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The surprise synthesis of α-GlcNAc 1-C-sulfonates

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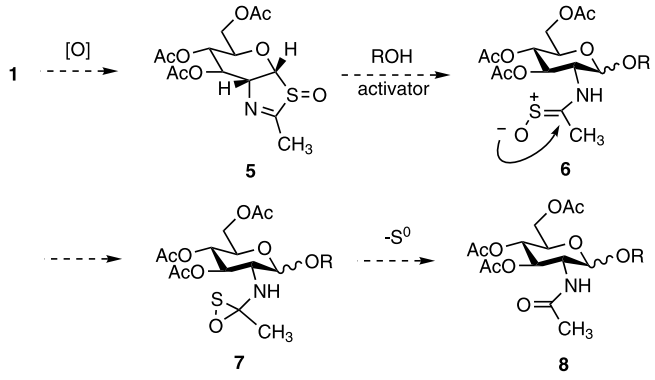
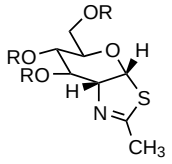
Abstract—Oxidation of GlcNAc thiazoline in the presence of an alcohol affords no glycosidation products, but rather the alkyl α-GlcNAc 1-C-sulfonate. E2 cleavage of the sulfonate ester and then *O*-deacetylation gives the α-GlcNAc 1-C-sulfonic acid, a new type of carbohydrate derivative.

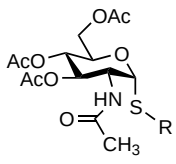
GlcNAc thiazoline, as its tri-*O*-acetate **1**,[1] can be hydrolyzed at the imine–S bond, and the resulting mercaptan **3** serves as an excellent precursor to a variety of α-GlcNAc[2] thioconjugates **4**.[3] The corresponding thiazoline triol **2** is an efficient inhibitor of those *N*-acetylhexosaminidases whose mechanism involves a structurally similar oxazolinium intermediate.[4] We further viewed **1** as a potential GlcNAc donor for glycosylations,[5] according to the process proposed in Scheme 1. Oxidation of **1** under acidic or other activating conditions and in the presence of an alcohol acceptor should convert the sulfur to its *S*-oxide (**5**), which might then undergo cleavage at the anomeric carbon[6] to give the *O*-glycoside **6**. Rearrangement of the thioamide *S*-oxide via **7** with loss of elemental sulfur[7] should generate the 2-acetamido group and afford the glycosylated product **8**.



Scheme 1. Proposed use of thiazoline **1** as a GlcNAc donor.



1: R = Ac
2: R = H



3: R = H
4: R = alkyl, aryl

One of the first sets of oxidizing reaction conditions tried, namely *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of ethanol, surprisingly gave no ethyl glycoside whatsoever, but rather the ethyl sulfinate **10** and the ethyl sulfonate **12** as the major isolated products (Scheme 2). The structure of sulfonate **12** was established by examination of its FAB mass (*m*/*z* 446, MLi^+) and ^1H and ^{13}C NMR spectra. The carbohydrate portion of **12** spectroscopically resembles other α-GlcNAc thioconjugates,[3] with the anomeric proton and carbon appearing at 5.35 ($J = 6.3$ Hz) and 86.1 ppm, respectively. The $-SO_2OC\underline{H}_2CH_3$ resonance appears at 4.34 ppm as a quartet rather than as a diastereotopic pair. The analogous tri-*O*-benzyl thiazoline **9**, which can be prepared from **2** by benzylation,[8] also gave an ethyl sulfonate (**13**, Scheme 2) under the same conditions. While a few pyranoside 6-C- and 3-C-sulfonic acids have been synthesized,[9] **12** and **13** are the first examples of anomeric sulfonates.

Each sulfinate (**10** and **11**) was formed as an apparent single diastereomer. Their characterization by mass and ^1H and ^{13}C NMR spectra also leaves no doubt as to their structures, except for the configuration at sulfur. Separate oxidation of **10** with an additional equivalent of *m*-CPBA at room temperature gave sulfonate **12** (82%), which corroborates their structures, and *m*-CPBA oxidation of **1** in the presence of 2 equiv. of

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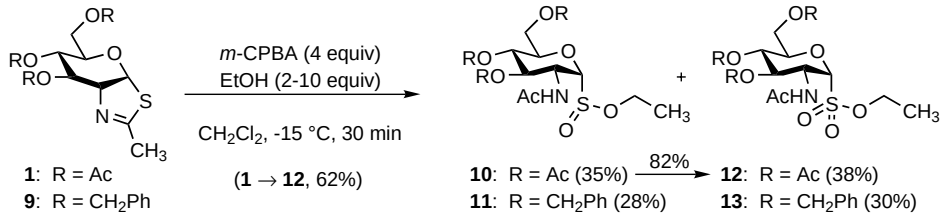
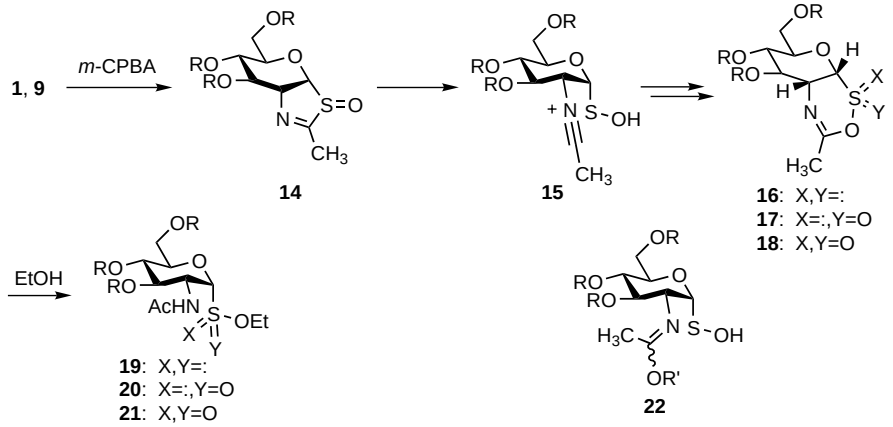


Scheme 2. Reaction of GlcNAc thiazolines with *m*-CPBA and ethanol.

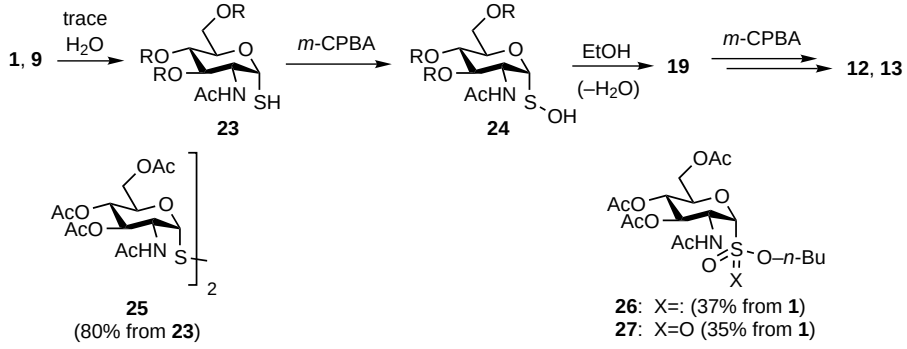
EtOH for 30 min at −15°C and then 2 h at room temperature caused complete conversion to sulfonate **12** (62%). To our knowledge **10** and **11** are likewise the first examples of anomeric sulfinates.

A mechanism for sulfonate formation is proposed in Scheme 3. In contrast to the corresponding oxazoline,[10] the thiazolines **1** and **9** probably undergo initial oxidation at the sulfur atom,[11] generating the thiazoline *S*-oxide, **14** (R = Ac or CH_2Ph). Ring expansion of **14** to **16**/**17**/**18** might occur via an intermediate nitrilium ion **15**, although imino ester (should *m*-chlorobenzoate add[12]) or imino ether intermediates (**22**) are alternative possibilities (see below). Oxidation of S(II) to the S(IV) stage could occur before ring closure to **17**, or after ring closure to **16**, or even after ring-opening (**19**→**20**). According to a separate control experiment, however, oxidation of sulfinate **10** is slow under these conditions at −15°C, so the first S(VI) intermediate (**18**) probably appears prior to ring-opening. Ring-opening reaction of **17**/**18** with ethanol generates the acetamido-containing products **20**/**21**.

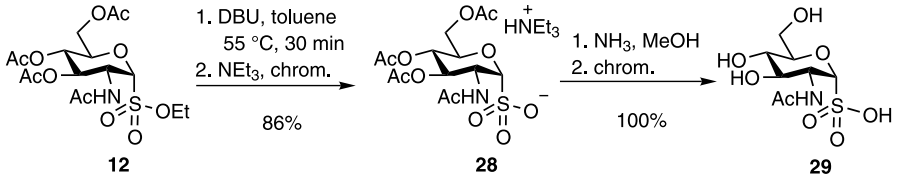
A plausible alternative scenario (Scheme 4) might involve hydrolysis, by adventitious moisture,[3] of the thiazoline **1** to the acetamido mercaptan **23**, and then oxidation of the mercaptan[13] in the presence of ethanol to afford the sulfonate. However, subjecting authentic **3** to identical reaction conditions (*m*-CPBA, EtOH, CH_2Cl_2, −15°C) led to neither **10** nor **12** in detectable amounts. Instead, the major product was the symmetrical disulfide **25**[14] (80%) which was not observed at all in the reaction of **1**. Furthermore, adding activated molecular sieves to the reaction of **1** gave the same products at about the same rate, and replacing ethanol with freshly distilled *n*-butanol gave the *n*-butyl sulfinate **26** and sulfonate **27** in analogous fashion. In our experience,[3] hydrolysis of **1** is slow in solvents less polar than methanol and at temperatures below 0°C. Thus, **1** was



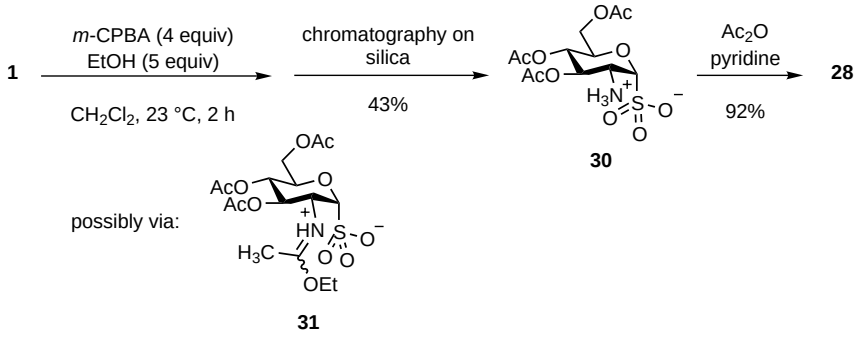
Scheme 3. Proposed mechanism for sulfonate formation.



Scheme 4. An alternative mechanism.



Scheme 5. Deprotection of GlcNAc sulfonate.



Scheme 6. Isolation of sulfonate zwitterion.

treated with *m*-chlorobenzoic acid (2 equiv.), ethanol (2 equiv.), and water (2 equiv.) in dichloromethane solution for 30 min at −15°C, mimicking the conditions for forming **10** and **12** (but without *m*-CPBA). TLC analysis showed only starting material **1**, and no evidence for hydrolysis to **23**. Hence, the mechanism in Scheme 4, involving prior hydrolysis of **1**, is probably not operating.

The deprotected sulfonic acid **29** (Scheme 5) was prepared from **12** by first cleavage of the ethyl sulfonate by an E2 process to give **28**, which was isolated as the chloroform soluble triethylammonium salt (NI-FAB-MS m/z 410, M^-). Subsequent ammonolysis of the acetates and Sephadex chromatography allowed isolation of **29** as the free sulfonic acid [NI-FAB-MS m/z 284, $(M-H)^-$].

TLC analysis of reactions of **1** with *m*-CPBA that were begun at room temperature, rather than taken through a temperature gradient, indicated substantial amounts of baseline material. By chromatographing the crude reaction mixture on silica with 1:9 $MeOH/CH_2Cl_2$ as the eluant, the amino sulfonic acid zwitterion **30** could be isolated in 43% yield (23% of **12** was also isolated), as shown in Scheme 6. The structure of **30** was confirmed by its *N*-acetylation to give **28**. Possibly the hydrolysis of acetamido occurs through the imino ether **31**,[15] itself formed by *m*-CPBA oxidation of the ring-opened imino ether **22** to the sulfonate stage. Ethanol may intercept **14** or **15** at the higher temperature, whereas at −15°C **22** either does not form, or does not oxidize, to an appreciable extent.

Common naturally occurring glycoconjugates that carry a negative charge include *O*-phosphates, *O*-sulfates, and C-oxidized sugars with components such as glucuronate and *N*-acetylneuraminate.[16] Synthetic pyranose C-sulfonates such as **29** can potentially mimic the natural charged species,[17] and perhaps better withstand chemical and enzymatic degradation. They thereby may find applications as enzyme inhibitors and biomechanistic probes.[18]

Acknowledgements

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18. Spectra for new compounds: **10** ^{1}H NMR (300 MHz, $CDCl_3$, δ, mult., integr., J in Hz) 6.43 (d, 8.4), 5.58 (dd, 10.5, 9.0), 5.11 (t, 9.3), 4.74 (d, 5.7), 4.66–4.74 (obscd ddd), 4.04–4.19 (m, 5 H), 2.04, 1.99, 1.98, 1.91 (4 s, 3H each), 1.34 (t, 3H, 6.6); FAB MS m/z 430 MLi^+, 424 MH^+. **11** ^{1}H NMR 7.19–7.25 (m, 15H), 5.33 (d, 7.9), 4.69 (d, 5.5), 4.46–4.82 (m, 7H), 4.01–4.27 (m, 3H), 4.05 (dd, 9.8, 8.5), 3.58–3.66 (m, 3H), 1.77 (s, 3H), 1.33 (t, 6.8); FAB MS m/z 574 MLi^+, 568 MH^+. **12** ^{1}H NMR 6.18 (d, 7.6), 5.65 (dd, 11.2, 9.2), 5.35 (d, 6.3), 5.17 (t, 9.6), 4.58 (ddd, 9.2, 7.6, 6.0), 4.34 (q, 2H, 7.2), 4.29–4.39 (obsc 1H), 4.21 (dd, 12.8, 4.4), 4.13 (dd, 12.8, 2.4), 2.08, 2.05, 2.04, 1.98 (4 s, 3H each), 1.41 (t, 3H, 9.6); ^{13}C NMR (75 MHz, δ) 171.1, 170.9, 170.2, 169.0, 86.1, 72.7, 69.5, 69.1, 67.1, 61.6, 50.6, 23.0, 20.7, 20.7, 20.6, 15.1. **13** ^{1}H NMR 7.20–7.25 (m, 15H), 5.32 (d, 7.8), 5.27 (d, 5.7), 4.83 (d, 12.0), 4.78 (d, 11.1), 4.64 (d, 12.0), 4.59 (d, 12.3), 4.58 (d, 11.1), 4.49 (d, 12.3), 4.42–4.50 (obscd ddd), 4.30 (q, 2H, 7.2), 4.21 (ddd, 8.4, 4.8, 2.7), 3.77 (dd, 11.1, 4.8), 3.71 (t, 8.4), 3.69 (dd, 11.1, 2.7), 1.75 (s, 3H), 1.32 (t, 3H, 7.2); ^{13}C NMR 170.6, 137.9, 137.7, 128.9, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 87.3, 77.4, 76.5, 74.9, 73.7, 69.3, 68.2, 50.4, 23.3, 15.4; FAB MS m/z 590 MLi^+. **26** ^{1}H NMR (400 MHz) 6.16 (d, 8.0), 5.66 (dd, 11.2, 9.2), 5.56 (d, 6.4), 5.18 (t, 9.6), 4.59 (ddd, 11.2, 8.0, 6.4), 4.38 (ddd, 8.0, 4.0, 2.0), 4.29 (t, 2 H, 6.4), 4.24 (dd, 12.8, 4.0), 4.13 (d, 12.8), 2.10, 2.06, 2.05, 1.99 (4 s, 3H each), 1.72 (quint, 2H, 7.2), 1.42 (sext, 2H, 6.8), 0.98 (t, 3H, 6.8); FAB MS m/z 490 MNa^+, 468 MH^+. **27** ^{1}H NMR (400 MHz) 6.14 (d, 8.8), 5.64 (dd, 10.8, 9.6), 5.18 (t, 9.6), 4.83 (d, 5.6), 4.76 (ddd, 10.8, 9.2, 6.0), 4.06–4.31 (m, 5H), 2.11, 2.05, 2.05, 1.97 (4 s, 3H each), 1.72 (quint, 2H, 7.2), 1.42 (sext, 2H, 7.4), 0.98 (t, 3H, 7.2); FAB MS m/z 474 MNa^+, 452 MH^+. **28** ^{1}H NMR (300 MHz) 9.82 (br s), 6.63 (d, 9.6), 5.76 (dd, 10.8, 9.2), 5.11 (t, 9.2), 4.64 (d, 6.0), 4.60–4.67 (m), 4.54 (ddd, 10.8, 9.6, 6.0), 4.12 (dd, 12.8, 3.6), 4.06 (dd, 12.8, 2.4), 3.07, (q, 6H, 7.2), 1.99, 1.91, 1.90, 1.85 (4 s, 3H each), 1.29 (t, 9H, 7.2); ^{13}C NMR 170.9, 170.8, 170.4, 169.4, 85.6, 71.3, 71.1, 68.6, 62.3, 50.1, 46.6 (3 C), 23.7, 21.1, 21.1, 20.9, 9.9 (3 C). **29** ^{1}H NMR (D_2O) 4.71 (d, 6.3), 4.10 (dd, 10.8, 8.4), 4.02 (dd, 10.8, 6.3), 3.89 (ddd, 10.2, 3.9, 2.1), 3.72 (dd, 12.3, 2.1), 3.64 (dd, 12.6, 4.2), 1.89 (s, 3H); ^{13}C NMR (D_2O) 174.9, 85.2, 75.8, 70.0, 69.9, 60.0, 52.1, 22.2. **30** ^{1}H NMR (D_2O) 5.82 (dd, 9.9, 8.1), 5.49 (dd, 9.3, 8.1), 5.07 (d, 5.4), 4.65–4.72 (m), 4.42 (dd, 12.8, 3.6), 4.24 (dd, 12.6, 2.1), 4.01 (dd, 9.0, 5.4), 2.15, 2.12, 2.10 (3 s, 3H each); ^{13}C NMR (D_2O) 173.7, 172.9, 172.7, 82.8, 72.0, 69.7, 68.5, 61.9, 49.6, 20.5, 20.4, 20.4; FAB MS m/z 370 MH^+.