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A Comprehensive Approach to the Synthesis of Sulfate Esters

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Abstract: A comprehensive approach to the synthesis of sulfate esters was developed. This approach permits the direct and high-yielding synthesis of protected sulfate monoesters. Subsequent deblocking to reveal sulfate monoesters is accomplished in near-quantitative yield. The exceptionally stable neopentyl protecting group and the labile isobutyl protecting group were utilized in the synthesis of aromatic and aliphatic sulfate monoesters. Strategies for tuning protecting group reactivity were also explored and developed.

Introduction and Background

Sulfate monoesters are widespread in biological systems, occurring in proteins, polysaccharides, steroids, and other small molecules (Figure 1). These molecules are important in a number of biological processes, including hormone regulation,[1] detoxification,[2] molecular recognition and cell-signaling,[3] and viral entry into cells.[4] Sulfation of protein tyrosine residues can function as a modulator of protein−protein interactions.[5] It appears likely that these interactions may be driven by specific recognition of the sulfate group itself. Sulfation of extracellular polysaccharides expands their structural diversity, allowing for the expression of enormous amounts of biological information.[6] Notably, the sulfated forms of some steroids may act as biosynthetic precursors of the active steroids.[1]

Given the growing information on the importance of sulfate monoesters in biochemistry, there is great interest in synthesizing sulfated molecules.[7] The most commonly used reagents for the synthesis of sulfate monoesters are complexes of sulfur trioxide with tertiary amines or amides (see examples in ref 7). Sulfation with these reagents is usually the last step in a synthesis, because the resulting sulfate monoesters tend to be water soluble and difficult to purify. Sulfate monoesters are also highly labile under acidic conditions, further limiting chemical manipulation following installation of the sulfate group. The regioselectivity of these reagents is often an issue in reactions with polyfunctional substrates, where the separation of multiple sulfated products is nearly impossible. The problems associated with the use of sulfur trioxide complexes frequently result in low yields of the desired sulfate monoesters.

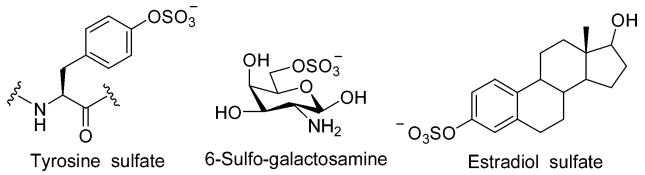
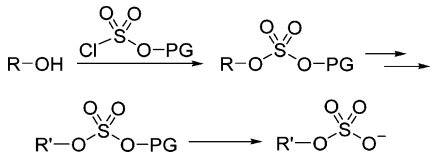


Figure 1. Sulfate monoesters in biological systems.

Because of these difficulties, a few strategies have been developed to convert hydroxyl groups to sulfate diesters. In essence, this generates a protected sulfate monoester that may later be deblocked. This is an attractive approach, because the initial products are uncharged, can be purified by silica gel chromatography, and may be amenable to subsequent chemical manipulations. Phenyl chlorosulfate has been used to functionalize carbohydrate hydroxyl groups as phenyl sulfate diesters.[8] Deblocking requires catalytic hydrogenation of the phenyl ring to a cyclohexyl group, which is base labile. Carbohydrate sulfates, generated with sulfur trioxide-pyridine, have been protected using 2,2,2-trifluorodiazoethane.[9] Subsequent removal of the trifluoroethyl group is accomplished by boiling in strong base. In these examples, the formation of sulfate diesters and the deblocking steps proceed in moderate yields. Furthermore, the deblocking conditions are quite vigorous and are incompatible with the synthesis of aryl sulfate monoesters and with protecting groups that are sensitive to catalytic hydrogenation or basic conditions. The reaction of phenols with 2,2,2-trichloroethyl chlorosulfate gives rise to sulfate diesters in one step.[10] Reductive conditions are required to remove the trichlo-

(1) Hobkirk, R. *Trends Endocrinol. Metab.* **1993**, *4*, 69−74.
(2) Falany, C. N. *FASEB J.* **1997**, *11*, 206−216.
(3) Bowman, K. F.; Bertozzi, C. R. *Chem. Biol.* **1999**, *6*, R9−R22.
(4) Farzan, M.; Mirzabekov, T.; Kolchinsky, P.; Wyatt, R.; Cayabyab, M.; Gerard, N. P.; Gerard, C.; Sodroski, J.; Choe, H. *Cell* **1999**, *96*, 667−676.
(5) Kehoe, J. W.; Bertozzi, C. R. *Chem. Biol.* **2000**, *7*, R57−R61.
(6) Hooper, L. V.; Manzella, S. M.; Baenziger, J. U. *FASEB J.* **1996**, *10*, 1137−1146.
(7) For examples, see: (a) Dusza, J. P.; Joseph, J. P.; Bernstein, S. *Steroids* **1985**, *45*, 303−315. (b) Kitagawa, K.; Aida, C.; Fujiwara, H.; Yagami, T.; Futaki, S.; Kogire, M.; Ida, J.; Inoue, K. *J. Org. Chem.* **2001**, *66*, 1−10. (c) Lee, J.-C.; Lu, X.-A.; Kulkami, S. S.; Wen, Y.-S.; Hung, S.-C. *J. Am. Chem. Soc.* **2004**, *126*, 479−477. (d) Tully, S. E.; Mabon, R.; Gama, C. I.; Tsai, S. M.; Liu, X.; Hsieh-Wilson, L. C. *J. Am. Chem. Soc.* **2004**, *126*, 7736−7737. (e) Young, T.; Kiessling, L. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3449−3451.
(8) Penney, C. L.; Perlin, A. S. *Carbohydr. Res.* **1981**, *93*, 241−246.
(9) Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett.* **1997**, *38*, 7243−7246.
(10) Liu, Y.; Lien, I.-F. F.; Ruttgaizer, S.; Dove, P.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 209−212.

Scheme 1. A Comprehensive Approach to the Synthesis of Sulfate Monoesters[a]



[a] PG = alkyl protecting group.

roethyl protecting group. These deblocking conditions can affect other functional groups and are incompatible with protecting groups that are sensitive to reductive conditions. The intermediate diester is stable to acids and weak bases, but reactive toward good nucleophiles or stronger organic bases.

Several problems clearly exist with the currently available methods for sulfation. Indeed, there is no broadly useful method for the introduction of a protected sulfate monoester that can be used at an intermediate step in a complex synthesis. For this reason, a comprehensive approach was sought that would permit the high-yielding synthesis of sulfate monoesters by way of transient sulfate diesters. An approach was envisioned that involved the reaction of an alcohol or phenol with an alkyl chlorosulfate. The resulting protected sulfate monoesters would be easily purified, stable to many chemical manipulations, and could be deblocked at the end of the synthesis in near quantitative yield (Scheme 1).

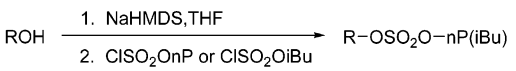
In this approach, the choice of alkyl protecting group would be dictated by the application for which the sulfation method is needed. By changing the alkyl group, in principle, one could dial-in the required reactivity. For instance, to create a protected sulfate monoester that is stable to acidic, basic, and reductive conditions, one could choose primary aliphatic protecting groups that are deblocked under nucleophilic conditions. While some primary aliphatic esters of sulfates, such as methyl or ethyl, are reactive alkylating agents,[11] isobutyl and neopentyl groups have been used to protect sulfonate esters and may also be useful in the protection of sulfate monoesters. In the protection of sulfonates, the neopentyl group is exceedingly stable and difficult to remove, usually requiring high temperatures and long reaction times.[12] The isobutyl group is more easily removed from sulfonates, but is less stable to bases and nucleophiles.[13]

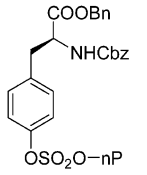
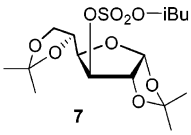
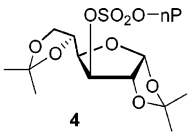
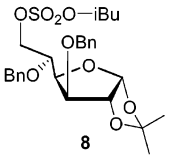
In this work, neopentyl and isobutyl groups were chosen to demonstrate the utility of this comprehensive approach for the synthesis of several sulfate monoesters. Variations on the alkyl group were investigated to search for protecting groups with reactivities that would be between those of neopentyl and isobutyl groups. These protecting groups demonstrate the potential for tuning reactivity, thus permitting the selection of a suitable sulfate monoester protecting group for a wide range of applications.

Results and Discussion

Synthesis of Protected Sulfate Monoesters. Neopentyl and isobutyl chlorosulfate were tested as reagents in the synthesis of protected sulfate monoesters.[14] Phenolic and carbohydrate substrates were treated with these reagents to effectively and easily produce protected sulfate monoesters in high yield (Table 1).

Table 1. Synthesis of Protected Sulfate Monoesters[a]



Product	Yield	Product	Yield
Ph−OSO_2O−nP **1**	95	Ph−OSO_2O−iBu **5**	80
E−OSO_2O−nP **2**	98	E−OSO_2O−iBu **6**	82
 **3**	99	 **7**	95
 **4**	95	 **8**	86

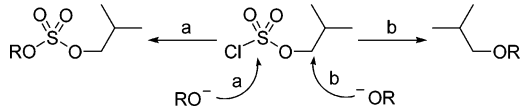
[a] E = estrone, ^{t}Bu = isobutyl, nP = neopentyl. Reactions to produce neopentyl-protected sulfate monoesters were performed at −75 °C and included 20% DMPU as a cosolvent. Reactions to produce isobutyl-protected sulfate monoesters were performed at −15 °C and employed 5−10 equiv of isobutyl chlorosulfate.

For the synthesis of neopentyl-protected sulfate monoesters, phenols and alcohols were treated with sodium hydride or sodium bis(trimethylsilyl)amide in THF (20% DMPU) at −75 °C, followed by the addition of a small excess of neopentyl chlorosulfate.[15] Using these conditions, neopentyl-protected sulfate monoesters of a variety of phenolic compounds and a protected carbohydrate were produced in 95−99% yield. Notably, even fairly complex molecules, such as a protected tyrosine derivative, underwent smooth reaction. The tyrosine neopentyl sulfate derivative **3** was desulfated and then checked for racemization of the amino acid α-carbon. A comparison of optical rotation measurements for the desulfated derivative and the original protected tyrosine derivative indicated that **3** had undergone less than 1% racemization.

Although the reactions to produce neopentyl-protected sulfate monoesters were high-yielding, the neopentyl group was expected to be extremely stable. Isobutyl-protected sulfate monoesters were also evaluated, because the isobutyl group should be significantly more labile. By investigating these two protecting groups, a range of reactivity would be established. Protecting groups with reactivities that lie within this range could be sought as needed for specific applications.

(11) Kaiser, E. T. Reactions of Sulfonate and Sulfate Esters. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum Press: New York, 1977; pp 649−679.
(12) (a) Kotoris, C. C.; Chen, M.-J.; Taylor, S. D. *J. Org. Chem.* **1998**, *63*, 8052−8057. (b) Roberts, J. C.; Gao, H.; Gopalsamy, A.; Kongsjahju, A.; Patch, R. J. *Tetrahedron Lett.* **1997**, *38*, 355−358.
(13) Xie, M.; Widlanski, T. S. *Tetrahedron Lett.* **1996**, *37*, 4443−4446.
(14) Neopentyl and isobutyl chlorosulfate can be easily prepared in large scale by the reaction of the respective alcohols with sulfuryl chloride. The crude chlorosulfates can be distilled and then stored under argon at −20 °C for several months without detectable decomposition. Buncel, E. *Chem. Rev.* **1970**, *70*, 323−337.
(15) Initial reactions of phenol with neopentyl chlorosulfate in the presence of a tertiary amine base gave diester **1**, but in unsatisfactory yields (<50%), even with reaction times of up to 3 days. Lithium aryloxides, produced using *n*-butyllithium or lithium bis(trimethylsilyl)amide, reacted slowly with neopentyl chlorosulfate. These reactions did not go to completion, even with extended reaction times.

Scheme 2. Production of Isobutyl Ether Side Products



During the synthesis of isobutyl-protected sulfate monoesters, the reaction conditions were adjusted slightly to diminish the production of isobutyl ether side products. Isobutyl ethers were presumably generated by the reaction of sodium alkoxides or phenoxides at the primary carbon of isobutyl chlorosulfate to release $^{-}OSO_2Cl$ (Scheme 2).

Minor adjustments to the reaction conditions included discontinuing the use of DMPU, lowering reaction concentrations, increasing the reaction temperature to −15 °C, and using 5−10 equiv of isobutyl chlorosulfate.[16] Using these modified conditions, an isobutyl-protected sulfate monoester of diacetone D-glucose was produced in 95% yield, while less sterically hindered alcohols and phenols produced slightly lower yields. For example, the reaction of estrone with isobutyl chlorosulfate gave an 82% yield of the desired sulfate diester **6** accompanied by 13% of the estrone isobutyl ether (Figure 2). In one difficult case, sulfate diester **5** was isolated in 80% yield.

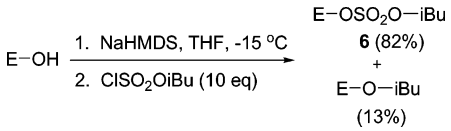


Figure 2. Reaction of estrone with isobutyl chlorosulfate. E = estrone, ^{i}Bu = isobutyl.

Stability of Protected Sulfate Monoesters. All protected sulfate monoesters were stable to purification using silica gel chromatography. Neopentyl-protected sulfate monoesters were stored at room temperature for several months without detectable decomposition. Isobutyl-protected sulfate monoesters were stable when stored at −20 °C, but slowly degraded at room temperature. The chemical stability of the sulfate monoester protecting groups was assessed by treatment with a variety of reagents in synthesis and by direct assays monitored by ^{1}H NMR.

Direct assays were designed to assess the stability of the neopentyl and isobutyl sulfate monoester protecting groups toward treatment with piperdine and trifluoroacetic acid (TFA) in chloroform. These acidic and basic conditions are similar to those typically used in carbohydrate and peptide syntheses, thus demonstrating the potential utility of these protecting groups for such applications. The extent of degradation effected by these reagents was determined by monitoring the appearance of ^{1}H NMR signals corresponding to degradation products (Table 2).

For the assessment of protecting group stability, phenyl sulfate esters **1** and **5** were chosen as model compounds. Degradation was not observed when phenyl neopentyl sulfate **1** was treated with 20% piperdine, even after 48 h. However, 6% piperdine reacted with phenyl isobutyl sulfate **5** through nucleophilic cleavage of the isobutyl group. The appearance of ^{1}H NMR signals corresponding to phenyl sulfate supports this mode of decomposition. Less than 10% degradation was observed for each diester after 48 h of treatment with 50% TFA. The degradation effected by TFA was monitored by the appearance of ^{1}H NMR signals corresponding to phenol.

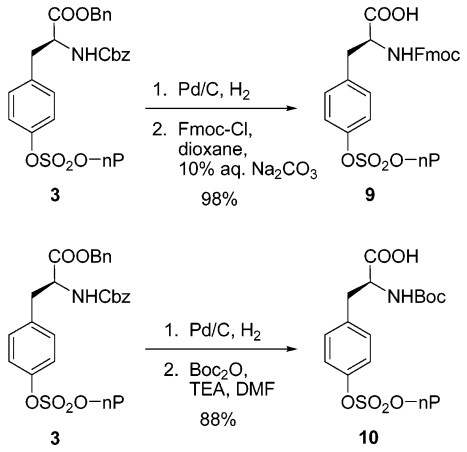
(16) Multiple equivalents of isobutyl chlorosulfate were used to increase the reaction rate and protect the diester product from degradation under the reaction conditions. Lithium phenoxides reacted with isobutyl chlorosulfate to give isobutyl ethers almost exclusively.

Table 2. Direct Assessment of Protecting Group Stability[a]

	substrate degradation (%)				
substrate (reagent)	3 h	6 h	12 h	24 h	48 h
1 (20% piperdine)					
1 (10% TFA)					0.4
1 (50% TFA)	1.9	2.3	4.0	6.9	9.7
5 (6% piperdine)	49.1	73.7	89.2	100	
5 (50% TFA)	1.2	2.3	3.6	7.1	8.7

[a] TFA = trifluoroacetic acid, (−) = no degradation was observed. All experiments were performed in deuterated chloroform.

Scheme 3. Transformation of Tyrosine Derivatives[a]



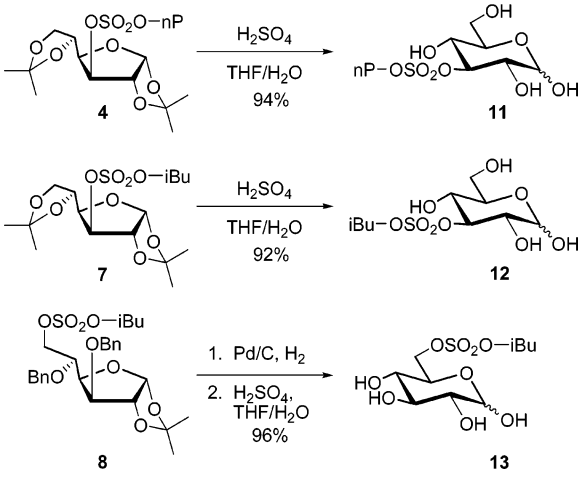
[a] nP = neopentyl.

These assays demonstrate some of the strengths and limitations of each protecting group. The neopentyl group is highly stable to strongly acidic, basic, and nucleophilic conditions. The isobutyl group is stable to strongly acidic conditions, but degrades under basic or nucleophilic conditions.

Chemical manipulation of protected sulfate monoesters further underscores the stability of the neopentyl and isobutyl protecting groups. Tyrosine derivative **3** was converted to the 9-fluorenylmethoxycarbonyl (Fmoc) and *tert*-butoxycarbonyl (Boc) derivatives, which could be useful for peptide synthesis (Scheme 3). Tyrosine derivative **3** was first treated with Pd/C and H_2 to remove benzyl and benzyloxycarbonyl (Cbz) groups in one step. An Fmoc protecting group was installed in 98% yield by stirring the resulting tyrosine derivative with 9-fluorenylmethyl chloroformate in dioxane and 10% aqueous sodium carbonate. A Boc protecting group was installed in 88% yield by heating the tyrosine derivative with di-*tert*-butyl dicarbonate in DMF and triethylamine. These high-yielding transformations clearly demonstrate the stability of the neopentyl protecting group toward hydrogenolysis conditions, weak aqueous base and tertiary amine bases.

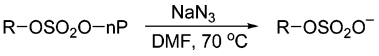
Other transformations demonstrate the stability of the neopentyl and isobutyl protecting groups toward hydrogenolysis conditions and brief treatment with strong aqueous acid. Benzyl and isopropylidene protecting groups were removed from protected carbohydrate sulfates **4**, **7**, and **8** by hydrogenolysis with Pd/C and H_2 and by treatment with aqueous H_2SO_4 in THF (Scheme 4). The high yields obtained in these reactions (92−96%) indicate that neopentyl- and isobutyl-protected sulfate monoesters may be useful in a complex carbohydrate synthesis.

Scheme 4. Transformation of Glucose Derivatives[a]



[a] nP = neopentyl, ^{i}Bu = isobutyl.

Table 3. Deblocking Neopentyl Protecting Groups[a]



Product	Yield	Product	Yield
Ph−OSO_2O^- **14**	96	E−OSO_2O^- **16**	98
15	96	**17**	98

[a] E = estrone, nP = neopentyl.

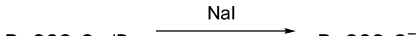
Deblocking To Reveal Sulfate Monoesters. The removal of neopentyl and isobutyl protecting groups was accomplished by the reaction of the protected sulfate monoester with a nucleophile in a polar aprotic solvent. A wide variety of nucleophiles were assessed for their ability to cleave these protecting groups.

Small nucleophiles such as azide and cyanide in hot DMF (60−70 °C) were effective for removal of the neopentyl group in near quantitative yields. Sodium azide was chosen as the reagent for removal of the neopentyl protecting group. The crude sodium sulfate monoesters were passed rapidly through a small silica column using CH_2Cl_2/EtOH (4:1) as the eluent. This effectively removed the excess sodium azide and gave pure sulfate monoester products in 96−98% yield (Table 3).

Nucleophilic substitution at neopentyl centers is considerably slower than at other alkyl groups because of increased steric hindrance.[17] Indeed, the reaction of iodide with phenyl neopentyl sulfate **1** resulted in apparent displacement at sulfur to release phenol rather than cleavage of the neopentyl group. Reaction of iodide with diester **4** did not yield diacetone D-glucose, nor was there cleavage of the neopentyl group after 6 h in hot acetone (55 °C). These results suggest that iodide will readily displace phenoxides, but not alkoxides, at the sulfur center (Scheme 5).

(17) Dostrovsky, I.; Hughes, E. D. *J. Chem. Soc.* **1946**, 157−161.

Table 4. Deblocking Isobutyl Protecting Groups[a]



Product	Yield	Product	Yield
20	97	**21**	96

[a] ^{i}Bu = isobutyl.

An additional experiment demonstrates the need for a range of protecting groups as a means to dial-in reactivity. Diester **11** was treated with sodium azide in DMF (Figure 3). Azide apparently reacted with substitution on the glucose ring to produce 3-azido-3-deoxy D-glucose **18** and neopentyl sulfate **19**.[18] This result suggests that neopentyl chlorosulfate is not useful for the sulfation of the secondary and primary alcohols of most carbohydrates, because the neopentyl group cannot be removed to reveal the desired sulfate monoester products.

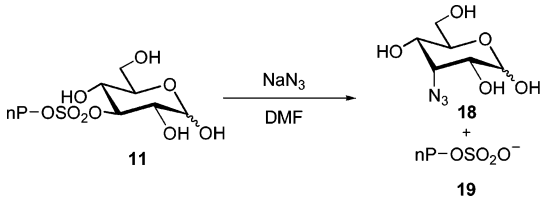
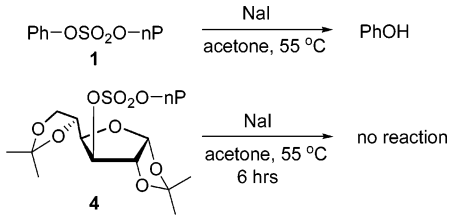


Figure 3. Reaction of sodium azide with an aliphatic neopentyl-protected sulfate monoester. nP = neopentyl.

A variety of nucleophiles were expected to cleave the isobutyl protecting group, because nucleophilic substitution at isobutyl centers is significantly faster than at the highly hindered neopentyl group. For example, iodide has been used to cleave isobutyl esters of sulfonates.[13] Thus, sodium iodide in acetone was expected to be effective and convenient because the sulfated products would precipitate, providing a simple workup. Isobutyl-protected sulfate monoesters **12** and **13** were treated with sodium iodide in hot acetone (55 °C). The completed reaction was filtered, and the precipitated sodium salts were washed with excess cold acetone. These conditions were used to produce D-glucose 3-sulfate **20** and D-glucose 6-sulfate **21** in 97% and 96% yield, respectively (Table 4). Previous syntheses of these derivatives were difficult because of regioselectivity issues and the inherent instability of the sulfate monoester products.[19]

Scheme 5. Reaction of Iodide with Neopentyl-Protected Sulfate Monoesters[a]



[a] nP = neopentyl.

(18) Products **18** and **19** were observed by analysis of the crude material using ^{1}H NMR, IR, and MS.
(19) Archbald, P. J.; Fenn, M. D.; Roy, A. B. *Carbohydr. Res.* **1981**, *93*, 177−190.

The reaction of estrone isobutyl sulfate **6** with sodium iodide resulted in an apparent displacement at sulfur to release estrone. As seen in the reaction of iodide with phenyl neopentyl sulfate **1** (Scheme 5), iodide has a propensity to displace phenoxides from aryl alkyl sulfate diesters. Thus, another nucleophile was required for removal of the isobutyl protecting group from aryl sulfate monoesters. Sodium thiocyanate effectively deblocked the isobutyl group without displacement at sulfur. Thus, estrone derivative **6** was treated with sodium thiocyanate in hot acetone and triethylamine (55 °C).[20] The completed reaction was filtered, and the precipitated sodium salt **22** was washed with excess cold acetone for a simple and effective isolation in 96% yield (Figure 4).

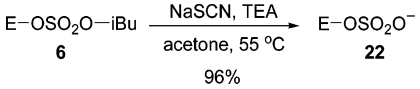
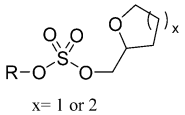


Figure 4. Deblocking the isobutyl group from an aryl sulfate monoester. E = estrone, ^{i}Bu = isobutyl.

The stability of isobutyl and neopentyl protecting groups and the conditions required for their removal direct the choice of which chlorosulfate reagent to use in a synthesis. The greatest utility for neopentyl chlorosulfate is in the synthesis of aryl sulfate monoesters, which were produced in 91−96% yield from the starting phenols. The exceptional stability of the neopentyl protecting group should allow it to be used effectively in complex syntheses. However, because of the strongly nucleophilic conditions required to remove the neopentyl group, neopentyl chlorosulfate is not suitable for the synthesis of most primary or secondary aliphatic sulfate monoesters. Isobutyl chlorosulfate is useful in the synthesis of a wide variety of sulfate monoesters by permitting the high-yielding production of stable, protected sulfate monoesters that can be easily and near-quantitatively deblocked. As demonstrated, the greatest utility for this reagent is in the synthesis of secondary and some primary aliphatic sulfate monoesters. The isobutyl group is less robust than the neopentyl group toward nucleophilic and basic conditions, limiting its usefulness in complex syntheses. However, for the synthesis of sulfate monoesters as the last step of a synthesis, isobutyl chlorosulfate is clearly a superior reagent to sulfur trioxide complexes.

Tuning Protecting Group Reactivity. A range of reactivity has been defined by neopentyl and isobutyl protecting groups for sulfate monoesters. Limitations have been identified and warrant the development of other protecting groups. Adjustment of the steric or electronic environment of the primary aliphatic scaffold should allow for the tuning of reactivity. In this work, two examples were tested, with the understanding that many additional possibilities are likely to exist and can be designed for use in specific applications.

Electron-withdrawing groups are deactivating in bimolecular substitution reactions.[21] Accordingly, β-ethers were expected to display lower reactivity toward nucleophiles. As a means of tuning reactivity in this way, tetrahydrofuran-2-methyl and tetrahydropyran-2-methyl protecting groups were initially chosen for evaluation (see below).



The requisite tetrahydropyran-2-methyl chlorosulfate **23** was produced in 81% yield from tetrahydropyran-2-methanol. Tetrahydrofuran-2-methyl chlorosulfate was also produced, but unfortunately was too unstable for routine use. This chlorosulfate degrades quickly, making it difficult to sufficiently purify or use effectively in subsequent reactions.[22] Thus, only tetrahydropyran-2-methyl chlorosulfate was further tested as a reagent in the synthesis of protected sulfate monoesters. To determine the relative reactivity of this protecting group, tetrahydropyran-2-methyl- and isobutyl-protected sulfate monoesters of diacetone D-glucose were selected as test molecules. The tetrahydropyran-2-methyl-protected sulfate monoester **24** was produced in 86% yield from diacetone D-glucose (Figure 5).

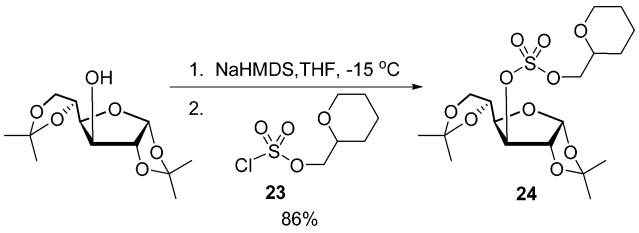


Figure 5. Synthesis of a tetrahydropyran-2-methyl protected sulfate monoester.

Isobutyl and tetrahydropyran-2-methyl protected sulfate monoesters **7** and **24** were treated separately with 2 equiv of sodium iodide in deuterated acetone at room temperature in a sealed NMR tube. NMR spectra were obtained periodically to follow the reaction progress. These experiments revealed that the tetrahydropyran-2-methyl protecting group is about an order of magnitude less reactive than the isobutyl group toward nucleophilic cleavage. Thus, the reactivity of this protecting group falls between the reactivities of neopentyl and isobutyl groups (Figure 6).

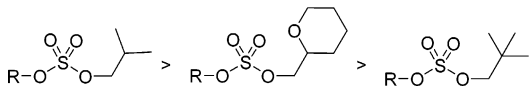


Figure 6. Order of reactivity for sulfate monoester protecting groups.

Conclusion

A comprehensive approach to the synthesis of sulfate esters has been developed that permits the high-yielding synthesis of protected sulfate monoesters and their subsequent deblocking in near quantitative yield. Due to its simplicity and effectiveness, this approach should be useful for the synthesis of a wide range of sulfate monoesters, including sulfated peptides and carbohydrates. As demonstrated by relevant examples, neopentyl and isobutyl protecting groups could be used for the installation of a sulfate ester as an intermediate step or at the end of a complex synthesis. Reactivity tuning can expand the usefulness of this comprehensive approach and suggests that one may be able to dial-in a required protecting group reactivity for use in specific applications.

(20) Triethylamine was used to keep the reaction mixture slightly basic and prevent decomposition of sulfate monoester products.
(21) Hine, J.; Brader, W. H. *J. Am. Chem. Soc.* **1953**, *75*, 3964−3966.
(22) A similar result was observed in the solvolysis of the analogous *p*-bromobenzenesulfonate esters of tetrahydrofuran-2-methanol and tetrahydropyran-2-methanol. Kwiatkowski, G. T.; Kavarnos, S. J.; Closson, W. D. *J. Heterocycl. Chem.* **1965**, *2*, 11−14.

Experimental Section

General. Solvents were distilled under a dry nitrogen atmosphere from potassium benzophenone ketyl (THF and Et_2O) or calcium hydride (triethylamine, pyridine, DMPU) or were fractionally distilled (methanol, acetone, DMF). Other commercial reagents were used as received unless otherwise noted. Sodium bis(trimethylsilyl)amide is commercially available as a 1 M solution in THF. An accurate molarity of this solution was determined by titration with the use of the 4-phenylbenzylidene benzylamine indicator.[23] All reactions were carried out in flame-dried flasks under a dry nitrogen or argon atmosphere and using magnetic stirring. Flash column chromatography was performed with 60 Å 230−400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Fourier transformed infrared spectra were recorded as neat liquids, solids, or thin films (obtained by evaporation from chloroform). High-resolution mass spectra were obtained by the methods indicated.

Synthesis of Neopentyl-Protected Sulfate Monester Esters. Representative Example: Phenyl Neopentyl Sulfate (1). Phenol (0.3043 g, 3.23 mmol) was dissolved in 4 mL of THF and 3 mL of DMPU, and the resulting solution was cooled to −75 °C. Sodium bis(trimethylsilyl)amide (0.93 M solution in THF, 3.8 mL, 3.53 mmol, 1.09 equiv) was added dropwise to the cooled solution and stirred for 10 min. Neat neopentyl chlorosulfate (0.56 mL, 3.52 mmol, 1.09 equiv) was added quickly to the reaction mixture. After 10 min, the reaction mixture was allowed to warm to room temperature. Upon completion (TLC), ethyl acetate and saturated aqueous $NaHCO_3$ were added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$, water and brine, and then dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (10% ethyl acetate/hexanes) gave **1** as clear liquid (0.750 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.30 (m, 5H), 4.09 (s, 2H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.42, 130.10, 127.42, 121.17, 83.54, 32.05, 26.07; IR (neat) 2964, 2873, 1587, 1489, 1410, 1370, 1206, 1175, 1149, 962, 880; HRMS (EI) *m*/*z* calcd for $C_{11}H_{16}O_4S$ (M^+) 244.0769, found 244.0776.

Synthesis of Isobutyl-Protected Sulfate Monester Esters. Representative Example: Phenyl Isobutyl Sulfate (5). Phenol (0.2016 g, 2.14 mmol) was dissolved in 40 mL of THF, and the resulting solution was cooled to −15 °C. Sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 2.4 mL, 2.4 mmol, 1.1 equiv) was added dropwise to the cooled solution and stirred for 10 min. Neat isobutyl chlorosulfate (1.5 mL, 10.58 mmol, 4.9 equiv) was added quickly to the reaction mixture. After 10 min, the reaction mixture was allowed to warm to room temperature. Upon completion (TLC), ethyl acetate and saturated aqueous $NaHCO_3$ were added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$, water and brine, and then dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (10% ethyl acetate/hexanes) gave **5** as a clear liquid (0.392 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.30 (m, 5H), 4.20 (d, J = 6.8 Hz, 2H), 2.09 (m, 1H), 0.99 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.41, 130.06, 127.41, 121.15, 80.38, 28.19, 18.61; IR (neat) 2968, 2878, 1587, 1489, 1408, 1207, 1149, 973, 879; HRMS (CI) *m*/*z* calcd for $C_{10}H_{15}O_4S$ ($M + H^+$) 231.0686, found 231.0687.

Deblocking Neopentyl-Protected Sulfate Monester Esters. Representative Example: Estrone Sulfate (16).[10] In a flask fitted with a reflux condenser, estrone neopentyl sulfate **2** (0.1011 g, 0.240 mmol) was dissolved in 1 mL of DMF. Sodium azide (0.0213 g, 0.328 mmol, 1.4 equiv) was added, and the solution was stirred and heated to 70 °C in an oil bath overnight. Removal of the solvent in vacuo and purification of the crude product by silica gel chromatography (20% ethanol/CH_2Cl_2) gave **16** as the sodium salt (0.088 g, 98%): ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.24 (d, J = 8.4 Hz, 1H), 7.06−7.03 (m, 2H), 2.89−2.87 (m, 2H), 2.52−1.88 (m, 7H), 1.66−1.40 (m, 6H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 151.76, 138.71, 137.51, 126.93, 122.48, 119.77, 45.46, 45.33, 39.59, 36.72, 32.79, 30.42, 27.52, 27.04, 22.52, 14.30, 14.21; IR (solid) 3453, 2930, 2867, 1724, 1493, 1227, 1049, 933; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{21}O_5Na_2S$ ($M + 2Na^+$) 395.0900, found 395.0909.

Deblocking Isobutyl-Protected Aliphatic Sulfate Monester Esters. Representative Example: D-Glucose 3-Sulfate (20).[19] In a flask fitted with a reflux condenser, D-glucose 3-isobutyl sulfate **12** (0.038 g, 0.120 mmol) was dissolved in 4 mL of acetone. Sodium iodide (0.0544 g, 0.363 mmol, 3.0 equiv) was added, and the solution was stirred and heated to 55 °C in an oil bath for 5 h. The precipitated product was washed several times with cold acetone to give **20** as a hydroscopic solid (0.033 g, 97%): ^{1}H NMR (400 MHz, D_2O) δ (α-anomer, 45%) 5.30 (d, J = 4.0 Hz, 1H), 4.51 (t, J = 9.6 Hz, 1H), 3.45 (m, 1H); (β-anomer, 55%) 4.77−4.74 (m, 1H), 4.33 (t, J = 9.2 Hz, 1H), 3.58−3.54 (m, 1H); (both anomers) 3.95−3.72 (m, 3H), 3.64 (t, J = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 96.45, 92.84, 85.11, 83.05, 76.22, 73.68, 71.99, 71.00, 69.13, 69.06, 61.48, 61.31; IR (solid) 3362, 1637, 1215, 1055, 999, 934, 816; HRMS (ESI) *m*/*z* calcd for $C_6H_{11}O_9Na_2S$ ($M + 2Na^+$) 304.9914, found 304.9910.

Deblocking Isobutyl-Protected Aryl Sulfate Monester Esters. Representative Example: Estrone Sulfate (22). In a flask fitted with a reflux condenser, estrone isobutyl sulfate **6** (0.0420 g, 0.103 mmol) was dissolved in 1 mL of acetone. Sodium thiocyanate (0.0177 g, 0.218 mmol, 2.1 equiv) and triethylamine (0.04 mL) were added, and the solution was stirred and heated to 55 °C in an oil bath for 2 h. The precipitated product was washed several times with cold acetone to give **22** as a white solid (0.037 g, 96%): ^{1}H NMR, ^{13}C NMR, IR, and HRMS identical to estrone sulfate **16**.

Supporting Information Available: Complete experimental procedures for the synthesis of all compounds, procedures for protecting group reactivity and stability studies, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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