Facile C_1 Epimerization of α-1-Sulfonamidyl-2-deoxy-2-iodo-glycopyranosides

Jane M. Owens, Bryan K. S. Yeung, Daniel C. Hill, and Peter A. Petillo*

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

alchmist@alchmist.scs.uiuc.edu

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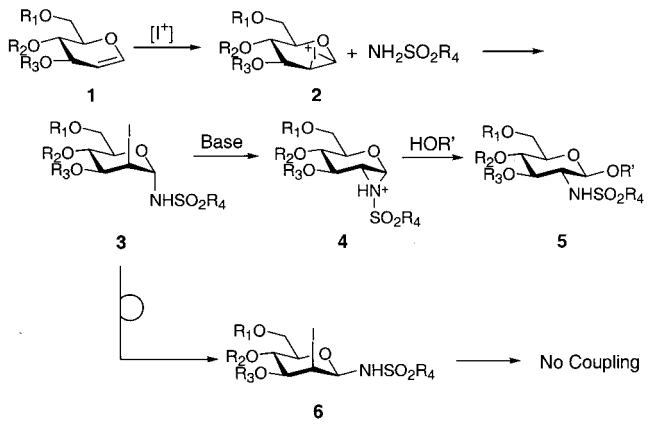
2-Amino-2-deoxy glycosides are essential components of glycosaminoglycans[1,2] and many other biologically important saccharides.[3] The Danishefsky iodosulfonamidation methodology has proven to be a powerful method for the synthesis and coupling of these sugars and has been successfully employed in a number of important syntheses.[4−6] In this procedure, a 1,2-glycal, **1**, is transformed to its *trans*-diaxial-1,2-iodosulfonamide counterpart, **3**, via treatment with I(*sym*-colidine)$_2$ClO$_4$ and a sulfonamide (Scheme 1). Treatment of the *trans*-1,2-iodosulfonamide intermediate with LiTMP and AgOTf in the presence of a glycosyl acceptor or with $AgBF_4$ in the presence of the stannyl alkoxide of the glycosyl acceptor results in β-coupled 2-amino-2-deoxy product.[4a−d] Alternatively, the *trans*-1,2-iodosulfonamide can be converted to the 1-β-thioethyl-2-sulfonamidyl-2-deoxy product,[4a,g−h] or the 1-β-azido-2-sulfonamidyl-2-deoxy product,[4a,i−k] under the appropriate conditions.

Recently, while attempting to employ this procedure in a synthesis of glycosaminoglycan fragments,[5,7] we encountered a number of iodosulfonamides which would not couple to a glycosyl acceptor under any conditions.

Scheme 1



While we originally thought this a failing of the coupling procedures, closer examination of the substrates revealed that the material isolated from the standard Danishefsky protocol was not the expected *trans*-diaxial-1,2-iodosulfonamide, **3**, but rather its C_1 epimer, **6**. We first encountered difficulties with the iodosulfonamidation methodology while attempting to utilize iodosulfonamide **3a**. Through use of the standard published procedure,[4b] the reaction of tri-*O*-benzyl-D-glucal, **1a**, in CH_2Cl_2 with *p*-nitrobenzenesulfonamide at room temperature for 1 h resulted in iodosulfonamide, **6a**, whose stereochemistry was ascertained only after a careful NOE study (Figure 1). A time and temperature study of the iodosulfonamidation reaction revealed that after five minutes at −10 °C, **3a** is formed in good yield but is quantitatively converted to **6a** in 1 h. Despite intensive effort, we failed to find conditions that prevented the isomerization of **3a** to **6a**. Because the reaction of **3** to **5** proceeds via the aziridine intermediate, **4**, the C_1 epimer, **6**, is inert to any coupling conditions.

These observations represent the first reported instance of such rapid and extensive isomerization of a *trans*-diaxial-1,2-iodosulfonamide to the corresponding *cis*-iodosulfonamide under the published reaction conditions. We have tested a variety of iodosulfonamides derived from tri-*O*-benzyl-D-glucal for this epimerization, including the phenylsulfonamide, 4-methylphenylsulfonamide, and β-trimethylsilylethylsulfonamide. In none of these cases did we observe the epimerization of C_1, even after extended reaction times. In our hands, these iodosulfonamides were robust and coupled without difficulty.[5,7]

To further probe the mechanism of isomerization, purified **3a** was reacted with catalytic hydroiodic acid in CH_2Cl_2 and with $HClO_4$ in CH_2Cl_2. Both resulted in the conversion of **3a** to **6a** and a series of new, unidentifiable byproducts. A mixture of pure **3a** and 1 equiv of I(*sym*-collidine)$_2$ClO$_4$ in CH_2Cl_2 or 1 equiv of *sym*-collidine in CH_2Cl_2 quantitatively converted **3a** to **6a** within 1 h with no observable byproducts. These results suggest that, in **3a**, the pyranosyl ring opens at C_1 catalyzed by either acid or water. The opened saccharide then undergoes a bond rotation similar to that proposed for the Amadori rearrangement and other related aminoglycoside isomerizations.[8,9] Subsequent ring closure generates the *cis*-glycoside **6a**, which is the thermodynamic product.

* To whom correspondence should be addressed. Tel.: (217) 333-0695. Fax: (217) 244-8559.

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Table 1. Significant ^{1}H and ^{13}C NMR Data for 3 and 6

	R_1	R_2	R_3	R_4	$J_{H1,H2}$[a]	δH_1[b]	δC_2[b]	δH_N[b]	δC_1[b]
3a	Bn	Bn	Bn	p-NO_2Ph	5.6	5.55	30.2	6.47	81.8
6a	Bn	Bn	Bn	p-NO_2Ph	1.4	4.23	41.0	5.78	80.2
3b	Piv	Piv	Piv	Ph	1.1	5.60	27.3	6.90	84.5
6b	Piv	Piv	Piv	Ph	1.6	4.26	38.2	5.64	80.0
3c	$(CH_3)_2C$		TES	Ph	0.6	5.66	36.7	6.69	86.2
6c	$(CH_3)_2C$		TES	Ph	1.8	4.21	46.7	5.61	81.1
3d[c]	Ac	Ac	Ac	Ph	2.9	5.56	27.3	6.81	83.7
6d	Ac	Ac	Ac	Ph	1.5	4.29	37.6	5.57	80.1
6e	Bz	Bz	Bz	Ph	1.4	4.61	38.2	5.82	80.1
6f	$(CH_3)_2C$		Ac	$(CH_2)_2$TMS	1.8	4.19	39.9	5.40	80.7
6g[d]	Ac	R[e]	Ac	$(CH_2)_2$TMS	1.5	4.08	38.9	5.31	79.5
3h[d]	Bn	R[f]	Bn	$(CH_2)_2$TMS	9.9	5.18	29.6	4.85	78.2
3i[g]	Bn	Bn	Bn	Ph	3.5	5.62	30.9	5.83	83.2
3j[g]	R[h]	Bn	Bn	Ph	7.8	5.33	29.0	6.25	na[i]

[a] In hertz. [b] In ppm from TMS. [c] Never isolated, data comes from a mixture of **3d** and **6d**. [d] From ref 6. [e] R = β-2,3,4,6-tetra-*O*-acetylglucopyranose. [f] R = β-2,3,4,6-tetra-*O*-benzylglucopyranose. [g] From ref 4b. [h] R = β-2-(benzenesulfonamido)-3,4,6-tri-*O*-benzyl-2-deoxy-glucopyranose. [i] na = not assigned.

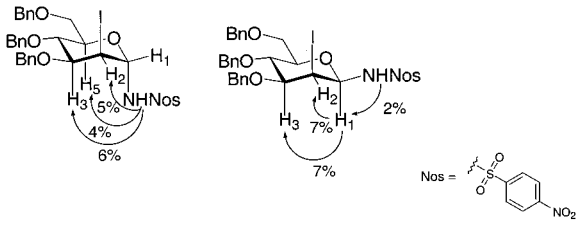

Figure 1. NOE measurements for **3a** and **6a**.

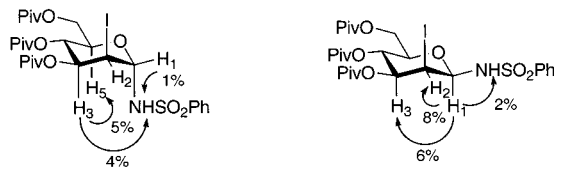

Figure 2. NOE measurements for **3b** and **6b**.

C_1 epimerization is also promoted by ester protecting groups and by protection of the 4- and 6-hydroxyls as an acetonide. Under the iodosulfonamidation conditions at 0 °C, tri-*O*-pivaloylglucal, **1b**, and 3-*O*-triethylsilyl-4,6-di-*O*-acetonide-D-glucal, **1c**, are largely converted to their corresponding *trans*-diaxial-1,2-iodosulfonamides, **3b** and **3c**, within 20 min. Longer reaction times result predominately, or exclusively, in the C_1 epimerized products. The identities of **3b** and **6b** were verified by extensive NOE study (Figure 2) while **3c** and **6c** were confirmed by chemical shift and coupling data.

Distinguishing between the *cis*- and *trans*-iodosulfonamides without NOE data is not trivial. Monitoring of the reaction by TLC is not effective since the R_f values of **3** and **6** are typically quite similar. There are some distinct differences between the ^{1}H NMR and ^{13}C NMR spectra of **6** and those of **3**, but, contrary to expectations, $J_{H1,H2}$ cannot be used to distinguish between these C_1 epimers. While values for $J_{H1,H2}$ of the *cis*-iodosulfonamides, **6**, generally range from 1 to 2 Hz, values for the *trans*-iodosulfonamides, **3**, vary from 0 to 10 Hz. The largest and most diagnostic differences between the spectra are the chemical shifts of H_1 and C_2. The resonance of H_1 in **6** (4.2−4.6 ppm) is at least 1 ppm upfield of its resonance in **3** (>5 ppm) with the difference dependent on the protecting groups employed. The chemical shift of C_2 in **6** (~40 ppm) is at least 10 ppm downfield of C_2 in **3** (~30 ppm). In the case of **3c** and **6c**, these resonances are each shifted 10 ppm downfield. Less diagnostic are the chemical shift differences of H_N and C_1. In the spectra of **3**, these resonances can be up to 1.5 ppm downfield and 5 ppm upfield of their positions in the spectra of **6** (Table 1). Thus, we can reliably use the chemical shifts of H_1 and C_2 to assign an arbitrary 1,2-iodosulfonamide as either **3** or **6**, though that of C_2 should be interpreted with care. The chemical shifts of H_N and C_1 can be used to support such assignments.

Though it can be difficult to ascertain the stereochemistry of the iodosulfonamidation transformation when only one epimer is isolated, examination of the iodosulfonamides that would not couple clearly showed that, in all cases, they were the undesired epimer, **6**.[10] These compounds possessed ester protecting groups or a 4,6-di-*O*-acetonide. In all the cases of the ester-protected compounds, presumably, the electron-withdrawing nature of these groups facilitates the epimerization at C_1. We hypothesize that the 1,3-dioxane ring in the 4,6-acetonide saccharides also facilitates the epimerization perhaps by enforcing a more chairlike conformation of **3**. TLC studies of the iodosulfonamidation of various 4,6-acetonide protected glucals indicated that the resulting *trans*-diaxial-1,2-iodosulfonamide always readily epimerizes to the undesired isomer.[11] The hypothesis that the conformation of **3** plays a role in its stability to epimerization is supported by the H_1-H_2 coupling constants. Except for **3a**, none of the *trans*-iodosulfonamides prone to epimerization have an H_1-H_2 coupling constant of greater than 4.0 Hz. The H_1-H_2 coupling constants of all other *trans*-iodosulfonamides vary between 2.5 and 10 Hz.

Trans-1,2-iodosulfonamides that are prone to epimerization under the reaction conditions are also susceptible to isomerization during purification. The use of CH_3Cl, Et_2O, or petroleum ether in solvent systems for silica chromatography results in rapid partial or complete

(8) *The Carbohydrates*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1980; Vol. IB, p 881.

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(10) **6g** is described in ref 6 where it is identified as the trans epimer **3g**. However, its coupling is not reported, and, after examination of the published spectral data, we feel confident that it is in actuality the cis isomer **6g**.

(11) Isolation of substantial cis product from the iodosulfonamidation of a 4,6-di-*O*-acetal protected glycal was previously reported in ref 2b where the α- and β-anomers of 3-*O*-benzyl-4,6-*O*-benzilidene-2-deoxy-2-iodo-altropyranosyl benzenesulfonamide were formed in a separable 3:1 mixture.

conversion of **3** to **6**. The iodosulfonamides are most stable with solvent systems of CH_2Cl_2, hexanes, and EtOAc, although some isomerization is still observed.

In summary, some *trans*-1,2-iodosulfonamides produced during Danishefsky's iodosulfonamidyl glycosylation procedures readily epimerize at C_1 to the cis isomers. This epimerization appears to be general acid- and general base-catalyzed and can occur during purification of the iodosulfonamide substrate. Differentiation between the cis and trans isomers must rely on chemical shift data from the ^1H *and* ^{13}C NMR spectra and not just on the H_1-H_2 coupling constant. Electron-withdrawing groups, either in the form of protecting groups such as esters or of an especially electron-withdrawing sulfonamide, promote this epimerization. Glycosides in which the hydroxyls at the 4- and 6-positions are protected as an acetonide are also highly susceptible to epimerization. Shortened reaction times and careful, rapid purification of iodosulfonamides prone to epimerization can usually minimize production of the undesired cis-isomer to maintain the utility of Danishefsky's iodosulfonamidyl glycosylation procedures.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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