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

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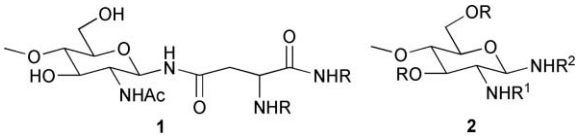
**Iodine catalyzes a facile one-pot direct diamination of glycals with chloramine-T to afford stereoselectively 2-amino-β-glycosylamine derivatives that serve as convenient precursors for the synthesis of *N*-linked glycopeptides.**

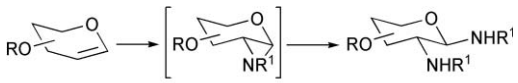
With the emergence of glycobiology as an inter-disciplinary research domain, organic chemists are provided with ample opportunities to develop strategies for the synthesis of biologically relevant glycoconjugates. *N*-Linked glycoproteins, typically containing a GlcNAc-β(1→N) linkage to Asn **1**, are 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




**1** **2**

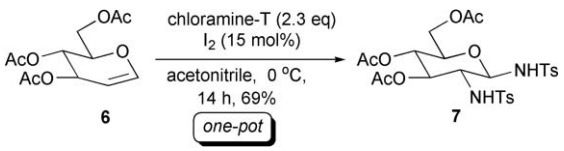
aziridines could be opened up, in a domino process, by the nucleophilic amino reagent itself, to afford 2-amino glycosylamines such as **5**, directly in one-pot (Eq. 1). Given the fact that a successful outcome would have significant prominence in the synthesis of amino-substituted carbohydrate scaffolds, 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**

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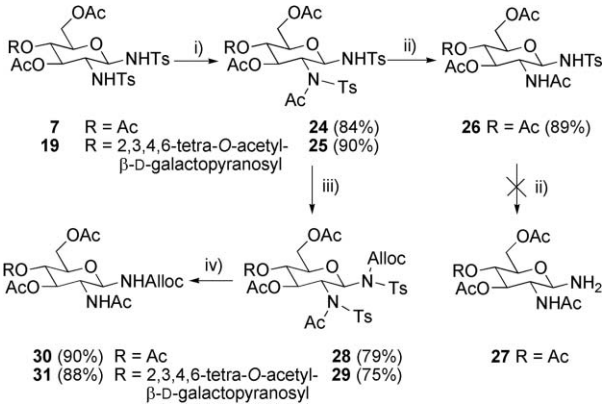
† Electronic supplementary information (ESI) available: Experimental procedure; spectral data for all compounds; $^1$H-NMR and $^{13}$C-NMR for important compounds. See DOI: 10.1039/b612151a

‡ 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.

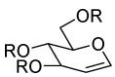
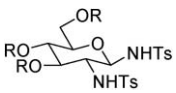
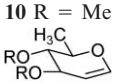
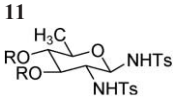
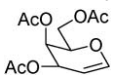
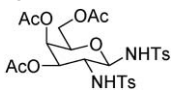
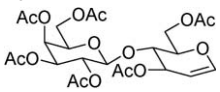
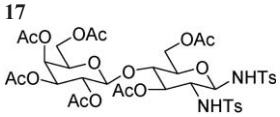
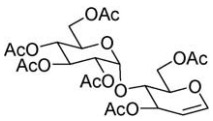
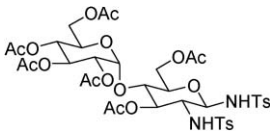
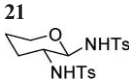
In order to utilize these disulfonamides in *N*-glycopeptide synthesis, it is essential to transform them into 2-acetamido-glycosylamines such as **27**, which requires the incorporation of an acetyl group at *C2* nitrogen. As revealed through the selective examples, an unprecedented chemoselective acetylation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



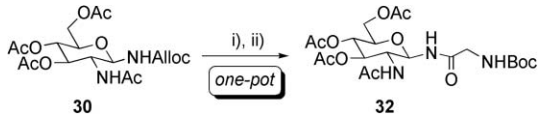

**Scheme 2** *Reagents and conditions*: i) $Ac_2O$ (2 equiv.), DMAP (1 equiv.), pyridine, RT, 24 h; ii) $SmI_2$ (8.5 equiv.), $H_2O$ (50 equiv.), RT, 25 min; iii) Alloc chloride (4 equiv.), DMAP (20 mol%), $Et_3N$ (2 equiv.), RT, 9–12 h; iv) $SmI_2$ (13–17 equiv.), $H_2O$ (75–100 equiv.), RT, 1 h.

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.

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## Notes and references


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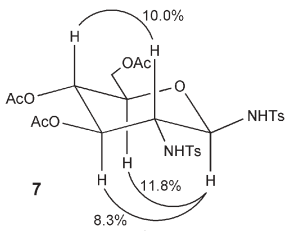
11 The β-D-gluco stereochemistry of **7** was established from the coupling constants between H-1 and H-2 (see ESI†) as well as by detailed NOE experiments. Thus, NOE irradiation of the H-1 signal resulted in an enhancement of the signals of H-3 and H-5 by 8.3% and 11.8% respectively. Similarly, irradiation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

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