.39, 127.45, 127.52, 127.5) 55.05, 56.89, 57.69, 67.99, 68.57, 72.90, 73.17, 74.49, 74.55, 75.06, 75.18, 75.53, 75.82, 78.42, 81.79, 82.77, 84.97, 104.51, 107.85, 113.64, 126.80, 126.85, 127.25, 127.39, 127.45, 127.52, 127.54, 127.59, 127.63, 127.75, 127.89,

127.92, 127.96, 128.11, 128.25, 128.38, 128.52, 129.30, 129.44, 130.97, 136.83, 137.96, 138.36, 138.38, 139.23; exact mass calcd for $C_{56}H_{64}NO_{11}$ = 926.4479, found = 926.4479 (HRFABMS, M + 1).

Acknowledgment. We gratefully acknowledge financial support from the Department of Chemistry at the University of Illinois, University of Illinois Research Board, and the Illinois Chapter of the American Heart Association. We wish to acknowledge members of the Petillo group and Dr. Mary Beth Carter for useful conversations during these studies. Assistance in the purification of **12** by Bryan Yeung is recognized.

Supporting Information Available: Detailed experimental procedures including ^{1}H NMR spectra and analytical and spectroscopic data for all compounds in this study (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970367V