Glycoconjugate Journal (1997) **14:** 497–499

EGC1
A new entry to glycosylamines

Francisco L. Merchán, Pedro Merino* and Tomás Tejero

Departamento de Química Orgánica, ICMA, Universidad de Zaragoza, Zaragoza, Spain

A new procedure for the introduction of a nitrogen atom into the anomeric centre leading to glycosylamines is described. The new reaction consisting of the condensation of a furanose with a hydroxylamine in the presence of a Lewis acid occurs with a complete degree of diastereoselectivity.

***Keywords*: carbohydrates, glycosylamines, nitrones, hydroxylamines, Lewis acid**

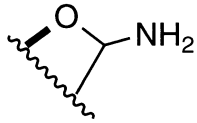
Introduction

Optically active glycosylamines (Figure 1) have been widely employed as versatile chiral auxiliaries for the synthesis of biologically active substances [1]. Glycosylamines permit effective synthesis of α-amino acids by Strecker [2] and Ugi [3] methods. They can also be used for the asymmetric synthesis of β-amino acids, alkaloids or homoallylamines [4]. From the point of view of their biological activity mono- and diglycosylamines (whose structure and conformation have been recently studied [5]) are considered as inhibitors of some glycosidases [6]. In addition synthetic glycosylamides (obtained from glycosylamines) can be considered as glycolipid analogues; many of these compounds are of interest due to their activity as immunomodulators [7].

Backgound

Several approaches have been described for the synthesis of glycosylamines the most used being the reaction of a reducing sugar residue with ammonia [8] or primary amines [9]. Ammonium hydrogen carbonate [10] and potassium cyanate [11] have also been use for the introduction of the amino functionality into the sugar moiety. Application of the thus prepared glycosylamines to the solid-phase synthesis of *N*-glycopeptides have been described [12]. Glycosylamines can also be prepared by reduction of glycosylazides; a number of synthetic procedures for the preparation of the later have been described [13]. The access to other derivatives of glycosylamines such as glycoamidines, *N*-thioformyl or *N*-thioacetylglycosylamines have also been investigated [14].

In particular the synthesis of *N*-hydroxyglycosylamines have been previously described through the condensation of an aldose and hydroxylamine hydrochloride [15]. The use of the latter makes that the obtained monosubstituted *N*-hydroxyglycosylamines are not configurationally stable at the anomeric centre due to the equilibrium with the corresponding oximes (Figure 2). Those glycosylhydroxylamines have been used for preparing the corresponding nitrones which have been further transformed into *N*,*N*-disubstituted glycosyl hydroxylamines after a nucleophilic addition step [16].

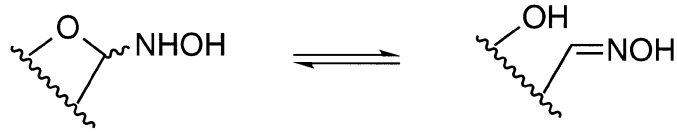


Glycosylamines

Figure 1.

Results and discussion

We present in this communication a new entry to disubstituted *N*-hydroxyglycosylamines. The new synthetic approach



hydroxylamine oxime

Figure 2.

* To whom correspondence should be addressed.

0282–0080

consists of the direct introduction of a nitrogen atom into the anomeric centre. The reaction takes place between an aldose derived from D-mannose and benzylhydroxylamine in the presence of a Lewis acid as an activating agent.

Experimental

When the protected furanose **1** was treated with benzylhydroxylamine in the presence of a drying agent such as magnesium sulfate, calcium chloride, sodium sulfate or molecular sieves in a variety of solvents such as dichloromethane, chloroform, methanol or toluene no reaction was observed in any case. These conditions, however, had been shown to be very efficient when applied to protected α-alkoxy and α-amino aldehydes [17]. Longer times of reaction and higher temperatures did not lead to better results.

Activation of the carbonyl group with a Lewis acid made the reaction proceed smoothly. In a similar way to that described by us for the condensation of benzylhydroxylamine with ketones [18] (or less reactive carbonyls) the best results were observed when zinc (II) chloride was used as an activating agent.

Thus, when a mixture of furanose **1**, benzylhydroxylamine and magnesium sulfate in dichloromethane was treated with a catalytic amount of zinc (II) chloride at ambient temperature hydroxylamine **2** (Figure 3) was obtained after 6 h with complete diastereoselectivity. The transdisposition between C-1 and C-2 was assigned on the basis of the coupling constant observed by ^{1}H NMR spectroscopy ($J_{1,2} = 0$ Hz).

The mechanism

Condensation between the aldehyde form **1b** of the protected D-mannose and benzylhydroxylamine leads to the intermediate γ-hydroxy nitrone **3** (Figure 4). The intramolecular cyclization of that compound is promoted by the action of the zinc (II) chloride which is present (although in a catalytic amount) in the medium of the reaction.

Unfortunately, attempts at isolating the intermediate **3** were unsuccessful, presumably due to the more rapid intramolecular cyclization. Both NMR studies and assays with less efficient activating agents are currently in progress in our laboratory in order to isolate (or characterize) the intermediate nitrone **3**. The dramatic change observed in the reactivity when a Lewis acid was added as well as the well-documented reactivity of nitrones in the presence of Lewis acids firmly support the proposed mechanism.

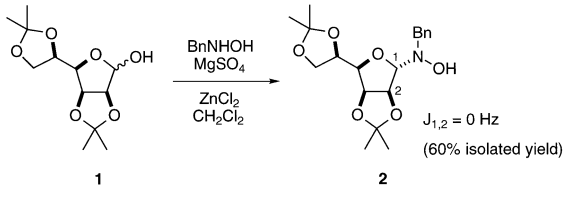


Figure 3.

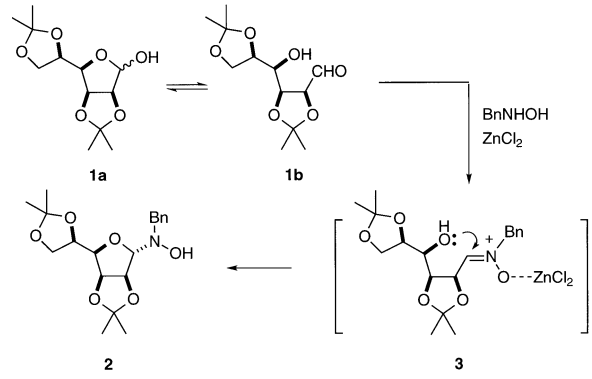


Figure 4.

Conclusions

The reactivity showed represents a new entry not only to *N*-hydroxyglycosylamines but also to the important glycosylamines, easily accessible by deoxygenation of the parent hydroxylamines. The extension of this reactivity (consisting of the direct introduction of a nitrogen into the anomeric centre) to other reducing sugars and subsequent applications of the obtained products are currently under development in our laboratory and they will be reported in due course.

Acknowledgement

Financial supports come from the DGICYT (Ministerio de Education y Ciencia, Madrid, Project PM94-0598).

References and Notes

1 Kunz H, Ruck K (1993) *Angew Chem Int Ed Engl* **32**: 336.
2 (a) Kunz H, Sager W (1987) *Angew Chem Int Ed Engl* **56**: 557. (b) Kunz H, Sager W, Schanzenbach D, Decker M (1991) *Liebigs Ann Chem* 649.
3 Kunz H, Pfrengle W (1988) *J Am Chem Soc* **110**: 651.
4 Laschat S, Kunz H (1991) *J Org Chem* **56**: 5883.
5 (a) Linek K, Alfoldi J, Durindova M (1993) *Chem Papers* **47**: 247. (b) Linek K, Alfoldi J, Defaye J (1993) *J Carbohydr Res* **247**: 329.
6 Lalegerie P, Legler G, Yon JM (1982) *Biochimie* **64**: 977.
7 Lockhoff O (1991) *Angew Chem Int Ed Engl* **30**: 1611.
8 (a) Isbell HS, Frush HL (1958) *J Org Chem* **23**: 1309. (b) Paulsen H, Pflughaupt KW (1980) in *The Carbohydrates*, Vol. 1B (Pigman W, Horton D, Eds) p. 881. New York, Academic Press.
9 Cipolla L, Lay L, Nicotra F, Pangrazio C, Panza L (1995) *Tetrahedron* **51**: 4679.
10 (a) Likhosherstov LM, Novikova OS, Derevitskaja VA, Kotchetkov NK (1986) *Carbohydr Res* **146**: c1. (b) Kallin E, Lonn H, Norberg T, Elofsson MJ (1989) *Carbohydr Chem* **597**: 8. (c) Urge L, Kollat E, Hollosi M, Laczko I, Worblewski K, Thurin J, Otvos Jr L (1991) *Tetrahedron Lett* **32**: 3445.

11 (a) Kovacs J, Pinter I, Lendering, U, Koll P (1991) *Carbohydr Res* **210**: 155.
(b) Kovacs J, Pinter I, Abeln D, Kopf J, Koll P (1994) *Carbohydr Res* **257**: 97.
12 Urge L, Otvos Jr L, Land E, Wroblewski K, Laczko I, Hollosi M (1992) *Carbohydr Res* **235**: 83.
13 For recent synthesis of glycosylazides see: (a) Giuliano RM, Davis RS, Boyko WJ (1994) *J Carbohydr Chem* **13**: 1135.
(b) Hamerschmidt F, Polsterer J-M, Zbiral E (1995) *Synthesis* 415.
(c) Praly J-P, Senni D, Faure R, Descotes G (1995) *Tetrahedron* **51**: 1697.
(d) Gyorgydeak Z, Thiem J (1995) *Carbohydr Res* **268**: 85.
14 Avalos M, Babiano R, Cintas P, Duran CJ, Jimenez JL, Palacios JC (1995) *Tetrahedron* **51**: 8043 and references cited therein.
15 Pfaltz A, Jaun B, Fassler A, Eschenmoser A, Jaenchen R, Gilles HH, Diekert G, Thauer RK (1982) *Helv Chim Acta* **65**: 828.
16 Huber R, Knierzinger A, Obrecht J-P, Vasella A (1985) *Helv Chim Acta* **68**: 1730.
17 Dondoni A, Franco S, Junquera F, Merchan F, Merino P, Tejero T (1995) *Synth Commun* **24**: 2537.
18 Franco S, Merchan F, Merino P, Tejero T (1995) *Synth Commun* **25**: 2275.