Water-promoted Synthesis of Stereoselective Oxazoline-fused Saccharides and Construction for 1, 2-cis Glycosylamines of Multi-modifications of Polyhydroxyl groups

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Abstract

The multi-modifications of polyhydroxyl groups and the stereoselective formation of 1,2-*cis* glycosidic bonds are difficult in glycochemistry. Herein we disclosed a concise synthesis of the oxazoline-fused saccharides (oxazolinoses) from acetyl saccharides and benzonitriles under acidic conditions promoted by the stoichiometric water. The oxazolinoses can be easily converted into 1,2-*cis* glycosylamines with differentiated modifications at 2,3-positions on the saccharide ring in few steps and the 1-NH₂ can further be simply transformed to the 1-OH. Oxazolinoses can also be directly used to synthesize complex chiral molecules such as schisandrins. Saccharides screening have shown that the oxazolinoses could be synthesized from various monosaccharides and oligosaccharides. Accordingly, 1- α - or 1- β -1,2-*cis* glycosylamines can be obtained from different oxazolinoses which are 1,2-*cis* stereoselectivity controlled by neighboring group participation. The density functional theory (DFT) calculations have revealed the origin of the stereoselectivity and the key role of water.

Introduction

Carbohydrates are one of the four major types of essential biological macromolecules, along with nucleic acids, proteins, and lipids. In organisms, the carbohydrates are often conjugated with amino acid residues to form glycopeptides and glycoproteins so as to perform biological functions [1]. For example, the glycopeptides are widely found in structurally diverse natural products such as the metabolites produced by bacteria (*e.g.* vancomycin) [2]. In addition, some glycoproteins that exist widely in organisms with bio-recognition function are N-glycosides which generally contain the core pentasaccharides and aspartic acid residues (*e.g.* erythropoietin, chlorovirus N-glycans) [3] (Scheme S1a, supporting information).

Due to the limited availability of natural-derived carbohydrates, chemical synthesis and modification to produce a richer variety of natural carbohydrates and non-natural analogs is not only conducive to the biological research of carbohydrates but also essential to the development of carbohydrate drugs [4]. As the saccharide molecule is a six- or five-membered ring of hemiacetal structure containing polyhydroxyl groups, the selective modification of hydroxyl groups in company with the control of the configuration of glycosylation at 1-position have long been two major research focuses in the field of glycochemistry [5]. Especially, due to the similar chemical properties of the hydroxyl groups at 2,3-positions on the saccharide ring, their differentiated modifications are especially difficult for synthesis and have not been resolved. In addition, 1,2-*trans* glycosidic bonds are relatively easy to construct, but the formation of 1,2-*cis* linkages are very difficult and have no general solution due to the influence of the neighboring group [6] (Scheme S1b, supporting information).

At present, the synthesis of glycoside and the chemical modification of the saccharide ring are mainly achieved through a complex process of hydroxyl protection, which has many steps and low efficiency. There is still a lack of simple and efficient synthetic strategies that can perform flexible multi-site modification of the saccharide ring to obtain a substrate that is easy to perform glycosylation reaction. In particular, because glycosylamines not only exist widely in organisms, but also can be used as

saccharide mimics for biofunction studies and the intermediates for synthesis of heterocyclic rings, the synthesis and multi-site modification of glycosylamines are becoming more and more important [7]. However, the existing methods are to synthesize glycosylamines through ene- or azide-saccharides *via* many synthetic steps with metal or dangerous reagents, or through protected saccharides using special reagents such as Burgess Reagent. These methods are almost impossible to simultaneously achieve selective modification of the 2 and 3 hydroxyl groups on the saccharide ring and the construction of 1,2-*cis* glycosidic bonds [8] (Scheme 1a).

Starting from the structural optimization of berberine [9], we previously developed a facile method to prepare 4-alkoxy-2-oxazoline derivatives from nitriles and β -hydroxyacetals [10]. Herein we disclosed a concise synthesis of the oxazoline-fused saccharide (oxazolinose) **3** from acetyl saccharide **1** and benzonitrile **2** under acidic condition promoted by the stoichiometric water (Scheme 1b). The oxazolinose **3** can be easily converted into 1,2-*cis* glycosylamine **12** with differentiated modifications at 2,3-positions on the saccharide ring in few steps and then the 1-amino group can further be transformed into a hydroxyl group in one step. Saccharides screening have shown that the oxazolinoses can be synthesized from various six- or five-membered monosaccharides and oligosaccharides. Therefore, the 1- α and 1- β glycosylamines can be obtained from different saccharides, respectively. Thus provides a general strategy for synthesizing multi-site modified saccharide building blocks from the new oxazolinoses. In addition, the oxazolinoses can be directly used to synthesize complex chiral molecules such as schisandrins.

Results And Discussion

In the process of screening the reaction conditions, we found that compound **3A** can be obtained with trifluoromethanesulfonic acid as a reagent and water as an additive in the solvent of dichloromethane (Table S1, Supporting Information) and then, more optimizations were carried out (Table 1). By investigating the amount of water (Entry 1–4), we found that one equivalent of water gave the highest yield of **3A** (40% yield, Entry 3). Then the amount of trifluoromethanesulfonic acid was studied (Entry 5–7) and two equivalents were found to give **3A** in the highest yield as of 74% (Entry 6). In addition, changing the temperature (Entry 8–9) and reaction time (Entry 10–11) did not obtain higher yield of **3A**. Several other solvents were also screened but no **3A** was observed (Entry 12–14).

According to the optimized reaction conditions, different benzonitrile substrates were then investigated to look for which have good stereoselectivity of products (Table 2). The yields of the compounds with substituents of electron-donating group are between 57% and 90% (**3B–3E**). However, the yields of which with electron-withdrawing substituents dropped significantly, to less than 40% (**3F–3G**). The stereoselectivity of product **3E** with the electron-donating substituent is much better than other compounds, similar to the un-substituted **3A**. The yields and stereoselectivity of compounds **3H–3I** with the halogen substituent at the *para* position of the benzene ring are obviously weaker than the compounds **3J–3L** with the halogen substituent at the *ortho* position of the benzene ring. When adding other electron-donating substituents on the benzene ring substituted by the *ortho*-halogen, there is no rule

to follow in the yields and configuration control (**3M-3T**). However, most products have good stereoselectivity, such as **3M**, **3N**, **3Q**, **3S** and **3T**. In addition, when the heterocyclic cyanide substrate is used, the high product yield would be obtained but with poor stereoselectivity (**3U-3V**). Finally, we also tried a nitrogen-containing cyanide substrate, but no product was obtained, which is probably due to the protonation of nitrogen atoms under acidic conditions (**3W-3X**). This also shows that the nucleophilicity of the cyano group is closely related to the reaction yields. In order to determine the structure of the product, we removed the acetyl protecting group of compound **3E** to obtain **3Y**, and then determined the X-ray single crystal structure of **3Y**.

Based on the above results, we have selected the benzonitrile substrates with good stereoselectivity of products and continue to screen various saccharides (Scheme 2). Different six-membered ring saccharides can successfully obtain the corresponding products (**3Ea-b**, **3Sa**). The C-N configuration at 1-position of the product is controlled by the configuration of the *ortho* group at 2-position on the saccharide ring. For example, glucose gives the *alpha* products **3E** and **3S**, while mannose gives the *beta* products **3Eb** and **3Sa**, which indicated that we can further obtain 1-*α* or 1-*β* glycosylamines originated from different saccharides. Moreover, both disaccharide and trisaccharide substrates can give the corresponding products (**3Ec-d**). In addition, five-membered ring saccharides can also generate oxazolinoses in high yields and with good stereoselectivity (**3a-g**). We have compared the ¹H-NMR spectra of several oxazolinoses and found visible differences of the hydrogen chemical shift at 1-position between 1-*α* and 1-*β* C-N configurations. The chemical shifts of hydrogen atom on C-1 for 1-*α* oxazolinoses are around at 6.10 ppm. Electron-donating or withdrawing substitutes can make the chemical shifts fluctuate slightly. Meanwhile, the chemical shifts of hydrogen atom on C-1 for 1-*β* oxazolinoses are around at 6.40 ppm. Therefore, the difference of two isomers can be recognized *via* ¹H-NMR spectra (Fig S1, Supporting Information).

The reaction mechanism is proposed in Scheme 3a. Acetyl glucose **1A** generates carbocation compound **T** under the action of trifluoromethanesulfonic acid. Then **T** is attacked by the benzonitrile **2A**, which might give 1-*S* and 1-*R* products. However, the experiment results mainly obtained 1,2-*cis* product **3A** (**C1**). In order to gain a further insight into the intramolecular cyclization mechanism and the preference of stereoselectivity for the oxazoline ring of target product **C1** (**3A**), a computational study using the density functional theory (DFT) method at M06-2X/6-311G(d) level was performed with Gaussian 16 B.01 [11, 12] for geometry optimization, frequency analysis and transition state search. The solvent effects of dichloromethane (DCM) were taken into consideration by using solvation model based on density (SMD) [13] during the calculations.

As shown in Scheme 3b, the intermediate **A1** was predicted to be more stable than **A2** by 5.0 kcal/mol, indicating that **A1** is the dominant configuration produced from the nucleophilic attack of benzonitrile. **A1** could undergo an intramolecular nucleophilic addition of its oxygen atom of the acetoxy group attacking the carbon atom of the imide bond to afford **B1**, *via* transition state **TS1** with the free energy barrier of 18.8 kcal/mol. On the other hand, **A2** might undergo a similar reaction path *via* transition state **TS2** to afford **B2** with the free energy barrier of 23.4 kcal/mol, 4.6 kcal/mol higher than **TS1**, which is consistent

with the experimental observation that **C2** almost cannot be detected at room temperature. The water existing in the environment promoted the departure of the **B1** acetyl group to generate target product **C1**, which is 14.1 kcal/mol more stable than **C2**, suggesting again that **C1** should be the main product of the reaction (Supporting Information).

We further investigated the potential application of the oxazolinoses in organic synthesis (Scheme 4A). For example, **3A** can perform ring-open reaction under acidic conditions to give the 1- α -amino compound **4A** with the benzoate group at 2-position. On the other hand, the acetyl protecting groups of **3A** can be removed to generate **5**. Then the benzyl protecting groups were introduced to give **6** which can be treated with acid to produce **4B**. After diazotization treatment, the 1- α -amino group of **4B** can be converted into a 1- β -hydroxyl group to obtain **7** with selective protecting group at 2-position. The 1- α -amino carbohydrate **4B** can smoothly undergo the synthesis of glycosylamines **10a-c**. Compound **5** can also undergo the simple conversion of the protective group on the saccharide ring through **8** and **9** to obtain glycosylamine **10d** with differentiated protecting groups at the 2,3-positions on the saccharide ring. Thus, the N-glycoside derivatives similar to **10a-c** can be further prepared *via* **10d**. In addition, **3S** can undergo Ullmann-coupling reaction under the action of copper powder to generate the axial chiral compound **11** with *P* configuration (Scheme 4B). It shows that the oxazolinoses have the potential as the chiral blocks in organic synthesis.

Conclusions

In summary, we have developed a novel method with readily available reagents for the synthesis of oxazolinoses which can be directly converted into 1,2-*cis* glycosylamines with benzoate group at the 2-position. The 1- α and 1- β glycosylamines can be obtained from different saccharides, respectively. Meanwhile, the selective modification at the 3-position of the saccharide ring can also be easily achieved from the oxazolinoses *via* three steps. Through a few simple transformations, the oxazolinoses can be used to prepare 1,2-*cis* glycosylamines with differentiated protections at the 2 and 3 positions. In addition, the 1-amino group of the saccharide ring can also be easily converted to a hydroxyl group. Thus, a library of building blocks of saccharide derivatives could be further established *via* the general strategy, which is expected to be widely used in the field of glycochemical synthesis. On the other hand, because the oxazolinose has an excellent chiral group of oxazoline, it can also be directly used for asymmetric synthesis to construct complex chiral molecules such as schisandrins.

Data Availability

All data are available in the manuscript or the supplementary materials. X-ray structure is deposited at the Cambridge Crystallographic Data Centre under reference number 2036191.

Declarations

Competing interests

Synthesis and applications of oxazolinoses have been put in a patent file (CN202011101903.0).

Author contributions

B.L., W. Z., and Q.J. conceived the work and contributed to the experimental design, manuscript revision and approval of the final version. B.L. and S.D. wrote the manuscript, with input from all other authors. B.L. contributed to the initial exploratory experiments and discovery of oxazolinoses. S.D. and Y.Z. contributed to the synthetic experiments for reaction conditions optimization, substrates screening and application of oxazolinoses. Y.S. and Z.X. contributed to the quantum chemistry calculation of the reaction mechanism. J.S., Y.L. and K.C. contributed to the frequent discussions of the experiments.

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Tables And Schemes

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