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Synthesis of Cyclic Sulfates by Halocyclization

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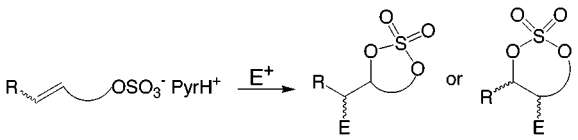
ABSTRACT



We report the synthesis of cyclic sulfates by halocyclization. The resulting cyclic sulfate products can be opened selectively with sodium azide to transform them into highly functionalized compounds that contain azide, alcohol, and halide groups.

Cyclic sulfates are versatile electrophiles.[1,2] They react with a variety of nucleophiles to facilitate the construction of natural products[3] and specific functionality, such as aziridines,[4] modified sugars,[5] and cyclopropane derivatives.[6,7] The use of cyclic sulfates was limited by the lack of an efficient method for their synthesis[8] until the advent of methods for the oxidation of cyclic sulfite intermediates.[9] The increased accessibility of cyclic sulfates has augmented our understanding of their reactivity and extended their use in synthesis. Access to cyclic sulfates incorporating a wider range of functional groups would expand further the scope of their applications. To this end, we report a new method for cyclic sulfate synthesis.

We hypothesized that unsaturated monosulfates could be transformed into cyclic sulfates through halocyclization reactions (Figure 1).[10,11] This approach would yield cyclic sulfate derivatives with the products containing a total of three electrophilic centers. Because each new electrophilic

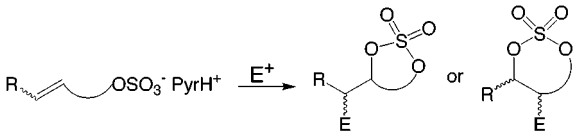


Figure 1. Scheme depicting cyclic sulfate generation by halocyclization.

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(1) Lohray, B. B. *Synthesis* **1992**, 1039.
(2) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
(3) For some examples, see: (a) Machinaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405. (b) Nicolaou, K. C.; Patron, A. P.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. *Chem. Eur. J.* **1996**, *2*, 847. (c) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732. (d) Trost, B. M.; Dudash, J.; Hembre, E. J. *Chem. Eur. J.* **2001**, *7*, 1619. (e) Waterson, A. G.; Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4305. (f) Stohlmeyer, M. M.; Tanaka, H.; Wandless, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 6100.
(4) Tanaka, K. *Sulfonic Acids, Esters, Amides and Halides as Synthons*; John Wiley & Sons Ltd.: New York, 1991.
(5) For some examples, see: (a) van der Klein, P. A. M.; Filemon, W.; Veeneman, G. H.; Van der Marel, G. A.; Van Boom, J. H. *J. Carbohydr. Chem.* **1992**, *11*. (b) Maracaurelle, L. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2001**, *123*, 1587. (c) Cohen, S. B.; Halcomb, R. L. *Org. Lett.* **2001**, *3*, 405.
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(7) Guijarro, D.; Guillena, G.; Mancheno, B.; Yus, M. *Tetrahedron* **1994**, *50*, 3427.
(8) (a) Bragg, P. D.; Jones, J. K. N.; Turner, J. C. *Can. J. Chem.* **1959**, *37*, 1412. (b) Kaiser, E. T.; Katz, I. R.; Wulfers, T. F. *J. Am. Chem. Soc.* **1965**, *87*, 3781. (c) Helferich, B. *Chem. Ber.* **1921**, *54*, 1082. (d) Denmark, S. E. *J. Org. Chem.* **1981**, *46*, 3144. (e) Latif, F.; Shekhani, M. S.; Voelter, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1573.
(9) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.
(10) Bartlett, P. A. *Olefin Cyclization Processes That Form Carbon-Heteroatom Bonds*; Academic Press: New York, 1984.
(11) Cardillo, G.; Miller, M. J. *Tetrahedron Lett.* **1990**, *46*, 3321.

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site should exhibit a different reactivity, the products could undergo independent sequential reactions with distinct nucleophiles. The conditions associated with sulfation and halocyclization reactions are mild; consequently, this synthetic approach could greatly expand the range of substrates from which cyclic sulfates can be generated.

The low nucleophilicity of the sulfate group and the anticipated high reactivity of the resulting cyclic products led to questions regarding the plausibility of the proposed halocyclization route. Our first objective was to determine its feasibility. Sulfates are poor nucleophiles, yet weakly nucleophilic species such as benzyl ethers, phosphotriesters, and phosphonic acid derivatives can participate in halocyclization reactions.[10−12] Our initial studies with pyridinium 4-(*p*-methoxybenzyl)oxy-(*Z*)-2-buten-1-sulfate (**1**) yielded promising results. When sulfate **1** was treated with *N*-iodosuccimide (NIS), the product[13] of *exo* cyclization, **2**, was the only one obtained (Figure 2, 40% yield). To optimize

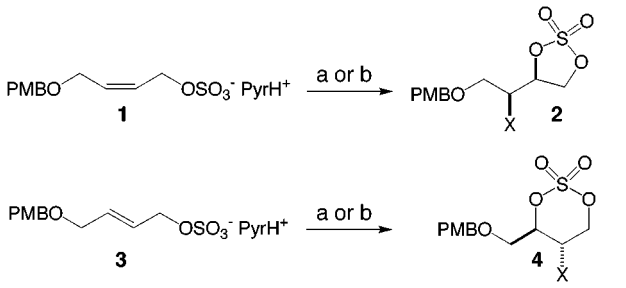
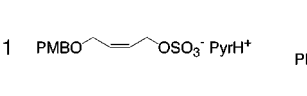
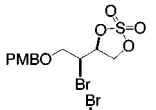
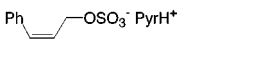
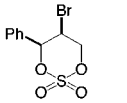
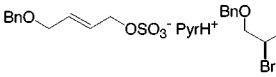
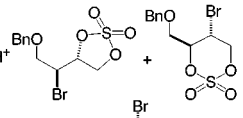
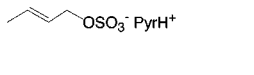
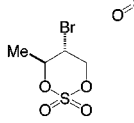
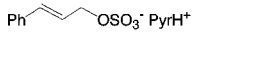
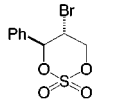
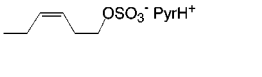
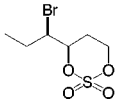
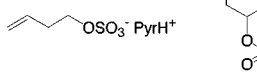
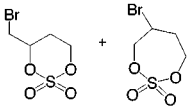
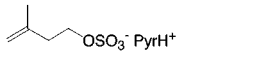
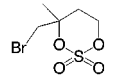
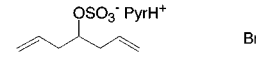
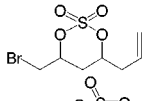
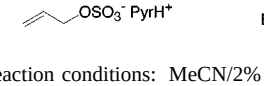
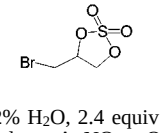


Figure 2. Effect of alkene geometry on the regiochemistry of cyclization. Conditions: (a) ICl, $AgNO_3$; (b) Br_2, $AgNO_3$.

the reaction, a variety of electrophiles and solvents were investigated. Electrophilic reagents such as *N*-bromosuccinimide and NIS promoted cyclic sulfate formation, but halogens and interhalogens were more effective. In the presence of excess halide, however, the cyclic sulfate products revert back to starting materials. Accordingly, we found that the combination of bromine or chloroiodine in the presence of silver nitrate afforded the highest yields. Alkene **1**, for example, affords the cyclic sulfate in 91% yield under these conditions (Table 1). These results demonstrate the feasibility and efficiency of this route to cyclic sulfates.

The effect of alkene geometry on the product structure was investigated using the diastereomeric pyridinium sulfates **1** and **3** (Figure 2). Each sulfate was synthesized by treatment of the corresponding alcohol with pyridine−sulfur trioxide complex.[14] In the absence of directing substituents on the substrate, halocyclization reactions typically afford the five-

Table 1. Synthesis of Cyclic Sulfates by Halocyclization[a]

entry	substrate	product	yield
1			91%
2[b]			41%
3[b]			90% (14 : 86)
4			64%
5			82%
6			69%
7			60% (82:18)
8			78%
9[c]			77% (2:1 *cis*:*trans*)
10			~5% (Volatile)

[a] Reaction conditions: MeCN/2% H_2O, 2.4 equiv of Br_2, 1.2 equiv of $AgNO_3$, 0 °C, 30 min. [b] K_2CO_3 used, not $AgNO_3$. [c] One equivalent of Br_2.

membered ring cyclic sulfate derived from *exo* cyclization over the six-membered isomer arising from *endo* cyclization.[15] As anticipated, the *Z*-isomer of pyridinium sulfate **1** afforded the five-membered ring isomer **2** as the only product (Figure 2). In contrast, the halocyclization reaction of *E*-allylic sulfate **3** yielded the six-membered ring isomer **4**. This outcome was unexpected but not unprecedented. Differences in regioselectivities for *cis* and *trans* isomers have been observed previously in the iodocyclization of allylic imidates.[16]

Steric and electronic effects can influence the regioselectivity of halocyclization reactions; consequently, we examined the effects of various substituents on cyclic sulfate

(12) Yokomatsu, T.; Shioya, Y.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1997**, *46*, 463.

(13) Bartlett, P. A.; Myerson, I. *J. Am. Chem. Soc.* **1978**, *100*, 395.

(14) A number of methods for converting alcohols to sulfates have been developed. For an overview, see: Sandler, S. R.; Karo, W. In *Organic Functional Group Preparations*; Academic Press: San Diego, 1989; Vol. 3, pp 129−161. For recent developments, see: (a) Lubineau, A.; Lemoine, R. *Tetrahedron Lett.* **1994**, *35*, 8795. (b) Guilbert, B.; Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1994**, *35*, 6563. (c) Manning, D. D.; Bertozzi, C. R.; Pohl, N. L.; Rosen, S. D.; Kiessling, L. L. *J. Org. Chem.* **1995**, *60*, 6254. (d) Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett.* **1997**, *38*, 7243. (e) Langston, S.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 234.

(15) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.

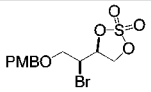
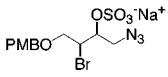
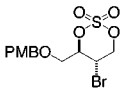
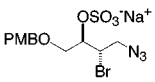
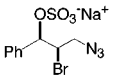
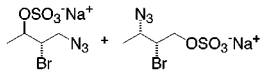
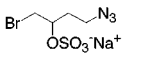
(16) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1986**, *51*, 4905.

formation (Table 1). For most substrates containing *cis*-alkenes, *exo* cyclization to form the five-membered ring was preferred. The *cis* cinnamyl derivative (Table 1, entry 2), however, was an exception; it underwent cyclization to form selectively the six-membered ring. Thus, groups that can stabilize electropositive centers influence the regioselectivity, a result that is consistent with a late transition state. The *trans* alkenes provided the more stable 6-membered cyclic sulfates as the reactions of *E*-alkenes containing methyl (Table 1, entry 4) or phenyl (entry 5) substituents illustrate. The bromocyclization reaction of a substrate with an allylic alkoxy group (Table 1, entry 3), however, was less regioselective (*exo* to *endo* ratio of 14:86). A diallyl derivative underwent selective reaction to afford the cyclized product possessing an unmodified alkene (Table 1, entry 9). With a simple homoallylic sulfate (Table 1, entry 7), both six- and seven-membered ring systems were generated, with the six-membered ring system predominating as expected. The reaction of a homoallylic sulfate with a more substituted alkene occurred with high regioselectivity (Table 1, entry 8). Overall, the results indicate that excellent and predictable regioselectivities are obtained in the halocyclization reactions of alkenyl sulfates. Significantly, many of the cyclic sulfates generated via halocyclization are not accessible from traditional oxidation approaches.

An important advantage of the halocyclization approach to forming cyclic sulfates is that the products possess contiguous electrophilic centers. We anticipated that the resulting cyclic sulfates would be versatile intermediates as if the electrophilic sites could be differentiated. We therefore examined the reactivity of a series of bromo cyclic sulfate derivatives with sodium azide. As anticipated, the nucleophilic azide reacts selectively with the five-membered cyclic sulfates at the primary carbon to afford the ring-opened monosulfate (Table 2, entry 1). No nucleophilic displacement of the bromide was observed. The selectivity for nucleophilic displacement of the cyclic sulfate group was maintained even in the case of less reactive six-membered-ring cyclic sulfates (Table 2, entries 2−5). Although the cyclic sulfate is always opened, the site of reactivity appears to be influenced by inductive effects (Table 2, compare entries 2 and 4).

Cyclic sulfate formation through halocyclization complements the Sharpless strategy and other cyclic sulfite oxidation methods.[9,8d] From halocyclization reactions, six-membered and larger cyclic sulfate ring systems can be generated; these compounds are difficult to access through cyclic sulfite intermediates. Moreover, a diversity of functional groups can be incorporated into the halocyclization substrates, including those that are incompatible with oxidants needed to convert cyclic sulfites to sulfates. The halocyclization process occurs with predictable regioselectivity, and the resulting products can be selectively modified. Nucleophilic addition reactions occur exclusively at the most reactive site of the cyclic sulfate; thus, sequential modifications of the cyclic sulfate products can be carried out. Significantly, this approach to cyclic sulfate formation introduces two new stereocenters, which could be used advantageously in both target- and diversity-oriented organic syntheses. Given the advantages and versatility of the halocyclization reaction, we anticipate it will provide access to a wide range of valuable synthetic intermediates.

Table 2. Reaction of Cyclic Sulfates with Sodium Azide[a]

entry	substrate	product	yield
1			93%
2			91%
3			76%
4			84% (60:40)
5			78%

[a] Reaction conditions: NaN_3/DMF.

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Supporting Information Available: Detailed experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, MS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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