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The preparation of 2-iodoamides from glucals and their further transformations into oxazolines

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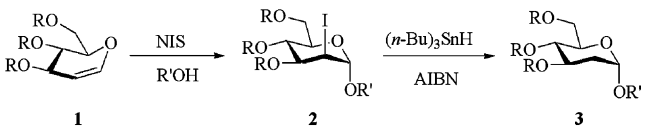
Abstract—2-Deoxy-2-iodo-glycosylamides have been prepared from a variety of protected D-glucals by their reaction with N-iodosuccinimide and amides. Benzyl protected 2-iodoamides, when treated with sodium hydride and 15-crown-5, gave stable C1 N-linked 2-glycooxazolines as the major products. Silyl protected 2-iodoamides afforded the C1 O-linked 2-glycooxazolines; presumably by the rearrangement of unstable N-acylaziridine intermediates.

The haloglycosylation reaction, developed by Lemieux et al.[1] and Thiem et al.[2] has been used extensively for the preparation of *trans*-configured 2-haloglycosides from glycals and alcohols. Although a variety of halogenating agents have been used to effect this transformation, the greatest selectivity is obtained when sources of I^+ (e.g., N-iodosuccinimide (NIS)) are employed. The α-manno products are obtained preferentially from protected D-glucals and axial, bridging, iodonium ion intermediates have been proposed. Subsequent reductive deiodination of the 2-iodoglycosides with trialkylstannanes leads to the formation of 2-deoxy-α-glycosides (Scheme 1).

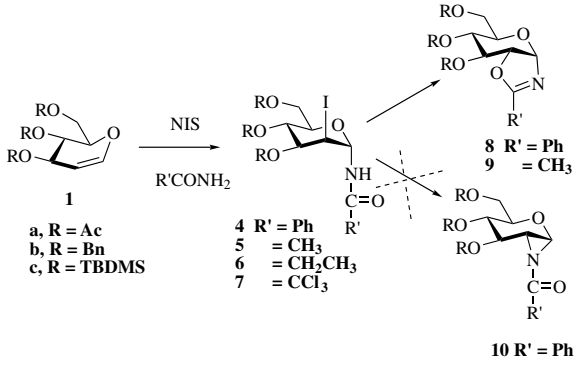
Other nucleophiles have also been incorporated at the C1 position of sugars using this protocol.[3–5] When the nucleophiles employed in the glycal addition reactions are weak, the imide anion byproduct formed from NIS is frequently observed to compete for the C1 position. This has lead to the isolation of glycosyl succinimides[6] that have been shown to exist preferentially in the alternate $^1C_4$ chair conformation.[7]



Scheme 1. Iodoglycosylation reaction of D-glucals.

As part of a research program aimed at the synthesis of carbohydrate-fused heterocycles, we became interested in the iodine promoted addition of primary, aliphatic, and aromatic amides to glycals. We envisioned that it should be possible to prepare both oxazolines and N-acylaziridines from the cyclization of the resulting 2-iodoamide products using different reaction conditions (Scheme 2).

There have been numerous reports detailing the synthesis and isolation of C1 O-linked 2-glycooxazolines from N-acyl-2-amino-2-deoxy-glycosyl acetates[8] and these cyclic molecules have been shown to be effective glycosyl donors.[9] However, there have only been limited



Scheme 2. Alternate cyclization routes for 2-iodoglycosylamides.

Keywords: Iodoamidation; Glucals; 2-Glycooxazolines.
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previous accounts detailing the synthesis and isolation of the C1 N-linked analogs by Ritter-like reactions.[10] The 1,2-aziridino sugars have been even more elusive targets and have been proposed as unstable intermediates in several reactions.[11–13]

Herein, we report on our synthetic studies towards the preparation of oxazolines and aziridines. The effects of the type of primary amide (alkyl or aryl) and the sugar protecting groups on the addition and subsequent cyclization reactions will be discussed.

Iodoamidation reactions were carried out on a variety of protected glucals: tri-O-acetyl-D-glucal, tri-O-benzyl-D-glucal and tris-O-*tert*-butyldimethylsilyl-D-glucal (Scheme 2, **1**) with several primary alkyl and aryl amides.[3,14,15] Diastereomeric mixtures of gluco and manno iodoamides **4**–**7** were obtained from these reactions (Table 1).

In general, the highest yields and greatest selectivities were obtained when benzamide was used as the nucleophile (Table 1, entries 1–3). In the reactions with benzamide, the benzyl protected sugar afforded primarily the α-manno addition product, whereas the acetyl protected glucal gave mainly the β-gluco product. Furthermore, the electron poor acetylated glucal reacted more sluggishly than the benzyl protected precursor and gave lower yields of product.

Interestingly, the *tert*-butyldimethylsilyl (TBDMS) protected glucal afforded only a single addition product in high yield when reacted with NIS and benzamide. Careful analysis of the proton NMR spectrum (500 MHz; $CDCl_3$) of this compound showed a large ^3J value (10.5 Hz) for coupling between the protons at C1 and C2, a small $^3J_{2,3}$ (1.5 Hz) and the remaining ring protons at C4 and C5 appeared as singlets. This suggests that the compound isolated from the reaction mixture exists in the alternate $^1C_4$ chair conformer. So it appears as if the tendency of the silyloxy groups to prefer axial positions[16] and the inverse anomeric effect, override the steric demands of the bulky substituents in the C1 and C2 position in this compound.[17] This conformation may be experiencing attractive steric interactions between the silicon groups and the aromatic ring of the amide, which help stabilize this conformer.[18] Similar diastereoselectivities were observed with the TBDMS protected glycal and propionamide, however, with acetamide and trichloroacetamide as the coupling partners, a higher proportion of the $^4C_1$ conformers were observed. This may be because of fewer stabilizing interactions in the alternate $^1C_4$ conformers with the less bulky alkyl groups. The addition of the electron deficient amide, trichloroacetamide, also gave rise to a reverse in diastereoselectivity similar to that observed with tri-O-acetyl-D-glucal.

Methods were then evaluated to cyclize the iodobenzamides using both the amide nitrogen and oxygen as the potential nucleophiles (Table 2).

We carried out the cyclization of the benzyl protected benzamide analog **4b** with sodium hydride and 15-crown-5 in dichloromethane (Table 2, entry 1), anticipating that we would isolate aziridine **10b**.[19] Spectroscopic analysis of the exclusive product isolated from this reaction suggested that instead, the C1 N-linked oxazoline **8b** was prepared; a result of cyclization through the amide carbonyl oxygen.[15]

When we applied these same conditions to the TBDMS protected iodobenzamide **4c** (Table 2, entry 2), unexpectedly, the C1 O-linked oxazoline **13c** (Scheme 4)[8b] was obtained and not the predicted aziridino sugar **10c**[20] nor the C1 N-linked oxazoline **8c**.[10a]

Table 1. Proportions of diastereomeric iodoamides obtained from glucals[a]

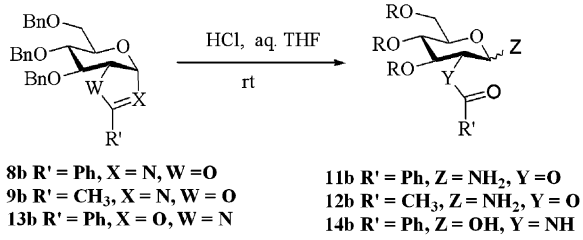
Entry	Iodoamide	Sugar R =	Amide R′ =	α-Manno	β-Manno	α-Gluco	β-Gluco	Isolated yield (%)[b]
1	**4a**	Ac	Ph	6	Trace	1	10	42
2	**4b**	Bn	Ph	2	0	0	1	85
3	**4c**	TBDMS	Ph	1 ($^1C_4$)	0	0	0	82
4	**5c**	TBDMS	CH_3	1 ($^1C_4$) 10 ($^4C_1$)	0	0	0	50
5	**6c**	TBDMS	CH_2CH_3	1 ($^1C_4$)	0	0	0	81
6	**7c**	TBDMS	CCl_3	Trace ($^4C_1$)	1.5	2	3	62

[a] Determined by integration of the anomeric protons in the ^1H NMR spectrum obtained in $CDCl_3$.
[b] Represents product recovered following extractive workup and subsequent chromatographic purification (SiO_2).

Table 2. Basic cyclization of iodobenzamides **4**

Entry	Iodoamide	Base	Conditions	N-Oxazoline[a]	O-Oxazoline[a]	N-Aziridine[a]
1	**4b**	NaH, 15-crown-5	CH_2Cl_2, −78 °C (2 h)—rt (5 h)	**8b**, 81%	—	—
2	**4c**	NaH, 15-crown-5	CH_2Cl_2, −78 °C (2 h)—rt (5 h)	—	**13c**, 82%	—
3	**4b**	NaH, 15-crown-5	CH_2Cl_2, 25 °C, 2 h	**8b**, 65%	**13b**, 25%	—
4	**4c**	NaH, 15-crown-5	CH_2Cl_2, 25 °C, 2 h	—	**13c**, 82%	—
5	**4b**	NaH	CH_2Cl_2, 25 °C, 24 h	—	**13b**, 95%	—
6	**4b**	NaH	THF, 25 °C, 48 h	**8b**, 77%	—	—
7	**4c**	NaH	THF, 25 °C, 5 h	—	**13c**, 79%	—

[a] Represents yields of isolated products.



Scheme 3. Hydrolysis of benzyl protected oxazolines.

The basic cyclization reactions were also carried out at room temperature both with and without added crown ether and in different solvents (Table 2, entries 3–7). For the benzyl protected sugar, the use of crown ether or coordinating solvent served to accelerate the cyclization reaction and favored nucleophilic attack at C2 by the amide oxygen. Without crown ether (Table 2, entry 5), C1 O-linked oxazoline was formed as the major product. For the TBDMS protected sugar, the C1 O-linked product was obtained under all reaction conditions studied.

Structural characterization of both the C1 N-linked and C1 O-linked oxazolines was carried out using spectroscopic techniques, elemental analysis, comparison to similar known reference compounds and by acid hydrolysis of the oxazolines to their acyclic products. Treatment of the C1 N-linked oxazoline **8b** with HCl in aqueous THF provided glycosylamine **11b** in 48% yield along with unreacted starting material (Scheme 3). Hydrolysis of the C1 O-linked analog **13b** gave 2-amino-2-deoxy-N-benzoyl-D-glucopyranose **14b** in 38% yield along with recovered oxazoline.

This surprising formation of two distinct oxazoline products from these reactions suggests two possible mechanistic pathways. Either the two oxazolines are directly equilibrating via dissociation and recombination, or an unstable, N-acylaziridino sugar intermediate is formed that rearranges via nucleophilic ring opening at C1 by the amide carbonyl oxygen to form the C1 O-linked oxazoline (Scheme 4). Attempts to interconvert C1 N-linked oxazoline **8b** into C1 O-linked oxazoline **13b** by stirring the compound with NaH in CH_2Cl_2 at room temperature failed to cause equilibration. Therefore, the aziridine intermediate seems likely. The aziridine forms more readily when the amide oxygen is coordinated to the sodium counter ion thus prohibiting cyclization to produce the C1 N-linked oxazoline. The exclusive formation of the C1 O-linked oxazoline from the TBDMS protected iodoamide is probably a consequence of stereoelectronic effects operating at the C1 position in the altered chair conformer, which lead to the facile formation of the equatorially disposed aziridine. The aziridine then rearranges to the O-linked oxazoline with retention of the $^1C_4$ chair. Further mechanistic studies are in progress to further validate the proposed pathway.

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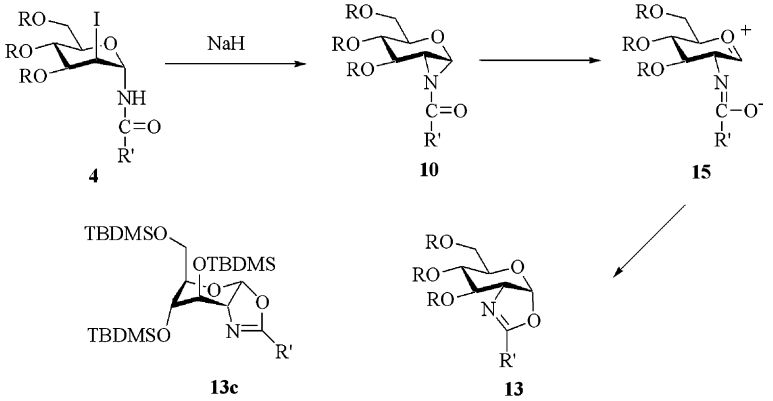

Scheme 4. Possible mechanism for the transformation from iodobenzamide to O-oxazoline.

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15. (a) Representative experimental procedures: Preparation of N-benzoyl-3,4,6-tri-O-benzyl-2-deoxy-2-iodo-α-D-mannosamine and N-benzoyl-3,4,6-tri-O-benzyl-2-deoxy-2-iodo-β-D-glucosamine **4b**: To tri-O-benzyl-D-glucal **1b** (0.25 g, 0.60 mmol) in dry propionitrile at −75 °C, was added N-iodosuccinimide (0.27 g, 1.20 mmol) and benzamide (0.43 g, 3.6 mmol). The mixture was kept at −75 °C for 8 h, warmed to rt, and stirred an additional 48 h. The mixture was quenched with water (20 mL), extracted with ethyl acetate (3×60 mL), and dried ($MgSO_4$). Purification (SiO_2, 230–400 mesh, 6:1 hexane–ethyl acetate) afforded 0.33 g (85%) of mixed diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) anomeric protons: α-manno 5.99 (b s), α-gluco 5.63 (dd, J=8.0, 4.0 Hz); 9:1 manno:gluco. MS (ES+) (M+1) *m/z* 665 (100), 536 (65). Preparation of the C1 N-linked oxazoline **8b**. To compound **4b** (0.5 g, 0.68 mmol) in CH_2Cl_2 (20 mL) at −78 °C, NaH (0.3 g, 1.02 mmol) and 15-crown-5 (0.1 mL, 0.50 mmol) were added. The reaction was kept at −78 °C for 5 h, then was quenched with the addition of water. The mixture was diluted to a volume of 50 mL with CH_2Cl_2 and was extracted with water (3×60 mL). The organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. Column chromatography (SiO_2, 1:1 ratio of hexane–ethyl acetate) on the crude mixture afforded 0.32 g (81%) of a light yellow oil. ^{1}H NMR (500 MHz $CDCl_3$): δ 6.10 (d, 1H, J=7.5 Hz), 4.86 (d, 1H, J=11.5 Hz), 4.76–4.71 (m, 2H), 4.68 (dd, 1H, J=8.0, 5.0 Hz), 4.61 (d, 1H, J=11.5 Hz), 4.52–4.48 (m, 2H), 3.89 (dd, 1H, J=7.0, 5.0 Hz), 3.83 (dd, 1H, J=9.0, 7.0 Hz), 3.73 (m, 2H), 3.63 (apparent d, 1H, J=9.0 Hz). ^{13}C NMR: δ 166.1, 138.5, 138.3, 132.5, 128.9, 128.7, 128.6, 128.55, 128.5, 128.3, 128.1, 127.9, 127.8, 127.1, 94.4, 81.4, 80.4, 74.7, 74.0, 73.8, 72.9, 71.9, 69.5. HR ES+ Calcd 536.2437; Found 536.2441; (b) Data for C1 O-linked oxazoline **13b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.23 (d, 1H, J=7.0 Hz), 4.77 (d, 1H, J=11.5 Hz), 4.68 (d, 1H, J=11.5 Hz), 4.54 (dd, 2H, J=9.0, 9.0 Hz), 4.48 (d, 1H, J=12 Hz), 4.47 (dd, 1H, J=7.0, 3.0 Hz), 4.29 (d, 1H, J=12 Hz), 4.14 (dd, 1H, J=3.0, 2.5 Hz), 3.72 (dd, 1H, J=2.5, 1.5 Hz), 3.60–3.53 (m, 3H). ^{13}C NMR: δ 164.5, 137.9, 137.8, 137.7, 131.8, 128.5, 128.4, 128.38, 128.3, 128.2, 128.0, 127.94, 127.92, 127.8, 127.7, 127.6, 126.9, 100.7, 76.8, 75.1, 73.3, 71.8, 71.6, 70.4, 69.4, 66.1; MS (API–CI+) 428, 536 (M+H), 558 (M+Na).
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