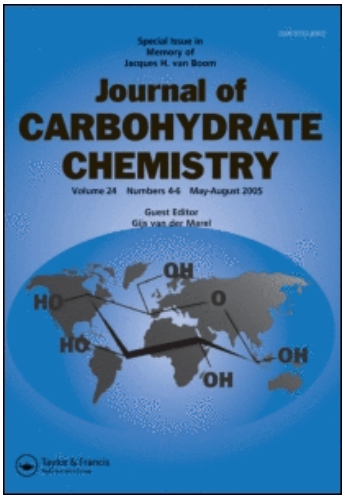


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Heterocycle-Substituted Carbohydrate Oxazolines

Michael DeCastro[a]; Cecilia H. Marzabadi[a]
[a] Department of Chemistry and Biochemistry, Seton Hall University, South Orange, NJ

To cite this Article DeCastro, Michael and Marzabadi, Cecilia H.(2005) 'Heterocycle-Substituted Carbohydrate Oxazolines', Journal of Carbohydrate Chemistry, 24: 2, 179 — 185
To link to this Article: DOI: 10.1081/CAR-200059963
URL: http://dx.doi.org/10.1081/CAR-200059963

Journal of Carbohydrate Chemistry, 24:179–185, 2005

ISSN: 0732-8303 print
DOI: 10.1081/CAR-200059963

Heterocycle-Substituted Carbohydrate Oxazolines

Michael DeCastro and Cecilia H. Marzabadi

Department of Chemistry and Biochemistry, Seton Hall University, South Orange, NJ

Glucooxazolines with appended heterocyclic rings have been prepared in a two-step process involving iodoamidation of protected D-glucals and subsequent basic cyclization.

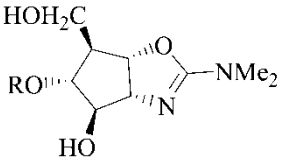
Keywords Iodoamidation, Glycooxazdines, Conformational effect, Heterocycles, Carbohydrate-fused oxazolines

INTRODUCTION

The importance of carbohydrates in living systems cannot be understated. This is particularly true for their roles in cellular recognition and signal transduction processes in the body. Enzymes such as glycosyltransferases and glycosidases regulate the activities of carbohydrate conjugates in these processes. Molecules such as allosamidin[1] **1** and trehazolin[2] **2** have been shown to be potent inhibitors of the glycosidase enzymes called chitinases and as such show promise as insecticides and antifungal agents. The activity of these molecules is believed to be due to their shape, which mimics the flattened transition state geometry of the transient oxocarbonium ion formed during glycoside hydrolysis.[3] Specifically, both of these molecules contain 2-oxazoline moieties; stabilized analogues of the intermediates formed from N-acetylated sugars present in chitin. Other oxazoline-containing molecules have also been reported to possess a range of biological activities. Aryl- and heteroaryl-substituted oxazolines have been developed as antibacterial,[4] antiviral,[5]

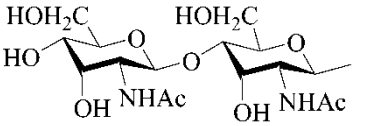
Received December 22, 2004; accepted January 7, 2005.
Address correspondence to Cecilia H. Marzabadi, Department of Chemistry and Biochemistry, Seton Hall University, 400 South Orange Ave., South Orange, NJ 07079. Tel.: 1-973-761-9032; Fax: 1-973-761-9772; E-mail: marzabce@shu.edu

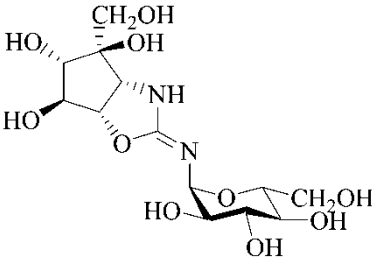
antimuscarinic,[6] and antidepressant[7] agents. Compounds such as **3** have been shown to be potent inhibitors of human rhinovirus.[8]



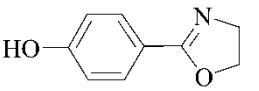
1

R =





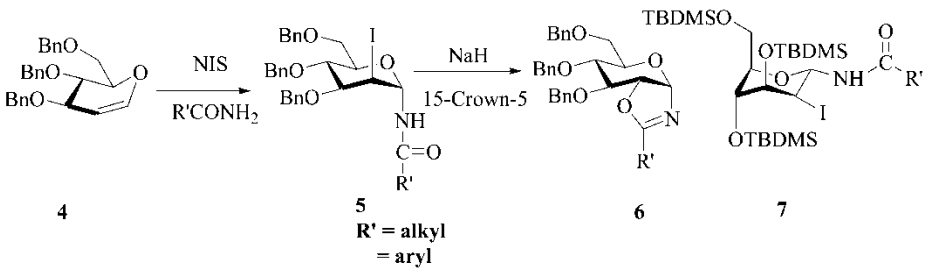
2



3

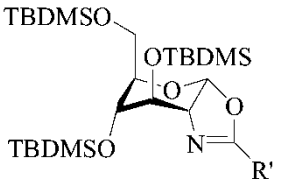
Because of the medicinal importance of the oxazoline moiety, we became interested in the synthesis of molecules containing this functionality. In particular, we wanted to explore the synthesis of carbohydrate-fused oxazolines because of their potential enhanced solubility and specificity for cellular targets. We believed that they were readily accessible from sugar precursors using a variation of the well-established iodoglycosylation reaction developed by Lemieux[9] and Thiem.[10] In this reaction, glycals are treated with N-iodosuccinimide (or other source of I+) and an alcohol acceptor to afford predominately the *trans*-2-deoxy-2-iodoglycosides. Addition to D-glucal derivatives affords predominately the α-manno diastereoisomers that can subsequently be deiodinated under free radical conditions to afford the 2-deoxy-α-glycosides. This methodology has been expanded to include the incorporation of a variety of other anomeric groups such as esters,[11] amino acids,[12] water,[13] and isothiocyanates.[14] Most relevant to our work were the reports from the Danishefsky group,[15] where they had employed this methodology to prepare 2-deoxy-2-iodo-benzenesulfonamido carbohydrate derivatives that were later converted to 2-amino-2-deoxyglycosides by treatment with base in the presence of a nucleophile. We decided to explore this addition chemistry with simple amide precursors. Subsequent treatment of the iodoamides with base should afford a range of glycooxazolines with nitrogen at the anomeric position of the sugar (Sch. 1).[16]

In prior studies, we determined that the yields and selectivities of glycal addition reactions were dramatically enhanced with the use of electron-rich amides (e.g., benzamide) and with the use of electron releasing (e.g., benzyl or silyl) protecting groups on the glycal hydroxyl groups. We also were successful



Scheme 1: Oxazoline formation from glucals.

in cyclizing these precursors to the desired glycooxazolines with a nitrogen at C1 of the sugar. An unusual protecting group effect in the addition reactions of *tert*-butyldimethylsilyl-protected glucals was observed. *trans*-Iodoamides were isolated in which the pyranose ring existed in the $^1C_4$ conformation **7**. When the TBDMS-protected iodoamides were treated with base, the glycooxazolines with oxygen at the anomeric position **8** were obtained. We believe this to be due to the formation of unstable, N-acylaziridine intermediates that rearrange to the observed products. The formation of these intermediates is favored by the equatorial disposition of nitrogen at C1 in the altered conformer.



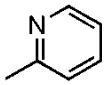
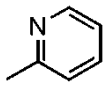
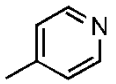
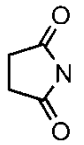
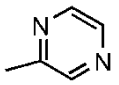
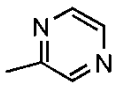
8

In this paper we describe further synthetic efforts utilizing novel aryl- and heteroaryl amides in reactions with 3,4,6-*tris*-O-*tert*-butyldimethylsilyl-D-glucal. The preparation of glucooxazolines from these precursors will be described. The biological testing of these compounds will be reported in due course.

RESULTS

Glucal addition reactions were carried out with N-iodosuccinimide and benzamide, picoloinamide, isonicotinamide, pyrazinecarboxamide, 2-thiophenecarboxamide, and furamide using an excess (2 equivalents) of iodinating agent and amide (6 equivalents). Because of the poor solubility of many of the amides in propionitrile, DMF was employed as the reaction solvent. The distribution and yields of products obtained from these addition reactions are shown in Table 1.

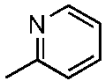
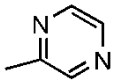
Table 1: Ratios of diastereomeric iodoamides 7 obtained from glucals.[a,b]

Entry	Amide R′ =	Iodoamide 7 R′ =	α-manno	β-manno	α-gluco	β-gluco	Isolated yield (%)[c]
a			2	0	0	1	79[d]
b			1	0	0	0	82
c			1	0	0	0	90
d			1	0	0	1	85
e			1	0	0	0	90
f			1	0	0	0	25[e]

[a]Determined by integration of the anomeric protons in the ^{1}H NMR spectrum obtained in $CDCl_3$.
[b]For sugar in $^1C_4$ conformation.
[c]Represents product recovered following extractive workup and subsequent chromatographic purification (SiO_2).
[d]Propionitrile was used as a solvent in the case of benzamide.
[e]Furamide reactions were carried out using two different solvents, propionitrile@ −78°C and DMF @ 0°C. Similar yields were obtained.

In most instances, good yields of the desired addition products were obtained. With isonicotinamide (Table 1, entry c), the amide failed to react; instead, the only addition product that was obtained was the succinimide adduct.[17] This was somewhat surprising in light of the fact that the 2-substituted analog, picolinamide (Table 1, entry b), gave good yields of addition product in this reaction. One possible explanation for the enhanced nucleophilicity of picolinamide is the ability of the amide protons to form a hydrogen bond with the pyridine ring nitrogen. This would prevent delocalization of electrons into the carbonyl, thereby increasing the nucleophilicity of the amide nitrogen relative to its isomer. Furamide gave only low yields of product under a variety of reaction conditions (Table 1, entry f). This could possibly be attributed to the nucleophilicity of the heterocyclic ring of the amide and its competition for iodonium ion.[18] All of the addition reactions gave the

Table 2: Yields of oxazolines 8 from basic cyclization of iodoamides.

Entry	R′ =	Isolated yield (%)[a]
a		75
b		80
c		82
d		95

[a]Represents product recovered following extractive workup and subsequent chromatographic purification (SiO_2).

α-manno diastereomers as the major products, with the exception of pyrazinecarboxamide, which gave a 1:1 mixture of the two *trans* addition products. The product stereochemistries were determined by the analysis of vicinal coupling constants (^3J) for the carbohydrate ring protons. This analysis showed that the sugar addition products existed in distorted chair conformers as evidenced by the smaller coupling constants for H3–H5 (5.5–7.5 Hz) and a large $^3J_{1,2}$ (10.0 Hz).

Cyclization of the iodoamides was affected using sodium hydride/15-crown-5 in THF. The yields from these reactions are shown in Table 2.

In all cases, the oxazoline with a C1 oxygen linkage was isolated. Spectroscopic data supported these assignments; the anomeric proton resonance was observed at a higher field than would be predicted for nitrogen at the C1 position.[a] Also, the chemical shifts observed are consistent with values reported for

[a]**Representative data.** 1-Deoxy-2-iodo-1-[{2-thienylcarbonyl}amino]-3,4,6- *tris*-O-*tert*-butyldimethylsilyl-α-D-mannopyranose **7e** ($^1C_4$): ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.06–7.56 (m, 3H, ArH), 6.38 (d, 1H, J = 9.5 Hz, N-H), 5.79 (dd, 1H, J = 9.5, 10 Hz, H-1), 4.65 (dd, 1H, J = 8.0, 5.5 Hz, H-2), 4.09 (appar. d, 1H, J = 5.5 Hz, H-3), 4.28 (dd, 1H, J = 7.0, 7.3 Hz, H-4), 3.95 (d, 1H, J = 7.5 Hz, H-5), 3.90–3.85 (m, H-6). ^{13}C NMR: δ 164.1, 131.1, 128.9, 127.8, 82.0, 76.7, 73.0, 68.9, 61.5, 34.1, 26.4, 26.1, 26.0, 18.5, 18.4, 18.2. HRMS-ESI (+): Calcd: 742.2231. Found: 742.2310. Data for C1 O-linked oxazoline **8d**: ^{1}H NMR ($CDCl_3$): δ 7.60–7.40 (m, 3H, ArH), 6.14 (d, 1H, J = 6.5 Hz, H-1), 4.22 (dd, 1H, J = 6.0, 2.0 Hz, H-2), 3.73 (dd, 1H, J = 2.0, 3.0 Hz, H-3), 3.70 (appar.d, 1H, J = 2.5 Hz, H-4), 3.66 (dd, 1H, J = 3.0, 5.0 Hz, H-5), 3.32 (m, 2H, H-6). ^{13}C NMR: δ 165.1, 137.4, 130.8, 110.0, 101.2, 74.6, 71.7, 70.4, 67.7, 64.1, 26.1, 25.8, 18.6, 18.0, 17.9. HRMS-ESI (+) Calcd: 614.3108. Found: 614.3187.

analogous structures.[19] Again, the conformation of the sugar rings were distorted, with medium to large $^3J_{1,2}$ (6.5–9.0 Hz) and medium to small vicinal couplings observed for the remainder of the ring protons (1.5–3.0 Hz). Because of the low yields of furamide addition product, no attempts were made to form the oxazoline from this precursor.

In conclusion, a novel series of aryl- and heteroaryl-substituted glucosylamides have been prepared that exist in the altered $^1C_4$ chair conformation. Cyclization of these molecules under basic conditions affords the C1 equatorially disposed oxazolines with oxygen at the anomeric center. They represent unique structures that may possess inhibitory activity for β-glycosidases and glycosyltransferases. The further transformations and bioassays of these molecules are ongoing.

REFERENCES

[1] Griffith, D.; Danishefsky, S. Total synthesis of allosamidin: an application of the sulfonamidoglycosylation of glycals. J. Am. Chem. Soc. **1991**, *113*, 5863–5864.

[2] Kobayashi, Y. Chemistry and biology of trehazolins. Carbohydr. Res. **1999**, *315*, 3–15.

[3] Ganem, B.; Papandreou, G. Mimicking the glucosidase transition state: shape/charge considerations. J. Am. Chem. Soc. **1991**, *113*, 8984–8985.

[4] Sasaki, T.; Otani, T.; Yoshida, K.; Unemi, N.; Hamada, M.; Takeuchi, T. Discovery of methyl-2-(2′-hydroxyphenyl)-2-oxazoline-4-carboxylate as a secondary metabolite from actinomadura. J. Antibiotics **1997**, *50* (10), 881–883.

[5] Diana, G. Inhibitors of picornavirus replication. Curr. Med. Chem.—Anti-Infective Agents **2003**, *2*, 1–12.

[6] Fotador, U.; Becu, C.; Borremans, F.; Anteunis, M. Synthetic and conformational aspects of trimethylammonium-methyl substituted 2-oxazolines as potential cholinergics. Tetrahedron **1978**, *34*, 3537–3544.

[7] Neau, B.; Damaj, I.; Lambrey, B.; Akbaraly, J.; Roux, J.; Perrissoud, D.; Jacquot, J. COR3224—a new antidepressant: pharmacokinetics and metabolism in rat. Eur. J. Drug Metab. Pharmacokinet. **1991**, Spec No 3: 77–79.

[8] Bibler-Muckelbauer, J.; Kremer, M.; Rossmann, M.; Diana, G.; Dutko, F.; Pevear, D.; McKinlay, M. Human rhinovirus 14 complexed with fragments of active antiviral compounds. Virology **1994**, *202*, 360–369.

[9] Lemieux, R.U.; Hendriks, K.B.; Stick, R.V.; James, K. Halide ion catalyzed glycosidation reactions. Syntheses of α-linked disaccharides. J. Am. Chem. Soc. **1975**, *97*, 4056–4062.

[10] Thiem, J.; Karl, H.; Schwenter, J. Synthese α-verknupfter-2′-deoxy-2-iododisaccharide. Synthesis **1978**, 696.

[11] Roush, W.; Briner, K.; Sebesta, D. Highly selective synthesis of α-L-olivomycosides via trimethylsilyl triflate mediated glycosidations of 1-O-acetyl-4-O-isobutyrl-2,6-dideoxy-2-iodo-3-C-methyl-α-L-mannopyranose. Synlett **1993**, 264–265.

[12] Kottenhahn, M.; Kessler, H. Synthese von 2-desoxy-α-O-glycopeptiden mit dem N-Iodsuccinimid-(NIS-) Verfahren. Liebigs Ann. Chem. **1991**, 727–744.

[13] Marzabadi, C.; Spilling, C.D. Stereoselectivity in glucal epoxide formation. J. Org. Chem. **1993**, *58*, 3761–3766.

[14] Isac-Garcia, J.; Hernandez-Mateo, F.; Calvo-Flores, F.; Santoyo-Gonzalez, F. Reactivity of 2-deoxy-2-iodoglycosyl isothiocyanates with O-, S-, and N- nucleophiles, synthesis of glycopyranoso-fused thiazoles. J. Org. Chem. **2004**, *69*, 202–205.

[15] Griffith, D.; Danishefsky, S. Sulfonamidoglycosylation of glycals. A route to oligosaccharides with 2-aminohexose subunits. J. Am. Chem. Soc. **1990**, *112*, 5811–5819.

[16] De Castro, M.; Marzabadi, C. The preparation of 2-iodoamides from glucals and their further transformations into oxazolines. Tetrahedron Lett. **2004**, *45*, 6501–6504.

[17] Thiem, J.; Klatke, W. Syntheses of deoxy oligosaccharides. In *Topics in Current Chemistry, Carbohydrate Chemistry*; Thiem, J., Ed.; Springer-Verlag: Berlin, 1990; Vol. 154, 285–330.

[18] Furan is generally considered the "least aromatic" of the five-membered ring heterocycles containing only a single heteroatom and has a greater tendency to react to give addition products. See Joule, J.; Mills, K. Furans: reactions and synthesis. In *Heterocyclic Chemistry*, 4th Edition; Blackwell Science: Oxford, 2000; 296–318.

[19] (a) Gordon, D.M.; Danishefsky, S.J. Ritter-like reactions of 1,2- anhydropyranose derivatives. J. Org. Chem. **1991**, *56*, 3713–3715; (b) Liu, J.; Gin, D. C2-Amidoglycosylation. Scope and mechanism of nitrogen transfer. J. Am. Chem. Soc. **2002**, *124*, 9789–9797.