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Carbohydrates

Direct Glycosidation of 2-Azido-2-deoxyglycosyl Nitrates

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Abstract: Glycosyl nitrates are important synthetic intermediates which had never been glycosidated before our recent discovery that glycosyl nitrates can be glycosidated in the presence of lanthanides. Presented herein is our preliminary attempt to enhance the utility of glycosyl nitrates as donors for *O*-glycosidation of 2-amino-2-deoxysugars.

Introduction

Amino sugars are commonly found as the components of more complex molecules, mainly antibiotics, glycoproteins, lipopolysaccharides, or mucopolysaccharides.[1] Glycosides of 2-amino-2-deoxysugars are present in many important classes of glycoconjugates and naturally occurring oligo-/polysaccharides such as chitin.[2] Because of the natural abundance of 2-amino sugars and their involvement in a variety of biological processes, the development of chemical methods for the synthesis of oligosaccharides containing these residues represents an important direction of modern glycosciences.[3] Azides have been successfully and widely used as amine precursors/protecting groups in the chemical synthesis of amino sugars. Beyond providing a relatively simple way to create a C–N linkage, azides have many advantages over other protecting groups used in synthesis. These include lower steric hindrance, greater solubility in organic media, stability under many reaction conditions used in other protecting group manipulations or during glycosylation reaction, and the absence of the rotamer formation.[4] In addition, this protecting group provides excellent atom economy and the absence of additional hydrogen or carbon nuclei that could complicate NMR spectra.[4,5] Furthermore, azides can be easily reduced to amines either concomitantly with other hydrogenation-labile protecting groups or orthogonally by Staudinger reaction or thiol-mediated reduction.[6] In addition, azide groups at C–2 position of glycosyl donors are especially valuable because of their non-participating effect during glycosylation reactions, allowing for the synthesis of 1,2-*cis* glycosidic linkages.[3] Until recent reports utilizing *N*-benzylidene protected donors by Nguyen and co-workers,[7] practically all 1,2-*cis* glycosylations for the synthesis of glycosides of 2-amino sugars have employed glycosyl donors equipped with the 2-azide moiety.[8]

One of the significant methods used to introduce the 2-azido moiety to glycals is the azidonitration protocol developed by Lemieux and Ratcliffe.[9] Inspired by early studies by Trahanovsky and Robbins on the synthesis of α-azido-β-nitroalkanes,[10] Lemieux and Ratcliffe anticipated that the azide radical-induced addition to glycals would provide 2-azido-2-deoxyglycosyl nitrates. This gave rise to the development of the azidonitration of glycals with sodium azide in the presence of ceric ammonium nitrate (CAN) in acetonitrile. Although this reaction may proceed with high regioselectivity, achieving the subsequent glycosidation is cumbersome because the anomeric nitrates have to be converted to suitable leaving groups such as hemiacetal,[11] halide,[9,12] acetate,[13] trichloroacetimidate,[11d,14] pentenyl,[15] phosphate,[16] thioglycoside,[17] xanthate,[13] etc.[3]

Recently, we discovered that glycosyl nitrates of the D-gluco, D-galacto- and D-manno series can be used as effective glycosyl donors for *O*-glycosylation.[18] Lanthanide triflates have been found to be suitable promoters for the activation of nitrate leaving groups of regular oxygenated sugars. This observation gave us an idea that the reaction can also be used for the direct glycosidation of glycosyl nitrates of the 2-azido-2-deoxy series. Reported herein is our first attempt to study glycosyl nitrates of 2-azido-2-deoxysugars as glycosyl donors in chemical glycosylation reactions.

Results and Discussion

For our preliminary screening we synthesized 2-azido-3,4,6-tri-*O*-benzoyl-2-deoxy-D-galactopyranosyl nitrate **1** by a refined protocol reported herein. According to our previous study, per-benzylated and per-benzoylated glycosyl nitrates of the D-glucose and D-galactose series could be activated efficiently by using a stoichiometric amount of ytterbium(III) trifluoromethanesulfonate [$Yb(OTf)_3$] in $Et_2O/ClCH_2CH_2Cl$ (1,2-DCE, v/v, 1:1).[18] However, the application of these reaction conditions to glycosidation of 2-azido donor **1** with primary acceptor **2**[19] afforded the desired disaccharide **3** in only 33 % yield with poor stereoselectivity (α/β = 1.6:1, Table 1, entry 1). This poor yield was on a par with previous results achieved with other unreactive nitrates of the disarmed mannosyl and superdisarmed glucosyl donor series.[18] To improve the utility of this glycosylation reaction, we endeavored to optimize the reaction conditions. The use of neat 1,2-DCE as the reaction solvent resulted in the

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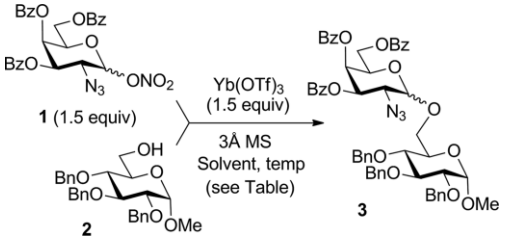
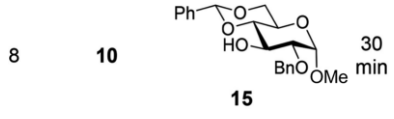
formation of disaccharide **3** in 19 % yield (α/β = 1.0:1, entry 2). When the same reaction was conducted in neat Et_2O as the reaction solvent, disaccharide **3** was produced in an enhanced yield of 52 % yield. This reaction proceeded with enhanced α-stereoselectivity (α/β = 3.7:1, entry 3), which is an anticipated outcome of reactions in ethereal solvents.[20] The use of 1,4-dioxane as the reaction solvent gave disaccharide **3** in a respectable yield of 77 %. A commendable 1,2-*cis* stereoselectivity (α/β = 4.8:1, entry 4) was obtained due to a known effect of 1,4-dioxane.[21] When neat CH_3CN was used as the reaction solvent, disaccharide **3** was obtained in 70 % yield. This reaction proceeded with preferential β-stereoselectivity (α/β = 1:3.6, entry 5), which is an anticipated outcome of reactions in nitrilic solvents.[20] Glycosylations performed in some other reaction solvents, such as DMF or toluene, were sluggish and inefficient. Since glycosylations in neat 1,4-dioxane provided the most advantageous combination of the reaction yield and stereoselectivity subsequent studies of this glycosylation reaction were based on 1,4-dioxane as the reaction solvent.

Table 1. Optimization of the reaction conditions for glycosidation of galactosyl nitrate donor **1**.



Entry	Solvent	Time	Yield of **3** (ratio α/β)
1	Et_2O/1,2-DCE (1:1, v/v), r.t.	18 h	33 % (1.6:1)
2	1,2-DCE, r.t.	18 h	19 % (1.0:1)
3	Et_2O, r.t.	18 h	52 % (3.7:1)
4	1,4-dioxane, r.t.	18 h	77 % (4.8:1)
5	CH_3CN, r.t.	18 h	70 % (1:3.6)
6	1,4-dioxane, 50 °C	5 h	78 % (3.1:1)
7	1,4-dioxane, 60 °C	3 h	71 % (2.8:1)



Having identified the most suitable reaction solvent, we turned our attention to optimizing the reaction temperature. As expected, the glycosidation of 2-azido donor **1** with acceptor **2** was accelerated at elevated temperatures. Thus, as shown in Table 1, the reaction performed at 50 °C was completed within 5 h to give disaccharide **3** in 78 % yield (α/β = 3.1:1, entry 6). Even faster reaction (3 h) was achieved at 60 °C, but both the yield and stereoselectivity of disaccharide **3** declined (71 % yield, α/β = 2.8:1, entry 7). Therefore, we concluded that room temperature experiments offer the optimal outcome.

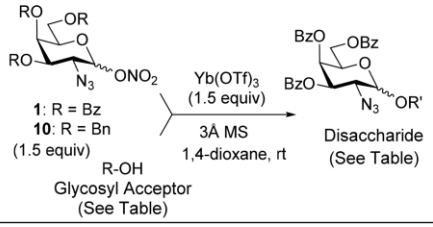
Having refined the reaction solvent and temperature, we decided to investigate the effect of promoters and additives. As reported previously, ytterbium(III) tris(trifluoromethanesulfonyl) methide (CTf_3^-) is more reactive than $Yb(OTf)_3$. This is because CTf_3^- is a more stable counteranion than OTf^-, which makes the lanthanide center more electrophilic for the "nitrate capture."[22] Han et al. reported that a laborious preparation of the catalyst containing a CTf_3^- counterion is unnecessary for the purposes of enhancing its reactivity.[23] A similar effect can be achieved by mixing commercial catalyst $Yb(OTf)_3$ with potassium tris(trifluoromethanesulfonyl) methide ($KCTf_3$) in situ. Unfortunately, the counteranion effect was proven insignificant in our glycosylation reactions. Thus, when $KCTf_3$ (0.15 equiv.) was used as an additive, the reaction was not accelerated, and the yield did not increase.

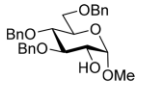
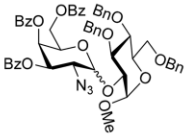
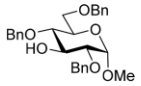
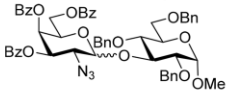
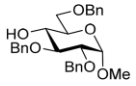
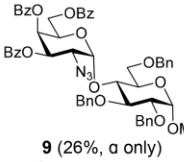
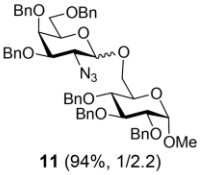
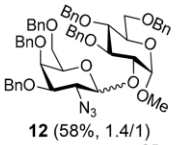
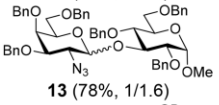
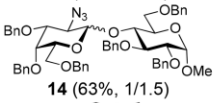
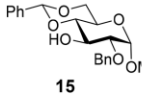
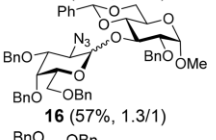
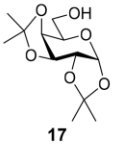
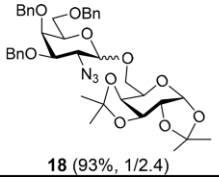
With the optimized reaction conditions, secondary acceptors were also investigated with 3,4,6-tri-*O*-benzoyl galactosyl nitrate donor **1**. The reaction between donor **1** and 2-OH acceptor **4**[19] led to disaccharide **5** in 65 % yield (α/β = 4.8:1, Table 2, entry 1). The reaction between donor **1** and 3-OH acceptor **6**[19] gave disaccharide **7** in 58 % yield (α/β = 10:1, entry 2). The reaction of donor **1** with the unreactive 4-OH acceptor **8**[19] gave disaccharide **9** in only 26 % yield, but with exclusive α-stereoselectivity (entry 3).

With the general success of glycosylations with the fairly unreactive glycosyl donor **1**, we switched to investigating known 3,4,6-tri-*O*-benzylated galactosyl nitrate donor **10**[24] that was expected to be more reactive (armed) due to the less deactivating nature of the remote ethereal substituents in comparison to that of esters.[25] Indeed, glycosyl donor **10** showed much greater reactivity than its tri-benzoylated counterpart **1**. Thus, glycosidation of donor **10** with the primary glycosyl acceptor **2** in the presence of $Yb(OTf)_3$ (1.5 equiv.) in 1,4-dioxane at r.t. produced disaccharide **11** in 1 h in 94 % yield (α/β = 1:2.2, Table 2, entry 4). The reactions with secondary acceptors were also quite swift, but generally provided somewhat lower yields, which were still well within the preparative value. The declined yields observed were due to competing hydrolysis of the donor. We also noted a general decline in stereoselectivity, which could be explained by a well-established inverse correlation between the reactivity and stereoselectivity.[8] A reaction between donor **10** and 2-OH acceptor **4** led to disaccharide **12** in 58 % yield in 1 h (α/β = 1.4:1, entry 5). The reaction between donor **10** and 3-OH acceptor **6** gave disaccharide **13** in 78 % yield in 1 h (α/β = 1:1.6, entry 6). The reaction between donor **10** and 4-OH acceptor **8** gave disaccharide **14** in 63 % yield in 20 min (α/β = 1:1.5, entry 7). The reaction between donor **10** and benzylidene-protected 3-OH acceptor **15**[26] gave disaccharide **16** in 57 % yield in 30 min (α/β = 1.3:1, entry 8). Finally, the reaction of donor **10** with di-*O*-isopropylidene protected 6-OH acceptor **17** gave disaccharide **18** in 93 % yield in 15 min (α/β = 1:2.4, entry 9).

Having investigated 2-azido-2-deoxy galactosyl nitrate donors, we switched our attention to 2-azido-2-deoxy glucosyl nitrate donors. Azidonitration of 3,4,6-tri-*O*-benzylated glucal is typically non-stereoselective and produces the C-2 epimers 2-azido-2-deoxy glucosyl and mannosyl nitrates.[27] When cyclic acetal protecting groups are used to conformationally constrain the pyranose ring, 2-azido-2-deoxyglucosyl nitrates are preferred.[28] Therefore, we chose known 2-azido-4,6-*O*-benzyl-

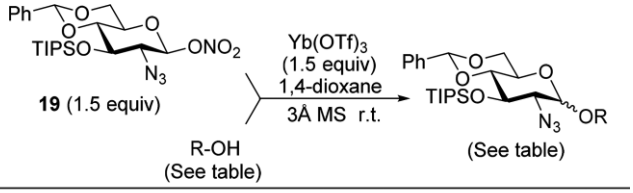
Table 2. Glycosylations with benzoylated and benzylated galactosyl nitrate donors **1** and **10**.

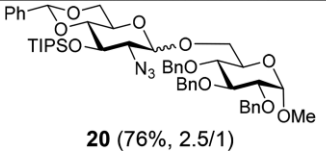
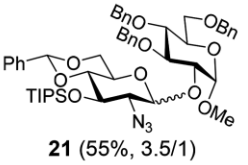
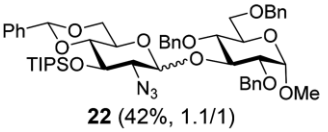
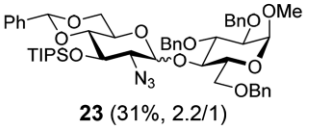
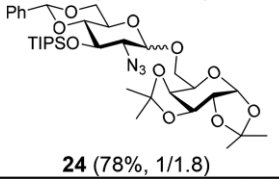


Entry	Donor	Acceptor	Time	Product (yield, ratio α/β)
1	**1**	 **4**	18 h	 **5** (65%, 4.8/1)
2	**1**	 **6**	18 h	 **7** (58%, 10/1)
3	**1**	 **8**	18 h	 **9** (26%, α only)
4	**10**	**2**	1 h	 **11** (94%, 1/2.2)
5	**10**	**4**	1 h	 **12** (58%, 1.4/1)
6	**10**	**6**	1h	 **13** (78%, 1/1.6)
7	**10**	**8**	20 min	 **14** (63%, 1/1.5)
8	**10**	 **15**	30 min	 **16** (57%, 1.3/1)
9	**10**	 **17**	15 min	 **18** (93%, 1/2.4)

idene-2-deoxy-3-*O*-triisopropylsilyl-β-D-glucosyl nitrate **19**[28] as a more readily accessible substrate to be investigated as the glycosyl donor. The reaction of donor **19** with primary acceptor **2** in the presence of $Yb(OTf)_3$ (1.5 equiv.) in 1,4-dioxane at r.t. produced disaccharide **20** in 76 % yield in 20 h (α/β = 2.5:1, Table 3, entry 1). The reactions with secondary acceptors were relatively sluggish, perhaps due to the known disarming effect of the benzylidene acetal.[29] The glycosidation between donor **19** and 2-OH acceptor **4** gave disaccharide **21** in 55 % yield in 20 h (α/β = 1.6:1, entry 2). The reaction between donor **19** and 3-OH acceptor **6** gave disaccharide **22** in 42 % yield in 20 h (α/β = 1.1:1, entry 3). The reaction between donor **19** and 4-OH acceptor **8** led to disaccharide **23** in 31 % yield in 20 h (α/β = 2.2:1, entry 4). Finally, the reaction of donor **19** with di-*O*-isopropylidene protected 6-OH acceptor **17** gave disaccharide **24** in 78 % yield in 6 h (α/β = 1:1.8, entry 5).

Table 3. Glycosylations with 2-azidoglucosyl nitrate donor **19**.



Entry	Acceptor	Time	Product (yield, ratio α/β)
1	**2**	20 h	 **20** (76%, 2.5/1)
2	**4**	20 h	 **21** (55%, 3.5/1)
3	**6**	20 h	 **22** (42%, 1.1/1)
4	**8**	20 h	 **23** (31%, 2.2/1)
5	**17**	6 h	 **24** (78%, 1/1.8)

Conclusions

Presented herein is our preliminary attempt to employ 2-azido-2-deoxyglycosyl nitrates as donors in *O*-glycosylation reactions. $Yb(OTf)_3$ was found to be an effective promoter and 1,4-dioxane was found to be the best reaction solvent for these glycosylations. The benzylated galactosyl azido nitrate donor showed high reactivity with both primary acceptors and secondary acceptors in comparison to its acylated counterpart. 2-Azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-triisopropylsilyl-β-D-glucosyl nitrate donor showed high reactivity with primary acceptors. The reac-

tion conditions were also found to be compatible with the acid-labile acetal protecting groups in glycosyl acceptors.

Supporting Information (see footnote on the first page of this article): Experimental details and NMR spectra of all new compounds.

Conflicts of Interest

There are no conflicts to declare.

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Keywords: Glycosylation · Carbohydrates · Amino sugars · Synthesis design · Glycans

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