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Note

Studies toward the synthesis of linear triazole linked pseudo oligosaccharides and the use of ferrocene as analytical probe

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ABSTRACT

Three different building blocks have been synthesised and used for the synthesis of linear triazole linked pseudo oligosaccharides with copper(I)-catalysed cycloaddition (CuAAC). Ethynylferrocene has been used as analytical probe to improve the UV/Vis properties and HPLC methods have been used and optimised for the analysis of the pseudo oligosaccharides. The smallest ones have been isolated and characterised by analytical HPLC, NMR, ESI-MS and elemental analysis.

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1. Introduction

The regiospecific biorthogonal copper(I) catalysed alkyne azide cycloaddition (CuAAC)[1,2] has been widely used as a tool for the synthesis of complex carbohydrate structures such as glycodendrimers,[3,4] glycoclusters,[5–7] polymer based glycoconjugates[8,9] or carbohydrate functionalised surfaces.[10–12] Most applications aim to study multivalent protein–carbohydrate interactions which are involved in multiple biological mechanisms like cellular recognition, cell–cell communication or molecular targeting.[13–15] However, carbohydrate structures have also been found to be promising compounds, in material sciences especially with biotechnical and biomedical applications in mind. Different CuAAC based approaches have been investigated in the past years such as the modification of existing biopolymers like cellulose,[16] where azides were introduced in the C-6 position of the glucose moieties and were afterwards modified with small organic alkines via CuAAC. Others are connecting alkine modified polymeric structures to azido-cyclodextrins, resulting in bigger, star-shaped polymeric structures.[17] Another approach is to build up alkine-functionalised synthetic polymers, *e.g.* based on alkine-modified methacrylates,[18,19] which can be modified with azido sugars after the polymerisation step. There are also reports on the synthesis of linear oligomeric structures built in a step by step approach.[20,21] To our knowledge, there are only a few reports up to now, on carbohydrate based pseudo poly- or oligomeric structures built from bifunctional carbohydrate monomers containing both azide and alkine moieties. For example there are reports on crystal lattice supported oligomerisation of such bifunctional monomers resulting in linear oligomeric structures.[22,23] There have also been reports on the synthesis of cyclic and linear pseudo oligomeric structures as potential therapeutic agents against the parasite Trypanosoma cruzi, which causes Chaga's disease.[24,25] Herein we want to present approaches toward the synthesis of linear triazole linked pseudo oligomeric carbohydrate structures by a one pot approach (Scheme 1).

To investigate the synthesis of linear oligomeric structures three different building blocks (**4, 5** and **7**) based on N-acetylglucosamin (GlcNAc, **1**) have been synthesised. We decided to use GlcNAc (**1**) because of its polymeric form chitin, which can be found in nature quite frequently *e.g.* in cell wall of fungi or exoskeleton of insects. Chitin exhibits interesting traits like high stability and low solubility. These properties make chitin an attractive polymer structure as new biomaterial in medicinal applications.[26] In analogy to the natural biopolymer a possible GlcNAc based oligomeric structure could also bear interesting properties. The synthetic approach allows additional modifications *e.g.* bearing a prodrug bound to a cleavable linker, which can be cleaved yielding a bioactive compound. This would be interesting for localised disease treatments. The building blocks used should either be commercially available or easily accessible (Scheme 2).

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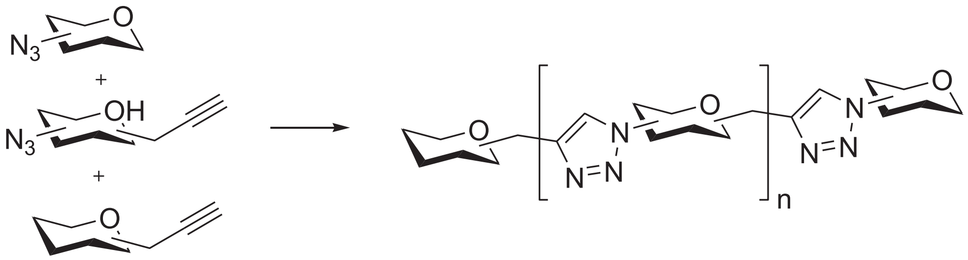


Scheme 1. General concept of the synthesis of linear triazole based oligosaccharides.

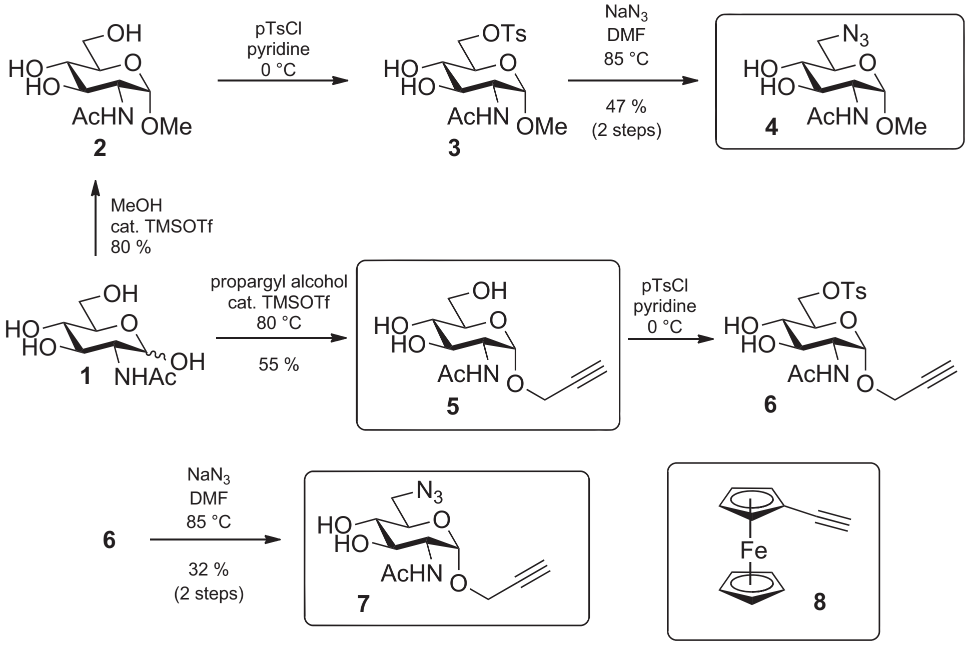
Compound **4** was synthesised according to literature procedures[27] starting from the Fischer glycoside **2** in two steps by tosylation followed by substitution reaction with NaN_3. Fischer glycosylation of GlcNAc **1** with propargylalcohol leads to compound **5**,[28] which again can be converted to the azide **7** by tosylation followed by substitution. Ethynylferrocene **10** has been used from the MCAT company stock. These protecting group free strategy on the one hand gave fast access to useable building blocks, and on the other hand resulted in anomeric alpha compounds (propargyl or methyl glycosides) and azides in 6-Position what limits the comparability to the natural biopolymers like chitin which shows a β–1,4 connection. Nonetheless we based our approach on these easy accessible compounds.

In a first approach we investigated the CuAAC reaction between **4** and **5** (Scheme 3). Both building blocks were used in equimolar amounts; the first reactions were performed once in a solvent mixture containing DCM/MeOH/H_2O in a 3:10:3 ratio and once in pure water, in both cases with 0.05 equiv. $CuSO_4$, 0.25 equiv. sodium ascorbate and 0.02 equiv. of TBTA. The reaction mixture was stirred at 60 °C for one hour and monitored by TLC, indicating complete reaction after 50 minutes. Then the solvents were evaporated and the residue was subjected to column chromatography. Although the desired compound **9** could be isolated in >90% yield (purity of the isolated compound > 90%) the work up of the very polar compound was very laborious and material consuming; thus we decided to perform an additional acetylation step after removal of the solvent in pyridine. As expected the peracetylated product **10** was much easier to purify and therefore we decided to go on with the additional acetylation step in further experiments.

Next we tried the reaction of azide **4** with ferrocene **8** in order to investigate **8** as an analytical probe, which should simplify the work up without an additional acetylation step and increase the UV/Vis activity to extend the analytical options. Once more, the building blocks **4** and **8** were used in equimolar amounts with DCM/MeOH/H_2O in a 10:10:3 ratio as solvent system and the same $CuSO_4$, sodium ascorbate and TBTA amounts as before. The reaction mixture was stirred at 60 °C for one hour and monitored by TLC indicating complete reaction after 20 minutes. The mixture was concentrated and purified by column chromatography to give **11** in 88% yield. Though both reactions have been finally worked up after one hour TLC monitoring shows a faster product formation for the reaction of **8** with **4** compared to the reaction of **5** with **4** indicating a higher reactivity for compound **8** what is an important information for the later discussion on the formation of the oligomeric structures.

Compounds **10** and **11** have both been analysed by HPLC, ESI-MS, NMR and CHN analysis. Especially HPLC analysis was very important, since for further oligomer synthesis experiments this method should be used as main analytical tool.

Moreover, interesting information for the characterisation of the longer oligomeric compounds could be obtained from NMR spectroscopy of compounds **10** and **11**. The signals have been assigned with additional apostrophes for each sugar ring starting from the methylglycosidic moiety.



Scheme 2. Synthesis of the building blocks **4**, **5** and **7**; ethynylferrocene **8.**

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