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Note

Stereospecific synthesis of α-*C*-glycosyl derivatives (“α-*C*-glycosides”) of *N*-acetylneuraminic acid by samarium-mediated reductive desulfonylation of a glycosyl phenylsulfone

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Abstract

A samarium-mediated Barbier reaction was performed to afford *N*-acetylneuraminic acid α-*C*-glycosyl compounds (“α-*C*-glycosides”) in excellent yield. The neuraminic acid phenyl sulfone or 2-pyridyl sulfone derivatives reacted with ketones or aldehydes resulting in the instantaneous and stereospecific formation of Neu5Ac α-*C*-glycosides. The phenyl and the 2-pyridyl sulfone derivatives were equally effective in this reaction. Finally, this procedure was successfully applied to the preparation of *C*-disaccharide, α-Neu5Ac-(2→6) Gal.

Keywords: Samarium diiodide; *C*-glycosyl compounds; *C*-glycosides; Phenylsulfone; Barbier reaction; Neu5Ac

Sialic acids are involved in a number of biological processes including cell–cell, cell–microorganism, cell–toxin, and cell–antibody binding. The importance of sialic acids, in processes with relevance to human diseases, has led to interest in the synthesis of both natural and modified sialic acids [1]. *C*-linked *N*-acetylneuraminic acid (Neu5Ac)-containing compounds are of particular interest for their potential pharmaceutical applications. These are expected to have both improved enzymatic hydrolytic stability and exoanomeric conformational similarity to the corresponding *O*-glycosides [2]. Except for several elegant methods for direct C–C bond formation at the anomeric center in aldoses and ketoses, few advances have been reported in the synthesis of Neu5Ac *C*-glycosides [3]. The major problem confounding such synthesis is the requirement that the C–C bond being formed results in a quaternary C atom. Presented here is the first application of phenyl sulfone for the stereocontrolled synthesis of carbon glycosides of Neu5Ac via a glycosyl samarium(III) intermediate [4].

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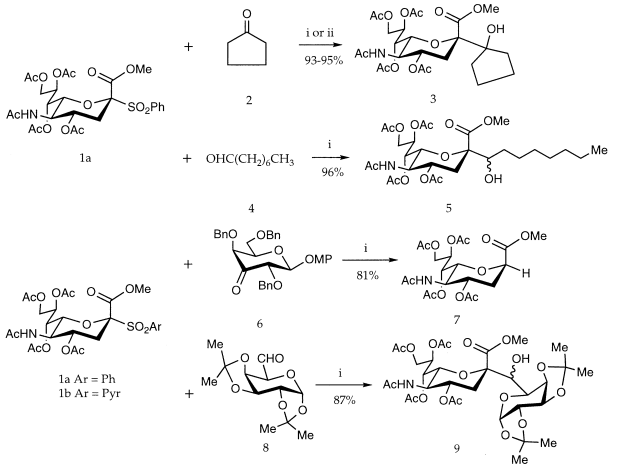
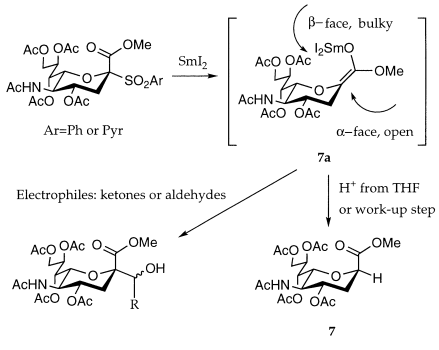
It was reported that the 2-pyridyl sulfone decreased the lowest unoccupied molecular orbital (LUMO) energy level of the SO_2Ar when compared to the phenyl sulfone moiety [5]. This decreased energy facilitated a one-electron transfer and homolytic fragmentation, affording the desired anomeric free radical. Subsequent work by Beau and co-workers [6] on the synthesis of *C*-mannopyranoside and *C*-galactosamine derivatives confirmed that the approach using 2-pyridyl sulfone is a useful method for the *C*-glycoside synthesis of aldoses. Encouraged by the reports of Sinaÿ [7] and Wong [8] on the samarium-mediated coupling of α-alkoxy sulfones with ketones, and glycosyl phosphates with ketones or aldehydes, we decided to investigate the use of SmI_2 as a reagent for mediating this same type of carbon radical and/or anionic reaction by using the Neu5Ac phenyl sulfone. Hexamethylphosphoric triamide (HMPA) reportedly accelerates rates of SmI_2 reductions, and it is usually used as a ligand in the samarium-mediated reactions [9]. Thus, our model studies were first directed towards the Neu5Ac phenyl sulfone **1a** [10] and ketone **2** (Scheme 1) treated with SmI_2–THF–HMPA. As expected [4], this reaction afforded Neu5Ac α-*C*-glycoside **3** stereospecifically in 95% yield. The α configuration was deduced by the empirical rules suggested by Hasegawa and coworkers [11]. The relatively downfield chemical shift of H-4 (4.77 ppm, compared to 5.25 ppm for the β-anomer), higher $J_{7,8}$ value (7.6 Hz, around 2.4 Hz for the β-anomer) and a small $\Delta\delta$ value of H_{9a}–H_{9b} (0.20–0.24 ppm, 0.66–0.79 ppm for the β-anomer) clearly indicated the α-configuration of the product. The reaction was next examined in the absence of added HMPA to study its role. Surprisingly, the same *C*-glycoside **3** was formed in 2 min. The characteristic blue color faded to a cloudy yellow as the reaction proceeded to completion. It appears that SmI_2 alone is sufficient for the formation of a relatively stable tertiary intermediate at the anomeric center of Neu5Ac. Thus, the use of the added HMPA can be conveniently avoided. The condensation of phenyl sulfone **1a** with octyl aldehyde **4** was next examined under Barbier conditions in the absence of HMPA. Neu5Ac α-*C*-glycoside **5** was obtained in 96% yield with a 1:1 diastereomeric mixture of both R and S chirality at C-1′.

When a fully protected sugar ketone **6** [12] was subjected to the same condensation reaction, no trace of the *C*-disaccharide was observed. Instead, the α-2-deoxy derivative **7**, an inhibitor of X-31 HA hemagglutinin after deacetylation [13], was obtained exclusively. The steric hindrance of sugar ketone **6** might be responsible for the failure of this glycosidation reaction. The stereochemical outcome of this reaction suggests that the reaction might proceed through an intermediate samarium enolate derivative **7a** (Scheme 2). Thus, Neu5Ac *C*-glycosides formed under Barbier conditions generate only α products because the α face of this intermediate is much less sterically hindered than the β-face. Finally, a very efficient stereoselective synthesis of *C*-disaccharide [α-Neu5Ac-(2→6)Gal] was performed using the above stratagem (Scheme 1). Coupling of the phenyl sulfone **1a** and sugar aldehyde **8** [14] instantaneously generated the desired α-*C*-disaccharide **9** in a 3:1 diastereomeric mixture at C-6 and an 87% yield based on Neu5Ac. The α configuration of **9** was in accordance with the empirical rules [11].

The reactions leading to **7** and **9** were also tested using Neu5Ac 2-pyridyl sulfone (**1b**) with the same stereochemical outcomes and yields. Based on this



Scheme 1. i. 4 equiv of SmI_2 (0.1 M in THF); ii. 4 equiv of SmI_2 and 4 equiv of HMPA in THF.



Scheme 2.

observation, we believe there is no advantage in using the 2-pyridyl sulfone electrophile for the reaction of Neu5Ac under Barbier conditions. It is noteworthy that, unlike the *C*-glycosylation via lithium enolates, the samarium-mediated *C*-glycosylation of Neu5Ac is carried out under extremely mild reaction conditions (room temperature) and tolerates a wide variety of protecting groups, including acetyl groups which are widely used in carbohydrate chemistry.

1. Experimental

General methods.—Melting points were uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter at ambient temperature. ^{1}H NMR (500 MHz) spectra were acquired using a Varian Unity-500 spectrometer equipped with a VXR 5000 computer system. Mass spectra were obtained using a VG ZAB-HF instrument in fast-atom bombardment (FAB) ionization mode. All reactions were monitored by thin-layer chromatography on aluminum sheets, Silica Gel 60 F_{254} (E. Merck); detection under short wavelength UV light (254 nm) or by dipping the plates into staining solution (1.0 g ammonium cerium(IV) sulfate and 24.0 g ammonium molybdate in 31 mL sulfuric acid and 470 mL water) then heating. Flash chromatography was performed using 230–400 mesh silica gel 60. All solvents and reagents were obtained from Aldrich Chemical Co. (Milwaukee, WI, USA).

General procedure for Neu5Ac C-*glycosidation*.—Neu5Ac phenyl sulfone (2–150 mg) and 1.2–2.0 equiv of electrophile (ketone or aldehyde) were dried together under high vacuum for 4 h, then dissolved in degassed anhydrous THF (0.5–1 mL). SmI_2 (4 equiv, freshly prepared from Sm and ICH_2CH_2I, 0.1 M in THF) was added in one portion at room temperature with vigorous stirring. After 10 min, the reaction mixture was directly filtered, and the filtrate was concentrated under reduced pressure, then purified on silica gel column with EtOAc as eluent.

*(*R,S*)-1-*C-*[Methyl-5-acetamido-4,7,8,9-tetra-*O-*acetyl-3,5-dideoxy-*D-glycero-α-D-galacto-*non-2-ulopyranosyl)onate]cyclopentan-1-ol* (**3**).—The *C*-glycoside was obtained as an oil in 95% yield from the reaction of **1a** and **2** using the general procedure described above: $[\alpha]_D^{20}$ −10° (ca. 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.60 (b s, 8 H), 1.90 (s, 3 H, CH_3CO), 1.95 (dd, 1 H, $J_{3ax,3eq}$ = 10.7 Hz, $J_{3ax,4}$ = 9.2 Hz, H-3ax), 2.03, 2.05, 2.12, 2.16 (4 s, 4 (×3 H, 4 CH_3CO), 2.51 (dd, 1 H, $J_{3e,4}$ 5.5 Hz, H-3eq), 2.81 (br s, 1 H, O*H*), 3.79 (s, 3 H, OCH_3), 4.04 (t, 1 H, $J_{4,5}$ = $J_{5,6}$ = 9.1 Hz, H-5), 4.10–4.14 (m, 2 H, H-6, H-9a), 4.34 (dd, 1 H, $J_{8,9b}$ 2.0, $J_{9a,9b}$ 11.9 Hz, H-9b), 4.77 (ddd, 1 H, H-4), 5.13 (d, 1 H, *J* 8.6 Hz, NH), 5.31 (dd, 1 H, $J_{6,7}$ 1.8 Hz, $J_{7,8}$ 7.6 Hz, H-7), 5.42 (ddd, 1 H, H-8). HRFABMS: calcd for $C_{25}H_{37}NO_{13}Na$ (M + Na): 582.2163. Found: *m*/*z* 582.2171 (M + Na).

*(*R,S*)-1-*C-*[Methyl 5-acetamido-4,7,8,9-tetra-*O-*acetyl-3,5-dideoxy-*D-glycero-α-D-galacto-*non-2-ulo pyranosyl)onate]octan-1-ol* (**5**).—The C-glycoside was obtained as an oil in 96% yield from the reaction of **1a** and **4** using the general procedure described above: ^{1}H NMR ($CDCl_3$): (R:S = 1:1) 0.90–1.40 (m, 15 H), 1.88, 2.03, 2.06, 2.12, 2.16 (2×5 s, 15 H), 2.36 (dd, 0.5 H), 2.45 (dd, 0.5 H), 2.59 (d, 0.5 H), 2.98 (d, 0.5 H), 3.60–3.70 (m, 2 H), 3.78 (2 s, 3 H), 4.00–4.20 (m, 3 H), 4.32 (dd, 0.5 H), 4.36 (dd, 0.5 H), 4.75–4.82 (m, 1 H), 5.10–5.19 (m, 1 H), 5.29–5.34 (m, 1 H), 5.40 (ddd, 0.5 H), 5.46 (ddd, 0.5 H); HRFABMS: calcd for $C_{28}H_{45}NO_{13}Na$ (M + Na): 626.2788. Found: *m*/*z* 626.2792 (M + Na).

*4-Methoxyphenyl 2,4,6-tri-*O-*benzyl-*α-D-xylo-*hex-3-ulopyranoside* (**6**).—The sugar ketone was synthesized from α-D-galactopyranose using identical conditions as described by Schmidt et al. [12] for the synthesis of the methyl α-D-glycoside. Flash chromatography of the final product gave **6** as a syrup (46% overall yield from α-D-galactopyranose): $[\alpha]_D^{20}$ −27° (ca. 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 3.74–3.80 (m, 6 H, H-5, 6a, 6b, MeO). 3.93 (s, 1 H, H-4), 4.34, 4.43 (2 d, 2 H, *J* 10.7 Hz, $PhCH_2$), 4.46, 4.52 (2 d, 2 H, *J* 10.2 Hz, $PhCH_2$), 4.60 (d, 1 H, *J* 9.2 Hz, H-2), 4.74, 4.78 (2 d, 2 H, *J* 12.4 Hz, $PhCH_2$). 4.94 (d, 1 H, *J* 9.2 Hz, H-1), 6.80, 7.02 (2 d, 2×2 H, aromatic H of MeOPh), 7.20–7.42 (m, 15 H, aromatic H of Bn); HRFABMS: calcd for $C_{34}H_{34}O_7Na$ (M + Na): 577.2202. Found: *m*/*z* 577.2206 (M + Na).

*Methyl 5-acetamido-4,7,8,9-tetra-*O-*acetyl-2,6-anhydro-2,3,5-trideoxy-*D-glycero-α-D-galacto-*nononate* (**7**).—Reaction of **1a** or **1b** with **6** using the general procedure described above afforded **7** as a syrup in 81% yield. The ^{1}H NMR data of compound **7** are in accordance with those in the literature [15].

*(*R,S*)-6-*C-*[(Methyl 5-acetamido-4,7,8,9-tetra-*O-*acetyl-3,5-dideoxy-*D-glycero-α-D-galacto-*non-2-ulopyranosyl)onate]-1,2:3,4-di-*O-*isopropylidene-*α-D-*galactopyranose* (**9**).—The *C*-disaccharide was

obtained as an oil in 87% yield from the reaction of **1a** or **1b** with sugar aldehyde **8** [14] using the general procedure described above. A small amount of pure major isomer was obtained by flash column chromatography using 1:3 petroleum ether–EtOAc as a eluent: $[\alpha]_D^{20}$ −3.7° (ca. 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): (major isomer) 1.32, 1.38, 1.50, 1.53, 1.86, 2.03, 2.05, 2.13, 2.17 (9s, 9×3 H), 2.63 (dd, 1 H), 3.14 (d, 1 H), 3.60 (d, 1 H), 3.79 (s, 3 H), 3.90–3.96 (m, 2 H), 4.03 (t, 1 H), 4.10 (dd, 1 H), 4.13 (dd, 1 H), 4.28 (br s, 2 H), 4.30 (dd, 1 H), 4.48 (d, 1 H), 4.58 (dd, 1 H), 4.76 (ddd, 1 H), 5.12 (d, 1 H), 5.29 (dd, 1 H), 5.47 (br d, 1 H), 5.52 (d, 1 H). HRFABMS: calcd for $C_{32}H_{48}NO_{18}$ (M + H): 734.2871. Found: *m/z* 734.2881 (M + H).

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