P5

Synthesis of Isoxazole-Linked Sugar Clusters

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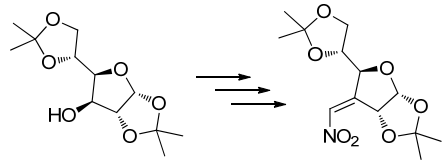
Isoxazoles are recognized as versatile structural elements in biologically active substances [1]. They are often used as linkers between different pharmacophores. Isoxazoles have found their way in carbohydrate chemistry together with triazoles that are other prominent azole congeners of the former [2].

Herein, a novel approach is reported to be used for the synthesis of sugar clusters that is based on sequential Michael addition – 1,3-dipolar cycloaddition reactions.

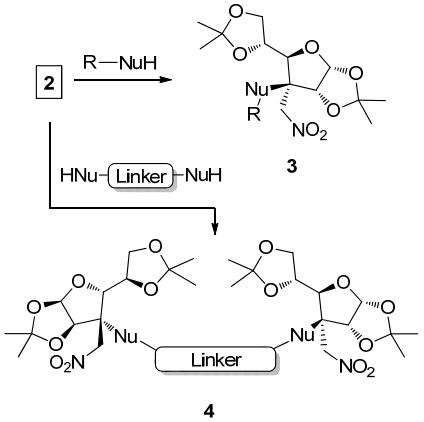
The starting material to prepare the different products of nuclephilic addition is nitromethylene derivative **2** that is prepared from diacetone-α-D-glucose (DAG) **1** in 3 steps: oxidation followed by Henry reaction with nitromethane provided diastereomeric mixture of nitroalcohols that were dehydrated into **2** by Moffatt procedure [3] (Scheme 1).



1 **2**

Scheme 1. General route for the preparation of Michael acceptor **2**

Michael addition of nucleophiles to corresponding acceptor **2** leads to the formation of novel sugar derivatives of type **3** and **4** (Scheme 2). Various *O-, S-* and *N*-adducts are possible, including addition of natural amino acid esters, thiol moiety containing sugars, monoamino or diaminosugars. Connection of symmetric dinucleophile as dithiole or diamine to nitromethylene **2** provides disaccharides **4**.



Scheme 2. Stereospecific Michael addition to nitromethylene derivative

Similarly to diacetone-α-D-glucose derived ketone, key-product **2** accepts nucleophiles selectively from its *si*-face [4] and all reactions proceed with excellent diastereoselectivity.

The resulting nitromethyl group can be transformed into nitrile oxides and then coupled with suitable terminal alkynes. In this way, artificial oligosaccharides are obtained in good isolated yields.

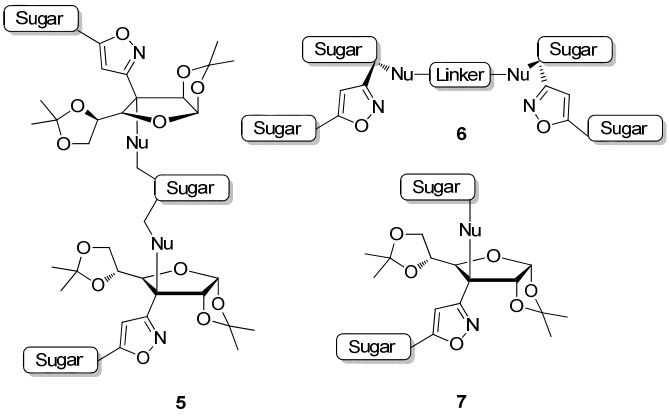


Figure 1. Examples of obtained tri-, tetra- and pentasaccharides **5**–**7**

Variation of nucleophiles and alkynes in Michael addition/1,3-dipolar reaction sequence leads to novel carbohydrates of type **5**, **6** and **7** (Figure 1).

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