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Sequential Michael Addition and 1,3-Dipolar Cycloaddition Reactions as a Simple Method for Combining of Carbohydrates

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I. Introduction

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 which are other prominent azole congeners of the former [2].

II. Discussions

Herein we report a novel approach for isoxazole- or/and thioether-amine-linked glycoconjugates which is based on sequential Michael addition – 1,3-dipolar cycloaddition reactions.

As a starting material to prepare the different products of nuclephilic addition we used inexpensive and commercialy available diacetone-α-D-glucose **1**. Its oxydation followed by Henry reaction with nitromethane provided diastereomeric mixture of nitroalcohols that were dehydrated into **2** by Moffatt procedure.

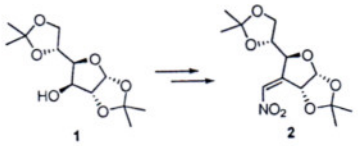

Fig.1. General route for the preparation of Michael acceptors.

We have identified glucose-derived nitroalkene **2** as a suitable structural motif which is capable to link a molecule possessing nucleophilic center and a molecule possessing terminal alkyne.

Michael addition of nucleophiles to corresponding acceptor **2** allows the formation of novel sugar derivatives. Various *O*-, *S*-, *N*-adducts are possible, including addition of natural amino acid esters. Futher, the Michael adducts can be converted either to spirocyclic sugar-piperazinones or they can serve as precursors for isoxazole synthesis.

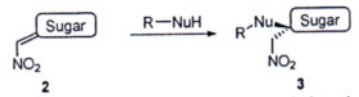

Fig.2. Stereospecific Michael addition to nitromethylene derivative.

Similarly to diacetone-α-*D*-glucose derived ketone **4**, key-product **2** accepts nucleophiles selectively from its *si*-face[3].

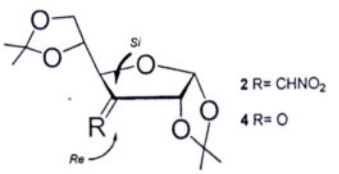

Fig.3. Diastereospecific addition of nucleophiles carbohydrates **2** and **4**.

The resulting nitromethylgroup can be transformed into nitrile oxides and then coupled with suitable terminal alkynes. Both the Michael addition and the cycloaddition occur with excellent isolated yields.

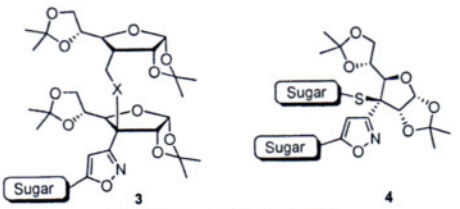

Fig.4. Trisaccharides illustration.

The overall process yields either disaccharides (only nucleophilic component is a carbohydrate) or trisacharides of type **3** and **4**.

III. References

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