



Intramolecular 1,3-dipolar cycloaddition of *N*-alkenyl nitrones *en route* to glycosyl piperidines

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ARTICLE INFO

Article history:

Received 11 September 2009

Revised 30 September 2009

Accepted 2 October 2009

Available online 8 October 2009

Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Keywords:

Nitrones

Intramolecular dipolar cycloaddition

Piperidines

Iminodisaccharides

ABSTRACT

Stereoselective intramolecular 1,3-dipolar cycloaddition of homochiral *N*-(alkenylglycosyl)nitrones, prepared by allylation of *C*-(glycosyl)nitrones and subsequent oxidation, is described. The previously described 2-aza-Cope rearrangement was not observed for these substrates, but evidences of *E/Z* isomerism during the cycloaddition were obtained. The obtained cycloadducts can serve as key precursors of imino disaccharide analogues. This is exemplified by a short route to a protected 2-furanosyl-4-hydroxy-6-phenyl piperidine.

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Carbohydrate mimics can play critical roles in many biological events such as cell–cell recognition and adhesion, cell growth and differentiation.¹ In particular, during the last years there has been a considerable interest in the synthesis of iminosugar di- and oligosaccharides² and their *C*-linked analogues,³ which can be regarded as imino-*C*-disaccharides of general type **1**. This interest has been propelled by the desire for synthetic imino-*C*-disaccharides **1** with increased hydrolytic stability, enzyme inhibition properties and/or unique conformational preferences in comparison to the natural counterparts.⁴ Other variations of the pseudoglycosidic linkage may consist of different sequences of atoms including nitrogen,⁵ sulfur⁶ and extended carbon-containing chains⁷ as in the case of the antidiabetic⁸ MDL25,637 **2** and compound **3**.⁹

On the other hand, compounds having a direct bond between subunits (Fig. 1, *n* = 0 in **1**) have also become the compounds of interest.¹⁰ In the *de novo* design of imino disaccharide analogues, the introduction of a direct link between the units can be very useful as it may contribute to fix a biologically active conformation. As a consequence, new synthetic methodologies leading to these classes of substrates are highly desirable. In this context, Goti and co-workers¹¹ have developed the synthesis of **4** in which a pyranose is directly linked to a hydroxylated pyrrolidine and, more recently, Sharma et al. reported¹² the synthesis of **5** from β -amino acids. We

initiated several years ago a research programme aiming at the synthesis of saturated nitrogen heterocycles bearing a glycosyl unit using nitrones as appropriate starting materials. In 2003, we reported¹³ the preparation of glycosyl pyrrolidines such as the galactosyl derivative **6** through an intermolecular 1,3-dipolar cycloaddition between *C*-glycosyl nitrones and methyl acrylate as the key step.

More recently, we have demonstrated that the intramolecular cycloaddition of *N*-alkenyl nitrones, prepared by stereoselective

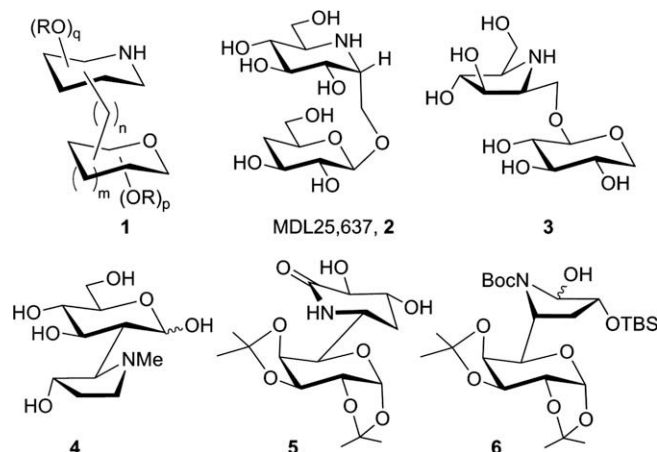


Figure 1. Imino-*C*-disaccharides.

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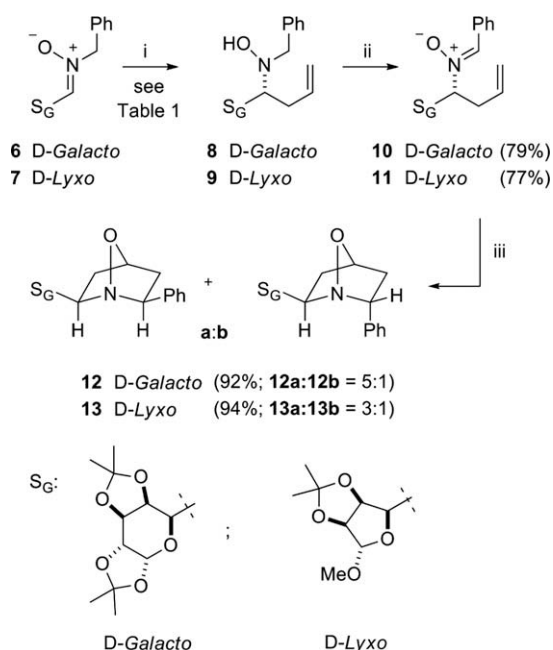
allylation of *N*-benzyl nitrones¹⁴ and subsequent oxidation of the resulting homoallyl hydroxylamines, is an excellent route for the synthesis of substituted 4-hydroxy-piperidines and, in particular, pipercolic acids.¹⁵ Such a type of intramolecular 1,3-dipolar cycloaddition presented some controversy regarding the actual course of the reaction, which has been proposed to take place in part via either a 2-aza-Cope rearrangement¹⁶ or an *E/Z* isomerization¹⁷ of the nitrones.

In this Letter we present a successful implementation of our intramolecular cycloaddition-based strategy represented by the synthesis of a protected glycosyl piperidine from the corresponding *C*-(glycosyl) nitrone. In addition, we present the structural proofs for *E/Z* isomerization¹⁸ during the course of the intramolecular cycloaddition, in a marked contrast with those findings previously reported by us for a *D*-glyceraldehyde nitrone, for which the existence of a 2-aza-Cope rearrangement was demonstrated.¹⁹

Starting *C*-(glycosyl) nitrones **6**, **7** and **14** were prepared from the corresponding aldehydes as described.²⁰ The diastereoselective allylation of nitrones²¹ **6** and **7**, to give hydroxylamines **8** and **9**, respectively, proceeded in excellent yields and moderate to good diastereomeric ratios depending on the substrate and the Lewis acid used as an additive (Scheme 1, Table 1).

In contrast to previously reported allylation of homochiral *C*-(α -alkoxy) nitrones,²¹ low stereocontrol was observed for nitrones **6** and **7**. In both cases the same major adduct was obtained whatever the conditions were employed. The absolute configuration of the obtained homoallylic hydroxylamine **8** was unambiguously determined by single-crystal X-ray analysis.²² In the case of **9** suitable crystals could not be obtained and the configuration was deduced by X-ray analysis of a further derivative as discussed below. Oxidation of hydroxylamines **8** and **9** with manganese(IV) oxide as reported by Goti and co-workers²³ afforded *N*-alkenyl nitrones **10** and **11**, respectively, in good yields.

Heating compounds **10** and **11** in toluene at 100 °C in a sealed tube afforded a mixture of cycloadducts from which the major adduct was identified (2D NMR) as the *exo-exo* isomer in both cases. The absolute configuration of the major adduct **12** was deduced from the precursor hydroxylamine **8**. The absolute configuration of



Scheme 1. Reagents and conditions: (i) allylMgBr, Et₂O, 0 °C, additive (see Table 1), 4 h; (ii) MnO₂, CH₂Cl₂, 0 °C, 8 h; (iii) toluene, sealed tube, 100 °C, 72 h.

Table 1
Stereoselective allylation of nitrones **6**, **7** and **14**^a

Entry	Nitrone	Additive ^b	Hydroxylamine	Yield ^c (%)	dr ^d
1	6	None ^e	8	96	1:4.4
2	6	ZnBr ₂	8	98	1:4.0
3	6	Et ₂ AlCl	8	98	1:1.0
4	7	None ^e	9	97	1:1.2
5	7	ZnBr ₂	9	97	1:1.5
6	7	Et ₂ AlCl	9	85	1:3.0
7	14	None ^e	15	98	3.3:1
8	14	ZnBr ₂	15	98	5.5:1
9	14	Et ₂ AlCl	15	97	1.2:1

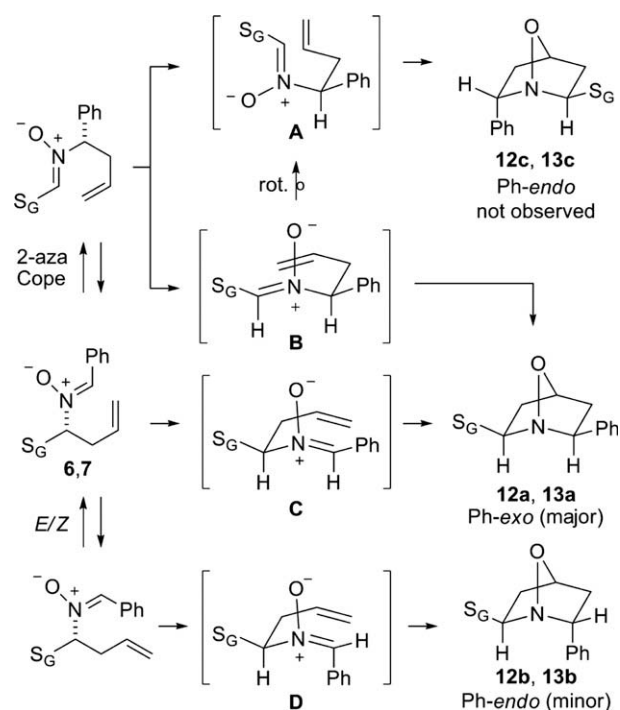
^a All the reactions were carried out using 1.2 equiv of allylmagnesium bromide in Et₂O as a solvent at 0 °C unless otherwise indicated.

^b 1.0 equiv of additive was employed.

^c Isolated yield after purification of the mixture of adducts.

^d *syn/anti* ratios determined by integration in ¹H NMR of the crude product.

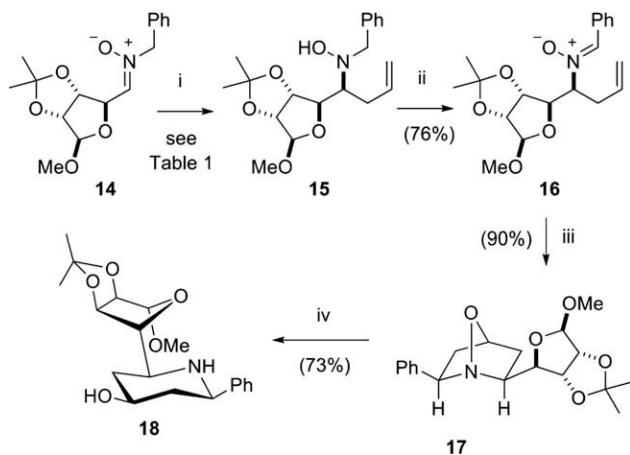
^e 2.0 equiv of Grignard reagent was used.



Scheme 2. Possible reaction paths for the intramolecular 1,3-dipolar cycloaddition of nitrones **6** and **7**. (S_G: see Scheme 1). Only transition structures leading to cycloadducts with the sugar moiety in an *exo* orientation have been considered.

cycloadduct **13a** was determined (and thus that of the precursor **9**) by single-crystal X-ray analysis.²² In addition to the *exo-exo* cycloadducts **12a** and **13a**, minor adducts in which the phenyl group adopted an *endo* orientation were obtained. Such *Ph-endo* isomers could arise, in principle, from either 2-aza-Cope rearrangement or *E/Z* isomerization of the corresponding *N*-alkenyl nitrone. In the previous reports^{16,17} it was not possible to determine the origin of the minor adduct (aza-Cope vs *E/Z* isomerism) because racemic compounds were used and in consequence the two possible *Ph-endo* isomers (Scheme 2, **b** and **c** series) were enantiomers. In our case the presence of the chiral sugar moiety (S_G) makes possible to distinguish between the two different *Ph-endo* compounds which actually are diastereomers (Scheme 2).

Fortunately, the configuration of both **12b** and **13b** was fully assessed by single-crystal X-ray crystallography.²² Such an ultimate confirmation of the absolute configuration of **12b** and **13b** demonstrates the existence of a partial *E/Z* isomerization of the



Scheme 3. Reagents and conditions: (i) allylMgBr, Et₂O, 0 °C, additive (see Table 1), 4 h; (ii) MnO₂, CH₂Cl₂, 0 °C, 8 h; (iii) toluene, sealed tube, 100 °C, 72 h; (iv) Zn, AcOH, 60 °C.

precursor *N*-alkenyl nitrones in contrast with the previous results observed in our laboratories with a *D*-glyceraldehyde-derived nitrone for which the 2-aza-Cope rearrangement was predominant.¹⁹ Whereas the major adducts (**a** series) were formed through transition structure **C**, minor compounds (**b** series) should be formed through transition structure **D**. Nevertheless, the absence in the crude product of the reaction of minor adducts **12c** and **13c** (which should be formed through **A**) does not allow to exclude the possibility of a 2-aza-Cope rearrangement since the rearranged nitrone may lead to major adduct (**a** series) through transition state **B**.

We also applied our strategy to *D*-ribose-*D*-nitrone **14** easily available from *D*-ribose as described.²⁰ Also in this case no stereocontrol was observed in the allylation reaction (Table 1, entries 7–9) but surprisingly, the *syn* adduct **15** was obtained in all cases as the major stereoisomer (Scheme 3).

In spite of the above-mentioned lack of stereocontrol, the observed trend of the additives is in agreement with the preferential formation of the *syn* adduct.²⁴ The absolute configuration of the hydroxylamine **15** was confirmed by a single-crystal X-ray analysis.²²

The opposite stereochemical outcome of the allylation reaction for **7** and **14** could be rationalized by the relative configuration of the dioxolane moiety at β -position of the reactive nitrone carbon atom; such a dioxolane establishes the preferred Houk model²⁵ in each case leading to the attack of the nucleophile by opposite faces in both nitrones (Fig. 2). Whereas for **14** it is possible to apply a typical Houk model, leading to the *syn* adduct, in the case of nitrone **7** there are important unfavourable steric interactions between the dioxolane and the incoming nucleophile thus the preferred (more reactive) conformation is that shown in Figure 2. A similar model is applicable for nitrone **6** which exhibits the same stereofacial selectivity as nitrone **7**, indicating that the observed

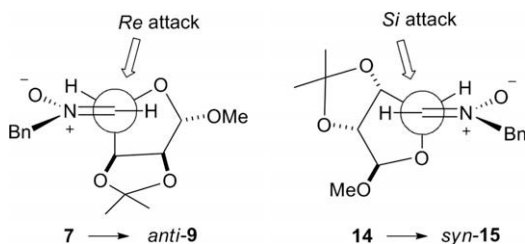


Figure 2. Proposed models of addition for allylation of nitrones **7** and **14**.

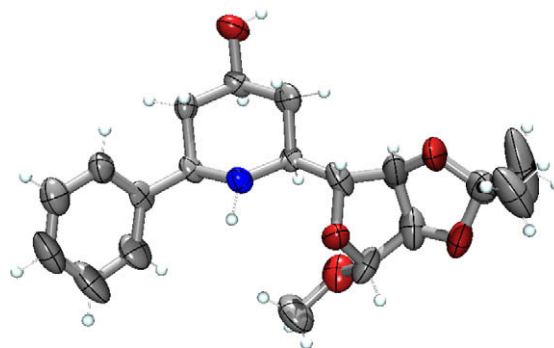


Figure 3. Perspective view (ORTEP) of **18**. Non-hydrogen atoms are drawn as 50% thermal ellipsoids while hydrogens are drawn at an arbitrary size.

stereochemical preferences are independent of the Lewis acid used.

Oxidation of **15** (MnO₂, 76%) and further intramolecular cycloaddition (toluene, sealed tube, 100 °C, 72 h, 90%) of the resulting *N*-alkenyl nitrone **16** exclusively furnished the *exo-exo* cycloadduct **17** in 90% isolated chemical yield. The absolute configuration of cycloadduct **17** could also be confirmed by an X-ray analysis.²² Finally, cleavage of the N–O bond with zinc in acetic acid provided the protected imino-C-disaccharide **18**. The all-*cis* configuration of the piperidine ring was revealed from the complete structural analysis (2D NMR) of **18**, which also comprised a single-crystal X-ray determination as illustrated in Figure 3.

In conclusion, a synthetic sequence starting from *C*-(glycosyl) nitrones and leading to imino-*C*-disaccharide analogues has been shown. The intramolecular dipolar cycloaddition of intermediate *N*-(alkenylglycosyl) nitrones took place with partial *E/Z* isomerization of the nitrones as demonstrated by the absolute configuration (determined by X-ray crystallography) of the obtained cycloadducts. Further studies on this sort of intramolecular cycloadditions as well as elaboration of different cycloadducts to other iminodisaccharide analogues will be described in the near future.

Acknowledgements

We thank the Ministerio de Educación y Ciencia (Spain, Grants CTQ2007-67532-C02-01/BQU and CTQ2007-67532-C02-02/BQU) and Gobierno de Aragón (Grupo Consolidado E-10) for financial support. E.M. thanks MEC (FPU Programme) for a pre-doctoral grant.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.023.

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22. The authors have deposited the atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. For general details of the X-ray structures of compounds **8**(CCDC 749562), **12b**(CCDC 749563), **13a**(CCDC 749564), **13b**(CCDC 749565), **15**(CCDC 749566), **17**(CCDC 749567) and (CCDC 749568) see [Supplementary data](#). The graphic view shown in [Figure 3](#) was made with ORTEP3 software (Copyright by Farrugia, L. J. University of Glasgow, 1997–2000) and rendered with POV-Ray software (Copyright by POV-Team, 1991–1999).
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25. Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7166. Models shown in [Figure 2](#) have been optimized after conformational minimization using semiempirical (PM3) methods.