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Synthesis and Protection of Aryl Sulfates Using the 2,2,2-Trichloroethyl Moiety

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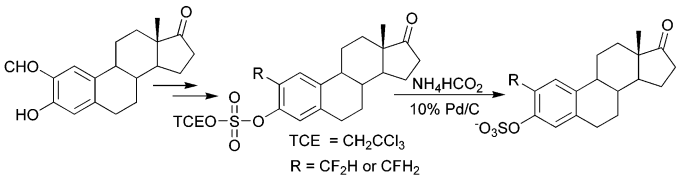
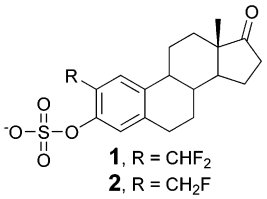
ABSTRACT



The 2,2,2-trichloroethyl (TCE) group was utilized as the first protecting group for aryl sulfates. Aryl sulfates, protected with the TCE group, were prepared in high yield by reacting phenols with chlorosulfuric acid TCE ester. Deprotection was accomplished using Pd/C-ammonium formate or with Zn-ammonium formate to give aryl sulfate monoesters in high yield. This approach to aryl sulfate synthesis was successfully applied to the construction of estrone sulfate derivatives, which could not be prepared by previous methodologies.

Sulfate monoesters are widespread in biochemistry and are crucial for many biological functions. In addition to alkyl sulfates such as carbohydrate sulfates, this class of compounds also includes aryl sulfates such as sulfotyrosine-bearing peptides and proteins and sulfated steroids. Despite their importance, the synthesis of aryl sulfates has not advanced to any significant extent over the last century. The most common approach to the construction of aryl sulfates is to sulfate the hydroxyl group at the end of the synthesis using sulfur trioxide−amine complexes[1] or chlorosulfuric acid.[2] One reason for this is that free sulfates or their salts are highly polar and often difficult to purify. Thus, to avoid a series of difficult purifications, the sulfate group is preferably introduced at the end of the synthesis. Another reason is that, to our knowledge, there are no protecting groups available for aryl sulfates.

Our interest in the synthesis of aryl sulfates stemmed from our desire to prepare estrone-3-sulfate derivatives **1** and **2**. These compounds are designed to act as suicide inhibitors



of estrone sulfatase by a mechanism similar to that proposed for the inhibition of phosphatases using 4-(fluoromethyl)-phenyl phosphates.[3,4] However, the standard approach to the synthesis of sulfate monoesters (sulfation of the phenolic OH) could not be employed for **1** and **2** since 2- and 4-difluoromethyl- or monofluoromethylphenols are highly unstable. Therefore, a route was envisioned that involved attaching an ester of chlorosulfuric acid to the hydroxyl group of 2-formyl estrone (Scheme 1). Thus, the sulfate group would be introduced and protected as a sulfate diester (**3**). Conversion of the formyl group to the mono- or difluoromethyl group followed by removal of the sulfate protecting group would yield the desired product. The main difficulty with

(1) For an example, see: Dusza, J. P.; Joseph, J. P.; Bernstein, S. *Steroids* **1985**, *45*, 303−315.

(2) For examples, see: Ragan, M. A. *Can. J. Chem.* **1978**, *56*, 2681−2685.

(3) Wang, Q.; Cechert, U.; Jirik, F.; Withers, S. G. *Biochem. Biophys. Res. Commun.* **1994**, *200*, 577−583.

(4) Myers, J. K. Widlanski, T. S. *Science* **1993**, *262*, 1451−1453.

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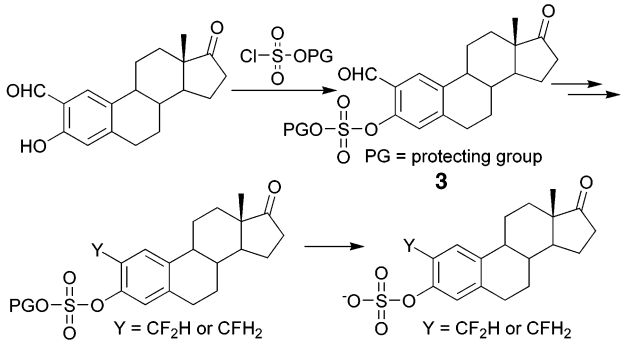
Scheme 1

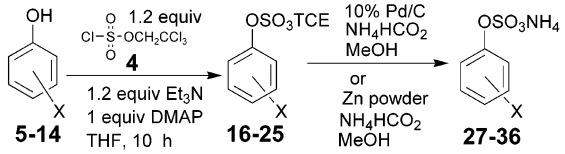


this approach was finding a protecting group that is compatible with aryl sulfate ester chemistry. Acid-labile protecting groups cannot be used due to the well-known instability of aryl sulfate monoesters to acid.[5] Protecting groups removed by hydrogenolysis or photolysis are usually benzyl-type moieties, and benzylic sulfate diesters are highly unstable. The two protecting groups that have been reported for sulfate esters were developed for alkyl sulfates, namely, carbohydrate sulfates, and are removed by base.[6,7] Perlin and Penney protected carbohydrate sulfates as phenyl sulfate esters. Deprotection was achieved by hydrogenation of the phenyl group to a cyclohexyl group followed by treatment with base.[6] Proud et al. used the 2,2,2-trifluoroethyl protecting group. Deprotection was achieved using a strong base.[7] These deprotection conditions are incompatible with aryl sulfate esters.

The 2,2,2-trichloroethyl (TCE) moiety has been used extensively as a protecting group for carbon and phosphorus acids.[8] It has never been seriously explored as a protecting group for sulfuric acid monoesters probably because it is usually removed using Zn/HOAc, which is not compatible with many aryl sulfate monoesters. Several years ago, Paquet reported the use of the TCE moiety as a phosphate protecting group for phosphoserine during solution-phase peptide synthesis using Boc chemistry.[9,10] Paquet noted that the TCE group could also be removed by hydrogenolysis (10% Pd/C, H_2) in aqueous ethanol. The TCE group was later used as a protecting group for phosphotyrosine during solution-phase peptide synthesis by Mora et al. using Boc chemistry.[11] Deprotection of the phosphate group was performed at the end of the syntheses using Paquet's hydrogenolysis conditions. On the basis of these studies, we reasoned that a TCE protecting group would be stable enough for the synthesis of **1** and **2** yet could be removed at the end of the synthesis

(5) Kice, J. L.; Anderson, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 5242−5245.
(6) Penney, C. L. Perlin, A. S. *Carbohydr. Res.* **1981**, *93*, 241−246.
(7) Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett.* **1997**, *41*, 7243−7246.
(8) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York; pp 397, 681−682.
(9) Paquet, A. *Int. J. Pept. Protein Res.* **1992**, *39*, 82−86.
(10) Paquet, A.; Blackwell, B.; Johns, M.; Nikiforuk, J. *J. Pept. Res.* **1997**, *50*, 262−268.
(11) Mora, N.; Lacombe, J. M.; Pavia, A. A. *Int. J. Pept. Protein Res.* **1995**, *45*, 53−63.

Table 1. Yields of Sulfate Diester Formation and Deprotection



X	% yield of **16**−**26**	% yield of **27**−**37**[a]	% yield of **27**−**37**[b]
4-F (**5**)	95 (**16**)	82 (**27**)	88 (**27**)
H (**6**)	92 (**17**)	83 (**28**)	82 (**28**)
4-NO_2 (**7**)	93 (**18**)	82 (**29**)	c (**29**)
4-CF_3 (**8**)	96 (**19**)	90 (**30**)	81 (**30**)
2,6-diF (**9**)	90 (**20**)	92 (**31**)	84 (**31**)
4-OMe (**10**)	71 (**21**)	84 (**32**)	88 (**32**)
2-Me (**11**)	74 (**22**)	83 (**33**)	86 (**33**)
4-I (**12**)	95 (**23**)	d (**34**)	92 (**34**)
4-Cl (**13**)	87 (**24**)	d (**35**)	93 (**35**)
4-CH_3CO (**14**)	91 (**25**)	e (**36**)	94 (**36**)
estrone (**15**)	90 (**26**)[f]	88 (**37**)[g]	87 (**37**)[g]

[a] Performed with 6 equiv of NH_4HCO_2, 10 wt % of 10% Pd/C, MeOH. [b] Performed with 2 equiv of Zn dust, 6 equiv of NH_4HCO_2, MeOH. [c] Partial reduction of the nitro group to the amine occurred. [d] Dehalogenation occurred. [e] Reduction of the carbonyl occurred. [f] Performed with 2 equiv of **4**, 2 equiv of Et_3N, and 1 equiv of DMAP. Product is the TCE ester of estrone-3-sulfate. [g] Reaction performed in MeOH/THF (1:1). Product is estrone-3-sulfate

by hydrogenolysis. In this letter, we report that the 2,2,2-trichloroethyl group is an effective moiety for the synthesis and protection of aryl sulfate esters and employ this protecting group to prepare compounds **1** and **2**.

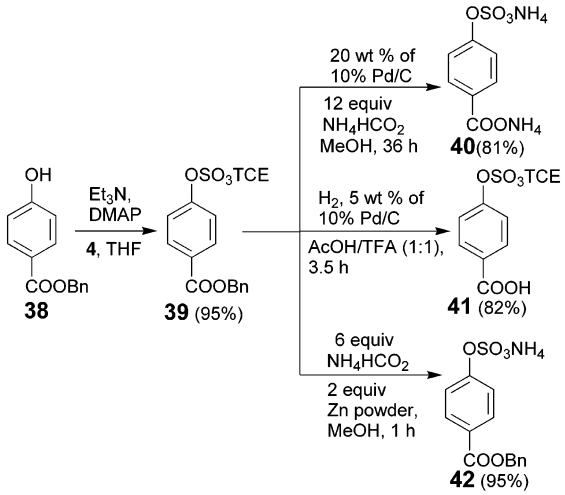
Hedayatullah et al. reported the synthesis of TCE esters of phenyl sulfates by reacting the TCE ester of chlorosulfuric acid (**4**, Table 1) with phenols in pyridine; however, no yields or specific procedures were reported.[12] Compound **4** was readily prepared in near quantitative yields using the procedure of Hedayatullah et al., which involved reacting sulfuryl chloride with 1 equiv of 2,2,2-trichloroethanol in the presence of 1 equiv of pyridine in ether.[13] Reagent **4** can be stored under an inert atmosphere at −20 °C for months without any detectable decomposition. 4-Fluorophenol (**5**, Table 1) was used as a model system for preparing TCE-protected sulfate esters. Reacting 1 equiv of **5** with 1.1 equiv of **4** in anhydrous pyridine for 24 h, followed by the addition of another 1 equiv of **4** and stirring for an additional 4 days, gave ester **16** in a modest 60% yield. However, the yield of ester **16** could be improved to 95% by adding a solution of **4** (1.2 equiv) in dry THF dropwise to a solution of **5** (1.0 equiv), Et_3N (1.2 equiv), and DMAP (1.0 equiv) in dry THF at room temperature and then stirring for an additional 10 h. This procedure worked well with a variety of phenols, including estrone (**16**−**26**, Table 1). These compounds are stable and exhibited no decomposition even when stored at room temperature over many months.

(12) Hedayatullah, M.; Leveque, J. C.; Denivelle, L. *C. R. Acad. Sc. Paris, Serie C* **1972**, *274*, 1937−1940.
(13) Hedayatullah, M.; Leveque, J. C.; Denivelle, L. *C. R. Acad. Sc. Paris, Serie C* **1971**, *273*, 1444−1447.

Not surprisingly, attempts to remove the TCE group using Zn/HOAc resulted in complete desulfation (loss of the TCE group and cleavage of the aryl S−O bond). Removal of the TCE group was attempted using the hydrogenolysis conditions of Paquet (10 wt % of 10% Pd/C, H_2 (balloon) in aqueous or dry ethanol). However, this also resulted in complete desulfation. It was hypothesized that HCl was formed during the reaction that resulted in desulfation of the deprotected product. An alternative to using H_2 for hydrogenolyses is to use an alkene, formic acid, or ammonium formate as the hydrogen source (catalytic transfer hydrogenolysis, CTH).[14] We reasoned that CTH using ammonium formate would be suitable for TCE sulfate deprotection because the ammonium formate would not only act as a source of hydrogen but also buffer the solution and prevent cleavage of the S−O bond of the monoester product. After some experimentation, it was found that the TCE group could be readily removed, usually within 5 h, using 6 equiv of ammonium formate and 10% Pd/C (10 wt %) in methanol. When the reaction was complete, the Pd catalyst was removed and the supernatant concentrated. The crude material was rapidly passed through a small silica column using CH_2Cl_2/MeOH/NH_4OH (10:2:0.5) as the eluant (to remove the ammonium chloride that is formed in the reaction). The pooled fractions were concentrated, and the residue was dissolved in water and then lyophilized to give the aryl sulfates as their ammonium salts. In general, the deprotection proceeded in good yield (for substrates **16**−**22** and **26**, Table 1) except in cases where certain groups on the aryl ring were present (substrates **23**−**25**, Table 1). Aryl halides **23** and **24** underwent both deprotection and dehalogenation.[15] The reaction with **25** resulted in a complex mixture of products due to reduction of the carbonyl group to the alcohol as well as reductive amination of the carbonyl group to the amine.[16] However, the ketone moiety at the 17-position in estrone derivative **26** remained intact. Surprisingly, the 4-nitro group on ester **18** was not reduced to the amine. Ram and Ehrenkaufer have reported that aromatic nitro groups are reduced to amino groups using CTH with ammonium formate.[17] However, these workers used anhydrous ammonium formate, 25−40 wt % of 10% Pd/C and dry MeOH.

Conditions that would selectively remove the TCE group in the presence of other reducible groups were explored. It has been reported that the TCE group can be removed in moderate yields from TCE esters of carboxylic acids using Zn/1 M NH_4OAc.[18] Therefore, we anticipated that the TCE groups in **16**−**26** could be removed using Zn/NH_4HCO_2. Subjecting compounds **16**−**26** to a mixture of 2 equiv of Zn dust and 6 equiv of NH_4HCO_2 in MeOH resulted in removal of the TCE group usually in less than 1 h. When the reactions were complete, they were filtered through Celite and the concentrated filtrates purified and lyophilized as described above. This gave the aryl sulfates as their ammonium salts generally in very good yield (Table 1). Using the Zn procedure, aryl halides **23** and **24** did not undergo dehalogenation and the carbonyl group in **25** was not reduced. However, the nitro group in substrate **18** was partially reduced to the amine.

Scheme 2



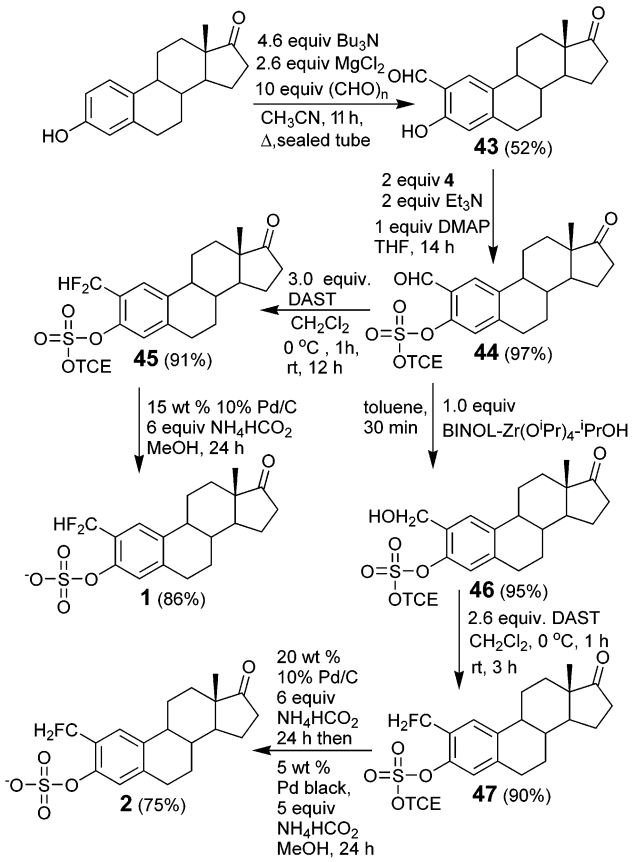
Paquet reported that TCE-protected phosphates were stable to hydrogenolysis when the reaction was performed in AcOH/TFA 1:1 (H_2, 10% Pd/C) and that benzyl esters could be selectively debenzylated in the presence of TCE-protected phosphates group using these conditions.[8,9] Using compound **39** as a model system, it was found that the benzyl ester moiety could be selectively deprotected under these conditions to give acid **41** in 82% yield (Scheme 2). Moreover, the sulfate group could be selectively deprotected using the Zn procedure to give **42** in 95% yield or both esters could be deprotected simultaneously using CTH to give **40** in 81% yield.

Stability studies were conducted using 4-fluoro ester **16** as a model system. This diester is remarkably stable to acids such as TFA, TFA containing 5% of 30% HBr/AcOH, 30% HBr/AcOH, and 4 M HCl in dioxane over a period of 24 h. It was also stable to weak organic bases such as 10% Et_3N in CH_2Cl_2, 20% *N*-ethylmorpholine in CH_2Cl_2 for at least 24 h, 2 equiv of aqueous LiOH in THF at 0 °C for 30 min, and $NaBH_4$/MeOH. However, it is not stable to good nucleophiles or stronger organic bases such as 20% piperidine or 20% DBU in DMF or CH_2Cl_2, MeONa/MeOH, or *t*-butoxide in THF.

This new methodology was applied to the synthesis of compounds **1** and **2** (Scheme 3). Heating a mixture of estrone, paraformaldehyde, $MgCl_2$, and tributylamine in a sealed tube for 11 h gave a mixture of 2-formyl and 4-formyl estrone in a 14:1 ratio. These two isomers could be separated by chromatography to give the 2-isomer, **43**, in a 52% yield.[19]

(14) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91−95.
(15) Rajagopal, S.; Spatola, A. F. *J. Org. Chem.* **1995**, *60*, 1347−1355.
(16) Ram, S.; Spicer, L. D. *Synth. Commun.* **1992**, *22*, 2673−2681.
(17) Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415−3418.
(18) Jou, G.; Gonzalez, F.; Albericio, P. L.-W.; Giralt, E. *J. Org. Chem.* **1997**, *62*, 354−366.
(19) This procedure is based on the work of Hofslokken and Skattebol: Hofslokken, N. U.; Skattebol, L. *Acta Chim. Scand.* **1999**, *53*, 258−262. A more detailed account on the formylation of estrogens using this and other procedures is forthcoming.

Scheme 3



Reaction of **43** with 2 equiv of **4**, 2 equiv of Et_3N, and 1 equiv of DMAP gave the protected sulfate ester **44** in 97% yield. The formyl group was converted into the difluoromethyl derivative **45** in 91% yield using 3.0 equiv of diethylaminosulfur trifluoride (DAST) without any competing fluorination at the 17-position. Hydrogenolysis of **45** using our CTH conditions gave compound **1** in 86% yield. To obtain compound **2**, it was found that the formyl group in **44** could be selectively reduced to the alcohol **46** in 95% yield using (±)-BINOL−$Zr(O^iPr)_4$−^{i}PrOH complex.[20] No concurrent reduction of the carbonyl at the 17-position was detected. The monofluoromethyl compound **47** was obtained in 90% yield using 2.6 equiv of DAST. Surprisingly, removal of the TCE group using CTH employing 20 wt % of 10% Pd/C and ammonium formate proceeded very slowly and, after 24 h, was far from complete. However, it was found that compound **2** could be obtained in 75% yield by adding in 5 wt % of palladium black and stirring for an additional 24 h.

In conclusion, chlorosulfuric acid 2,2,2-trichloroethyl ester is an effective reagent for the synthesis and protection of aryl sulfate esters. This reagent enabled us to construct compounds (**1** and **2**) that could not be prepared using previous methodologies.[21] To our knowledge, this report is the first describing a protecting group for aryl sulfates and presents the first effective alternative to using SO_3−amine complexes or chlorosulfuric acid for synthesizing aryl sulfates. We expect that this methodology will find widespread use in the preparation of this class of compounds. Of particular note is the stability of the aryl TCE sulfates to the highly acidic conditions that are commonly used during solid-phase peptide synthesis using Boc chemistry. The synthesis of sulfotyrosine bearing peptides is still fraught with difficulties.[22] Thus, we are currently examining the use of TCE-protected sulfotyrosine for the synthesis of sulfotyrosine bearing peptides using Boc chemistry. We are also exploring this methodology for the synthesis of alkyl sulfates such as sulfated carbohydrates.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada.

Supporting Information Available: Preparation procedures and characterization data for **1**, **2**, **16**−**37**, and **39**−**47**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036157O

(20) Lorca, M.; Kuhn, D.; Kurosu, M. *Tetrahedron Lett.* **2001**, *42*, 6243−6246.

(21) The results of the inhibition studies with **1** and **2** and estrone sulfatase will be reported elsewhere.

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