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A Sulfitylation−Oxidation Protocol for the Preparation of Sulfates

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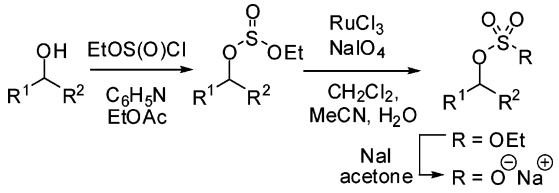

A novel, high-yielding method for sulfation of alcohols has been developed, proceeding via sulfite- and sulfate diester intermediates. Sulfite diesters serve as versatile sulfate monoester precursors, allowing for transformations that are difficult or impossible with the latter compounds.

One of the body's regulatory mechanisms involves the functional modification of heteroatoms with a sulfate group. For example, extracellular traffic and cell−cell communication involves the covalent modification of glycoproteins with a sulfate moiety.[1,2] Carbohydrate sulfates, found extensively at the cell surface or in the extracellular space in the form of proteoglycans[3] or mucins,[4] play an essential role in cellular communication. Sulfate functionality is found in sulfotyrosine-bearing peptide hormones[5] and sulfated steroids,[6] and the number of glycoproteins and glycolipids shown to bear sulfates is also rapidly growing. Consequently, sulfotransferases[7] and sulfatases,[8] the enzymes responsible for regulation of addition and removal of sulfates, respectively, have become the focus of intense interest, both from a fundamental point of view as well as for therapeutic intervention.[9]

To accurately establish the biological role of a (de)sulfating enzyme or structure−activity relationship of a particular sulfated structure, a pure amount of a selected sulfated substrate is often required. Isolation from natural sources, however, can be a tedious task due to low or transient availability of sulfates or microheterogeneity problems. Consequently, the preparation of organic sulfates or sulfamidates by chemical synthesis is a worthwhile alternative. To this end, an alcohol (or amine) is converted to a sulfate monoester (or sulfamidate) by reaction with a sulfur trioxide−nitrogen base complex or chlorosulfonic acid, typically by subjection to excess of reagents (2−10 equiv, see Figure 1).[10,11] More disturbingly, since the anionic nature of a sulfate encumbers straightforward purification on silica gel, introduction of the sulfate is inevitably postponed to the last stage of a synthesis. A logical consequence of such a strategy is that an alcohol targeted for eventual sulfation requires temporary protection during earlier steps of the synthesis.

We reasoned that the latter disadvantages could be circumvented by development of a strategy proceeding through intermediate diesters sulfite **I** and sulfate **II** (see Figure 1). Such diesters are neutral, can be introduced at a convenient stage of a synthesis, and if chosen carefully can be compatible with subsequent transformations before final deprotection to the desired sulfate monoester. We here wish to report that such a strategy is successful in the preparation of organic sulfates.

A few papers report *sulfate* diesters as protected precursors of the final monosulfate. Early studies[12] employed phenyl sulfate intermediates, which could be unmasked in a two-step protocol involving hydrogenation (phenyl → cyclohexyl) and base hydrolysis. Trifluoroethyl (TFE) esters were shown[13,14] to be compatible with a variety of conditions, including TFA, TBAF, hydrogenation, Zemplén conditions, and heat, whereas removal of the TFE group could be effected in good yield, usually by *tert*-butoxide in refluxing *tert*-butyl alcohol. Two years ago, a report[15] on the application of trichloroethyl (TCE) intermediates en route to aryl sulfates demonstrated that TCE esters can be carried several steps through a synthesis without decomposition, before final conversion to the sulfate monoester by hydrogenolysis. Widlanski et al. most recently further elaborated such an approach by application of neopentyl and *iso*-butyl sulfate diester precursors in the synthesis of aryl sulfates and two selected aliphatic sulfates.[16] Nevertheless, each of these procedures is associated with some specific disadvantages, like harsh deprotection conditions, low yields, requirement of large excesses of (hazardous) reagents, or limited application, e.g aromatic alcohols and sterically hindered secondary alcohols.

Inspiration for our approach came from the synthetic strategy for the conversion of diols to cyclic *sulfates* via cyclic *sulfite*

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(11) Most recently, the use of isobutene as proton scavenger was also reported: Papy-Garcia, D.; Barbier-Chassefière, V.; Rouet, V.; Kerros, M. E.; Klochendler, C.; Tournaire, M. C.; Barritault, D.; Caruelle, J. P.; Petit, E. *Macromolecules* **2005**, *38*, 4647−4654.
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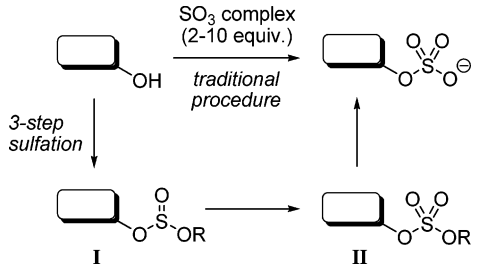


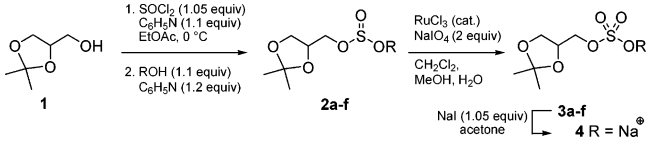
FIGURE 1. Concept of three-step sulfation.

TABLE 1. Two-Step Synthesis (See Scheme 1) of Sulfate Diesters 3a−f via Sulfite Intermediates, Followed by Unmasking to Sulfate 4

R	sulfite	yield (%)	sulfate	yield (%)
Me	2a	24[a]	3a	−
Et	2b	35	3b	95
i-Pr	2c	25	3c	88
t-Bu	2d	40[b]	3d	−
neopentyl	2e	21	3e	63
Bn	2f	36[a]	3f	−

[a] Decomposition, before or during oxidation. [b] Ten equiv of *t*-BuOH used.

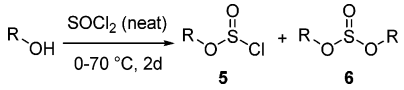
SCHEME 1. Preparation of Solketal Sulfate via Sulfite and Sulfate Esters



diesters.[17] Such a procedure proceeds under mild conditions and requires minimal excess of reagents. Furthermore, the sulfite intermediates appeared of particular interest, due to the reduced electrophilicity, and hence better stability, of sulfites with respect to sulfates. Nevertheless, it was apparent from the outset that the choice of the most suitable sulfite/sulfate protective group R is fundamental in balancing the stability of the intermediates with ease of deprotection in the final step.

With 1,2-*O*-isopropylidene-*rac*-glycerol (**1**) as a model compound, we set out to investigate the synthetic feasibility of a three-step sulfation technology. Conversion of the alcohol to a sulfite ester was initially investigated in a two-step one-pot procedure, involving sequential treatment with thionyl chloride and condensation with an alcohol (**1** → **2**, Table 1).As becomes clear from Table 1, the desired sulfite esters were successfully obtained, albeit with mediocre yields due to concomitant formation of symmetrical sulfite diester from the in situ formed alkyl chlorosulfite. Moreover, both methyl (**2a**) and benzyl (**2f**) sulfite diester were found unsufficiently stable for practical application, while preparation of the *tert*-butyl ester **2d** required large excess of *tert*-butyl alcohol. In contrast, we were delighted to find that the ethyl, *i*-propyl, and neopentyl esters were stable and that the subsequent oxidation (**2** → **3**) proceeded rapidly, cleanly, and in excellent yield under the action of two equivalents of $NaIO_4$ and catalytic $RuCl_3$. During this process, the initially formed diastereomeric mixture of sulfite diesters converges into a single product. The sulfate diesters were found sufficiently stable for silica gel column chromatography. Finally, conversion of sulfate diester into sulfate monoester (**3** → **4**) was found to proceed smoothly upon subjection of compound **3b** or **3c** to a single equivalent of NaI in acetone at ambient temperature, leading to a quantitative production of **4**. After evaporation of solvent and in situ formed iodoalkane (ethyl or isopropyl iodide, respectively), the pure sulfate monoester remains as the sole product. It is important to note that the last transformation—the result of nucleophilic attack of iodide at the alkyl carbon leading to S_N2 displacement of sulfate—proceeds with regiospecificity for both **3b** and **3c**. In contrast, the neopentyl substituent of **3e** proved unsuitable for generation of solketal sulfate **4**, because deprotection led to a mixture consisting of mostly neopentyl sulfate (20:1 ratio with **4**).[18] This reversal in regioselectivity is probably caused by the greatly increased steric hindrance of the alkyl moiety.

TABLE 2. Preparation of Alkyl Chlorosulfites



products	R	ratio[a] (**5**:**6**)	stability
5a + **6a**	Et	4:1	++
5b + **6b**	*i*-Pr	5:2	−
5c + **6c**	*t*-Bu	−[b]	NA
5d + **6d**	neopentyl	>100:1	+

[a] Based on NMR analysis after distillation. [b] Isobutene formation.

In order for the sulfation route to be synthetically useful, we focused our attention on an alternative approach for the generation of sulfite diesters involving condensation with an alkyl chlorosulfite reagent of type **5** (Table 2). Alkoxychlorosulfites are readily produced upon the condensation of thionyl chloride (neat) with an alcohol.[19,20] The concomitant formation of minor amounts of symmetrical dialkyl sulfites (**6**) was not disturbing, since the symmetrical diesters **6** are inert in the subsequent sulfitylation (Table 3, step *i*).

At this point, we decided to focus on ethyl protected sulfate esters for two reasons: first, the isopropyl chlorosulfite **5b** was rather unstable (complete decomposition in matter of days) and, second, because unmasking of isopropyl sulfate esters was expected to have a higher likeliness to lead to problems during deprotection.[21] Indeed, we were delighted to find that subjection of solketal **1** to 1.2 molar equivalents of ethyl chlorosulfite **5a** in the presence of pyridine (0 °C, EtOAc) led to a near quantitative production of ethyl sulfite ester (95%, entry 1 in Table 3).[22]

Having achieved high yields for each step of the sequence, the iterative sulfation protocol was applied to a number of

(17) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539.

(18) Poor regioselectivity was also encountered by Widlanski in deprotection of neopentyl glucose 3-sulfate with sodium azide. It was also reported that, in contrast to our findings, a neopentyl sulfate derivative is completely inert to deprotection with sodium iodide.

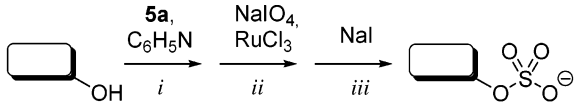
(19) Sharman, S. H.; Caserio, F. F.; Nystrom, R. F.; Leak, J. C.; Young, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 5965.

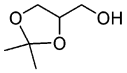
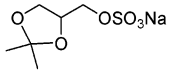
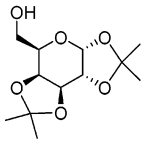
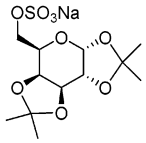
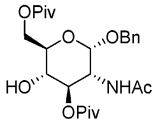
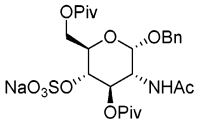
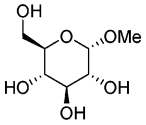
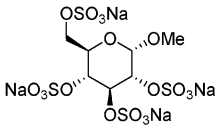
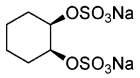
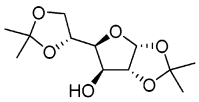
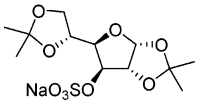
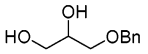
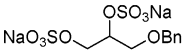
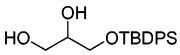
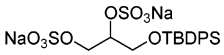
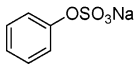
(20) Carré, P.; Libermann, D. *Bull. Soc. Chim. Fr.* **1933**, *53*, 1050−1075.

(21) Xie, M.; Widlanski, T. S. *Tetrahedron Lett.* **1996**, *37*, 4443−4446.

(22) A one-step conversion of alcohols into ethyl sulfate esters using (commercially available) $EtOSO_2Cl$ was found unsatisfactory due to the extremely unstable nature of the reagent. Second, ethyl sulfate esters are less suitable for a synthetic strategy involving early introduction of a sulfate precursor due to the lower stability with respect to sulfite esters.

TABLE 3. Application of the Three-Step Sulfation Protocol to the Sulfation Alcohols



entry	starting material	*i*	*ii*	*iii*	final product		overall (%)
1		95	95	100		**4**	90
2		95	96	100		**7**	91
3		80	95	99		**8**	76
4		83	93	99		**9**	77
5		97	93	99		**10**	89
6		95	97	99		**11**	91
7		96	100	100		**12**	96
8		100	91	100		**13**	91
9		93		100		**14**	93[a]

[a] Adapted procedure, see text.

different aliphatic primary and secondary alcohols, diols, sugars, and aromatic alcohols (Table 3). As becomes clear from Table 3, all three steps usually proceed in excellent yield, under mild conditions, and with near stoichiometric amounts of reagents. Purification of intermediates and products was generally unnecessary or rather disadvantageous (see below). The potential of the methodology is nicely reflected in the successful tetrasulfation of methyl β-D-glycoside **9**.[23]

It was found that sulfation of phenol requires an adapted procedure, involving sulfitylation−oxidation without intermediate purification, because phenyl ethyl sulfite is rather unstable and easily decomposes back to phenol. Much to our surprise, phenyl ethyl sulfate diester was more stable than the sulfite intermediate. In this particular case, deprotection also required special attention, as the standard sodium iodide conditions yielded phenol instead of phenyl sulfate.[16] Fortunately, the desired product was obtained uneventfully upon treatment with sodium methoxide in methanol, leading to quantitative production of the desired product.

In summary, with the exception of phenyl ethyl sulfite, sulfite and sulfate esters of aliphatic alcohols were found to be apolar, stable compounds, which readily dissolved in common organic solvents and allowed for silica gel column chromatography. The ultimate question to be addressed on the described three-step sulfation strategy is the suitability of application sulfite/sulfate diesters in reaction sequences that would otherwise be inconvenient due to the polarity of free sulfates. Thus, sulfite **11a** was subjected[24] to a variety of typical conditions for *O*-protective group interconversion (Figure 2).

First, removal of the 5,6-*O*-isopropylidene group ($AcOH/H_2O$ = 1/1) proceeded in excellent yield (**11a** → **15**). Subsequent acetylation (Ac_2O, pyridine) to **16a** or silylation to **16b** (TBDMSCl, imidazole, DMF) of the primary alcohol was also

(23) Wessel, H. P.; Bartsch, S. *Carbohydr. Res.* **1995**, *274*, 1−9.

(24) Only the ethyl sulfite diester was investigated, as ethyl sulfate diesters are considerably less stable.

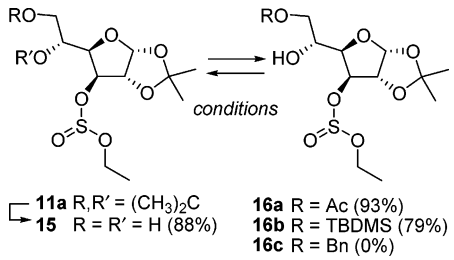


FIGURE 2. Compatibility of ethyl sulfite diester functionality with typical carbohydrate protective group manipulations.

well tolerated, as was the subsequent desilylation of **16b** to **11a** (pyridine·HF, pyridine, 63%).[25] Some other transformations were less satisfactory, for example full deacetonation (TFA/H_2O = 1/1) or benzylation (NaH, BnBr, TBAI, THF or BnOC(NH)CCl_3, TMSOTf, THF) led predominantly to decomposition. These findings demonstrate the potential of ethyl sulfite esters as sulfate precursors in organic sequences, but further optimization is still required.

In conclusion, a new sulfation methodology has been developed with several advantages over conventional sulfation procedures.[26] Yields are high, purification is easy or redundant, and reactions proceed with near stoichiometric amounts of reagents. Moreover, the sulfite diesters show promise as protected sulfate precursors, although compatibility with common reaction conditions requires further fine-tuning. We are currently addressing this issue with alternative sulfate precursors.

Experimental Section

General Procedure for Sulfite Diester Formation by Consecutive Thionyl Chloride and Alcohol Addition. Thionyl chloride (1.05 equiv) and pyridine (1.1 equiv) are dissolved in EtOAc. The solution is cooled to 0 °C, and the starting material is added dropwise. After 30 min a solution of an alcohol (1.1 equiv) and pyridine (1.1 equiv) is added dropwise. After another 30 min the reaction mixture is quenched with water and extracted with water and brine. The organic layer is dried (Na_2SO_4), filtered, and concentrated. The crude product is purified by flash chromatography with EtOAc/heptane mixtures.

(25) Glycosylation of **15** was also carried out with the trichloroacetimidate derived from 2,3,4,6-tetra-*O*-benzyl-α/*β*-D-glucopyranose under the influence of BF_3·OEt_2. The reaction was found to proceed smoothly and in excellent yield (90%) to give a mixture of four diastereomeric products, as confirmed by NMR and mass spectrometric analysis.

(26) Condensation of reagent **5a** with primary amines failed to lead to sulfamidite, presumably due to sulfinylamine formation via elimination of EtOH from the intermediate.

Preparation of Ethyl Chlorosulfite (5a). Thionyl chloride (25.46 g, 2.14 mol) and ethanol (82.95 g, 1.80 mol) were reacted as described in the general chlorosulfite synthesis procedure. Distillation was performed at 43 °C (63 mbar), yielding **5a** as a colorless liquid (∼75%). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 4.63 (dq, 1H, J = 7.1, 10.1 Hz), 4.49 (dq, 1H, J = 7.1 Hz, 10.1 Hz), 1.49 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) δ: 63.9, 14.7.

General Procedure for Sulfite Diester Formation by Condensation with Ethyl Chlorosulfite (Step *i* in Table 3). The starting material and pyridine (1.3 equiv) are dissolved in EtOAc. The solution is cooled to 0 °C, and ethyl chlorosulfite **5a** (1.2 equiv) is added dropwise. After about 1 h (depending on TLC analysis), the reaction mixture is quenched with water and extracted with water and brine. The organic layer is dried ($NaSO_4$), filtered, and concentrated. Further purification is usually unnecessary but can optionally be done by means of flash chromatography with EtOAc/heptane mixtures.

General Sulfite Oxidation Procedure (Step *ii* in Table 3). The sulfite diester is dissolved in a 2/2/3 MeCN/CH_2Cl_2/water mixture, to which $NaIO_4$ (2 equiv) and $RuCl_3$ (cat.) are added. The mixture is stirred vigorously for 1 h. TLC analysis (usually EtOAc:heptane 1:1) shows a spot-to-spot conversion into a slightly lower running (sometimes co-running) product. The reaction mixture is diluted with CH_2Cl_2 (about 2 reaction volumes) and is then extracted with water and brine. After drying (Na_2SO_4) the organic layer is filtered and concentrated. The crude product is then subjected to flash chromatography (often a short column suffices). The product fractions are pooled and concentrated, yielding the product.

General Sulfate Deprotection Procedure (Step *iii* in Table 3). Sodium iodide is added to a solution of the sulfate diester in acetone. The reaction is left at room temperature for 3 to 18 h. When TLC analysis (usually EtOAc:heptane 1:1) shows the starting material is gone, the reaction mixture is concentrated. After EtOAc addition, the organic layer is extracted twice with water. The aqueous layer is concentrated, yielding the crude product. Traces of sodium iodide can be removed by flash column chromatography with acetonitrile/water mixtures.

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Supporting Information Available: General experimental methods, procedures for the synthesis of selected compounds with full characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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