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Trifluoroethylsulfonate protected monosaccharides in glycosylation reactions

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Abstract—A variety of sulfo-protected monosaccharide donors and acceptors were investigated in glycosylation reactions. Trifluoroethylsulfonate (SO_3TFE) group was compatible with a wide range of activation conditions commonly used with fluoride, imidate, and sulfide donors. In addition, the influence of a SO_3TFE group, at the critical 2-position in glycosyl donor, on the stereoselectivity of the glycosylation reaction was studied.
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Glycosaminoglycans (GAGs) are linear, polydisperse acidic polysaccharides that occur ubiquitously in animal tissues, membranes, intracellularly in secretory granules or extracellularly in the matrix. GAGs contain repeating units of hexosamine, either glucosamine (GlcN*p*) or galactosamine (GalN*p*), and uronic acid, either glucuronic acid (GlcA*p*) or iduronic acid (IdoA*p*). The biological significance of these sulfated oligosaccharides have made them the object of numerous studies for synthetic carbohydrate chemists for several decades.[1] However, due to their structural complexity, GAG synthesis has remained an important challenge. Recent advances in oligosaccharide preparation, such as automated solid phase synthesis, have shown promising results, allowing faster access to the molecules of interest.[2,3] Nevertheless, these approaches still require preparation of suitably designed monomers. Positions that will ultimately contain sulfo groups must be masked with temporary protecting groups, deprotected after assembly of the oligosaccharide and sulfonated. Thus, such strategies require long multi-step synthetic sequences and intensive protecting group manipulation. Additionally, sulfonation reactions can be troublesome and often sluggish at the higher oligosaccharide level.[4] Sulfo esters are highly polar, making the products of sulfonation reactions difficult to manipulate and to purify. The protection of sulfo esters offers an attractive alternative to solve these problems. The introduction of protected sulfo esters, into monosaccharide or disaccharide building blocks at the early stages of the synthesis, should reduce protecting group manipulation and decrease the polarity of these molecules, making them easier to handle and purify. Phenylsulfonate and trifluoroethylsulfonate derivatives were introduced as sulfo-protection groups in carbohydrates in 1981 and 1997 by Penney and Perlin[5] and Flitsch and co-workers.[6] With the exception of our recently reported use of trifluoroethylsulfonate group in the preparation of sulfo-protected hexosamine building blocks,[7] no further reports of sulfo protection in oligosaccharide synthesis can be found. In the current study, we have extended the application of this protection chemistry to the synthesis of different hexosamine and uronic acid precursors and studied their behavior in glycosylation reactions.

The syntheses of 6-sulfo protected fluorides **1** and **2** and 4-sulfo protected trichloroacetimidate **3** (Fig. 1) have been described in our previous report.[7] In the course of these studies, we found that the trifluoroethylsulfonate (SO_3TFE) group at the primary 6-position, could act as a good leaving group under basic conditions, affording 1,6-anhydro derivatives. As a result preparation of 6-SO_3TFE trichloroacetimidate donors was

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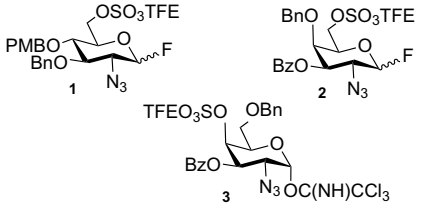
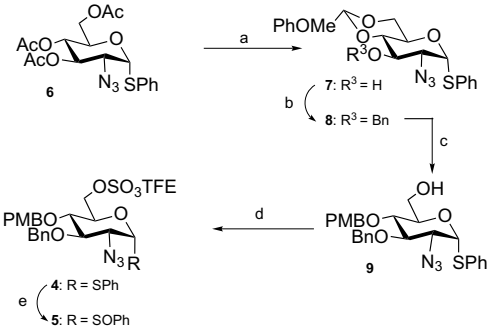


Figure 1. TFE-protected donors **1**–**3**.

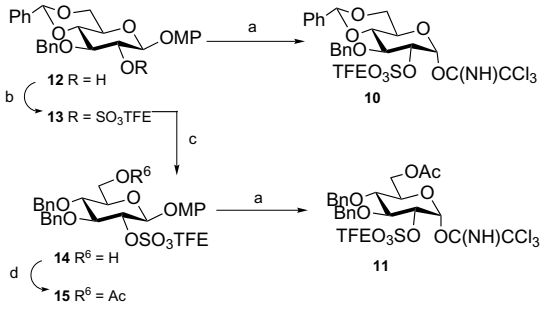
found difficult, thus we decided to investigate other types of activation. In the GlcN*p* series, the α-thiophenylglycosyl donor **4** was synthesized since it could either be directly used in glycosylation or transformed into a more reactive sulfoxide donor **5** (Scheme 1). Differentially protected thiophenylglycoside **4** was synthesized from the known thiophenylglycoside **6**.[8] After deacetylation and introduction of a *p*-methoxybenzylidene acetal at the 4,6-positions, the remaining 3-hydroxyl was benzylated, to give **8** in 80% yield. Regioselective opening of the benzylidene acetal by treatment with Bu_2BOTf[9] afforded the expected 6-hydroxyl derivative **9** in 91% yield. Selectivity was confirmed by NMR studies and subsequent acetylation of the primary position. Introduction of SO_3TFE at the 6-position was achieved in two steps, sulfonation and sulfo protection with a freshly prepared solution of trifluorodiazoethane[10] in presence of citric acid, affording donor **4** in 70% yield. Subsequent oxidation of **4** with *m*CPBA afforded the corresponding sulfoxide donor **5**.

The uronic acid residues in GAGs, both GlcA*p* (chondroitin sulfate D) and IdoA*p* (heparin, dermatan sulfate) units can contain 2-*O*-sulfo groups. For example, IdoA2SO_3 is an essential saccharide residue in the heparin pentasaccharide structure that binds to antithrombin, promoting its anticoagulant activity. Thus, we next directed our studies toward the preparation of the 2-sulfo protected uronic acid precursors glucose (Glc*p*). 2-SO_3TFE protected Glc*p* derivatives **10** and **11** were prepared to study the influence of SO_3TFE protecting group, in the critical 2-position, on the outcome of the glycosylation reaction stereoselectivity. The common intermediate **12** was synthesized from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose as described in literature,[11] and submitted to the two steps sequence of sulfonation/sulfo-protection, affording compound **13** in 87% yield (Scheme 2). Regioselective opening of the benzylidene ring in **13** afforded **14** (93%), which was subsequently 6-*O*-acetylated to give compound **15**. The activation of **13** and **15** proved to be troublesome in both cases and imidates **10** and **11** were obtained in modest 40% and 34% yield, respectively. The limiting step of activation was found to be the oxidative removal of the MP group with CAN. NMR studies of the major side-product recovered from the reaction revealed the presence of SO_3TFE group, which withstood the oxidative conditions of the reaction, and showed perturbation of the MP aromatic signals. No formal identification of this intermediate could be achieved.

Donors **1**–**4**, **10**, and **11** were investigated under a variety of glycosylation conditions with acceptors **17**, **18**,[7] **19**,[12] and **20**[12] (Fig. 2). The strong electron-withdrawing character of the SO_3TFE group was an initial concern in the glycosylation reactions. Its presence contributed to disarm the sugar, and it was expected that the reactivity of both donors and acceptors would be lowered. To our satisfaction, glycosylation of a reactive acceptor **17**, with fluorides, sulfide, and imidate donors gave good to excellent results (Table 1, entries 1–5, 7–8). Partial loss of the PMB protection was observed under AgClO_4/Cp_2ZrCl_2 initiation used with fluoride donor **1**. The use of acid scavenger, norbornylene,[13] did not



Scheme 1. Reagents and conditions: (a) (i) MeONa, MeOH; (ii) $MeOPhCH(OMe)_2$, CSA, MeCN 82% (two steps, α:β 7:1); (b) NaH, BnBr, DMF 80%; (c) BH_3·THF, Bu_2BOTf 91%; (d) (i) $Me_3N{\cdot}SO_3$, DMF, 50 °C; (ii) $TFEN_2$, citric acid, MeCN 70% (two steps); (e) *m*CPBA, DCM 86%.



Scheme 2. Reagents and conditions: (a) (i) CAN, MeCN, PhMe, H_2O; (ii) Cl_3CCN, DBU, DCM **10** 40%, **11** 34%; (b) (i) $Me_3N{\cdot}SO_3$, DMF, 50 °C; (ii) $TFEN_2$, citric acid, MeCN 87% (two steps); (c) BH_3·THF, Bu_2BOTf 93%; (d) Ac_2O, pyridine 99%.

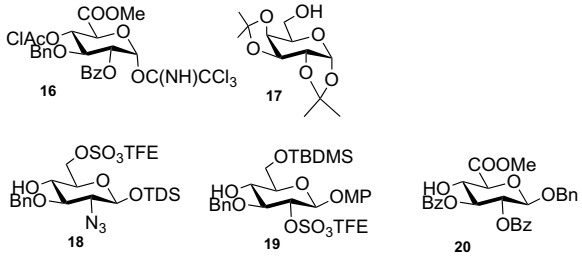
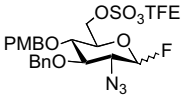
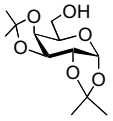
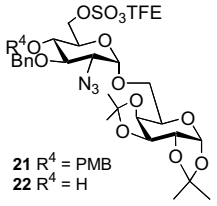
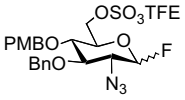
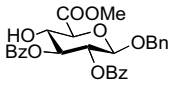
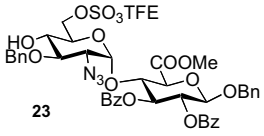
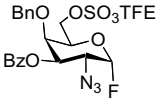
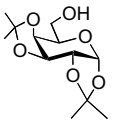
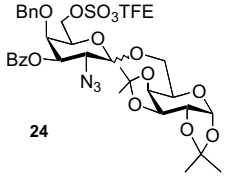
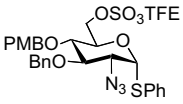
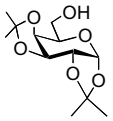
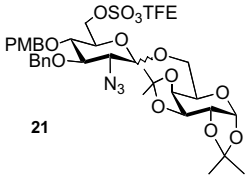
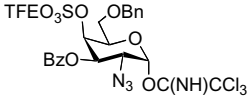
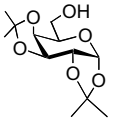
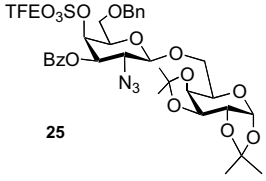
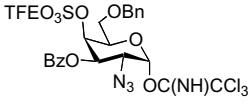
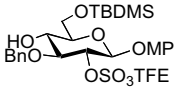
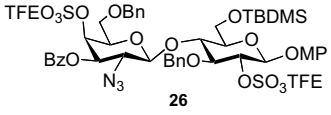
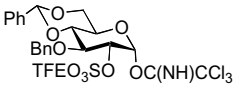
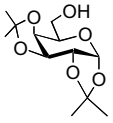
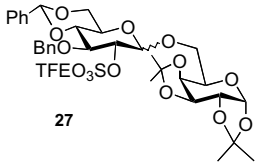
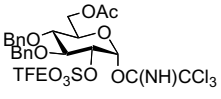
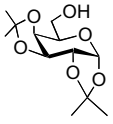
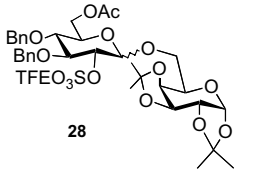
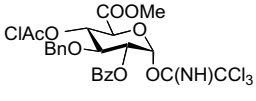
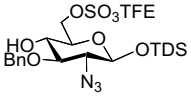
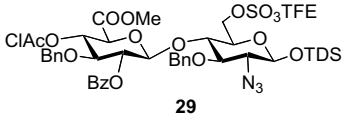


Figure 2. Donor **16** and acceptors **17**–**20** employed in the glycosylation reactions.

Table 1. Glycosylation of SO_3TFE donors and acceptors

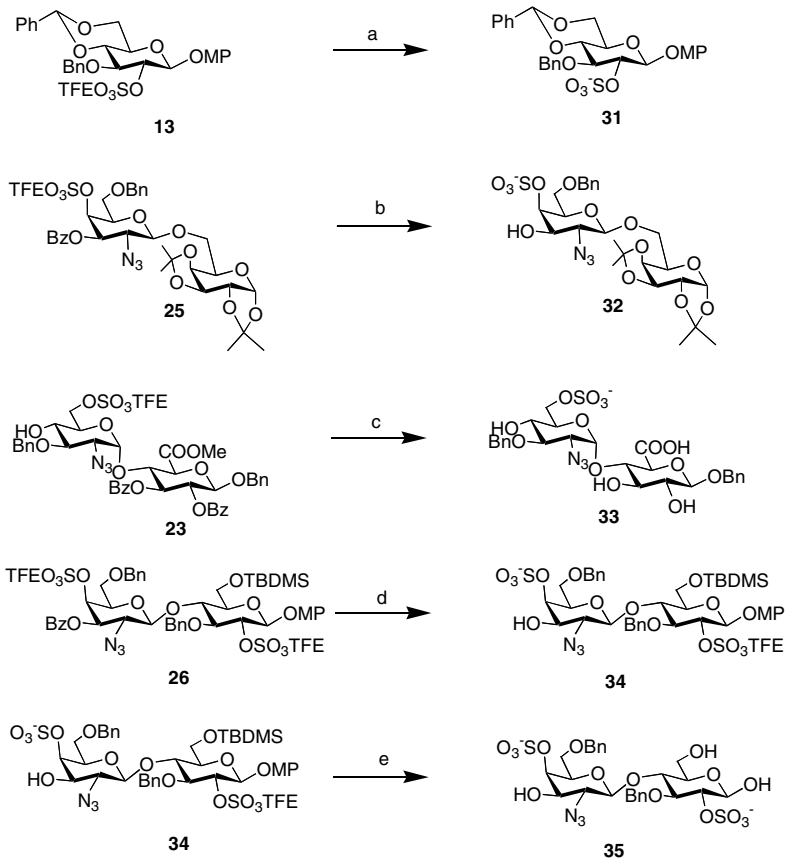
Entry	Donor[a]	Acceptor[a]	Disaccharide	Promoter (equiv)	Yield, α:β ratio
1			 **21** R^4 = PMB **22** R^4 = H	$AgClO_4$ (2.0) Cp_2ZrCl_2 (2.0)	71% α only
2			 **23**	$AgClO_4$ (2.0) Cp_2ZrCl_2 (2.0)	50% α only
3[b]			 **24**	$AgClO_4$ (3.0) Cp_2ZrCl_2 (3.0)	64% α:β 4:1
4[c]			 **21**	NIS (2.5) TfOH (0.5) Ph_2SO (2.8) Tf_2O (1.4)	72% α only 64% α:β1:2
5[b]			 **25**	$BF_3{\cdot}Et_2O$ (0.45)	49% β only
6			 **26**	$BF_3{\cdot}Et_2O$ (0.2)	10% β only
7			 **27**	TMSOTf (0.2) $BF_3{\cdot}Et_2O$ (0.2)	76% α:β 1:1.1 75% α:β 1:5.7
8			 **28**	TMSOTf (0.2) $BF_3{\cdot}Et_2O$ (0.2)	91% α:β 1.2:1 90% α:β 1:2
9			 **29**	TMSOTf (0.25)	44% β only

[a] All glycosylation reaction were carried on in DCM, except for entry 6 conducted in toluene, and with 1 equiv of donor and excess acceptor (1.2–1.5 equiv) except where otherwise specified.

[b] Referred to Ref. 7 for characterization of disaccharides **24** and **25.**

[c] See Ref. 15, DTBMP (3.0 equiv) was used as a base.

improve the outcome of the reaction. In the case of sulfide **4**, activation under the traditional NIS/TfOH conditions using 0.5 equiv of catalyst[14] was complete in less than 30 min. However, when the amount of catalyst



Scheme 3. Reagents and conditions: (a) *t*-BuOK, *t*-BuOH 82%; (b) MeONa, MeOH 70%; (c) (i) MeONa, MeOH; (ii) *t*-BuOK, *t*-BuOH 60% (two steps); (d) MeONa, MeOH 90%; (e) *t*-BuOK, *t*-BuOH 50%.

was decreased (0.2 equiv), the overnight reaction was incomplete and a large amount of unreacted donor was recovered. The use of less reactive acceptors, such as 4-OH containing GlcA*p* methyl ester **20** or 2-SO_3TFE Glc*p* derivative **19**, resulted in a drop of reactivity, low to poor yields and the recovery of a large amount of unreacted acceptors (Table 1, entries 2 and 6). This trend was confirmed by glycosylation studies with donor **16**, prepared as described in literature,[4b] and acceptor **18**, affording **29** in a modest 44% yield (Table 1, entry 9). Glycosylation performed with 2-SO_3TFE donors **10** and **11** under TMSOTf conditions resulted in an equal amount of products in the α- and β-anomeric form. Lowering the reaction temperature (−15 °C) did not improve stereo selectivity, suggesting that SO_3TFE group at the 2-position acted as a nonparticipating group. An increase of the β-selectivity could, however, be achieved using $BF_3{\cdot}Et_2O$ as a catalyst (Table 1, entries 7 and 8).

Preliminary studies aimed at the deprotection of these products focused on compounds **13**, **23**, **25**, and **26** (Scheme 3). The 2-sulfo protected monosaccharide **13** was deprotected using standard conditions, *t*-BuO^-K^+/*t*-BuOH affording 82% yield of **31**.[6] Similar conditions proved too harsh resulting in decomposition of the 4-sulfo protected disaccharide **25**. The use of milder conditions, 1 equiv sodium methoxide/methanol, afforded **32** yield of 70%. Deprotection of the 6-sulfo compound **23** also posed the greatest challenge, as the major product formed on treating **23** under standard conditions[6] was desulfonated. Removal of the OBz groups in **23**, followed by standard deprotection conditions[6] resulted in only minor loss of sulfo group, affording **33** in 60% yield. To remove the 2- and 4-sulfo groups from **26**, a stepwise approach was required. Treatment under sodium methoxide/methanol resulted in 4-sulfo group deprotection affording **34**, followed by *t*-BuO^-K^+/*t*-BuOH to deprotect the 2-sulfo group. The 2,4-disulfo product **35** was obtained in a 45% overall yield with partial decomposition resulting in loss of the 6-OTBDMS and OMP protecting groups. Further optimization studies on the deprotection of these groups will be required to make the sulfo-protection strategy useful in glycosaminoglycan synthesis.

In summary, the SO_3TFE protecting group proved to be compatible under a wide range of activation conditions. The 6-, 4-, and 2-SO_3TFE glycoside fluoride, sulfide, and imidate donors showed satisfactory results in the glycosylation of reactive acceptors. Glycosylation proved more difficult with less reactive acceptors, such as uronic acids, presumably due to the strong electron-withdrawing character of the SO_3TFE group. Investigation of highly reactive donors, such as sulfoxide, is now underway to improve glycosylation yields.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2004.06.131.

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