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# Practical synthesis of *N*-alkyl-*N*-glycosylhydroxylamines, multitalented precursors of enantiomerically pure nitrones

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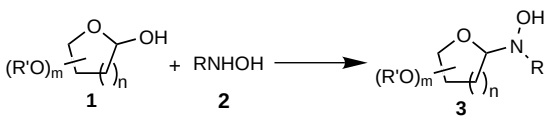
**Abstract**—A practical synthesis of *N*-benzyl-*N*-glycosylhydroxylamines **3** (R = $CH_2Ph$) is reported. The ability of these compounds to act as versatile synthetic intermediates is demonstrated by their oxidation followed by cycloaddition to *N*-glycosyl isoxazolidines and by the novel direct cycloaddition as masked acyclic, highly functionalized chiral nitrones. 

*N*-Glycosylhydroxylamines **3** (R = H) have received considerable attention as chiral equivalents of the simple hydroxylamine, the glycosyl moiety acting as an auxiliary which can be easily removed by acid treatment at an advanced stage of a synthetic sequence after reacting the hydroxylamine function. This concept has been extensively applied, demonstrating the synthetic utility of intermediates **3** (R = H), particularly by Vasella and co-workers.[1]

Conversely, *N*-substituted *N*-glycosylhydroxylamines **3** (R ≠ H) have been the object of only two reports, to the best of our knowledge, specifically dealing with *N*-benzyl derivatives. The first, by Merino and co-workers, details the synthesis of several compounds of structure **3** (R = $CH_2Ph$) by reaction of the corresponding monosaccharides **1** with 1.5 equiv. of *N*-benzylhydroxylamine in the presence of $MgSO_4$ (3 equiv.) and $ZnCl_2$ (1.5 equiv.) (Scheme 1).[2] In the second, published while this work was in progress, Dondoni and co-workers have synthesized an *N*-benzyl-*N*-arabinosylhydroxylamine by a modification of the above procedure and have used the compound as a hidden nitrone in an alkylation reaction.[3]




**Scheme 1.**

In this communication we report an alternative, practical synthesis of *N*-benzyl-*N*-glycosylhydroxylamines **3** (R = $CH_2Ph$) which can be extended to other *N*-alkyl congeners. Also, their usefulness as versatile intermediates in organic synthesis is addressed, since we demonstrate that they are either precursors of chiral nitrones with the glycosyl moiety working as a chiral auxiliary or highly functionalized hidden chiral nitrones by themselves, which are able to undergo highly stereoselective 1,3-dipolar cycloadditions.

The *N*-benzyl-*N*-glycosylhydroxylamines **3a–g** were obtained by reacting the corresponding sugar derivative **1a–g** with *N*-benzylhydroxylamine (**2a**) (1.2 equiv.) in dry pyridine at room temperature.[4] The hydroxylamines were purified and isolated in good yield after column chromatography (see Table 1).[5] The same method can be extended to the synthesis of other *N*-alkyl-*N*-glycosylhydroxylamines, as demonstrated by the synthesis of **3h** (entry 8). The products are obtained at the end of the reaction simply by a filtration and removal of the solvent and purified by a flash column chromatography over silica. The yields compare with those obtained with the previous method.[2] The final *N*-glycosylhydroxylamines are obtained as an anomeric mixture, where the thermodynamically most stable isomer prevails. In several cases the major isomer is the only detectable one by $^1H$ NMR spectroscopy. This observation suggests the occurrence of a rapid equi-

*Keywords*: monosaccharides; nitrones; isoxazolidines; chiral auxiliary; enantiospecific synthesis.

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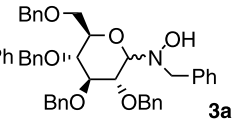
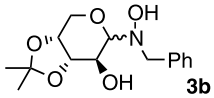
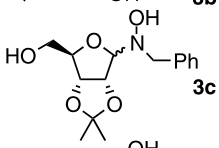
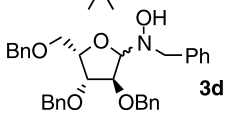
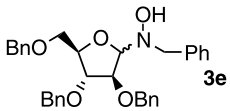
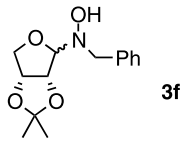
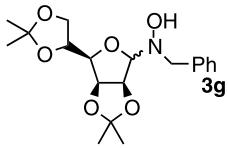
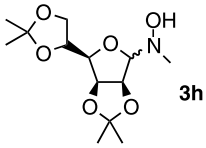
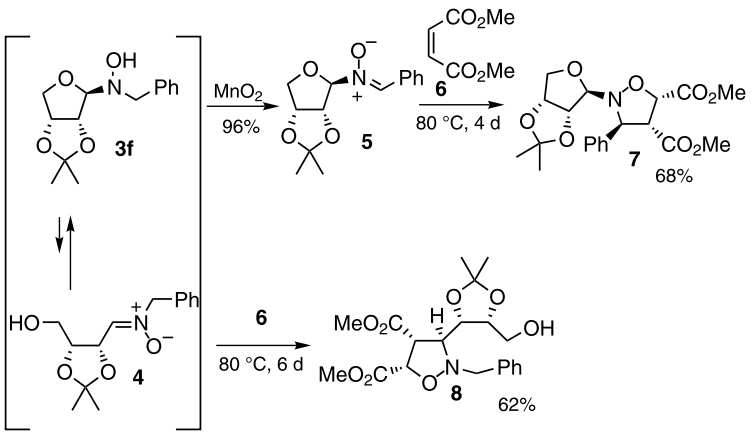
**Table 1.** Synthesis of *N*-alkyl-*N*-glycosylhydroxylamines from the corresponding lactols

| Entry | Lactol | RNHOH | Product | Yield | α/β |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** R = $CH_2Ph$ |  **3a** | 79% | 0/100 |
| 2 | **1b** | **2a** |  **3b** | 61% | 75/25 |
| 3 | **1c** | **2a** |  **3c** | 66% | 0/100 |
| 4 | **1d** | **2a** |  **3d** | 60% | 50/50 |
| 5 | **1e** | **2a** |  **3e** | 66% | 85/15 |
| 6 | **1f** | **2a** |  **3f** | 88% | 0/100 |
| 7 | **1g** | **2a** |  **3g** | 73% | 100/0 |
| 8 | **1g** | **2b** R = Me |  **3h** | 70% | 100/0 |

librium between the two isomers through an open-chain nitrone functionality, i.e. via an uncommon 1,4 H-shift. This same explanation has been advanced by Dondoni and indirectly proved by alkylation of the acyclic nitrone in equilibrium with the stable *N*-benzyl-*N*-arabinosylhydroxylamine.[3] In the single case of compound **3f** confirmation of this hypothesis was collected by a careful $^1H$ NMR analysis (500 MHz), which showed the signals of the open-chain nitrone tautomer **4** (Scheme 2), present in 6% amount at the equilibrium in $CDCl_3$.[6]




**Scheme 2.**

Compound **3f** was then chosen to demonstrate the versatility of this class of compounds in 1,3-dipolar cycloaddition chemistry (Scheme 2). We tested the reactivity of this compound with dimethyl maleate by itself, through the tautomeric nitrone form, and after oxidation to the *N*-glycosyl nitrone. The latter is a useful class of nitrones, affordable as well by condensation of hydroxylamines **3** (R = H) with aldehydes,[1] albeit *C*-phenyl nitrones have never been synthesized by this way. The nitrone **5**, obtained in high yield by oxidation of **3f** with $MnO_2$[7] (or HgO)[8] reacted with dimethylmaleate (**6**) affording the adduct **7** in good yield with a high diastereoselectivity. Since the *N*-glycosyl bond can be cleaved by acid treatment,[1] this class of nitrones is a tool for the enantioselective synthesis of simple isoxazolidines, the glycosyl moiety acting as a chiral auxiliary.

On the other hand, compounds **3** are also able to undergo cycloaddition reactions through species such as **4**, when heated in the presence of dipolarophiles. With dimethyl maleate (**6**), **3f** afforded, also with a high degree of stereoselectivity, the highly functionalized isoxazolidine **8** possessing the appendage deriving from the sugar skeleton in the 3-position.

This novel reactivity opens the way to a variety of isoxazolidines which can be envisaged as useful precursors of natural products, such as pyrrolizidine alkaloids, and biologically active compounds, and expands the range of useful chiral nitrones available for synthetic purposes.[9,10]

Further studies are currently underway in our laboratories to fully explore the synthetic potential of this new class of chiral nitrones.

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3. Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1999**, *40*, 9375.
4. *General procedure*: A solution (0.3 M) of lactol **1** (1–6 mmol) in dry pyridine was added with 3 Å molecular sieves (1–5 g) and *N*-benzyl- (or methyl-) hydroxylamine hydrochloride (1.2 equiv.). The resulting suspension was stirred overnight at room temperature, then filtered, concentrated and purified by flash column chromatography.
5. All new compounds gave satisfactory spectroscopic and analytical data.
6. Detectable signals of **4**: $^1$H NMR: $\delta = 6.89$ (d, $J = 6.0$ Hz, 1H), 5.32 (t, $J = 5.5$ Hz, 1H), 5.06 (s, 1H), 1.43 (s, 3H), 1.39 (s, 3H) ppm.
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9. For leading references on acyclic chiral nitrones, see: (a) Merino, P.; Franco, S.; Merchan, F. L., Tejero, T. *Synlett* **2000**, 442; (b) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
10. For recent works on cyclic chiral nitrones, see: Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367 and references cited therein.