JOC The Journal of Organic Chemistry

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Use of *N*,*O*-Dimethylhydroxylamine As an Anomeric Protecting Group in Carbohydrate Synthesis

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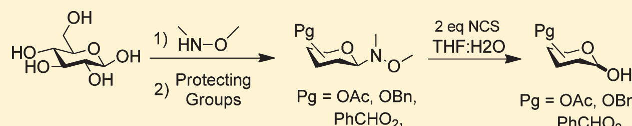
Supporting Information

ABSTRACT: The *N*,*O*-dimethyloxyamine-*N*-glycosides are introduced as anomerically protected building blocks for carbohydrate synthesis. These *N*-glycosides are stable to a variety of protecting group manipulations including acylation, alkylation, silylation, and acetal formation. The alkoxyamine-*N*-glycosides can be cleaved selectively with *N*-chlorosuccinimide to give the desired hemiacetals in excellent yield. Furthermore, these *N*-glycosides are stable to the activation conditions required for glycosylation using thioglycoside and trichloroacetimidate glycosyl donors suggesting *N*,*O*-dialkoxyamine-*N*-glycosides will be useful for complex oligosaccharide synthesis.



Anomeric protecting groups are often used in convergent oligosaccharide syntheses which require that complex glycosyl donors be generated late in a synthesis.[1] An ideal anomeric protecting group would be one that is easily installed, is stable under conditions necessary for protecting group manipulations, and is readily hydrolyzed to yield the desired hemiacetal. Further versatility in an anomeric protecting group would be provided if the protecting group could be activated to serve as a leaving group for glycosidation. Many anomeric protecting groups have been developed with these criteria in mind. Some of the most commonly used groups include allyl, pentenyl,[2,3] thioglycosides,[4] TMSEt,[5] *p*-methoxyphenyl,[6] and most recently the propargyl glycosides.[7] These groups are robust to many protecting group manipulations and they can be cleaved under an orthogonal set of conditions. But the formation of these glycosides is not ideal, as they are introduced either via a Fischer glycosidation, requiring separation of anomers, or through a multistep route decreasing the overall efficiency of oligosaccharide synthesis. Here we introduce the use of *N*,*O*-dimethylhydroxylamine as an anomeric protecting group for use in oligosaccharide synthesis. The advantage of *N*,*O*-dimethyloxyamine-*N*-glycosides is that they can be directly introduced on an unprotected mono- or oligosaccharide, reducing the number of chemical steps required in an oligosaccharide synthesis.

In a very important contribution, the synthesis of *N*,*O*-dialkyloxyamine-*N*-glycosides was demonstrated by Dumy et al.[8] These glycosidations were shown to give primarily the equatorial glycosides in high yield when glycoside formation was carried out under concentrated mildly acidic (pH 4−5) aqueous conditions.[8,9] The simplicity of the glycosylation and the stability of the resulting glycosides has made this glycosidation exceptionally useful for the generation of glycoconjugates,[10−14] the formation of glycoside mimics,[8,15,16] glycopeptide mimics,[17,18] and to "sweeten" natural products.[19] However, despite the ease of installation, the compatibility of *N*,*O*-dialkyloxyamine-*N*-glycosides with protecting group chemistry and glycosylation conditions associated with oligosaccharide synthesis has not been explored. Here we show that these glycosides are compatible with numerous protecting groups, that the glycosides can be selectively hydrolyzed with *N*-chlorosuccinimide (NCS), and that *N*,*O*-dialkyloxyamine-*N*-glycosides are stable to thioglycoside and trichloroacetimidate glycosylation conditions.

Similar to the synthesis previously reported, the *N*,*O*-dialkyloxyamine-*N*-glycoside **1** was formed in high yield under mildly acidic conditions.[8] An equal molar solution of sodium acetate, *N*,*O*-dimethylhydroxylamine hydrochloride, and glucose (0.7 M) gave the desired glycoside **1** in 92% yield. The protection of **1** with a range of common protecting groups was explored. Peracetylation under standard conditions (Ac_2O/Pyr) and perbenzylation (NaH, BnBr/DMF) proceeded smoothly to give **2** and **3** in greater than 90% yield. Similarly the regioselective addition of a TBDPS ether, using TBDPS-Cl in pyridine, gave high yields of the desired selectively protected glycoside **4**. We were pleased to find that the *N*,*O*-dimethyloxyamine-*N*-glycoside was also stable to acetal formation giving 71% yield of the protected 4,6-*O*-benzylidene glycoside **5** (Scheme 1).

The chemoselective deprotection of the hydroxylamine was explored under various conditions using the acetylated glycoside **1**. As was expected, treatment under standard acetal cleavage conditions (AcOH/H_2O, 4:1) cleaved the glycoside giving the free hemiacetal **7** in 80% yield. Unfortunately these conditions also led to partial removal of the protecting groups on compounds **4** and **5** leading to poor yields. A variety of Lewis acids were explored in water/organic solutions for hydrolysis of the *N*-glycosides but overall this process led to low yields of the desired hemiacetals. Given our previous success activating anomeric hydrazides under oxidative conditions we explored the use of halosuccinimides for cleavage of the *N*-glycosides.[20] The glycosides proved stable to NIS and NBS but were cleanly hydrolyzed with NCS in THF/water solutions (9:1) at 50−60 °C. These conditions proved to be compatible with the acetyl, benzylidene, benzyl, and TBDPS protecting groups on compounds **1**−**5**, giving high yields of the desired hemiacetals (Table 1).

Received: December 4, 2010
Published: February 18, 2011

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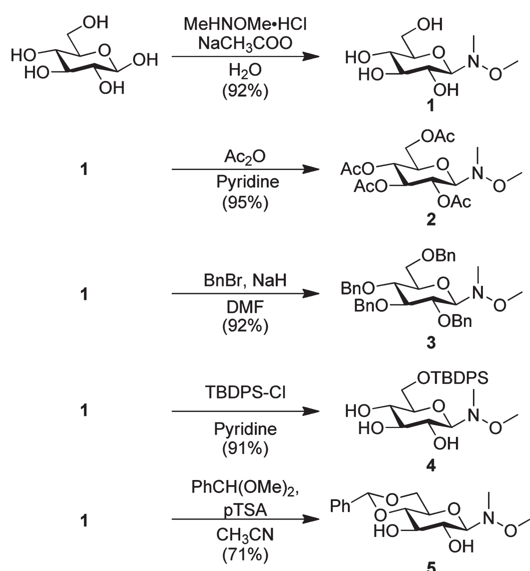
Scheme 1. Protection of *N,O*-Dimethyloxyamine Glucosides



We explored the possibility of forming *O*-glycosides under solvolysis conditions using NCS. Unfortunately, the acetylated derivative **2** did not give clean conversion into the methyl glycoside upon activation with NCS in methanol. After extended reaction times (24−48 h) glycosidation was evident but many deacetylation products were also produced. The more reactive benzylated *N*-glycoside **4** was converted to the methyl glycoside under similar conditions in moderate yield (60% 1:10 (α:β)). Given that the more armed benzylated glycoside could be activated for glycosidation we explored the tribenzylated *N*-acetylglucosamine donor **11**. This donor provides an acetyl group at the 2-position to control the stereochemistry of the glycosidation and donating benzyl groups to activate the donor toward glycosidation. The *N,O*-dimethylalkoxyamine-*N*-glycoside (**11**) was synthesized without difficulty using a similar approach as that detailed above, in a two-step, one-pot, 64% overall yield (Scheme 2). The *N*-glycoside **11** could be activated with NCS and gave glycosides of simple alcohols in good to moderate yield (54−60%). These results indicate that only in the case of strongly armed donors can these *N,O*-dimethyloxyamine-*N*-glycosides be glycosidated in synthetically useful yields. Further work is required before they can serve as donors in oligosaccharide synthesis.

Finally given the stability of these glycosides to protection and deprotection conditions, we sought to explore the stability of the *N,O*-dimethyloxyamine-*N*-glycosides as glycosyl acceptors. We focused our attention on the synthesis of two disaccharides containing (1→6) linked and (1→4) rhamnose linkages. We examined typical glycosylation conditions commonly used for thioglycoside activation (NIS/TMSOTf)[21] and trichloroacetimidate[22] activation.

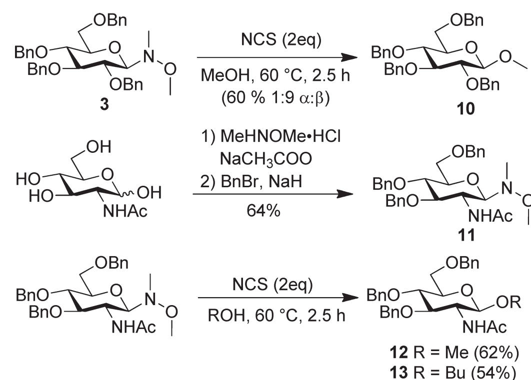
The glycosyl acceptors were prepared starting from compound **4**; after acetylation the TBDPS group was removed by using TBAF. Under the deprotection conditions the expected partial acetyl migration was observed giving the expected 6-OH (**15**, 55%) glucoside as well as the 4-OH (**16**, 30%).[23] Glycosylation of the *N*-glycoside acceptor **15** with 2,3,4-tri-O-acetyl-α-L-rhamnosyltrichloroacetimidate[24] using TMSOTf activation gave disaccharide **17** in 91% yield. Reaction between known ethyl-2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnoside donor[25] and *N,O*-dimethyloxyamine acceptor **16** under NIS/TMSOTf

Table 1. *N,O*-Dimethyloxyamine-*N*-glycoside Hydrolysis

glycoside	reaction conditions[a]	product	yield (%)
2	A	**6**	80
3	A	**7**	77
4	A	**8**	61
5	A	**9**	30
2	B	**6**	64
3	B	**7**	65
5	B	**9**	20
2	C	**6**	91
3	C	**7**	90
4	C	**8**	91
5	C	**9**	81

[a] Conditions: (A) AcOH/H_2O (4:1), 60 °C, 1 h; (B) $FeCl_3$ (2 equiv), THF/H_2O (9:1), 60 °C, 2 h; (C) NCS (2 equiv), THF/H_2O (9:1), 60 °C, 1 h.

Scheme 2. Glycosidation with *N*-Glycosides



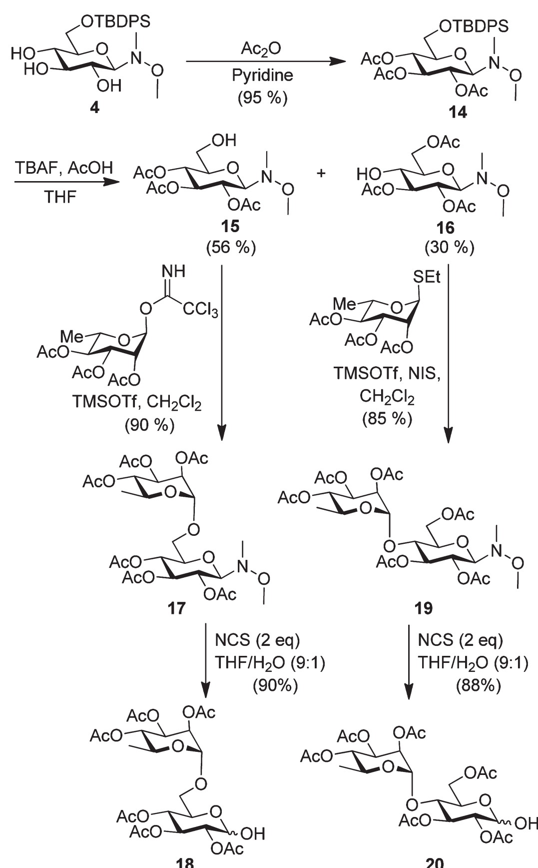
activation conditions led to disaccharide **19** in 85% yield. These reactions demonstrate that the *N,O*-dimethyloxyamine-*N*-glycosides are stable to standard glycosylation conditions.

It was possible to hydrolyze both *N*-glycoside disaccharides (**17** and **19**) with NCS to give hemiacetals in high yield. These hemiacetals could be used as precursors for the formation of disaccharide glycosyl donors in oligosaccharide synthesis (Scheme 3).

In conclusion, we have demonstrated that the *N,O*-dimethylhydroxyamine can be used as an anomeric protecting group under a range of conditions. These glycosides are tolerant of a range of protecting group manipulation conditions and are stable under glycosylation conditions. *N,O*-Dialkoxyamine-*N*-glycosides can be activated for glycosidation but in their current form these glycosides lack the reactivity required of effective glycosyl donors. Future work to increase the activity of these glycosides or find alternate conditions for activation is ongoing.

dx.doi.org/10.1021/jo102372m |*J. Org. Chem.* 2011, 76, 1918–1921

Scheme 3. Glycosylation of *N,O*-Dimethyloxyamine-*N*-glycoside Acceptors



EXPERIMENTAL SECTION

Representative Procedures

Formation of *N,O*-Dimethylamine-*N*-glycosides

***N,O*-Dimethyl-*N*-(*β*-D-glucopyranosyl)hydroxylamine (1).** Glucose (2.00 g, 11.1 mmol) was dissolved in water (15 mL) in a round-bottomed flask. *N,O*-Dimethylhydroxylamine hydrochloride (1.19 g, 12.2 mmol) and sodium acetate (1.00 g, 12.2 mmol) were dissolved in approximately 1 mL of water and the solution was added slowly to the glucose solution at 0 °C. The reaction was allowed to proceed for 20 h at rt at which time TLC analysis showed conversion of the starting material to a faster moving product (CH_2Cl_2:MeOH 5:1, R_f 0.4). The water was evaporated from the reaction in vacuo and the product was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (6:1) to give compound **1** (2.27 g, 92%) as a white solid. Analytical data agree with previous reports.[8]

Hydrolysis of *N,O*-Dimethylamine-*N*-glycosides

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-D-glucopyranose (18). Compound **17** (50 mg, 0.08 mmol) was dissolved in THF:water (3 mL, 9:1) and to it was added NCS (21.5 mg, 0.16 mmol). The solution was warmed to 60 °C for 1 h after which time TLC analysis showed complete conversion of starting material to a slower moving product (EtOAc:*n*-pentane 1:1, R_f 0.2). The solvent was evaporated and the crude oil was purified by flash chromatography eluting with *n*-pentane:EtOAc (1:1) to furnish 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-D-glucopyranose (**18**) (42 mg, 90%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (t, 1H, J = 10 Hz), 5.40 (d, 1H, J = 3.6 Hz), 5.34−5.22 (m, 4H), 5.05 (t, 1H, J = 9.9 Hz), 4.95−4.78 (m, 2H), 4.30 (dd, 1H, J = 4, 10.8 Hz), 3.91−3.87 (m, 1H), 3.76 (dd, 1H, J = 3, 13 Hz), 3.62−3.55 (m, 1H), 2.16, 2.14, 2.08, 2.04, 2.01, 1.98 (6s, 18H), 1.21 (d, 3H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.4, 170.3, 170.1, 170.0, 169.9, 169.7, 169.6, 98.4, 98.2, 95.2, 89.7, 73.7, 72.8, 72.4, 71.0, 70.8, 70.7, 69.8, 69.7, 69.3, 69.2, 69.1, 69.0, 68.8, 67.5, 66.7, 29.6, 20.9 (2), 20.7 (3), 20.6, 20.5, 17.3; ESI-HRMS calcd for $C_{24}H_{34}O_{16}Na$ $[M + Na]^+$ 601.1745, found 601.1741.

Glycosidation Procedure

Butyl 2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-*β*-D-glucopyranoside (13). Compound **11** (100 mg, 0.18 mmol) was dissolved in butanol (5 mL) and to it was added NCS (63 mg, 0.47 mmol). The solution was warmed to 60 °C for 2.5 h after which time TLC analysis showed conversion of the starting material to a new product (EtOAc:*n*-pentane, 1:1, R_f 0.6). The solvent was evaporated and the crude oil was purified by flash chromatography eluting with *n*-pentane:EtOAc (2:1) to furnish butyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-*β*-D-glucopyranoside (**13**) (53 mg, 54%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.18 (m, 15H, ArH), 5.57 (d, 1H, J = 7.8 Hz), 4.82−4.76 (m, 3H), 4.67−4.52 (m, 4H), 4.11 (dd, 1H, J = 7.8, 7.9 Hz), 3.86 (ddd, 1H, J = 7.8, 7.9, 7.4 Hz), 3.77−3.71 (m, 2H), 3.64−3.58 (m, 2H), 3.47−3.36 (m, 2H), 1.84 (s, 3H), 1.57−1.48 (m, 2H), 1.36−1.30 (m, 2H), 0.89 (t, 1H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 138.5, 138.2, 138.0, 128.4 (4), 128.3 (2), 127.9 (2), 127.8 (2), 127.7 (4), 127.5, 99.7, 80.3, 78.7, 74.7, 74.5 (2), 73.4, 69.2, 69.0, 57.1, 31.5, 23.5, 19.1, 13.8; ESI-HRMS calcd for $C_{33}H_{41}NO_6Na$ $[M + Na]^+$ 570.2832, found 570.2828.

ASSOCIATED CONTENT

Supporting Information. General experimental methods, full experimental procedures, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

The authors are grateful for financial support from the Natural Science and Engineering Research Council of Canada (NSERC).

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