

Synthesis of Carbohydrate-Isoxazole Conjugates

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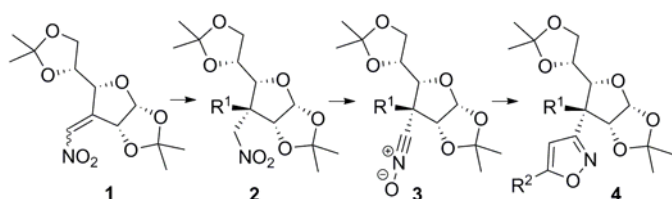
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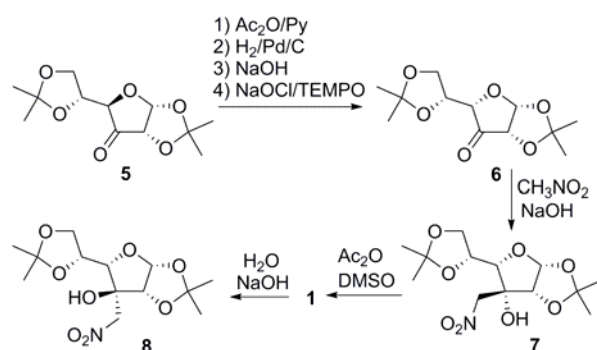
On many occasions, isoxazole cycle can serve as a linker between different structural motifs. This approach has been demonstrated in carbohydrate chemistry by preparation of isoxazole-linked steroidal glycoconjugates [1], C-glycosyl α -amino acids containing isoxazole linker [2], various nucleoside derivatives [3], and others [4]. In most cases, modifications have been performed at glycosidic or terminal positions (C(5) or C(6)) of carbohydrate core.

Herein, we report the synthesis of galactose and glucose derivatives that contain isoxazole moiety at C(3) position. Nitromethylene derivative **1** was chosen as a key intermediate, which could accept various nucleophiles and thus liberated nitromethyl moiety in compound **2** served as a precursor of nitrile oxide **3**, which formed isoxazoles **4** upon treatment with various alkynes.



Scheme 1. General approach to carbohydrate-isoxazole conjugate **4**

The required starting material, diacetone- α -D-glucose derived ketone **6**, was obtained in four synthetic steps from ketone **5** with *gluco* configuration (Scheme 2).



Scheme 2. Synthesis of Michael acceptor **1** and its reaction water

Highly diastereoselective Henry reaction on ketone **6** produced adduct **7**. Its dehydration provided product **1** [5]. Water was chosen as a nucleophile in preliminary studies on diastereoselective Michael additions into nitromethylene

system. This gave nitro alcohol **8** with *galacto* configuration. Molecular structures of both nitro alcohols were unambiguously proved by X-ray analysis (Figure 1).

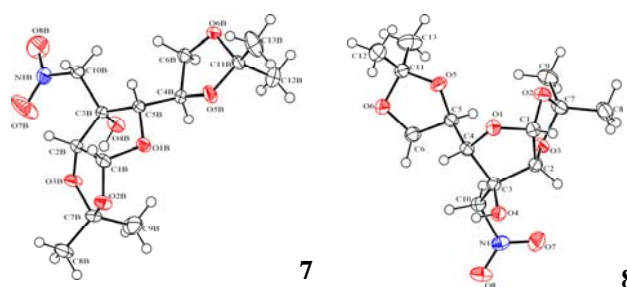


Figure 1. ORTEP representations of nitro alcohols **7** and **8**

With Michael acceptor **1** in hand, we proceeded to nucleophile additions. Various *N*-, *O*- and *S*-nucleophiles ($R^1H = NuH$) gave adducts of type **2** in good isolated yields and excellent diastereoselectivity. Further, isoxazole formation from **2** and different terminal alkynes ($R^2-C\equiv C-H$) was achieved under conditions that use ethyl chloroformate and triethylamine as a dehydrating system [6]. Under given conditions, carbohydrate-isoxazole conjugates **4** were obtained in good isolated yields. The detailed experimental conditions of the above-mentioned synthetic transformations and the efforts towards small combinatorial library of galactose- and glucose-derived isoxazoles will be discussed.

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