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C-Silylation of Secondary Amides: GlcNAc Peracetate Derivatives

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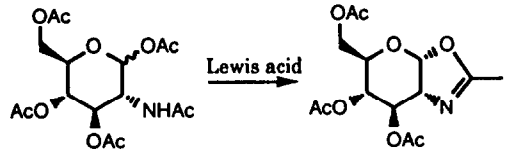
Abstract: The Me_3SiOTf-promoted formation of GlcNAc 1,2-cis oxazoline from GlcNAc peracetates can give significant amounts of nonpolar by-products. We identified these by-products to be C-silylated esters and amides. Secondary amides are readily C-silylated by treatment with a mixture of Me_3SiOTf and NEt_3. These C-silylated secondary amides are useful, as they undergo fluoride ion promoted aldol condensation.

Introduction

A useful derivative in the synthesis of glycoconjugates containing 2-acetamido-2-deoxy-β-glucose (GlcNAc) is the 1,2-cis oxazoline **2**.[1] Oxazolines have been used to prepare β-O-glycopeptides,[2] β-N-glycopeptides,[3] and glycosyl phosphates.[4] The GlcNAc oxazoline **2** has two advantages as a glycosyl donor. First, the oxazoline can be prepared from GlcNAc peracetate **1** (eq. 1) using Lewis acids such as $FeCl_3$,[5] $SnCl_4$,[6] Me_3SiOTf,[7] and $BF_3{\cdot}OEt_2$.[8] Thus, the "chloroacetolysis" conditions of Koenigs-Knorr glycosylation are avoided. Second, nucleophilic addition to the oxazoline C-1 position is stereospecific, giving the 1,2-trans β-glycoside.



1a = α
1b = β

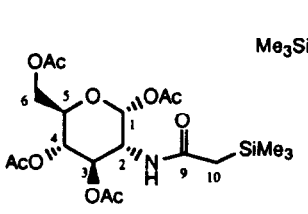
2

(1)

While there are numerous methods for their preparation,[5-8] little is known about by-products that arise during GlcNAc oxazoline synthesis. For example, a popular Lewis acid for oxazoline formation is Me_3SiOTf.[7-9] With this reagent, GlcNAc oxazolines are prepared in high yield from peracetyl mono- and disaccharides. However, preparation of certain oligosaccharide oxazolines with Me_3SiOTf may be compromised by glycosidic cleavage.[8] Also, Prestegard has reported that Me_3SiOTf gave uncharacterized side products during GlcNAc oxazoline synthesis.[9]

This paper describes the identification of C-silylated GlcNAc peracetate side products **3-5** formed in the presence of Me_3SiOTf and NEt_3, conditions for quantitative C-silylation of secondary amides, and lastly, the use of C-silylated secondary amides in C-C bond formation.

Results and Discussion. *C-Silylation Side Products:* The β-GlcNAc peracetate (**1b**)[10] cyclizes to give oxazoline **2** much more readily than does the corresponding α anomer (**1a**).[7,8] Prestegard has reported that Me_3SiOTf gave uncharacterized side products during oxazoline synthesis from a mixture of GlcNAc peracetates **1a** and **1b**.[9] While doing oxazoline optimization experiments, we found that C-silylated GlcNAc peracetates **3-5** can be formed during the work-up of the Me_3SiOTf promoted reaction. Thus, treatment of α-GlcNAc peracetate **1a** [10] with excess Me_3SiOTf for 30 min at room temperature, followed by neutralization with NEt_3, and immediate aqueous work-up of the reaction mixture gave various amounts of C-silylated peracetates **3-5**.



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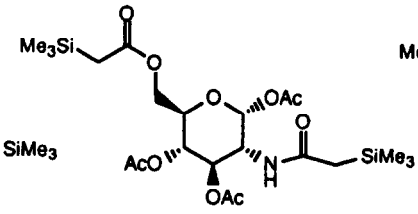

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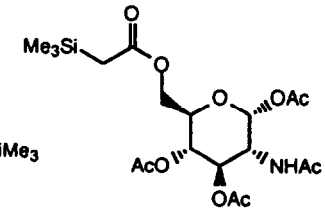


5

The predominant C-silylation product formed depends on the number of equivalents of Me_3SiOTf and NEt_3. Side product formation also depends on the duration of exposure to NEt_3 prior to aqueous work-up. For example, tlc analysis indicated that treatment of α-GlcNAc peracetate **1a** with 2.2 equiv of Me_3SiOTf at 0 °C for 1 hour gave no new products. In fact, if the reaction mixture was quenched with $NaHCO_3$ solution, the starting peracetate **1a** was recovered in quantitative yield. However, if NEt_3 was added to the reaction mixture immediately before aqueous work-up, one major product was obtained. Thus, addition of NEt_3 (2.2 equiv) to a solution of **1a** and Me_3SiOTf (2.2 equiv), followed by stirring for 1 min at 0 °C and immediate aqueous work-up gave the C-10 silylated GlcNAc peracetate **3** in 85% yield.

The identity of C-silylated peracetate **3** was confirmed by MS and NMR data. The MS data indicated that one Me_3Si group had been added to the GlcNAc peracetate. In addition, the 400 MHz ^1H NMR data showed that this Me_3Si group was attached to the GlcNAc's acetamido C-10 carbon. Specifically, two C-10 methylene protons occurred as an AB doublet (^2J=12.4 Hz) at 1.70 ppm, an upfield shift of 0.30 ppm from the acetamido methyl protons (δ= 1.99 ppm, 3H) in peracetate **1a**. Peracetate **3** was not N-silylated, as it had a D_2O-exchangeable amide NH resonance at 5.36 ppm. Also, the ^{13}C NMR spectrum showed a significant downfield shift for the silylated C-10 position, from 23.2 ppm in peracetate **1a** to 29.0 ppm in **3**.[11]

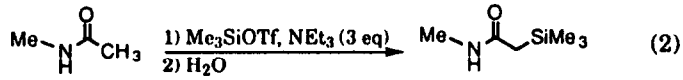
A different silylated GlcNAc peracetate was obtained with excess Me_3SiOTf and base. Treatment of GlcNAc peracetate **1a** with 6 equivalents of Me_3SiOTf and NEt_3, followed by immediate aqueous work-up, gave bis-C-silylated peracetate **4** as the major product (75%). The structure of bis-silyl peracetate **4**, was consistent with the MS and NMR data. The ^1H NMR spectrum showed that **4** had two separate Me_3Si resonances, at 0.03 ppm and -0.02 ppm respectively. Also, bis-silylated **4** had an AB pattern centered at 1.83 ppm for the diastereotopic methylene protons of the α-silyl acetate, indicating that C-silylation had occurred at only one of the OAc groups. Diagnostic changes in chemical shifts and $^3J_{HH}$ coupling constants revealed that this second C-silylation site was at the primary C-6 ester. The H6,H6' AB quartet in **4** was significantly different than the corresponding pattern in α-peracetate **1a**. One of the diastereotopic H6 methylene protons underwent an upfield shift from 4.20 ppm in **1a** to 4.05 ppm upon C-silylation; the other H6 resonance showed a smaller upfield shift from 4.01 ppm to 3.98 ppm. By contrast, the ^1H chemical shifts and $^3J_{HH}$ values for H1, H3 and H4 were nearly identical for GlcNAc peracetate **1a** and bis-silylated **4**. Although not observed in the crude reaction mixture, the C-6 monosilylated peracetate **5** was obtained as a

minor product after silica gel chromatography. It is likely that **5** arises from acid-catalyzed desilylation of the acetamido Me_3Si group in **4**.

The yields of C-silylated **3** and **4** depend on the duration that NEt_3 is allowed to react with the GlcNAc α-peracetate **1a** and Me_3SiOTf prior to aqueous work-up. Short reaction times, such as 1 min at 0 °C, gave excellent yields of C-silylation products **3** and **4**. Longer reaction times, however, resulted in decreasing amounts of C-silylation. For example, if NEt_3 was stirred with **1a** and Me_3SiOTf for 12 h before aqueous work-up, recovered starting peracetate **1a** (ca. 90%) and oxazoline **2** (ca. 10%) were obtained. Only trace amounts of C-silylated products were observed under these conditions.

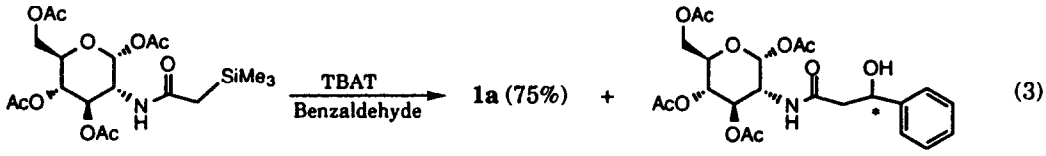
While C-silylation of ester enolates,[12] and N,N-dialkylamide enolates,[13,14] is known, as is the Me_3SiOTf /NEt_3 catalyzed silylation of carbonyl compounds,[15,16] direct C-silylation of a secondary amide is rare.[17] C-silylation of secondary amides likely occurs via separate steps. The first equivalent of Me_3SiOTf forms an O (or N)-silylated imidate. Treatment of this imidate with NEt_3 would generate an amide enolate, which could be readily C-silylated by excess Me_3SiOTf. Aqueous work-up would give the C-silylated secondary amide **3**.

We have found kinetic C-silylation of secondary amides to be a general reaction. Thus, treatment of N-methyl-acetamide **6** with excess Me_3SiOTf (3 equiv) and NEt_3 (3 equiv) at 0°C for 2 min, followed by aqueous work-up, gave quantitative formation of the C-silylated acetamide **7** (eq. 2). Newcomb has previously shown that an N-silylated amide is obtained when N-methyl-acetamide is treated with excess Me_3SiOTf and NEt_3.[18,19] Newcomb's experimental conditions differ from ours in that he allowed the Me_3SiOTf and NEt_3 to react longer (12-18 h) and also he did not do an aqueous work-up. Therefore, depending on the reaction conditions, secondary amides can be either C-silylated or N-silylated.



6 **7** (2)

Secondary Amide Enolates: C-Silylated secondary amides are of potential synthetic utility.[20] Indeed, fluoride ion catalyzes an aldol condensation between C-silylated amide **3** and benzaldehyde (eq. 3). When a mixture of **3** and benzaldehyde in THF at 0 °C was treated with tetra-butyl ammonium triphenyldiflurosilicate (TBAT) [21] the major product obtained was GlcNAc α-peracetate **1a** (75%). Peracetate **1a** probably arises by proton transfer from a secondary amide (pK_a=16-18) to the amide's C-enolate (pK_a=27). More importantly, however, the β-hydroxy-amide aldol product **8** was also isolated in 12% yield after silica gel chromatography as a 2:1 diastereomeric mixture. The diastereomeric ratio was determined by integration of the ^1H NMR resonances for the C-10 methylene, which occurs as a distinctive AB quartet at 2.98 ppm. The fact that aldol products are obtained indicates that secondary amide enolates can indeed form C-C bonds, even under conditions where proton transfer would be expected to quench the amide enolate.



3 **8** (12%) (3)

Conclusion

We demonstrated that reaction with Me_3SiOTf and NEt_3 under kinetic conditions is a useful method for C-silylation of secondary amides. The C-silylated secondary amides can be used as enolates for C-C bond formation.

Experimental Example (3): C-silylation of GlcNAc α-peracetate 1a. To a solution of GlcNAc α-peracetate **1a** (0.415 g, 1.07 mmol) in dichloroethane (6.0 mL) was added Me_3SiOTf (0.40 mL, 2.9 mmol). After stirring for 5 min at 0 °C, NEt_3 (0.40 mL, 2.9 mmol) was added. The reaction mixture was stirred for 30 sec and then poured into 20 mL of sat. $NaHCO_3$. The organic layer was washed with $NaHCO_3$ (2 x 10 mL), H_2O (2 x 20 mL), brine (2 x 20 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (Et_2O: MeOH 100:1) on silica gel gave amide **3** in 85% yield: TLC R_f (98:2 Et_2O: MeOH + 1% NEt_3) = 0.55. ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, H1, J=3.5), 5.36 (d, NH, J=9.0), 5.24-5.14 (m, H3, H4), 4.43 (m, H2, J= 9.0, 3.6), 4.20 (dd, H6', J= 12.5, 3.9), 4.03 (dd, H6", J= 12.4, 2.1), 3.94 (m, H5), 2.14 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.70 (d, AB, 2H, J= 12.4), 0.06 (s, 9H, Me_3Si); ^{13}C NMR (110 MHz, $CDCl_3$) δ 171.7, 171.0, 170.6, 169.0, 168.5, 90.7, 70.5, 69.6, 67.7, 61.5, 51.0, 29.0, 20.8, 20.6, 20.5, -1.6; IR (cm^{-1}) 1750, 1665; MS CI (m/z %) : (M^+ + 1) 462 (2), 402 (17), 359 (5), 304 (10), 266 (7), 228 (14), 199 (37), 114 (81), 73 (100). HRMS: calcd ($C_{19}H_{31}NO_{10}Si$) 462.1795, obsd. 462.1800.

Characterization of Aldol Product 8. TLC R_f (98:2 Et_2O: MeOH + 1% NEt_3) = 0.63. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H, Ar), 6.08 (dd, 1H, H11, J=8.5, 4.8), 5.92 (d, 1H, NH, J=9.0), 5.25 (d, 0.67 H, H1 of major diastereomer, J= 3.5), 5.22 (d, 0.33 H, H1 of minor diastereomer, J=3.5), 5.20-4.95 (m, 2H, H3, H4), 4.33 (ddd, 1H, H2, J= 3.5, 9.0, J=10.2), 4.20-3.99 (m, 3H, H5, H6', H6"), 2.78 (dd, H10', J=8.5, 15.0), 2.57 (dd, H10", J=4.8, 15.0); 2.05-2.00 (4s, 12H, Ac); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.5, 171.0, 170.6, 169.0, 168.5, 128.7, 128.3, 126.4, 125.5, 91.5, 80.0, 72.6, 70.6, 68.1, 62.0, 52.3, 43.5, 29.7, 20.8, 20.7, 20.6; MS FAB (m/z %) : (M^+ + Na^+) 518 (7), (M^+ + H^+) 496 (15), 478 (20), 436 (37), 418 (20), 298 (31), 212 (29), 194 (59), 168 (45), 152 (41), 131 (100). HRMS CI: calcd ($C_{23}H_{30}NO_{11}$) 496.1815, obsd 496.1819.

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