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Development of a Protecting Group for Sulfate Esters

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Abstract: The trifluoroethyl ester was studied as a protection group for sulfate monoesters in carbohydrates. The ester was formed from the sulfate by treatment with trifluorodiazoethane and was compatible with other common protecting groups used in carbohydrate chemistry. Selective cleavage of the trifluoroethyl ester was achieved with potassium *t*-butoxide. © 1997 Elsevier Science Ltd.

Biochemical studies are increasingly implicating sulfated oligosaccharides as key structures in important biological interactions. This has led to a growing interest in their use as preliminary targets for pharmaceutical investigation. Although there are a wide range of methods available to sulfate a hydroxyl group, few are suitable for use with complex sugar structures and those that are, generate anionic sulfates. Free sulfates and their salts are difficult to handle and to characterise and hence sulfation is usually carried out as one of the last steps in a synthesis. A protecting group which was stable to conditions usually used in carbohydrate synthesis would clearly be useful for extending synthetic strategies for sulfated oligosaccharides and might also find applications in preparations of other natural products such as sulfated peptides.

An obvious way to mask the anionic nature of the sulfate is to form the sulfate diester (Fig 1.). Such diesters are normally unstable and highly susceptible to nucleophilic attack, which can occur at any one of three positions **(a)-(c)** (Fig. 1[1]).

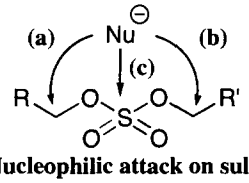


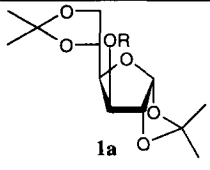
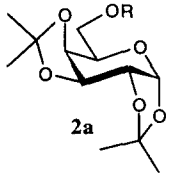
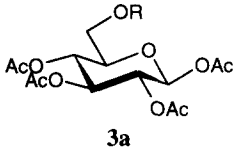
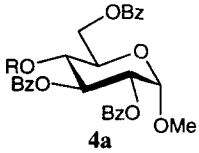
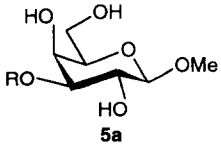
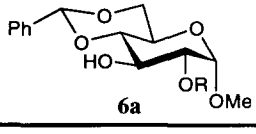
Figure 1: Nucleophilic attack on sulfate diester.

Substitution by route **(a)** is generally slow when R is a carbohydrate, in particular for the sulfate esters of secondary alcohols. The problem therefore remains to choose R' such that it disfavours attack by route **(b)** but still contains a reactive handle to allow selective removal to unmask the sulfate monoester. Perlin *et al*[2] have described the use of phenyl sulfates, which can be hydrogenated to a cyclohexyl sulfate which is then susceptible to base hydrolysis. Unfortunately, both formation of the sulfate diester and cleavage only give moderate yields and the reaction conditions are incompatible with protecting groups that are sensitive to base and to hydrogenation.

We have therefore investigated the use of trihaloethyl sulfate esters, which would be deactivated to nucleophilic attack as in **(b)** and **(c)** for both steric and electronic reasons. Our initial attempts focused on trichloroethyl sulfate esters of carbohydrates. Trichloroethyl esters have been used as phosphate and carboxyl protection and can be selectively removed using Zn/AcOH. Unfortunately, we found that yields

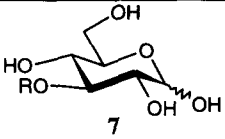
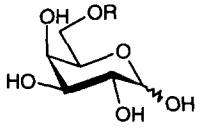
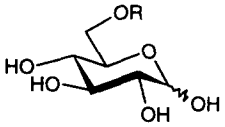
of synthesis were very poor using a range of reaction conditions, possibly due to steric hindrance. Thus, instead we concentrated on trifluoroethyl sulfate esters. Attempts to introduce both the sulfate and the protection in one step by reacting the free alcohol groups of sugars with 1,1,1-trifluoroethyl chlorosulfate failed to give the desired product and instead yielded a number of unwanted by-products. However, the trifluoroethyl ester was successfully formed directly from the sulfate by using 2,2,2-trifluorodiazoethane as the reagent. This had previously been successfully used by Meese for the highly selective alkylation of sulfonic acids in preference to carboxylic acids and hydroxyl groups[3]. We have found a similar selectivity for sulfate esters. 2,2,2-Trifluorodiazoethane could safely be prepared from trifluoroethylamine[4] in reasonable quantities (40 mmole)[5] and was used to esterify[6] a number of sulfated monosaccharides in reasonable to good yields (Table 1).

Table 1: Formation of Trifluoroethyl Esters of Carbohydrate Sulfates.

Entry	Substrate R=H	Product $R=SO_3CH_2CF_3$	Sulfation Method	Overall Yield from Alcohol
1	 **1a**	**1b**	Ref. [7]	51%
2	 **2a**	**2b**	Ref. [7]	60%
3	 **3a**	**3b**	Ref. [7]	93%
4	 **4a**	**4b**	Ref. [7]	80%
5	 **5a**	**5b**	Ref. [8]	46%
6	 **6a**	**6b**	Ref. [9]	75%

The intermediate sulfates were directly prepared from the partially protected carbohydrates **1a-6a** and used without purification often allowing one pot synthesis of the fully protected sulfates **1b-6b**[10].

Table 2: Deprotected Monosaccharides.

Entry	Substrate	Deprotected Sugar R=$SO_3CH_2CF_3$	Method	Yield	Deprotected Sulfate[11] R=SO_3^-	Yield
1	**1b**	 **7**	4:1 TFA:EtOH 25°C 2hrs	75%	**1c**[12]	82%
2	**2b**	 **8**	4:1 TFA:EtOH 25°C 2hrs	97%	**2c**[12]	96%
3	**3b**	 **9b**	NaOMe MeOH 2hr	66%	**9c**[13]	88%

The stability of the trifluoroethyl protecting group was then investigated. The 2',2',2'-trifluoroethyl sulfate esters were found to be stable to a variety of conditions commonly used to remove carbohydrate protecting groups (see Table 2). The esters were stable to strong organic acids (Table 2; entries 1 and 2) but not to mineral acids such as dilute sulfuric acid (the entire sulfate moiety was cleaved). The protecting group appeared to be stable to hydrogenation conditions (the 4,6-*O*-Benzylidene of **6b** was removed in 73% yield), was thermally stable (refluxing methanol) and was not cleaved when treated with TBAF.

The 2',2',2'-trifluoroethyl ester was surprisingly stable to sodium methoxide in methanol (Table 2; entry 3) such that acetate groups could be selectively removed under Zemplen conditions even at reflux. On the other hand, refluxing in potassium *tert* butoxide in *tert* butyl alcohol lead to the removal of the sulfate protecting group in good yields (Table 2). A possible mechanism involves attack of butoxide at the sulfur of the sulfate (see Fig. 1; Route (**c**)) displacing 2,2,2-trifluoroethoxide, followed by elimination to release 2-methylpropene. The potassium salt of the sulfated sugars **1c**, **2c** and **9c** could be isolated with the minimum of purification and without the need for ion exchange resins. However deprotection of compounds **5b** and **6b** resulted in some isomerisation of the sulfate ester, which is currently being investigated.

In conclusion, the 2',2',2'-trifluoroethyl ester seems to be a useful protecting group for sulfate esters, which can easily be formed from the sulfate monoester and can be cleaved in good yields, while being orthogonal to a number of common carbohydrate protecting groups.

Acknowledgements
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References and Notes:

1. Kaiser, E. T. *The Organic Chemistry of Sulfur*; Oae, S.; Plenum Press: New York and London, 1944; pp. 48-74.
2. Penney, C.L.; Perlin, A.S. *Carbohydr. Research* 1981, **93**, 241-246.
3. Meese, C. O. *Synthesis* 1984, 1041-1042.
4. Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* 1994, **116**, 6611-6621.
5. Preparation of 2,2,2-trifluorodiazoethane: CAUTION:- This compound is potentially explosive and must be considered as highly toxic. All experiments using this reagent were carried out in glassware with Clear-Seal joints and behind blast screens:- Sodium Nitrite (3.0g, 1eq) in water (10ml) was added to a solution of 2,2,2-trifluoroethylamine hydrochloride (5.4g, 1eq) in water (20ml) at 0°C. A stream of Nitrogen gas was bubbled through the liquid, the mixture of gas and 2,2,2-trifluorodiazoethane was passed over KOH pellets before being trapped in acetonitrile (40ml) at -40°C. After 1hr at 0°C the aqueous mixture was warmed to room temp over 1hr. The solution of 2,2,2-trifluorodiazoethane was used without further purification.
6. General method for sulfate protection:- 2,2,2-Trifluorodiazoethane solution (10ml, ~10eq) was added to a solution of the crude monosaccharide (~150mg, 1eq) in acetonitrile (10ml). After 5mins citric acid (1g) was added. The mixture was then stirred at room temperature for 24hrs, the solvent removed *in vacuo* and the resulting solid was dissolved in water. The mixture was extracted with diethyl ether and the combined organic layers were washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by column chromatography.
7. General sulfation method:- The sugar (1.0eq) and pyridine/sulfur trioxide complex (1.0-5.0eq) were heated (80°C) in acetonitrile until no starting material remained (1-2 hrs).
8. Guilbert, B.; Davis, N. J.; Pearce, M.; Aplin, R. T.; Flitsch, S. L. *Tetrahedron: Asymmetry* 1994, **5**, 2163-2178.
9. Langston, S.; Bernot, B.; Vasella, A. *Helv. Chim. Acta.* 1994, **77**, 2341-2353.
10. Selected data for trifluoroethyl protected monosaccharide sulfates: **1b**; HRMS: $C_{14}H_{22}F_3O_9S$ requires 423.09367, found 423.09308. **2b**; HRMS: $C_{14}H_{22}F_3O_9S$ requires 423.09367, found 423.09357. **3b**; Anal. Calcd for $C_{16}H_{21}F_3O_{13}S$: C, 37.65; H, 4.15%. Found: C, 37.62; H, 4.21%. **4b**; Anal. Calcd for $C_{30}H_{27}F_3O_{12}S$: C, 53.89; H, 4.07%, Found: C, 54.04; H, 4.21%. **5b**; ^{1}H-NMR (250 MHz, CD_3OD) : δ 3.65 (1H, ddd, *J* = 6.6, 5.5, 0.9 Hz, 5-H), 3.81 (3H, s, OMe), 3.82 (1H, dd, *J* = 9.9, 7.6 Hz, 2-H), 4.30 (1H, dd, *J* = 3.3, 0.9 Hz, 4-H), 4.31 (1H, d, *J* = 7.6 Hz, 1-H), 4.64 (1H, dd, *J* = 9.9, 3.3 Hz, 3-H), 4.91 (2H, q, *J* = 8.1 Hz, CH_2CF_3) 4.83-5.06 (2H, m, 6-Ha, 6-Hb). ^{13}C-NMR (250 MHz, CD_3OD) : δ 55.58, 59.99, 66.03, 66.13 (q, *J* = 37.9 Hz, CH_2CF_3) 67.86, 73.76, 86.68, 103.70, 121.68 (q, *J* = 276.4 Hz, CF_3). ^{19}F-NMR (250 MHz, CD_3OD) : δ -78.30 (3F, s). **6b**; HRMS: $C_{16}H_{20}F_3O_9S$ requires 445.07802, found 445.07860.
11. General method for deprotection of trifluoroethylsulfate esters:- Substrate (10mg, 1eq) was dissolved in tert butyl alcohol, potassium *tert* butoxide (5eq) was added and mixture refluxed until reaction was complete (1-2hrs). The product was purified by column chromatography.
12. Mumma, R. O.; Hoiberg, C.P.;Simpson, R. *Carbohydr. Res.* 1970, **14**, 119-121.
13. Lupescu, N.; Arad, S.; Geresh, S.; Bernstein, M. A.; Glaser, R. *Carbohydr. Res.* 1991, **210**, 349-352.

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