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Effective protection of the *N*-sulfate of glucosamine derivatives with the 2,2,2-trichloroethyl group

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Abstract

The 2,2,2-trichloroethyl (TCE) group was utilized as the first protecting group for *N*-sulfates (chlorosulfuric acid TCE ester, Et_3N, DMAP, DMF). Glycosylation with 3,4,6-tri-*O*-acetyl-*N*-trichloroethylsulfuryl-α-D-glucosaminosyl trichloroacetimidate provided the corresponding β-glucosaminosides stereoselectively and in excellent yields. The TCE protection stayed stable under a variety of conditions for the manipulation of other protecting groups, and was readily removable with zinc in the presence of ammonium chloride in methanol.

Keywords: 2,2,2-Trichloroethyl (TCE) group; *N*-Sulfate; Glucosamine; Protecting group; Glycosylation

The *O*- and *N*-sulfate decoration is a prominent feature of the heparin-like glycosaminoglycans, which are found protein-conjugated in the extracellular matrix and free in the circulatory system. These sulfated polysaccharides are involved in a number of signaling functions, such as regulation of the coagulation cascade, growth factor interactions, and viral entry into cells, via binding to the corresponding functional proteins.[1] The 'sulfo-form' of the integral fragments of the polysaccharides determines the specific binding.[2] Chemical synthesis of these oligosaccharide fragments is highly demanding but notoriously difficult.[3] Introduction of the sulfate substitutions is among one of the major challenges in the synthesis. Conventionally, the sulfonation is performed at a later stage of the synthesis with a sulfur trioxide-amine or -amide complex, that requires an additional level of protective group manipulation to distinguish the hydroxyl and amino groups requiring sulfonation. In addition, the resulting sulfonated products are highly polar and are difficult to manipulate for the subsequent transformations. And multiple O- and N-sulfonation is always difficult to complete. To by-pass these difficulties, the sulfate substitution could be introduced in a masked sulfate ester form at an early stage and then be released at the final step. Perlin and Penney tried phenyl as a protecting group for sulfate,[4] Flitsch et al. introduced trifluoroethyl group.[5] However, deprotection of these two groups, requiring harsh conditions, is problematic in the synthesis of complex targets.[6] Recently, Simpson and Widlanski showed that a variety of the alkyl groups (e.g., neopentyl and isobutyl groups) could serve the purpose.[7] Taylor et al. disclosed that 2,2,2-trichloroethyl (TCE) group was an ideal choice as a sulfate protecting group for the synthesis of aryl and carbohydrate sulfates.[8] Here, we report for the first time the use of TCE group as an *N*-sulfate protecting group and its applicability in the synthesis of glucosamine-*N*-sulfate derivatives.

Treatment of the readily available 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride (**1**)[9] with chlorosulfuric acid TCE ester **2**[8,10] in the presence of DMAP and Et_3N gave the TCE-protected D-glucosamine *N*-sulfate **3** in 82% yield (Scheme 1). Subjection of acetate **3** to ammonia in THF/MeOH led to the selective removal of the anomeric

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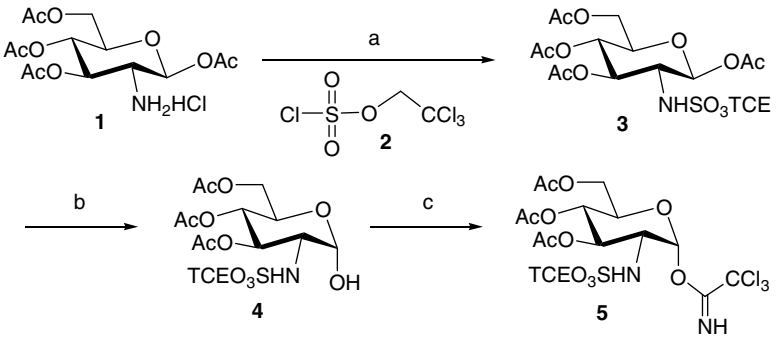


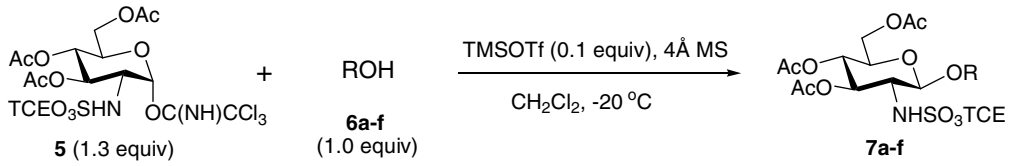
Scheme 1. Reagents and conditions: (a) Et_3N (3.5 equiv), DMAP (1 equiv), DMF, 0 °C, 2 h, 82%; (b) NH_3, THF/MeOH (7:3), 0 °C, 15 min, 81%; (c) $CNCCl_3$ (3.0 equiv), K_2CO_3 (1.2 equiv), CH_2Cl_2, rt, 10 h, 88%.

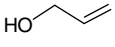
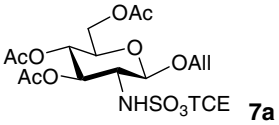
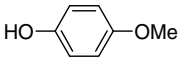
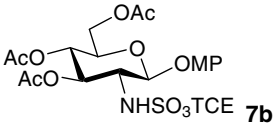
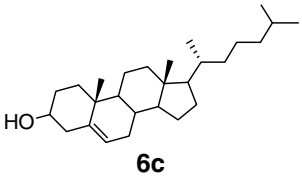
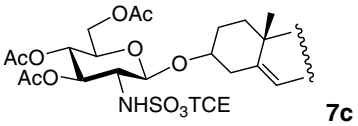
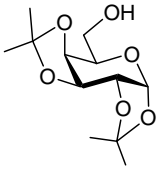
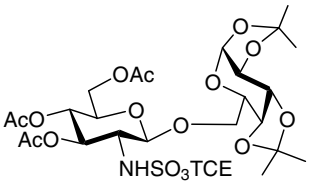
O-acetyl group, providing α-lactol **4** in good yield. Treatment of lactol **4** with CCl_3CN in the presence of K_2CO_3 in CH_2Cl_2 afforded α-trichloroacetimidate **5** in 88% yield, which was found stable under storage. The corresponding β-anomers were not detected in the last two steps.

The donor properties of the TCE-protected *N*-sulfo-glucosaminosyl imidate **5** were then explored using a series of alcohols (**6a**–**f**) as acceptors under a typical set of conditions for glycosylation with trichloroacetimidates (0.1 equiv of TMSOTf, 4 Å MS, CH_2Cl_2, rt).[11] The results are listed in Table 1. All the coupling reactions gave the corresponding β-glycosides (**7a**–**f**) in satisfactory yields (76–92%). The reaction is highly stereoselective, with no α-anomers being detected.

The stability of the TCE protecting group was further examined in the subsequent protecting group manipulations (Scheme 2). The three *O*-acetyl groups in glycoside **7b** were removed quantitatively with K_2CO_3 in MeOH.

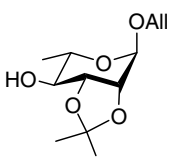
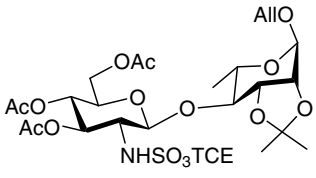
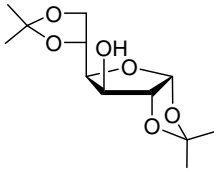
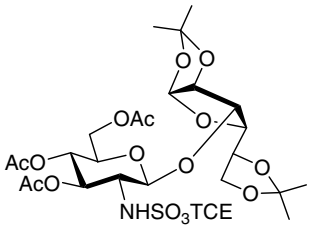
Table 1
Glycosylation of alcohols (**6a**–**f**) with 3,4,6-tri-*O*-acetyl-*N*-trichloroethylsulfuryl-α-D-glucosaminosyl trichloroacetimidate (**5**)[a]



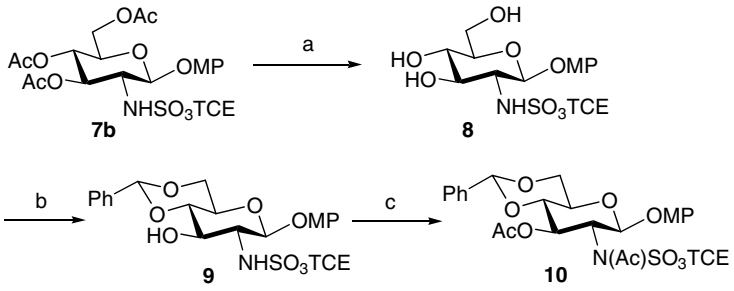
Entry	ROH	Product	H-1 (ppm, *J*)	Yield (%)
1	 **6a**	 **7a**	4.51, 8.1 Hz	92
2	 **6b**	 **7b**	4.93, 8.4 Hz	86
3	 **6c**	 **7c**	4.64, 8.1 Hz	81
4	 **6d**	 **7d**	4.83, 8.4 Hz	86

(*continued on next page*)

Table 1 (*continued*)

Entry	ROH	Product	H-1 (ppm, *J*)	Yield (%)
5	 **6e**	 **7e**	4.93, 8.1 Hz	76
6	 **6f**	 **7f**	4.75, 8.4 Hz	82

[a] For a typical procedure: To a stirred mixture of **5** (220 mg, 0.33 mmol), alcohol **6b** (33 mg, 0.26 mmol), and pulverized 4 Å molecular sieves (300 mg) in CH_2Cl_2 (3 mL) at −20 °C, was added dropwise a solution of TMSOTf in CH_2Cl_2 (0.1 M, 0.33 mL) under an atmosphere of Ar. After stirring for 0.5 h, the temperature was allowed to warm up naturally to room temperature and the stirring continued for another 1.5 h. The mixture was then filtered through a pad of Celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 1.8:1) to afford **7b** (143 mg, 86%) as a white solid.

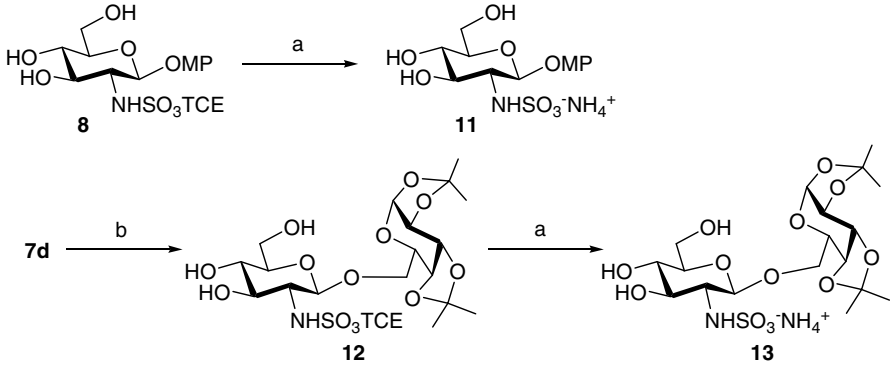


Scheme 2. Reagents and conditions: (a) K_2CO_3 (1.0 equiv), MeOH, rt, 1 h, 100%; (b) benzaldehyde dimethyl acetal (1.2 equiv), TsOH (0.1 equiv), DMF, 40 °C, 8 h, 82%; (c) Ac_2O (3.0 equiv), Et_3N (5.0 equiv), DMAP, CH_2Cl_2, rt, 3 h, 86%.

Treatment of triol **8** with benzaldehyde dimethyl acetal in the presence of TsOH in DMF at 40 °C provided 4,6-*O*-benzylidene derivative **9** in high yield. Acetylation of **9** with Ac_2O gave **10**, where both the –OH and –NH were acetylated. The *N*-sulfate TCE protecting group survived well in the above acidic and basic conditions.

Finally, the literature conditions (i.e., Zn, NH_4Cl, MeOH, rt) were found to work well on the deprotection of the TCE group (on **8** and **12**), providing the *N*-sulfate derivatives (**11** and **13**, respectively) in excellent yields (Scheme 3).[12]

In summary, the 2,2,2-trichloroethyl (TCE) group was utilized as the first protecting group for *N*-sulfates. The



Scheme 3. Reagents and conditions: (a) Zn dust (4 equiv), NH_4Cl (7 equiv), MeOH, rt, 88% (for **11**); 92% (for **13**); (b) K_2CO_3 (1.0 equiv), MeOH, rt, 1 h, 100%.

3,4,6-tri-*O*-acetyl-*N*-trichloroethylsulfuryl-α-D-glucosaminosyl trichloroacetimidate was readily prepared. Glycosylation with this donor provided the corresponding β-glucosaminosides stereoselectively and in excellent yields. The TCE protection on glucosamine-*N*-sulfate derivatives stayed stable under a variety of conditions for the manipulation of other protecting groups, and was readily removable with zinc in the presence of ammonium chloride in methanol.

Acknowledgments

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12. Selected data for the new compounds. Compound **5**: $[\alpha]_D^{23}$ 47.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.07 (s, 3H), 2.08 (s, 3H), 2.14 (s, 3H), 4.01 (dd, *J* = 10.8, 3.3 Hz, 1H), 4.09–4.15 (br m, 2H), 4.20–4.31 (m, 1H), 4.62 (2d, *J* = 11.1 Hz, 2H), 5.24 (t, *J* = 9.6 Hz, 1H), 5.35 (t, *J* = 9.9 Hz, 1H), 6.55 (d, *J* = 3.6 Hz, 1H), 8.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4, 20.57, 20.58, 56.1, 61.2, 67.4, 69.6, 69.9, 78.2, 90.4, 93.0, 94.4, 160.0, 169.1, 170.6, 171.6. Compound **7b**: $[\alpha]_D^{23}$ −23.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.03 (s, 3H), 2.04 (s, 3H), 2.08 (s, 3H), 3.77 (s, 3H), 3.80–3.85 (m, 2H), 4.07–4.16 (m, 2H), 4.28 (dd, *J* = 12.3, 5.1 Hz, 1H), 4.69 (s, 2H), 4.92 (d, *J* = 5.4 Hz, 1H), 5.10 (t, *J* = 9.3 Hz, 1H), 5.22 (t, *J* = 9.9 Hz, 1H), 6.81–6.84 (m, 2H), 7.01–7.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.5, 20.7, 20.8, 55.6, 58.7, 61.9, 68.5, 71.7, 72.6, 78.6, 93.2, 100.0, 114.6, 118.8, 150.4, 155.9, 169.5, 170.8, 171.6; ESIMS *m*/*z* 644.1 $[M+Na]^+$. Compound **9**: $[\alpha]_D^{23}$ −28.7 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.59–3.71 (br m, 3H), 3.75 (s, 3H), 3.83 (t, *J* = 9.9 Hz, 1H), 3.99 (t, *J* = 9.3 Hz, 1H), 4.31 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.93 (2d, *J* = 11.1 Hz, 2H), 5.15 (d, *J* = 8.1 Hz, 1H), 5.66 (s, 1H), 6.87 (d, *J* = 9.3 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.37–7.42 (m, 3H), 7.50–7.52 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 55.6, 62.1, 66.8, 68.7, 72.2, 78.8, 82.0, 94.8, 101.6, 101.9, 115.0, 118.9, 127.0, 128.6, 129.4, 138.6, 152.0, 156.1; ESIMS *m*/*z* 583.8 $[M+H]^+$. Compound **10**: $[\alpha]_D^{23}$ −8.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.14 (s, 3H), 2.60 (s, 3H), 3.68 (dd, *J* = 9.6, 4.5 Hz, 1H), 3.76 (s, 3H), 3.74–3.82 (m, 2H), 4.31 (dd, *J* = 10.5, 5.7 Hz, 1H), 4.44 (dd, *J* = 10.2, 7.5 Hz, 1H), 4.83 (2d, *J* = 10.8 Hz, 2H), 5.50 (s, 1H), 5.91 (t, *J* = 9.3 Hz, 1H), 6.07 (d, *J* = 8.1 Hz, 1H), 6.80–6.83 (m, 2H), 6.92–6.95 (m, 2H), 7.34–7.36 (m, 3H), 7.42–7.46 (m, 2H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 20.8, 20.4, 55.5, 64.9, 66.3, 68.45, 68.49, 79.4, 79.7, 92.1, 98.6, 101.6, 114.7, 119.1, 126.2, 128.2, 129.2, 136.7, 149.3, 156.1, 170.5, 170.9; ESIMS *m*/*z* 690.1 $[M+Na]^+$. Compound **11**: $[\alpha]_D^{23}$ −12.0 (*c* 1.0, CH_3OH); ^1H NMR (CD_3OD, 300 MHz): δ 3.50–3.59 (br m, 5H), 3.69–3.74 (br m, 2H), 4.00–4.02 (br m, 5H), 4.13–4.20 (br m, 1H), 7.06–7.12 (m, 2H), 7.31–7.37 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 56.4, 62.1, 62.8, 71.9, 77.6, 78.0, 102.2, 115.7, 119.8, 153.4, 156.9; ESIMS *m*/*z* 364.1 $[M-H]^-$. Compound **13**: $[\alpha]_D^{23}$ −59.8 (*c* 1.0, CH_3OH); ^1H NMR (CD_3OD, 300 MHz): δ 1.32 (s, 6H), 1.39 (s, 3H), 1.54 (s, 3H), 3.04 (t, *J* = 8.7 Hz, 1H), 3.30–3.37 (br m, 3H), 3.62–3.78 (m, 3H), 3.87 (dd, *J* = 15.3, 1.8 Hz, 1H), 3.97 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.05–4.10 (br m, 1H), 4.31–4.36 (m, 2H), 4.50 (d, *J* = 8.1 Hz, 1H), 4.61 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.50 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz): δ 24.8, 25.4, 26.6, 26.7, 61.9, 63.1, 69.3, 69.6, 72.1, 72.2, 72.3, 72.6, 78.2, 97.9, 103.1, 110.4, 110.7; ESIMS *m*/*z* 500.1 $[M-H]^-$.