Iodine catalyzed one-pot diamination of glycals with chloramine-T: a new approach to 2-amino-β-glycosylamines for applications in *N*-glycopeptide synthesis†‡

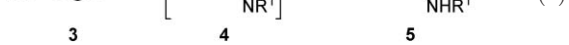
Vipin Kumar and Namakkal G. Ramesh*

Received (in Cambridge, UK) 23rd August 2006, Accepted 19th September 2006
First published as an Advance Article on the web 9th October 2006
DOI: 10.1039/b612151a

Iodine catalyzes a facile one-pot direct diamination of glycals with chloramine-T to afford stereoselectively 2-amino-β-glycosylamine derivatives that serve as convenient precursors for the synthesis of *N*-linked glycopeptides.

With the emergence of glycobiology as an inter-disciplinary research domain, organic chemists are provided with ample opportunities to develop strategies for the synthesis of biologically relevant glycoconjugates. *N*-Linked glycoproteins, typically containing a GlcNAc-β(1→N) linkage to Asn **1**, are among the most extensively explored glycoconjugates due to their implication in various biological processes.[1] 2-Amino-β-glycosylamines **2** are the central core in *N*-linked glycoproteins and glycopeptides and play a crucial role in cell-recognition and signal transduction during their biological processes. It has been further established that an acetamido group at *C2* (**2**, R^1 = Ac) and the anomeric β-stereochemistry are crucial in inducing a well-defined β-turn in the peptide backbone of *N*-linked glycoproteins.[2] 2-Amino-glycosylamines **2** are also the key building blocks in the convergent synthesis of *N*-linked glycopeptides and glycoproteins.[1] Current methods for the synthesis of **2** (R^1 = Ac, R^2 = H) such as reduction of 2-acetamido glycosyl azides,[1c,3] Kochetkov's amination and its modification,[4] reductive cyclization of δ-hydroxynitriles[5] all rely on the extensive synthetic modification of glucosamine. Alternative strategies that efficiently introduce two nitrogen substituents at *C1* and *C2* of a readily available glycal **3** are fewer in number despite the significant advantages.[6] Synthetic applications of these protocols are sometimes limited due to protecting group (especially ester group) intolerance, lack of substrate-generality, special reaction conditions and the use of hazardous chemicals and/or reagents such as azides. In this communication we report an efficient *one-pot* stereoselective diamination of glycals using simple and inexpensive reagents under very mild conditions.[7] The reaction is functional group tolerant, successful over a wide range of glycals including disaccharides and amenable to large-scale synthesis.

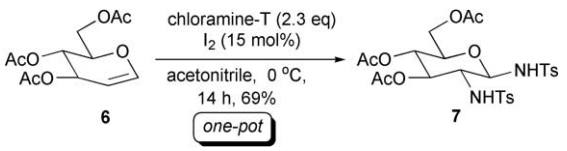
Taking advantage of the instability of glycal aziridines **4**,[6a,8] we envisaged that under suitable aziridination conditions and in the presence of an appropriate nitrogen source, these incipient glycal aziridines could be opened up, in a domino process, by the nucleophilic amino reagent itself, to afford 2-amino glycosylamines such as **5**, directly in one-pot (Eq. 1). Given the fact that a successful outcome would have significant prominence in the synthesis of amino-substituted carbohydrate scaffolds, we began identifying proper aziridination conditions that could directly lead to **5**. After extensive experimentation, we were finally successful in realizing our hypothesis when we investigated the aziridination reaction of tri-*O*-acetyl-D-glucal **6** with chloramine-T[9] in the presence of iodine as a catalyst.[10]



3 4 5 (1)

Treatment of **6** with 1 equiv. of chloramine-T and 15 mol% of iodine in acetonitrile at 0 °C, although affording a product (in 30% yield), did not lead to the completion of the reaction. Such an observation was consistent with our proposition, as the formation of the expected diamine **7** requires two equivalents of chloramine-T. Upon careful analysis, the product was indeed identified to be the disulfonamidated compound **7**. Subsequently, on treatment with 2.3 equiv. of chloramine-T and 15% of iodine, **6** was completely converted to **7**, in 14 h in an isolated yield of 69%, as a single diastereomer possessing essentially the same stereochemistry as in **1** (Scheme 1).[11] The chloramine-T–iodine combination proved to be the best choice of reagent for this transformation, without the need for any buffer.[10,12,13] Interestingly, products arising out of iodine catalyzed Ferrier rearrangement have not been observed under these conditions.[14]

Encouraged by the initial results, we tested the reaction with a variety of glycals possessing different carbohydrate templates. In



6 7

Scheme 1

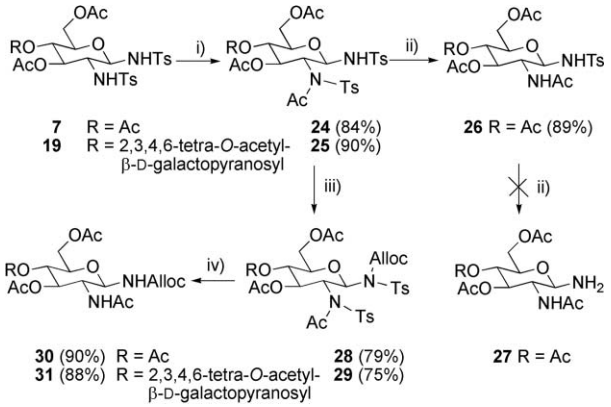
Department of Chemistry, Indian Institute of Technology – Delhi, Hauz Khas, New Delhi – 110016, India. E-mail: ramesh@chemistry.iitd.ac.in; Fax: +91 11 26581102; Tel: +91 11 26596584

† Electronic supplementary information (ESI) available: Experimental procedure; spectral data for all compounds; ^{1}H-NMR and ^{13}C-NMR for important compounds. See DOI: 10.1039/b612151a

‡ Dedicated to Prof. Alfred Hassner on the occasion of his 76th birthday.

all the cases, the reaction proceeded smoothly affording the corresponding *hitherto unknown* disulfonamides as a single diastereomer in good yields (Table 1); the only exception being tri-*O*-acetyl-D-galactal where the yield was moderate. The nature of the protecting group seems to have little effect on the reaction time as well as the yield; the reaction works equally well with ester and ether protected substrates (Entries 1–5). Synthetically rewarding is the facile transformation of disaccharide glycals **18** and **20** to the corresponding disulfonamides **19** and **21**, in high yields. To our knowledge, direct introduction of two nitrogen functionalities onto a disaccharide glycal in *one-pot* has no precedence. A salient feature is that the reaction has been performed with a few glycals on a five-gram scale without much loss in the efficiency. The success of the reaction with dihydropyran **22** demonstrates its application to other enol ethers. The formation of a diastereomeric mixture in this case may be attributed to its conformational flexibility.

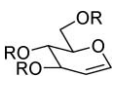
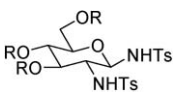
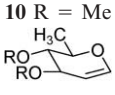
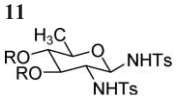
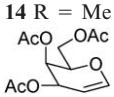
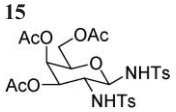
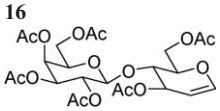
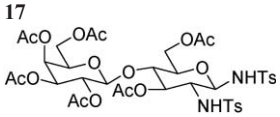
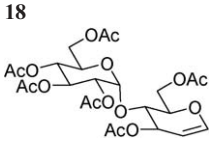
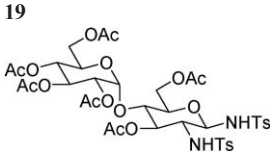
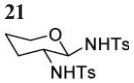
In order to utilize these disulfonamides in *N*-glycopeptide synthesis, it is essential to transform them into 2-acetamido-glycosylamines such as **27**, which requires the incorporation of an acetyl group at *C2* nitrogen. As revealed through the selective examples, an unprecedented chemoselective acetylation of these disulfonamides, for instance **7** and **19**, installed the essential acetyl group *exclusively* at *C2* nitrogen in excellent yields (Scheme 2).[15]



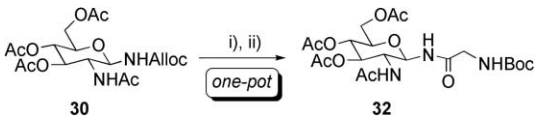
Scheme 2 *Reagents and conditions*: i) Ac_2O (2 equiv.), DMAP (1 equiv.), pyridine, RT, 24 h; ii) SmI_2 (8.5 equiv.), H_2O (50 equiv.), RT, 25 min; iii) Alloc chloride (4 equiv.), DMAP (20 mol%), Et_3N (2 equiv.), RT, 9–12 h; iv) SmI_2 (13–17 equiv.), H_2O (75–100 equiv.), RT, 1 h.

Judicious choice of the reagent was found to be crucial for subsequent detosylation of **24**. Compound **24** and even its benzyl-protected analogue were found to be extremely sensitive to common acidic or basic desulfonating reagents. With SmI_2 in the presence of water or HMPA as a co-solvent,[16] mono *N*-detosylation of tertiary sulfonamide at *C2* to afford **26** was

Table 1 Iodine catalyzed direct disulfonamidation of glycals with chloramine-T[a]

Entry	Starting Material	Product	Time (h)	Yield (%)[b]
				
1	**6** R = Ac	**7**	14	69
2	**8** R = Bn	**9**	13	57
3	**10** R = Me	**11**	13	60
				
4	**12** R = Ac	**13**	14	63
5	**14** R = Me	**15**	14	60
				
6	**16**	**17**	72[c]	38[d]
				
7	**18**	**19**	96	71[e]
				
8	**20**	**21**	96	65[e]
				
9	**22**	**23**[f]	14	61

[a] Unless otherwise mentioned, all reactions were performed at 0 °C using 2.3 equiv. of chloramine-T and 15 mol% of iodine in acetonitrile. [b] Isolated yield after column chromatography. [c] The reaction was incomplete. [d] Yield based on recovered starting material; isolated yield 21%. [e] 3.0 equiv. of chloramine-T and 20 mol% of iodine were used. [f] Mixture of diastereomers, at 0 °C *dr* was 1 : 1 and at −25 °C *dr* was ~ 4 : 1.



Scheme 3 *Reagents and conditions*: i) $Pd(PPh_3)_4$ (10 mol%), Et_2NH (10 equiv.), RT, 20 min; ii) Boc-glycine (1.5 equiv.), DCC (1.8 equiv.), DMAP (1.5 equiv.), RT, 12 h, 72% for two steps.

the sole reaction and the anomeric sulfonamide group remained unaffected. Use of a large excess of the reagent or step-wise detosylation in attempts to obtain **27** did not meet with success. Consequently, protection of the anomeric nitrogen of **24** and **25** before detosylation is imperative. Gratifyingly, this could be achieved smoothly by way of allyloxycarbonyl protection to obtain **28** and **29** in good yields. Subsequently, on exposure to SmI_2–water, compounds **28** and **29** readily underwent a very facile didetosylation affording **30** and **31** respectively, as stable *N*-glycans for glycopeptide synthesis, in excellent yields (Scheme 2). While free glycosylamines such as **27** are known to be highly unstable and prone to facile anomerization,[1c,4c,17] the Alloc derivatives **30** and **31** are notably stable with a long shelf-life. Preferential choice of Alloc protection was influenced by the availability of well-established deprotection protocols.[18,19] As an illustrative example, compound **30** was smoothly deprotected using a catalytic amount of $Pd(PPh_3)_4$ and the liberated free amine, without isolation, was coupled with Boc-glycine in *one-pot* to obtain the *N*-linked glycopeptide **32** in a high yield (72% for two steps) (Scheme 3). It is noteworthy that the anomeric-β-stereochemistry remained intact during the entire synthetic sequence.

In conclusion, we have reported a new and stereoselective approach to 2-amino-β-glycosylamines for use in the convergent synthesis of *N*-linked glycopeptides *via* iodine-catalyzed one-pot disulfonamidation of glycals with chloramine-T as the key step. The simplicity of the protocol and scope for further expansion to complex oligosaccharides are likely to contribute to the research developments in the area of glycobiology.

We are grateful to the DST, India for financial support and the CSIR, India for a fellowship to V. K. We are also grateful to Dr. K. P. Kaliappan for helping us with the HRMS data.

Notes and references

1 For some very recent reviews and articles on *N*-linked glycoproteins and glycopeptides see: (*a*) L. Liu, C. S. Bannett and C.-H. Wong, *Chem. Commun.*, 2006, 21; (*b*) C. M. Kaneshiro and K. Michael, *Angew. Chem., Int. Ed.*, 2006, **45**, 1077; (*c*) K. J. Doores, Y. Mimura, R. A. Dwek, P. M. Rudd, T. Elliot and B. G. Davis, *Chem. Commun.*, 2006, 1401; (*d*) B. Wu, J. D. Warren, J. Chen, G. Chen, Z. Hua and S. J. Danishefsky, *Tetrahedron Lett.*, 2006, **47**, 5219; (*e*) Z.-G. Wang, J. D. Warren, V. Y. Dudkin, X. Zhang, U. Iserloh, M. Visser, M. Eckhardt, P. H. Seeberger and S. J. Danishefsky, *Tetrahedron*, 2006, **62**, 4954; (*f*) J. Chen, J. D. Warren, B. Wu, G. Chen, Q. Wan and S. J. Danishefsky, *Tetrahedron Lett.*, 2006, **47**, 1969; (*g*) B. Wu, J. Chen, J. D. Warren, G. Chen, Z. Hua and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2006, **45**, 4116.

2 C. J. Bosques, S. M. Tschampel, R. J. Woods and B. Imperiali, *J. Am. Chem. Soc.*, 2004, **126**, 8421.

3 For some recent examples, see: (*a*) N. Wagner, S. Dziadek and H. Kunz, *Chem.–Eur. J.*, 2003, **9**, 6018; (*b*) P. R. Sridhar, K. R. Prabhu and S. Chandrasekaran, *J. Org. Chem.*, 2003, **68**, 5261 and references cited therein.

4 (*a*) L. M. Likhosherstov, O. S. Novikova, V. A. Derevitskaja and N. K. Kochetkov, *Carbohydr. Res.*, 1986, **146**, C1; (*b*) L. M. Likhosherstov, O. S. Novikova and V. N. Shibaev, *Dokl. Chem.*, 2002, **383**, 89, (*Chem. Abs.*, 2002, **140**, 28003); (*c*) M. Bejugum and S. L. Flitsch, *Org. Lett.*, 2004, **6**, 4001.

5 A. D. Dorsey, J. E. Barbarow and D. Trauner, *Org. Lett.*, 2003, **5**, 3237.

6 (*a*) R. S. Dahl and N. S. Finney, *J. Am. Chem. Soc.*, 2004, **126**, 8356; (*b*) J. Liu, V. D. Bussolo and D. Y. Gin, *Tetrahedron Lett.*, 2003, **44**, 4015 and references cited therein; (*c*) J. Liu and D. Y. Gin, *J. Am. Chem. Soc.*, 2002, **124**, 9789; (*d*) B. B. Snider and H. Lin, *Synth. Commun.*, 1998, **28**, 1913; (*e*) F. E. McDonald and S. J. Danishefsky, *J. Org. Chem.*, 1992, **57**, 7001.

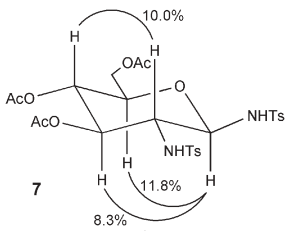
7 Part of this work was presented as a poster at the IUPAC International Conference on Biodiversity and Natural Products (ICOB-5 and ISCNP-25), Kyoto, Japan, July 23–28, 2006.

8 D. A. Griffith and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1990, **112**, 5811.

9 Chloramine-T used was purchased from Aldrich or Fluka Chemicals.

10 T. Ando, D. Kano, S. Minakata, I. Ryu and M. Komatsu, *Tetrahedron*, 1998, **54**, 13485.

11 The β-D-gluco stereochemistry of **7** was established from the coupling constants between H-1 and H-2 (see ESI†) as well as by detailed NOE experiments. Thus, NOE irradiation of the H-1 signal resulted in an enhancement of the signals of H-3 and H-5 by 8.3% and 11.8% respectively. Similarly, irradiation of the signal due to H-2 enhanced the signal due to H-4 by 10%. Structure **7** showing NOE experiment details:



12 We have observed that a stoichiometric amount of iodine monochloride also effects the reaction. However, it has obvious operational disadvantages as compared to iodine.

13 Very recently, a tin(II) iodide catalyzed aziridination or diamination of simple olefins with chloramine-T under reflux conditions was reported, see: Y. Masuyama, M. Ohtsuka, M. Harima and K. Yasuhiko, *Heterocycles*, 2006, **67**, 503.

14 For reports on iodine catalyzed Ferrier rearrangement see: (*a*) J. S. Yadav, B. V. Subba Reddy, K. Premalatha and T. Swamy, *Tetrahedron Lett.*, 2005, **46**, 2687; (*b*) B. K. Banik, O. Zegrocka, M. S. Manhas and A. K. Bose, *Heterocycles*, 1997, **46**, 173; (*c*) B. K. Banik, M. S. Manhas and A. K. Bose, *Tetrahedron Lett.*, 1997, **38**, 5077; (*d*) M. Koreeda, T. A. Houston, B. K. Shull, E. Klemke and R. J. Tuinman, *Synlett*, 1995, 90.

15 Other disulfonamides also underwent chemoselective acetylation in yields ranging from 82–87%.

16 (*a*) A. Dahlen and G. Hilmersson, *Eur. J. Inorg. Chem.*, 2004, 3393; (*b*) H. B. Kagan, *Tetrahedron*, 2003, **59**, 10351; (*c*) E. Vedejs and S. Lin, *J. Org. Chem.*, 1994, **59**, 1602; (*d*) H. Künzer, M. Stahnke, G. Sauer and R. Wiechert, *Tetrahedron Lett.*, 1991, **32**, 1949.

17 (*a*) S. J. Danishefsky, S. Hu, P. F. Cirillo, M. Eckhardt and P. H. Seeberger, *Chem.–Eur. J.*, 1997, **3**, 1617; (*b*) M. Amadori, *Atti. Accad. Naz. Lincei, Cl. Sci. Fis. Mat. Nat., Rend.*, 1925, **2**, 337; (*c*) D. Vetter and M. A. Gallop, *Bioconjugate Chem.*, 1995, **6**, 316.

18 (*a*) K. C. Nicolaou, S. A. Snyder, A. Z. Nalbandian and D. A. Longbottom, *J. Am. Chem. Soc.*, 2004, **126**, 6234; (*b*) A. Ishiwata, M. Takatani, Y. Nakahara and Y. Ito, *Synlett*, 2002, 634.

19 (*a*) R. H. Szumigala, E. Onofiok, S. Karady, J. D. Armstrong and R. A. Miller, *Tetrahedron Lett.*, 2005, **46**, 4403; (*b*) U. Jacquemard, V. Beneteau, M. Lefoix, S. Routier, J.-Y. Merour and G. Coudert, *Tetrahedron*, 2004, **60**, 10039; (*c*) H. Tsukamoto, T. Suzuki and Y. Kondo, *Synlett*, 2003, 1105; (*d*) P. Gomez-Martinez, M. Dessolin, F. Guibé and F. Albericio, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2871; (*e*) F. Guibe, *Tetrahedron*, 1998, **54**, 2967 and references cited therein.

