Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 343 (2008) 936–940
Carbohydrate RESEARCH

Note

Investigation into an efficient synthesis of 2,3-dehydro-*N*-acetyl neuraminic acid leads to three decarboxylated sialic acid dimers

Evan J. Horn, Jonel P. Saludes and Jacquelyn Gervay-Hague*

Department of Chemistry, University of California, Davis, One Shields Ave., Davis, CA 95616, USA

Received 7 November 2007; received in revised form 19 January 2008; accepted 24 January 2008
Available online 2 February 2008

Abstract—Sialic acid, an important carbohydrate found incorporated on the cell surface of many organisms, has been modified for use in a wide range of biological and pharmaceutical applications. We hypothesized that 4,7,8,9-tetra-*O*-acetyl-2-deoxy-2,3-dehydro-*N*-acetyl neuraminic acid methyl ester (**4**) could be efficiently synthesized in a one-pot reaction by heating peracetylated sialic acid (**2**) in pyridine and acetic anhydride to induce β-elimination. When reduced to practice, this reaction produced only modest yields of **4**. Six compounds, including three new decarboxylated sialic acid dimers, were also found to have been synthesized in the reaction. In an effort to better understand the chemistry and the mechanisms of this reaction, all of the side products were isolated and fully characterized.
© 2008 Elsevier Ltd. All rights reserved.

Keywords: Sialic acid; Decarboxylation; Neu5Ac2en

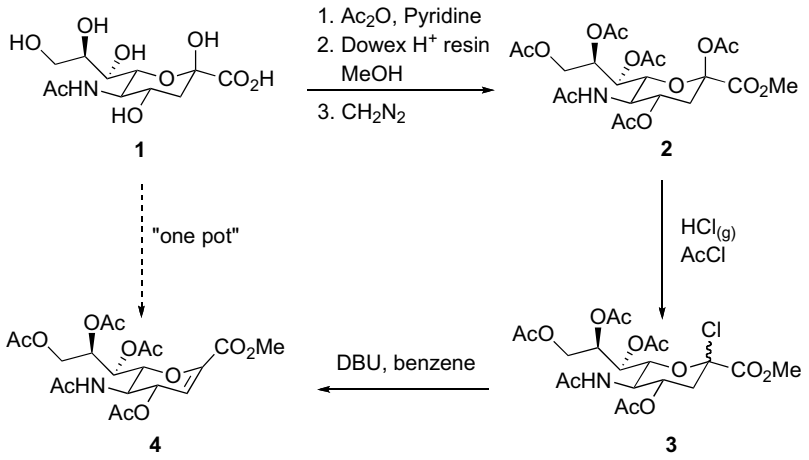
Sialic acid (*N*-acetylneuraminic acid; Neu5Ac, **1**) has been modified for use in a wide range of biological and pharmaceutical applications. The 2,3-dehydro derivative of Neu5Ac (Neu5Ac2en, **4**) is a key intermediate in the preparation of the commercial anti-influenza drug, Zanamivir, which was found to be more effective than adamantane-based compounds.[1,2] Because of its synthetic importance, several methods have been reported for the synthesis of **4**.[3,4] These include the most widely used β-elimination of peracetylated Neu5Ac glycosyl chloride **3**[5] catalyzed by Et_3N or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1),[6,7] TMSOTf-catalyzed elimination of peracetylated Neu5Ac methyl ester **2**,[8] and oxidation[9] or elimination[10] of Neu5Ac thioglycoside. A recent approach to the preparation of **4** from **3** utilized Na_2HPO_4 in refluxing acetonitrile for 3 h.[11] Although this method gave an almost quantitative yield, the preparation of **3** required several steps and careful handling of HCl gas.

Our laboratory has found derivatives of **1** and **4** to be useful building blocks for constructing amide-linked homooligomers with stable secondary structures,[12,13] and we typically employed DBU-catalyzed β-elimination to make **4**. However, it was our hypothesis that the C-2 acetate could be a sufficiently good leaving group under the basic conditions of peracetylation, and that by simply heating **2** in a one-pot technique, we could induce β-elimination to afford **4.** To test this hypothesis, **1** was peracetylated to yield nearly pure product as evidenced by ^{1}H NMR and MS. The solution was then heated to 100 °C for 4 h. The crude reaction mixture was carried forward and treated with ethereal diazomethane to methylate the carboxylic acid to facilitate purification (Scheme 2).

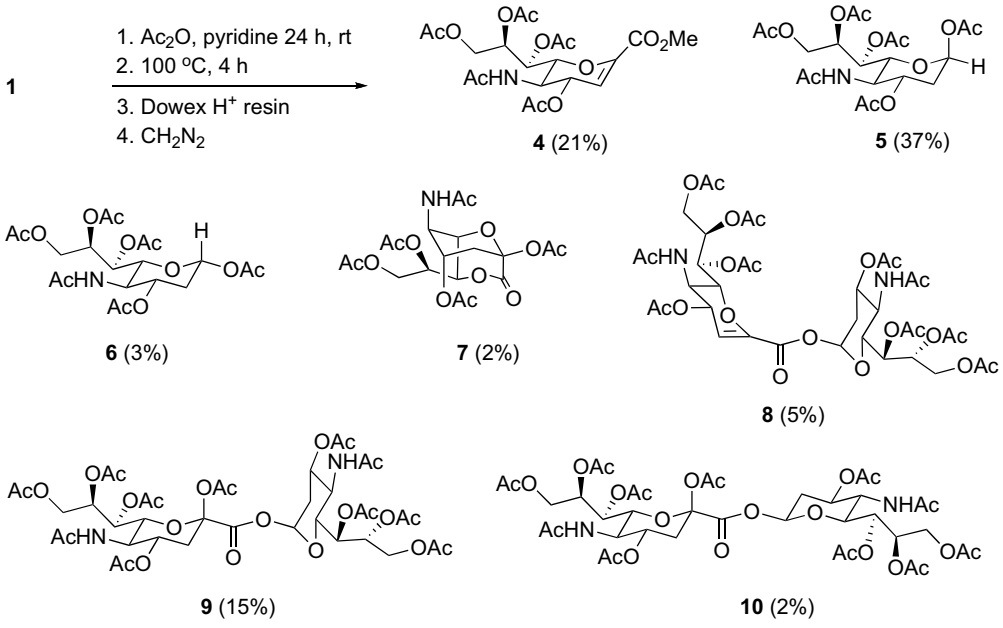
Initial ^{1}H NMR analysis showed that several products were formed in the reaction (Scheme 2), including compound **4** (confirmed via a doublet at δ 6.08, $J = 1.8$ Hz). The mixture was purified by a series of chromatographic procedures (Fig. S6, Supplementary data) to yield a total of seven compounds, with **4** isolated in only 21%. Two other products **5** (37%) and its anomer **6** (3%) were quite unexpected, with both having undergone

* Corresponding author. Tel.: +1 530 754 9577; fax: +1 530 752 8995; e-mail: gervay@chem.ucdavis.edu

0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.01.033



Scheme 1. The most widely used route to **4**, and our proposed one-pot synthesis.



Scheme 2. Products isolated from one-pot reaction.

decarboxylation. Both **5** and **6** were previously synthesized using 4:1 toluene–pyridine in the presence of lead(IV) acetate.[14] Formation of these compounds under standard peracetylation conditions was unprecedented. Compound **7**, a 1→7 lactone which is a common side product of peracetylation,[15] was also found in small amounts (2%).

Compounds **8**, **9**, and **10** are novel compounds. We first believed these to be dimers based on a few observations. Their mass spectra showed molecular ions close to twice that of the previously isolated monomers, and the number of acetate peaks in the ^{1}H NMR spectra corresponded to dimeric, peracetylated structures. In addition, their ^{1}H NMR spectra showed similarities to **2**, **4**, **5**, and **6**, leading us to believe that each of these dimers are composed of a combination of any two of these previously isolated compounds. Compound **9**, being the dimer isolated in highest yield, was characterized first. Its low-resolution mass of m/z 957.3 $[M+Na]^+$ suggest that it was composed of a combination of **2** and either **5** or **6**. Deuterium exchange and ^{1}H NMR studies revealed two exchangeable protons from NHAc, indicating that the dimer is connected via an ester linkage. The mass difference of 74 amu between **9** and the sum of **2** (m/z 533.2 $[M]^+$) and **5** (or **6**) (m/z 475.2 $[M]^+$) indicate the absence of an acetate and Me of the methyl ester. Heteronuclear correlation by HSQC revealed that the downfield ^{1}H NMR peak at δ 6.15 is anomeric (^{13}C NMR δ 93.5), and not due to an olefinic proton. The configuration of this anomeric center was determined

Download English Version:

https://daneshyari.com/en/article/1389749

Download Persian Version:

https://daneshyari.com/article/1389749

Daneshyari.com