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Selective synthesis of Neu5Ac2en and its oxazoline derivative using $BF_3{\cdot}Et_2O$

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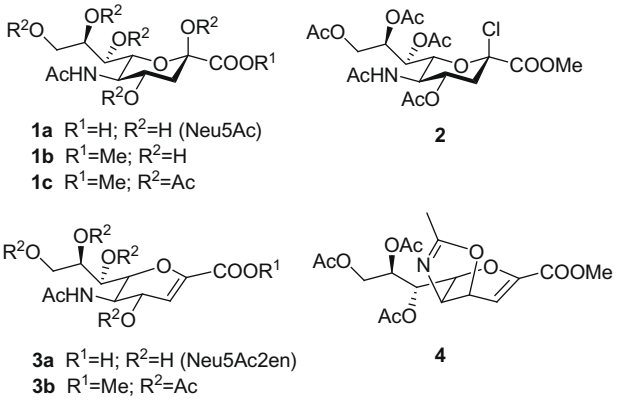
ABSTRACT

Application of the Lewis acid $BF_3{\cdot}Et_2O$ to the selective synthesis of 5-acetamido-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonic acid (Neu5Ac2en) and the related oxazoline, methyl 7,8,9-tri-*O*-acetyl-2,3,4,5-tetradeoxy-2,3-didehydro-2,3-trideoxy-4′,5′-dihydro-2′-methyloxazolo[5,4-*d*]- D-*glycero*-D-talo-non-2-enonate is described.

N-Acetylneuraminic acid **1a** (sialic acid, Neu5Ac, Fig. 1) is commonly found on the surface of mammalian cells and is of particular importance in cellular recognition processes, cell adhesion and disease states.[1] Hence there is great interest in the synthesis of sialosides, either as biological probes or as enzyme inhibitors. Many of the procedures to obtain such analogues proceed through the intermediate 2-chlorosialic acid **2** (Fig. 1), but a disadvantage to its use is competitive elimination of the chlorine atom, which is aided by the electron-withdrawing nature of the protected carboxylic acid at the 2-position. This commonly leads to the formation of a 2-deoxy-2,3-dehydro-Neu5Ac derivative (Neu5Ac2en **3a**, Fig. 1). Neu5Ac2en and its *N*-glycolyl analogue are metabolic products found in body fluids and secretions[2] and as a result are of interest *per se*. Neu5Ac2en[3] is a potent sialidase inhibitor, as are analogues modified at C-4.[4–6] It has been used as the basis for the design and synthesis of sialidase inhibitors with anti-influenza activity,[7–9] the best example being Zanamivir (4-guanidino-Neu5Ac2en). In addition, inhibition of other sialidases has been achieved by z2,3-unsaturated analogues.[10–12] Chemically, per-*O*-acetylated 2,3-unsaturated sialic acid derivative **3b** has been used for the preparation of analogues of sialic acid via the epoxide,[13–16] synthesis of *N*-acetyl-3-fluoroneuraminic acid by treatment of the glycal **3b** with $X_2Fe{-}BF_3{\cdot}Et_2O$,[17] molecular fluorine[18] or TEDA–$CH_2Cl{\cdot}2BF_4$ (Selectfluor)[19] and for the synthesis of C-4 substituted sialic acid analogues via the 4,5-oxazoline derivative **4**.

Typically, the preparation of **3b** involves the base-promoted elimination of 2-chlorosialoside **2**, using bases such as DBU,[13,20,21] anhydrous H_2PO_4 in refluxing MeCN[22] and pyridine.[16] In addition, one group has reported the synthesis of **3b** from per-*O*-acetyl methyl ester **1c** when treated with $PPh_3{\cdot}HBr$ in MeCN.[19] The respective 4-epimer can be readily prepared from methyl ester **1b** when treated with Ac_2O in H_2SO_4 at 80 °C,[10,23] or from the 2-bromosialic acid derivative when treated with *syn*-collidine.[20]

Also of importance is the corresponding 2,3-unsaturated 4,5-oxazoline derivative **4**, particularly in the synthesis of C-4 modified sialosides.[4,7,24] Compound **4** is prepared easily by the Lewis acid-promoted internal nucleophilic attack of the acetamido group (lone pair of the oxygen) on the electrophilic centre at the 4-position with inversion of configuration. Two different strategies have



1a R^1=H; R^2=H (Neu5Ac)
1b R^1=Me; R^2=H
1c R^1=Me; R^2=Ac

2

3a R^1=H; R^2=H (Neu5Ac2en)
3b R^1=Me; R^2=Ac

4

Figure 1.

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been reported in the literature: (a) synthesis of the 4,5-oxazoline **4** from the Neu5Ac2en per-*O*-acetate **3b** using $BF_3{\cdot}Et_2O$[25] or $SnCl_4$[26] and (b) synthesis of the 4,5-oxazoline **4** from per-*O*-acetylated sialic acid **1c**, using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst.[4,6,27]

The chemical scope of oxazoline **4** is diverse. Catalytic hydrogenation (Pd/C) produces the respective 4-deoxy Neu5Ac2en derivative[4] whereas acidic cleavage by trifluoroacetic acid gives the 4-*epi*-Neu5Ac2en derivative.[4] This 4-*epi*-Neu5Ac2en has been prepared previously by refluxing Neu5Ac with sulfuric acid and acetic anhydride.[10] Nucleophiles have also been introduced to this molecule, for example, sulfur and nitrogen at C-4; the oxazoline ring was opened stereoselectively via an S_N2 reaction to obtain the 4-α diastereomer.[25] 2,3-Unsaturated derivatives were also synthesised by acetolysis of β-methyl glycosides of sialic acid in a one-pot reaction using Ac_2O in concentrated sulfuric acid with further hydrolysis to the 4-*epi*-acetate or 4-*epi*-hydroxy derivative at pH 5 and pH 2, respectively.[28] Recently, a 3,4-unsaturated sialic acid derivative was prepared via a Lewis acid-catalysed Ferrier reaction of the activated allylic oxazoline **4**.[29]

Our attempts to prepare a *C*-allyl-sialoside directly from the per-*O*-acetate using $BF_3{\cdot}Et_2O$, in a manner similar to that reported with aldoses,[30] resulted in a mixture of products with an olefinic hydrogen. Prompted by this finding, a series of experiments were carried out to investigate the effect of $BF_3{\cdot}Et_2O$ on sialic acid derivative **1c** in the absence of a nucleophile (Scheme 1). Conditions were varied, including equivalents of $BF_3{\cdot}Et_2O$, reaction times and solvents (Table 1). Interestingly, selectivity as to the formation of either per-*O*-acetylated Neu5Ac2en **3b** or the 2,3-unsaturated 4,5-oxazoline sialic acid **4** could be achieved according to the solvent used. Performing the reaction in acetonitrile resulted in 2,3-unsaturated sialic acid **3b** whereas use of dichloromethane led almost exclusively to 2,3-unsaturated 4,5-oxazoline sialic acid **4** (entries 2 and 3). It was found that selectivity was both time and temperature dependent. By monitoring the reaction using ^1H NMR spectroscopy, it was observed that reaction times longer than 1.5 h increased the proportion of **4** (decreasing the ratio of **3b**:**4**) in dichloromethane. Compound **4** was selectively formed when the reactions were carried out in dichloromethane overnight. It was found that 1.2 equiv of the Lewis acid $BF_3{\cdot}Et_2O$ was sufficient to complete the reaction (entry 5). Fewer equivalents of $BF_3{\cdot}Et_2O$ led to a slight increase in formation of compound **4** (entry 7) and incomplete conversion (entry 8). In contrast, compound **1c** was completely converted to **3b** after 1.5 h when the reaction was carried out in acetonitrile at 25 °C (entry 3). As a comparison, the reactions were also attempted using $SnCl_4$, which produced a ratio of **3b**:**4** of 1:1 over a similar reaction time. $BF_3{\cdot}Et_2O$ clearly delivers a significantly higher degree of selectivity.

In further experiments, we observed that reacting sialic acid methyl ester **1b** with $BF_3{\cdot}Et_2O$ and acetic anhydride also promoted formation of oxazoline **4**. It should be noted that these conditions were recently used in a similar manner for per-*O*-acetylated aldoses.[31] In this case, a mixture of **1c**, **3b** and **4** was obtained. Interestingly, an excess of Ac_2O led to that mixture whereas an excess of $BF_3{\cdot}Et_2O$ led to only **3b** and **4**, with a predominance of **4** (Scheme 2). The von Itzstein group has reported the synthesis of **4** in one step when treating 1-methylsialoside methyl ester with acetic anhydride using TMSOTf as catalyst, but the use of $BF_3{\cdot}Et_2O$ led only to peracetylation and no elimination product was observed.[28]

Table 1

1c $\xrightarrow[\text{overnight}]{\text{Lewis acid}}$ **3b** + **4**

Entry	Lewis acid	Equivalents	Solvent	Yield[a] (%)	Ratio **3b**:**4**[b]
1	$BF_3{\cdot}Et_2O$	6.0	CH_2Cl_2	93	1:99
2	$BF_3{\cdot}Et_2O$	3.0	CH_2Cl_2	74	1:99
3	$BF_3{\cdot}Et_2O$	3.0	CH_3CN[c]	92	9:1
4	$BF_3{\cdot}Et_2O$	3.0	CH_2Cl_2[c]	51	5:1
5	$BF_3{\cdot}Et_2O$	1.2	CH_2Cl_2	95	1:99
6	$BF_3{\cdot}Et_2O$	1.0	CH_2Cl_2[d]	ND	2:3
7	$BF_3{\cdot}Et_2O$	1.0	CH_2Cl_2	98	1:5
8	$BF_3{\cdot}Et_2O$	0.5[e]	CH_2Cl_2	56	1:4
9	$SnCl_4$	1.2	CH_3CN	91	1:1

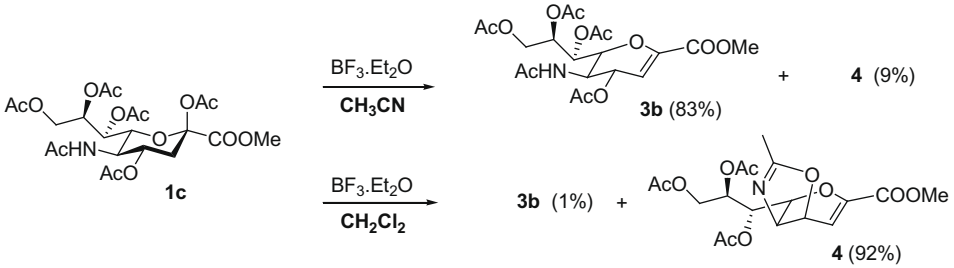
ND—not determined.
[a] Total isolated yield of **3b** + **4**.
[b] Ratio determined by ^1H NMR.
[c] 1.5 h, 25 °C.
[d] 4.5 h, rt.
[e] 7.5% of starting material was recovered.

The structural assignment of **4** was aided by data reported in the literature.[10] It should be noted that the coupling constant between H-4 and H-5 changes from 2.5 to approximately 9 Hz on formation of the oxazoline ring. In addition, the double doublet attributed to H-6 is shielded by the oxazoline ring and is therefore shifted to higher field (δ 3.41).

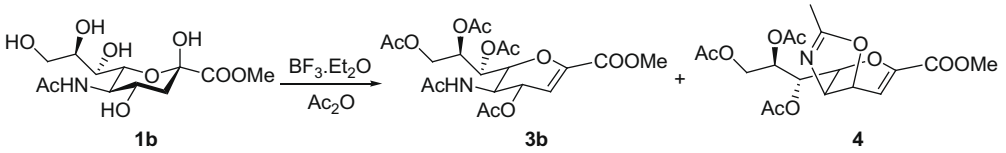
It is believed that the stability of the oxazoline **4** is limited, showing a high susceptibility to ring opening and consequent formation of C-4 substituted analogues. Thus, the preparation of oxazoline **4** directly from methyl ester **1b** or from the per-*O*-acetate sialic acid **1c** to obtain Neu5Ac2en derivatives is a significant advantage, given that transformations such as hydrogenation, halogenation or oxidations have been shown to have drawbacks when carried out with Neu5Ac2en itself.

In summary, the Lewis acid $BF_3{\cdot}Et_2O$ can be utilised to selectively prepare Neu5Ac2en **3b** or the related oxazoline **4**, depending on the conditions used. Acetonitrile affords Neu5Ac2en per-acetate **3b** whereas dichloromethane affords oxazoline **4** (Scheme 1). The methodology to synthesise Neu5Ac2en **3b**, in particular, offers significant advantages over published methods involving chlorosialoside **2**.

*Synthesis of methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-*D*-glycero-*D*-talo-non-2-enonate* (Neu5Ac2en, **3b**):[13,32] $BF_3{\cdot}Et_2O$ (72 μL, 0.57 mmol) was added to a solution of methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*galacto*-2-α/β-nonulopyranosonate (100 mg, 0.19 mmol) in



Scheme 1.



Scheme 2.

dry acetonitrile (2 mL) under a nitrogen atmosphere at 25 °C. After 90 min, the reaction mixture was diluted with dichloromethane (25 mL) and $NaHCO_3$ powder was added. The reaction mixture was filtered and concentrated to give **3b** (quant.).

*Synthesis of methyl 7,8,9-tri-O-acetyl-2,3,4,5-tetradeoxy-2,3-didehydro-2,3-trideoxy-4′,5′-dihydro-2′-methyloxazolo[5,4-d]-*D*-glycero-*D*-talo-non-2-enonate* (**4**):[10,33] $BF_3{\cdot}Et_2O$ (29 μL, 0.23 mmol) was added to a solution of methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*galacto*-2-α/β-nonulopyranosonate (100 mg, 0.19 mmol) in dry dichloromethane (2 mL) under a nitrogen atmosphere at room temperature. After stirring overnight, the reaction mixture was diluted with dichloromethane (25 mL) and $NaHCO_3$ powder was added. The reaction mixture was filtered and concentrated to give **4** (77 mg, 95%).

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32. *Compound* **3b**:[13] ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H, NAc), 2.01, 2.02, 2.05, 2.09 (4s, 12H, 4OAc), 3.77 (s, 3H, COOMe), 4.17 (dd, 1H, H-9a, $J_{8,9a}$ = 6.9 Hz, $J_{9a,9b}$ = 12.3 Hz), 4.35–4.38 (m, 2H), 4.57 (dd, 1H, H-9b, $J_{8,9b}$ = 3.4 Hz, $J_{9a,9b}$ 12.3 Hz), 5.33–5.34 (m, 1H), 5.42–5.34 (m, 2H), 5.58 (m, 1H), 5.98 (d, 1H, ^3J 2.7 Hz); ESI MS $C_{20}H_{27}O_{12}N$ (473.15) *m/z* 474 $[M+H]^+$, 496 $[M+Na]^+$.
33. *Compound* **4**:[10] ^{1}H NMR ($CDCl_3$) δ 1.99, 2.04, 2.04, 2.14 (4s, 12H, 3OAc and CH_3), 3.41 (dd, 1H, H-6, $J_{6,7}$ = 2.5 Hz, $J_{5,6}$ = 9.9 Hz), 3.79 (s, 3H, COOMe), 3.93 (dd, 1H, H-5, $J_{4,5}$ = 8.7 Hz, $J_{5,6}$ = 9.9 Hz), 4.22 (dd, 1H, H-9a, $J_{8,9a}$ = 6.3 Hz, $J_{9a,9b}$ = 12.5 Hz), 4.58 (dd, 1H, H-9b, $J_{8,9a}$ 2.5 Hz, $J_{9a,9b}$ = 12.5 Hz), 4.81 (dd, 1H, H-4, $J_{3,4}$ = 3.9 Hz, $J_{4,5}$ = 8.7 Hz), 5.53 (ddd, 1H, H-8, $J_{8,9a}$ = 2.5 Hz, $J_{6,7}$ = 6.0 Hz, $J_{8,9a}$ = 6.3 Hz), 5.62 (dd, 1H, H-7, $J_{6,7}$ = 2.5 Hz, $J_{6,7}$ = 6.0 Hz), 6.37 (d, 1H, H-3, $J_{3,4}$ = 3.9 Hz); ESI MS $C_{18}H_{23}NO_{10}$ (413.38) *m/z* 414 $[M+H]^+$.