Stereoselective Synthesis of Carbohydrate-Derived *N*-Sulfonyl Aziridines

Humberto Rodríguez-Solla,*[a] Carmen Concellón,[a] Noemí Alvaredo,[a] Ricardo Llavona,[a] Santiago García-Granda,[a] M. Rosario Díaz,[a] Raquel G. Soengas[b]

[a] Departamento de Química Orgánica e Inorgánica and Química Física y Analítica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain
Fax +34(985)102971; E-mail: hrsolla@uniovi.es

[b] Departamento de Química & QOPNA, Universidade de Aveiro, 3810-193 Aveiro, Portugal

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Abstract: A novel reaction of iodomethyllithium with a variety of sugar-derived *N*-sulfinyl imines, under very mild conditions, is described. *N*-Sulfonyl aziridines were easily obtained in high yields and in moderate to good stereoselectivities through an addition/oxidation protocol. A mechanism is proposed that is supported by the results of X-ray diffraction studies.

Key words: aziridines, carbohydrates, imines, iodomethyllithium, sulfonamides

Chiral aziridines are important building blocks in organic synthesis.[1] Due to their highly strained nature, aziridines readily open with excellent stereo- and regiocontrol to relieve ring strain, affording a wide variety of chiral amines,[2] and can be employed as starting materials for the synthesis of important biomolecules such as amino acids and alkaloids.[3] In addition, aziridines can function as sources of chirality in stereocontrolled reactions and have found use both as ligands and auxiliaries in asymmetric synthesis.[1b,c]

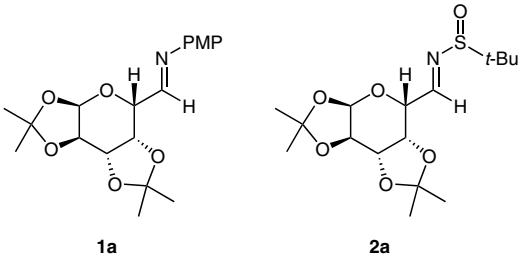
Moreover, the aziridine ring is present in a number of molecules that show biological activity, which is intimately associated with the reactivity of the strained heterocycle. Naturally occurring compounds containing the aziridine moiety exhibit antitumor and/or antibiotic activity, due to their ability to cross-link DNA,[4] or inhibit the bacterial enzyme diaminopimelic acid epimerase.[5] Other molecules related to mitosanes and mytomycins and bearing the aziridine ring have been synthesized and shown to possess activity against a variety of cancers.[6]

Despite the importance of chiral aziridines in biological systems and as intermediates in the synthesis of biologically important compounds, sugar aziridines have been much less exploited.[7] This is somewhat surprising given the interest in using aziridines for the preparation of amino-substituted sugar derivatives of great biological value[8] such as azasugars[9] and sugar amino acids.[10] As the nucleophilic opening of the aziridine ring of sugar aziridines is strongly influenced by the configuration of the starting sugar and by its conformational flexibility, this process is usually highly selective, giving just one of the possible isomers.[11]

Although synthetic routes toward aziridines have included many procedures such as the addition of nitrenes to alkenes,[12] nucleophilic substitutions of derivatives of epoxides[13] or β-amino alcohols[14] and methods based on the use of imines as starting materials,[15] almost all the reported syntheses of carbohydrate aziridines are based on S_N2 intramolecular nucleophilic substitution.[16] Generally, these methods are multistep procedures, requiring long reaction times and taking place in only moderate overall yields.

In this context, the development of a novel and efficient procedure to obtain aziridines derived from sugars in good yields and stereoselectivities would be desirable. We have previously described an efficient, simple, and rapid aziridination process by reaction of imines derived from *p*-toluenesulfonamide with iodomethyllithium generated in situ.[17] Taking into account the inherent usefulness of this procedure for the rapid preparation of sugar aziridines, we decided to investigate the application of this methodology for the aziridination of carbohydrate-derived imines.

First attempts focused on the synthesis of carbohydrate-based imines derived from either *p*-toluenesulfonamide or *tert*-butylsulfonamide. In this sense, methods based on the synthesis of these substrates according to different procedures previously reported in the literature[18] failed, and no *p*-toluene or *tert*-butylsulfonyl imines were isolated. For this reason, we also explored the use of other protecting groups on the imine group such as *p*-methoxyphenyl and *tert*-butylsulfinyl. In both cases, the corresponding imines **1a** and **2a** were successfully prepared according to literature procedures (Figure 1).[19,20]



1a **2a**

Figure 1 Galactose-derived imines **1a** and **2a**

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Initial attempts to prepare aziridines were performed starting from imine **1a**. Iodomethyllithium was generated in situ by treatment of diiodomethane with methyllithium in the presence of imine **1a** at –78 °C using tetrahydrofuran (THF) as solvent. Unfortunately, no addition of iodomethyllithium to imine **1a** took place under a range of reaction conditions. A similar behavior was observed in the addition of iodomethyllithium to *N*-PMP imines derived from octanal or benzaldehyde.[17b]

When the same reaction was performed on a stereoisomeric mixture of sulfinyl imine **2a**,[21] a complex mixture of stereoisomers was isolated; for this reason, oxidation of *N*-sulfinilaziridines was carried out in the presence of MCPBA, with the galactose-derived *N*-sulfonyl aziridine being isolated as a single stereoisomer in 86% yield (Table 1, entry 1).[22] It is important to remark that, when the reaction was carried out on either (*S*)- or (*R*)-*tert*-butylsulfinylimine, similar results were observed in terms of yield and stereoselectivity. Thus, in the case of (*S*)-*tert*-butylsulfinylimine or (*R*)-*tert*-butylsulfinylimine derived from galactose, single stereoisomers of aziridine **3a** were isolated in 83 and 82% yield, respectively, after application of the oxidation protocol. This result supported the idea that the *tert*-butylsulfinyl group does not act in the reaction as a chiral auxiliary. As a consequence, all the aziridination reactions were finally performed on stereoisomeric mixtures of sulfinyl imines **2**.

Aziridination reactions on other sugar-based imines are summarized in Table 1. From a general point of view, reactions took place in good yields (>70%) and in stereoisomeric ratios ranging from 72:28 to >98:2 (Table 1).

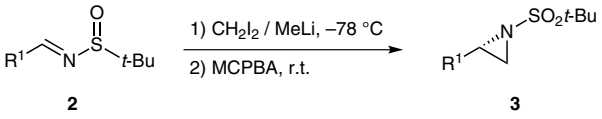
The diastereoisomeric ratio (dr) of sugar-based *N*-sulfonyl aziridines **3** was determined on the basis of ^{1}H NMR spectroscopic analysis (300 MHz) of the crude reaction products.

It is worth mentioning that this process tolerates a broad scope of sugar-derived imines with different protecting moieties on the hydroxyl groups. Furthermore, all the reactions took place with good stereoselectivities and in high yields with no epimerization of any stereogenic center. In general terms, it is noteworthy that this approach to the synthesis of aziridines **3** is experimentally simple and the reaction times are short.

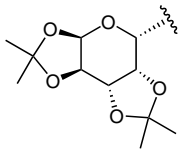
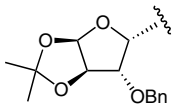
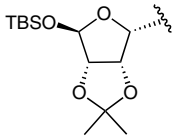
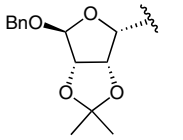
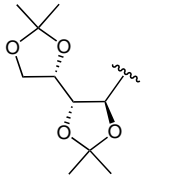
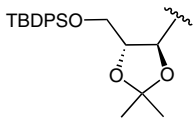
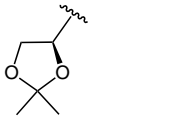
The structure of sugar-based aziridines **3** (as depicted in Table 1) were established on the basis of ^{1}H and ^{13}C NMR spectroscopic analysis, and the absolute configuration of the major stereoisomer was established for **3d** by X-ray diffraction (Figure 2).[23] The structure and the absolute configuration of other sulfonyl aziridines **3** were assigned by analogy.

The absolute configuration obtained after the addition of iodomethyllithium **4** to imines **2** can be easily explained through the Felkin–Ahn model. Thus, iodomethyllithium would attack the *si* face giving preferentially *anti*-stereoisomers (Scheme 1) through a model similar to that used to explain the stereoselectivity observed in the addition of

Table 1 Synthesis of Carbohydrate-Derived *N*-Sulfonyl Aziridines **3**



2 **3**

Entry[a]	**3**[b]	R^1	dr	Yield (%)[c]
1	**3a**		>98:2	86
2	**3b**		80:20	81
3	**3c**		87:13	79
4	**3d**		80:20	95
5	**3e**		72:28	80
6	**3f**		80:20	70
7	**3g**		79:21	85

[a] All reactions were carried out on mixtures of imine stereoisomers derived from (±)-*tert*-butylsulfinylimine.
[b] Diastereoisomeric ratio (dr) was determined on the basis of ^{1}H NMR (300 MHz) analysis of the crude products **3**.
[c] Isolated yield (based on **2**) of analytically pure compounds **3** after column chromatography.

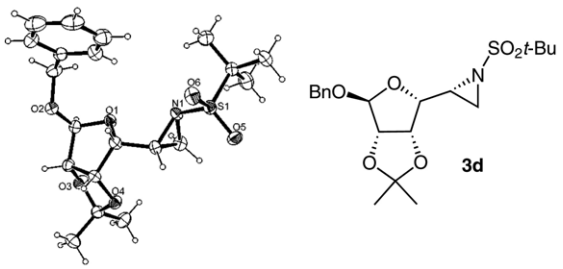
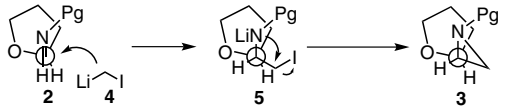


Figure 2 ORTEP diagram for **3d**

nitronate and bromonitronate anions to *N*-*p*-methoxyphenylimines.[19] By assuming an addition process of iodomethyllithium to the imine group, iodated lithium amide **5** is generated, which undergoes spontaneous heterocyclization to afford the corresponding aziridine **3**. This mechanistic proposal was supported by X-ray diffraction analysis of compound **3d** (Figure 2). The same stereochemical course was recently used to explain other nucleophilic addition reactions to similar sugar-based imines.[19,24]



Scheme 1 Mechanistic proposal for the addition of iodomethyllithium to sugar-derived imines **2**

In conclusion, we have described the reaction of iodomethyllithium with a variety of imines to afford, in high yields, sugar-based *N*-sulfonyl aziridines. This process took place with good to high stereoselectivities while maintaining the stereochemical integrity of the sugar backbone. The aziridines **3** obtained were those predicted by the Felkin–Ahn model.

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(20) **Synthesis of 6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6[(4-methoxyphenyl)imino]-α-D-galactopyranose (1a):**[19] *N*-*p*-Methoxyphenylimine **1a** was prepared in nearly quantitative yields by stirring a solution of the corresponding aldehyde (10 mmol, 1.0 equiv) in CH_2Cl_2 with *p*-anisidine (10 mmol, 1.0 equiv), in the presence of $MgSO_4$ (2 g) for 16 h. Yield: 3.4 g (93%); orange oil; $[\alpha]_D^{20}$ +7.2 (*c* 0.6 in $CHCl_3$); R_f = 0.62 (hexane–EtOAc, 3:1). IR (neat): 3060, 1674, 1510, 1260 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 4.0 Hz, 1 H), 7.03 (d, *J* = 8.6 Hz, 2 H), 6.78 (d, *J* = 8.6 Hz, 2 H), 5.56 (d, *J* = 4.9 Hz, 1 H), 4.58 (dd, *J* = 7.7, 2.3 Hz, 1 H), 4.45–4.22 (m, 2 H),4.28 (dd, *J* = 5.0, 2.4 Hz, 1 H), 3.69 (s, 3 H), 1.48 (s, 3 H), 1.39 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9 (CH),

158.1 (C), 143.7 (C), 121.8 (2 × CH), 113.9 (2 × CH), 109.2 (C), 108.5 (C), 96.0 (CH), 73.1 (CH), 70.3 (CH), 70.2 (CH), 55.1 (CH_3), 53.2 (CH), 25.8 (CH_3), 25.7 (CH_3), 24.6 (CH_3), 24.0 (CH_3); MS (ESI^+): *m*/*z* (%) = 364 (100) $[M + H]^+$, 338 (7), 322 (30), 306 (4); HRMS (ESI^+-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}NO_6$: 364.1760; found: 364.1755.

(21) **Synthesis of *N*-*tert*-Butylsulfinyl Imines 2:** To a solution of the corresponding aldehyde (0.5 mmol, 1 equiv) in anhydrous CH_2Cl_2 (10 mL), $[Ti(OEt)_4]$ (2 mmol, 4 equiv) was added slowly by using a syringe. *N*-*tert*-Butanesulfinamide (0.5 mmol, 1 equiv) was added in one portion and the reaction mixture was stirred at r.t. for16 h. The excess $[Ti(OEt)_4]$ was decomposed by slow addition of the reaction mixture to a solution of brine. The resulting suspension was filtered through a pad of Celite, washed with ethyl acetate, the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to yield crude *N*-*tert*-butylsulfinyl imines **2** without further purification.
6-Deoxy-6-(*N*-*tert*-butylsulfinyl)imino-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2a): Yield: 155.8 mg (86%); yellow oil; R_f = 0.36, 0.33 (hexane–EtOAc, 3:1). IR (neat): 3051, 1633, 1458, 1071, 735, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 2.7 Hz, 1 H), 5.62 (d, *J* = 4.9 Hz, 1 H), 4.64 (dd, *J* = 7.8, 2.4 Hz, 1 H), 4.60 (app. t, *J* = 2.7 Hz, 1 H), 4.49 (dd, *J* = 7.8, 2.4 Hz, 1 H), 4.35 (dd, *J* = 4.9, 2.4 Hz, 1 H), 1.52 (s, 3 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.20 (s, 9 H); δ (minor isomer) = 8.00 (d, *J* = 2.6 Hz, 1 H), 5.65 (d, *J* = 5.2 Hz, 1 H), 4.64 (dd, *J* = 7.7, 2.4 Hz, 1 H), 4.56 (dd, *J* = 7.6, 2.6 Hz, 1 H), 4.40–4.37 (m, 1 H), 4.31–4.20 (m, 1 H), 1.43 (s, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 1.28 (s, 3 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (CH), 109.6 (C), 109.4 (C), 96.1 (CH), 72.6 (CH), 70.4 (2 × CH), 70.2 (CH), 57.2 (C), 25.9 (CH_3), 25.6 (CH_3), 24.6 (CH_3), 24.1 (CH_3), 22.2 (3 × CH_3); δ (minor isomer) = 165.2 (CH), 109.8 (C), 109.7 (C), 96.1 (CH), 71.9 (CH), 70.4 (2 × CH), 70.1 (CH), 57.1 (C), 25.9 (CH_3), 25.6 (CH_3), 24.6 (CH_3), 24.1 (CH_3), 22.3 (3 × CH_3); MS (ESI^+): *m*/*z* (%) = 400 (5) $[M + K]^+$, 386 (9) $[M + 2 + Na]^+$, 385 (20) $[M + 1 + Na]^+$, 384 (100) $[M + Na]^+$; HRMS (ESI^+-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{27}NO_6SNa$: 384.1457; found: 384.1462.

(22) **Synthesis of *N*-Sulfonyl Aziridines 3:** To a mixture of the corresponding *N*-sulfinyl mine **2** (0.4 mmol, 1 equiv) and CH_2I_2 (0.6 mmol, 1.5 equiv) in anhydrous THF (2 mL), was added a solution of MeLi (1.5 M in Et_2O, 0.48 mmol, 1.2 equiv) at –78 °C. The solution was stirred at –78 °C for 30 min, and then allowed to warm to r.t. and stirred for an additional 30 min. The reaction was then quenched with aq. NH_4Cl and the organic layer was extracted with Et_2O (3 × 10 mL). The combined extracts were dried with Na_2SO_4 and concentrated under vacuum to yield crude *N*-sulfinyl aziridines. Finally, to a solution of the corresponding sulfinyl aziridine in CH_2Cl_2 (1 mL), anhydrous MCPBA (0.4 mmol, 1 equiv) was added at r.t. in one portion. When the reaction was complete (less than 1 min), the reaction was diluted with CH_2Cl_2 (2 mL) and washed with sat. $NaHCO_3$ (3 × 3 mL). Organic layers were dried over anhydrous Na_2SO_4 and the solvents were evaporated, giving the corresponding *N*-sulfonyl aziridines **3**, which were purified by flash chromatography on silica gel (hexane–EtOAc, 3:1).
6,7-Deoxy-6,7-(*N*-*tert*-butylsulfinyl)imino-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptapyranose (3a): Yield: 135.1 mg (86%); white solid; m.p. 84–85 °C (Et_2O–hexane); $[\alpha]_D^{20}$ –9.2 (*c* 1.0, $CHCl_3$); R_f = 0.30 (hexane–EtOAc, 3:1). IR (neat): 1640, 1458, 1308, 1067, 724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.50 (d, *J* = 4.9 Hz, 1 H), 4.61 (dd, *J* = 7.9, 2.4 Hz, 1 H), 4.33 (dd, *J* = 7.9, 1.5 Hz, 1 H), 4.30 (dd, *J* = 4.9, 2.4 Hz, 1 H), 3.63 (dd, *J* = 5.2, 1.5 Hz, 1 H), 3.09 (dt, *J* = 6.9, 5.2 Hz, 1 H), 2.64 (d, *J* = 6.9 Hz, 1 H), 2.33 (d, *J* = 5.2 Hz, 1 H), 1.49 (s, 9 H), 1.47 (s, 3 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.3 (C), 108.4 (C), 96.0 (CH), 71.4 (CH), 70.3 (2 × CH), 67.0 (CH), 59.1 (C), 37.0 (CH), 31.2 (CH_2), 25.8 (CH_3), 25.7 (CH_3), 24.6 (CH_3), 24.1 (CH_3), 23.9 (3 × CH_3); MS (ESI^+): *m*/*z* (%) = 430 (18) $[M + K]^+$, 416 (14) $[M + 2 + Na]^+$, 415 (32) $[M + 1 + Na]^+$, 414 (100) $[M + Na]^+$; HRMS (ESI^+-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{29}NO_7NaS$: 414.1562; found: 414.1558.

(23) CCDC 900247 contains the supplementary crystallographic data for compound **3d**. This data can be obtained free of charge via: www.ccdc.cam.ac.uk/conts/retrieving.html [or the Cambridge Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44(1223)336033; or deposit@ccdc.cam.ac.uk].

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