Advances in Glycosyl Azide Preparation via Hypervalent Silicates†

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The chemistry and biology of *N*-linked glycoconjugates is a topic of intense interest due to the significant role that these compounds have in biological processes.[1−3] To thoroughly study their function, a general and high-yielding method for the preparation of useful intermediates is required due to the low bioavailability of naturally occurring *N*-linked glycoconjugates and the need for model substances. One approach to the synthesis of *N*-linked glycoconjugates has been to prepare glycosyl azides[4−11] that can be efficiently converted to a variety of *N*-linked functional groups.[12−14]

We have recently reported the application of hypervalent silicate derivatives for nucleophilic displacements by fluoride,[15,16] azide and cyanide,[17] and as aryl transfer reagents.[18−20] An aspect of this methodology included the treatment of azidotrimethylsilane (TMS-N_3) with tetrabutylammonium fluoride (TBAF) which provided, presumably via hypervalent azidosilicate **1**, a nucleophilic source of azide anion.[17] Our initial studies, which extended the studies of the Takaya lab,[21] demonstrated the versatility of azidosilicate **1** in the preparation of glycosyl azides.

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Since our recent report on azide displacements via silicate anion **1**,[17] several improvements in the methodology have been made. The most important improvement is that the displacement has been shown to require less than a full equivalent of TBAF. Previously, it had been reported that a stoichiometric quantity of TBAF was required for the displacement. Under substoichiometric conditions, α-bromo glucose **2** efficiently underwent azide displacement to provide azido glucose **3**β (Scheme 1). In the first entry, 100 mol % (with respect to TMS-N_3) of TBAF was used and the expected β-azide **3**β was formed in high yield. When the amount of TBAF was reduced to 50 mol %, the reaction still provided **3**β in high yield; however, the reaction time was substantially longer at 20 h. Finally, by reducing the amount of TBAF to 20 mol %, azide **3**β was still obtained with complete inversion of configuration and in high yield; however, the displacement required 40 h to proceed to completion. Under the substoichiometric conditions, we propose that bromide ion generated by the displacement "attacked" TMS-N_3, generating a bromo analogue of silicate **1** which delivered azide anion in the subsequent displacement. Two lines of evidence support this proposal: first, in the absence of fluoride (or bromide), azide displacement was not observed; second, when glycosyl bromide **2** was allowed to react with TMS-N_3 and tetrabutylammonium bromide for 72 h at 65 °C, azide **3**β was isolated in 36% yield, along with decomposition of starting material. We propose that the diminished yield of azide obtained under these more forcing conditions is the result of decomposition of the glucosyl bromide at higher reaction temperatures.

A second important observation was that the fluoride source did not have to be TBAF. A limitation of the TBAF protocol, even in the substoichiometric mode, was that solutions of commercially available TBAF contain approximately 2−5% water, and with hydrolytically sensitive glycosyl derivatives such as trichloroimidates (i.e., **7**, Scheme 3), hydrolysis of the activated glycosyl derivative occurred. Tetrabutylammonium triphenyldifluorosilicate (TBAT, **4**) could replace TBAF as the source of nucleophilic fluoride.[15,16] TBAT is an excellent fluoride surrogate for TBAF because TBAT is a crystalline, nonhygroscopic solid that is soluble in a wide range of organic solvents. Comparison of TBAF versus TBAT as the fluoride source indicated that it is superior in every respect: the reaction times were shorter, yields of azide were equivalent or higher, and the stereoselectivity of the displacement was superior (see Scheme 3). For example, α-bromide **2** underwent displacement with azidosilicate generated by either TBAF/TMS-N_3 or TBAT/TMS-N_3 in high yield and with complete stereocontrol (Scheme 2). However, when TBAT was used as the fluoride source, the reaction occurred more quickly. The disadvantage of employing TBAT was that these transformations required a full equivalent of the fluoride source. The reason that 1 equiv of TBAT is required is

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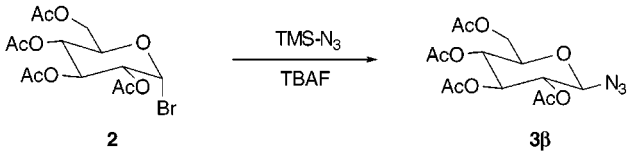
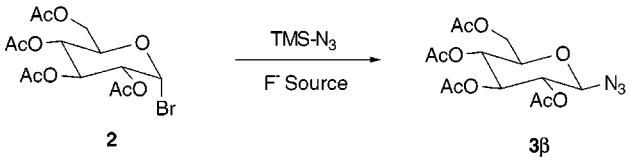
Scheme 1



2 3β

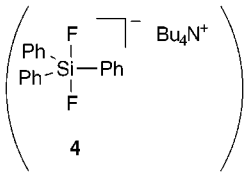
TBAF	Temp (°C)	Time (h)	Yield (%)
100 mol%	25	3	93
50 mol%	25	20	91
20 mol%	25	40	92

Scheme 2



2 3β

TBAF vs. TBAT



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F⁻ Source	Temp (°C)	Time (h)	Yield (%)
TBAF	25	3	93
TBAT	25	1.5	96

not obvious, but suggests a complex equilibrium of fluorosilicate and mixed bromofluorosilicates is produced during the course of the displacement. Experiments to elucidate the silicate species produced during these displacements are underway.[22]

It was possible that the observed displacements were the result of in situ generation of tetrabutylammonium azide by a disproportionation reaction. ^{19}F NMR experiments have conclusively demonstrated, however, that trimethylsilyl fluoride, the other product of this disproportionation, is not formed under these reaction conditions. As noted above, additional experiments are underway to conclusively characterize the silicate species that is responsible for the displacement.[22]

The advantages of employing TBAT as the fluoride source were demonstrated in displacements that had proven problematic with TBAF (Scheme 3). Glucosyl chloride **5** underwent azide displacement with silicate generated by TBAF/TMS-N_3 to afford azide **3**β in slightly lower yield than corresponding α-bromide **2**. When the fluoride source was changed from TBAF to TBAT, the conversion of **5** to the β-anomer of **3** was achieved in higher yield and required a slightly shorter reaction time. Another transformation which proved difficult using the silicate generated by TBAF/TMS-N_3 was the conversion of β-chloride **6** to the α-anomer of **3**. When TBAF was employed as the fluoride source, the reaction afforded a 9:1 (α/β) anomeric mixture of azide **3**. However, when TBAT was used as the fluoride source, the reaction proceeded in a completely stereoselective manner to provide the α-anomer of **3**.

The last entries are the conversion of α-trichloroimidates **7** and **9** to corresponding β-azides **8** and **3**. When TBAF was used with **7**, the reaction time was very long, anomeric selectivity was poor (resulting in a 1:1, α/β mixture of **8**), and half of the starting material was hydrolyzed, presumably due to the water in TBAF solutions. By changing the fluoride source to TBAT, the reaction time was greatly reduced, the anomeric selectivity was improved (only the β-anomer of **8** was obtained), and the overall yield was improved. When TBAF was used with trichloroimidate **9**, the only product observed was the peracetylated pyranose which resulted from hydrolysis. When TBAT was used as the fluoride source, only a small amount of desired azide **3**β (20%) was obtained with a substantial amount of hydrolyzed material (65%).

In conclusion, the preparation of glycosyl azides in a catalytic and stereocontrolled manner was successfully achieved under mild conditions. This method provides a viable alternate route for the preparation of glycosyl azides. The mechanism of this process is currently being investigated and will be reported in due course.

Experimental Section

General Methods. All ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$. Tetrahydrofuran (THF) was distilled over sodium and benzophenone. Tetrabutylammonium fluoride (TBAF) was used as a 1.0 M solution in THF, TBAT was prepared as described by Pilcher,[15] and α-bromo glucose **2** was purchased from Acros (cat. 27093-0100) and recrystallized from diisopropyl ether prior to use. The remaining solvents and chemicals were used as received. Flash chromatography was performed using 230−400 mesh silica gel. Reactions were monitored by analytical TLC carried out on silica gel plates and visualized by charring with vanillin/sulfuric acid solution. All reactions utilizing TBAF as the fluoride source, in a noncatalytic amount, have been reported. Analytical data (IR, ^{1}H and ^{13}C NMR, MS, and optical rotations) for glycosyl derivatives **2**−**9** were reported in our earlier paper.[17]

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl Azide (3β). Catalytic Studies. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**) (89 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Azidotrimethylsilane (40 μL, 0.30 mmol) was added via syringe followed by TBAF. TBAF was added in three different volumes, 0.30 mL (0.30 mmol, 100 mol %), 0.15 mL (0.15 mmol, 50 mol %), and 0.06 mL (0.06 mmol, 20 mol %). Each solution was stirred at ambient temperature for the time indicated in Scheme 1. Each solution was filtered through a plug of silica gel, dried over Na_2SO_4, and concentrated in vacuo to give a yellow amorphous solid. Each residue was crystallized from absolute ethanol to afford azide **3**β as a white solid in the amount indicated in Scheme 1: mp 126−127 °C (lit.[23] mp 126−127 °C). Physical and spectroscopic properties of **3**β were identical to previously reported values.[23,24]

Reaction with Tetrabutylammonium Bromide. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**) (89 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Azidotrimethylsilane (40 μL, 0.30 mmol) was added via syringe followed by tetrabutylammonium bromide (97 mg, 0.30 mmol). The solution was stirred 65 °C for 72 h. The organic solution was evaporated and chromatographed (4:1, hexanes/EtOAc) to afford 50 mg (56%) of starting α-bromide **2** and 30 mg (37%) of azide **3**β, both as white solids.

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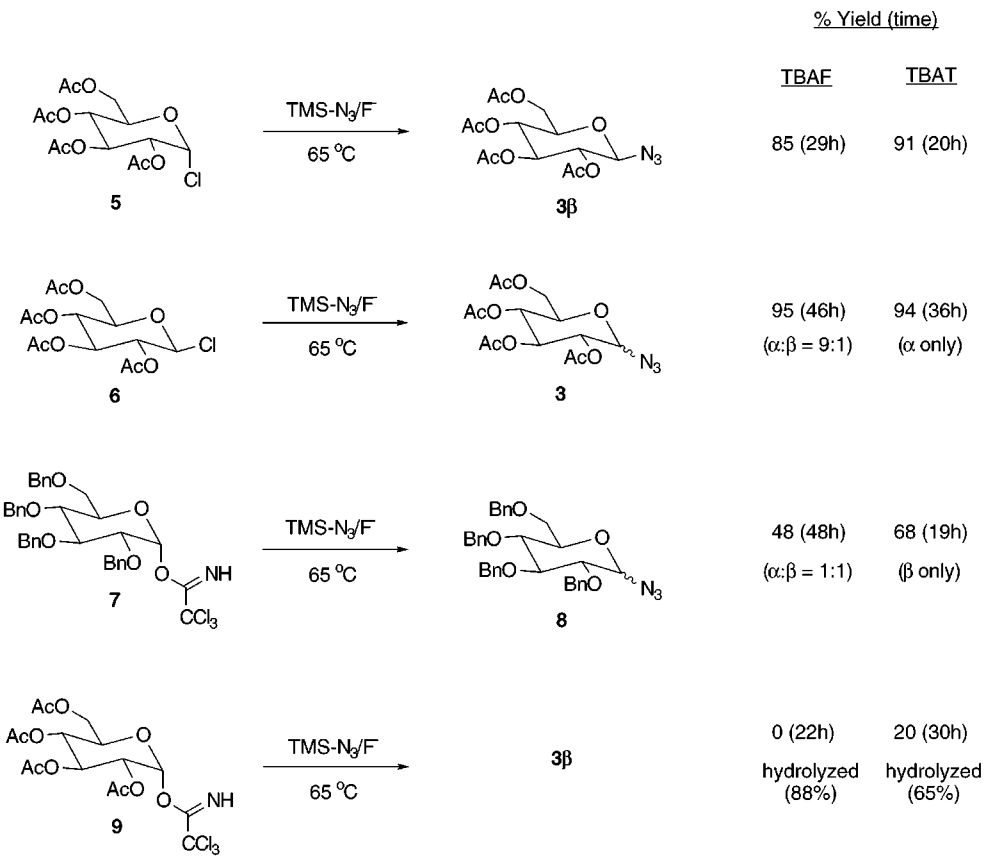
Scheme 3



TBAT as Fluoride Source. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**) (89 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Azidotrimethylsilane (40 μL, 0.30 mmol) was added via syringe followed by TBAT (162 mg, 0.301 mmol). The solution was stirred at ambient temperature for 1.5 h. The organic solution was concentrated in vacuo and chromatographed (4:1, hexanes/EtOAc) to give a yellow amorphous solid. The residue was crystallized from absolute ethanol to afford 78 mg (96%) of azide **3**β as a white solid.

From α-Chloride 5. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride (**5**)[25] (80 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Azidotrimethylsilane (40 μL, 0.30 mmol) was added via syringe followed by TBAT (162 mg, 0.301 mmol). The solution was stirred at 65 °C for 20 h. The organic solution was concentrated in vacuo and chromatographed (4:1, hexanes/EtOAc) to give a yellow amorphous solid. The residue was crystallized from absolute ethanol to afford 74 mg (91%) of azide **3**β as a white solid.

This reaction has been performed on the 1-g scale without incident.

From α-Trichloroimidate 9. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl trichloroimidate (**9**)[26](430 mg, 0.87 mmol) was dissolved at 25 °C in 10 mL of THF. Azidotrimethylsilane (150 μL, 1.13 mmol) was added via syringe followed by TBAT (610 mg, 1.13 mmol). The solution was stirred at 65 °C for 30 h. The organic solution was concentrated in vacuo and chromatographed (4:1, hexanes/EtOAc) to give 189 mg (65%) of hydrolyzed sugar and 65 mg (20%) of azide **3**β, both as white solids.

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl Azide (3α). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**5**)[27](80 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Azidotrimethylsilane (40 μL, 0.30 mmol) was added via syringe followed by TBAT (162 mg, 0.301 mmol). The solution was stirred at 65 °C for 36 h. The organic solution was concentrated in vacuo and chromatographed (4:1, hexanes/EtOAc) to give a yellow amorphous solid. The residue was crystallized from diisopropyl ether to afford 76 mg (94%) of azide **3**α as a white solid: mp 98−99 °C (lit.[23]mp 98−99.5 °C). Physical and spectroscopic properties of **3**α were identical to previously reported values.[23,28]

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl Azide (8β). 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl trichloroimidate (**7**)[29] (150 mg, 0.22 mmol) was dissolved at 25 °C in 3 mL of THF. Azidotrimethylsilane (40 μL, 0.30 mmol) was added via syringe followed by TBAT (162 mg, 0.301 mmol). The solution was stirred at 65 °C for 19 h. The organic solution was concentrated in vacuo and chromatographed (9:1, hexanes/EtOAc) to give 84 mg (68%) of azide **8**β as a yellow syrup. Physical and spectroscopic properties of **8**β were identical to previously reported values.[8,23]

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