Nitrogen-Centered Radical Mediated Anomeric Specific Cascade Amidoglycosylation of Glycals

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Article

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Abstract

A nitrogen-centered radical-mediated strategy to prepare 1,2-\textit{trans} 2-amino-2-deoxyglycosides in one step was established. The cascade amidoglycosylation was initiated by a benzenesulfonimide radical generated from NFSI under the catalytic reduction of TEMPO. The benzenesulfonimide radical electrophilic added to the glycals, then the resulted glycosidic radical was converted to oxocarbenium upon oxidation by TEMPO+, and enabled the following anomeric specific glycosylation.

Introduction

2-Amino-2-deoxyglycosides, in particular, 2-\textit{N}-acetamido-2-deoxyglycosides, are widely distributed in living organisms as glycoconjugates and naturally occurring oligosaccharides with important biological roles.\textsuperscript{1-3} The 2-amino-2-deoxyglycosides are connected with other carbohydrates, lipids, or amino acids via either 1,2-\textit{cis} or, more frequently, 1,2-\textit{trans} glycosidic linkage.\textsuperscript{2,4} Therefore, the stereoselective formation either 1,2-\textit{cis} or 1,2-\textit{trans} glycosidic linkage of 2-amino-2-deoxyglycosides is of high significance due to its essentiality for oligosaccharide assembly.\textsuperscript{5-8} A variety of synthetic approaches to 2-amino-2-deoxyglycosides have been developed and considerable progresses have been made.\textsuperscript{9-12} Since some of the mono 2-amino-2-deoxy sugars are naturally available or easily prepared, they have widely employed in synthesis of 2-amino-2-deoxyglycosides.\textsuperscript{5,13} And many different types of glycosamide precursors, including thioglycoside\textsuperscript{14-17}, trichloroacetimidate,\textsuperscript{18-20} phosphate ester\textsuperscript{21,22}, and OABz\textsuperscript{23}, have been extensively explored. However, these protocols commonly start from glycosamides with masking amino groups\textsuperscript{24-26} such as Azide\textsuperscript{16,27-29}, PhthN\textsuperscript{30}, AcNH\textsuperscript{21,31,32} or TrocNH\textsuperscript{33}. Normally, these glycosamide precursors are need to be prepared in multiple steps, including the specific protecting/deprotecting procedures, thus decrease the efficiency of synthesis (Scheme 1a).

Meanwhile glycals are also considered as building blocks for construction of 2-amino-2-deoxyglycosides. In this regard, the applicability of dipolar cycloaddition with azides,\textsuperscript{34} [4+2] cycloaddition with azadicarboxylates,\textsuperscript{9,35} or aziridination with \textit{N}heterocyclic carbine (NHC)\textsuperscript{36-39} to the synthesis of 2-amino-2-deoxyglycosides from glycals have been investigated (Scheme 1b, up equation). In the meantime, the installation of an azide moiety at the C-2 position of glycal as a source of an amino group has also been widely applied in preparation of 2-amino-2-deoxyglycosides (Scheme 1b, down equation).\textsuperscript{40-46} However, the stereoselectivities at C-1 and C-2 are dependent on the structure of the glycal substrates and glycosylation often proceed nonstereoselectively. In addition, a further C-1 derivatization and construction of stereoselective glycosidic linkage were found to be a considerable challenge.

The N-F reagents, such as Selectfluor\textsuperscript{TM} and \textit{N}-fluorobenzenesulfonimide (NFSI), are mild electrophilic fluorinating reagents and well explored.\textsuperscript{47} It was reported that when glycals were treated with N-F reagents, the 2-deoxy-2-fluoro carbohydrates were obtained by fluorination of glycals at C2 position (Scheme 1c).\textsuperscript{48-50} Recently, nitrogen-centered radicals (NCRs) have aroused increasing concern in synthetic chemistry since NCRs could be used as key intermediates for effective construction of C-N
bonds. Based on considerable synthetic potential of glycals for preparation of 2-amino-2-deoxyglycosides, we proposed that it would be an ideal strategy if the N-F reagents were converted to nitrogen-centered radicals and added to glycal at C-2 position, followed by glycosylation with acceptors at C-1 position. Herein, we reported the nitrogen-centered radical cascade regioselective amination of glycal and anomeric specific glycosylation (scheme 1d).

Results

Radical addition of glycals. As shown in scheme 2, we hypothesized that the nitrogen-centered benzenesulfonimide radical A, generated from NFSI by reduction with TEMPO, might regioselectively electrophilic add the alkenyl of glycal to give radical D. The radical D would then be oxidized by the TEMPO$^+$ B to afford the oxocarbenium E and recycle the catalysis TEMPO$^{54,55}$. We considered that the steric hindrance of benzenesulfonimide and/or the neighboring effects of sulfonyl group would direct the glycosylation in 1,2-trans manner to furnish the anomerically specific product F.

Our initial investigation of the nitrogen-centered radical involved amidoglycosylation was conducted between the tri-O-benzyl-D-glucal 1 and diisopropylidene-D-glucose 2. After treatment with NFSI and catalytic amount of TEMPO in DCE at room temperature, the glycosylation product 3 was obtained in 22% yield (Table 1, entry 1). The NMR analysis showed that the acceptor 2 was β-selectively coupled with the glucal 1 as we proposed. We noticed that the glycal 1 was not completely consumed. To accelerate the reaction and increase the yield, the reaction temperature was raised to 50 °C. The glycosylation was slightly improved with 38% yield (entry 2). Screening the solvents, such as DCM, THF, MeNO$_2$, and toluene (entries 3 - 6), identified MeCN as the optimal solvent with 56% yield (entry 7). Meanwhile, a byproduct was also isolated from the reaction mixture as results of Ferrier-rearrangement. According to the mechanism of Ferrier-rearrangement, the C-3 elimination was resulted from the HF formation in the reaction. However, attempts to neutralize the HF with base (NaHCO$_3$, Na$_2$CO$_3$, Na$_3$PO$_4$ et al.) did not significantly suppress the Ferrier-rearrangement. Instead, we found that reducing the amount of NFSI considerably decreased the Ferrier-rearrangement byproduct and the glycosylation product 2 was afforded in 75% (Table 1, entry 8 and 9). The amount of catalysis TEMPO was also evaluated and 0.2 equivalent of TEMPO gave the highest yield (entries 10 and 11). To demonstrate the practicability of this method, the reaction was conducted in 2 grams scale and 64% yield was achieved.

Scope of glycals. With the optimized reaction conditions established, various glycal donors were examined to explore the scope of the NCR-mediated amidoglycosylation (Scheme 3). Besides the benzyl ether, the methyl ether, benzylidene, and diisopropylidene were also suitable protecting groups and the corresponding disaccharides 4 – 6 were afforded in good yields as well as excellent selectivities (β/α > 20:1 or β only). However, we found that the glycal with acetyl protecting group only gave the product 7 in 37% yield. The low yield was due to the lower HOMO energies of the double bond. The D-galactals and L-rhamnals were also subjected for the amidoglycosylation. The related disaccharides 8 - 11 were
harvested in good yields too. These results demonstrated that the nitrogen-centered radical was practical protocol for the preparation of β-selective 2-amino-2-deoxyglycosides using glycals as glycosylation donors.

**Scope of acceptors.** The scope of acceptors for amidoglycosylation was also evaluated (scheme 4). Different monosaccharide acceptors with primary alcohols were subjected for the radical glycosylation. The products 12 – 14 were obtained in good yields and excellent anomeric selectivities. The acceptors with secondary alcohols were then conducted for the glycosylation. But we found that the yields were obviously decreased (30% for 15 and 42% for 16). We originally considered that the low yield was due to formation Ferrier-rearrangement byproducts too. However only trace amount of the rearrangement byproduct was isolated from the reaction mixture. Instead, we found that a 1-fluorosaccharide was formed as the major byproduct. We reasoned that the formation of 1-fluorosaccharide was due to the competition of NFSI-derived fluoride anion with the bulky secondary saccharide acceptors.\(^{60,61}\) It was found that addition of Na\(_2\)HPO\(_4\) to the reaction mixture significantly avoided the formation of 1-fluorosaccharide and the yields were increased to 53% and 64%.

Besides the glycosylated serine 17, a salidroside analog 18 with protective activities against the hypoglycemia and serum limitation induced cell death in rat pheochromocytoma cells,\(^{62,63}\) was also synthesized. Finally, the epiandrosterone was subjected as acceptor and the corresponding glycan 19 was furnished in moderate yield as a single anomeric product. The disulfonyl group is a stable protecting group for subsequent reactions in polysaccharides synthesis. The benzenesulfonimide glycosides also can be easily converted to 2-N-acetamido-2-deoxyglycosides by simple treatment. As shown in scheme 5, the disulfonyl group of disaccharide 3 was efficiently removed by treatment with Sml\(_2\).\(^{64}\) Then the reaction mixture was treated with acetyl anhydride to introduce the acetyl group and gave the NAc-disaccharide 20 in 77% yield in one-pot manner.

In summary, we have established an efficient protocol for cascade synthesis of 1,2-trans 2-amino-2-deoxyglycoside, which gives a novel and useful example for radical-mediated glycosylation. The reaction involves a nitrogen-centered radical-mediated amination of glycals and followed by glycosylation. The utilities of this method was illustrated with different glycals and acceptors with highly anomeric selectivities. Moreover, the disulfonyl group was easily converted to acetyl group by one-pot treatment.

**Methods**

**Methods for amidoglycosylation of glycals.** To an oven-dried 15 mL reaction tube equipped with a stir bar in the glove box, 0.3 mmol NFSI, 0.3 mmol glycosyl acceptor and 0.05 mmol TEMPO were added. Then dry MeCN (500 µL) was added to dissolve the reactants and reagents. The reaction tube was sealed and moved out of the glove box. Glycal donor (0.25 mmol) was dissolved in dry MeCN (500 µL) and added to the above reaction mixture at a constant speed by a syringe over 2 h at 50°C. Then the reaction was stirred for additional 1 hour at 50°C until glycal donor was completely consumed (monitored by TLC).
The reaction solution was concentrated *in vacuum* to give the residue, which was subjected to flash chromatographic column to afford the corresponding amidoglycosylation products.

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Declarations

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Author contributions

W.S. and C.X. conceived this project. W.S., C.Z., F.P., Z.P. and Y.D. carried out the experiments. W.S. and C.X. wrote the paper. All authors discussed the results.

Competing interests

The authors declare no competing interests.

Table And Schemes

The table and schemes are available in the Supplementary Files.

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