Enolate and Other Carbon Nucleophile Alkylation Reactions Using 1,2-Cyclic Sulfates as Terminal Epoxide Equivalents

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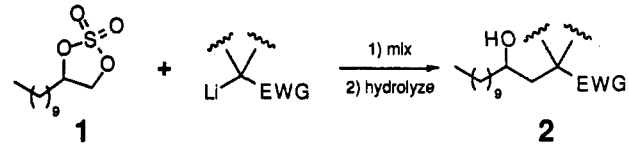
Summary: Enolates of esters and amides as well as α-sulfonyl-, α-cyano-, and α-phosphonyl-substituted anions react with cyclic sulfate 1 to give hydroxylated products arising from nucleophilic attack, on this terminal epoxide equivalent, at the primary carbon.

The γ-hydroxy carbonyl moiety is a commonly encountered structural element. Nucleophilic opening of an epoxide by an enolate is one obvious approach for constructing this substructure. There are only a limited number of reports of simple enolates (i.e., those having a single electron-withdrawing group) successfully opening epoxides. An early example is the use of dilithioacetate and related dianions.[1] Taylor has described the reaction of Al-enolates of esters with epoxides,[2] and Crotti has reported the lithium perchlorate catalyzed reaction of ketone enolates with epoxides.[3] There are a few reports on the reaction of amide enolates with epoxides.[4] Davies has achieved the reaction of Fe-acyl enolates with epoxides.[5]

Cyclic sulfates have been known for a number of years. They have been exploited as electrophilic epoxide equivalents. As summarized recently by Lohray,[6] cyclic sulfates have several features that distinguish them from epoxides. Although they are less strained (~5 vs ~27 kcal/mol), five-membered cyclic sulfates contain a better leaving group. They occasionally show complementary regioselectivity to epoxides in nucleophilic ring-opening reactions. They are apparently always more reactive than the corresponding epoxides. Moreover, Sharpless has recently developed an improved and facile conversion of 1,2-diols into cyclic sulfates, which has resulted in the easy availability of this class of compounds in an optically pure form.[7]

Most examples of nucleophilic opening of cyclic sulfates involve the use of heteroatom-based nucleophiles (e.g., amine, azide, carboxylate, chloride, fluoride, hydride, phenoxide, and thiocyanate).[6] To the best of our knowledge, the only carbon nucleophiles that have been used are phenyllithium,[8] sodium phenylacetylide,[8] cyanide,[9] benzyl magnesium bromide (Li_2CuCl_4 catalyzed),[10] malonate,[10] α-dithiaaryl carboxylate anions,[11] 2-dithianyllithium species,[11] and 2-(phenylthio)-2-dihydropyranyllithium species.[12]

We report here the reactions of a number of carbanions with the representative cyclic sulfate 1 (readily prepared by the literature method)[7,10,13] to provide the secondary alcohols 2 resulting from regiospecific ring opening at the primary carbon of 1. The nucleophiles used represent readily available, commonly encountered anions. A number of electron-withdrawing group-stabilized carbanions were surveyed, specifically the anions of representative nitriles, esters, amides, ketones, lactones, sulfones, and phosphonates. These reactions significantly extend the utility of this procedure.



1 2

The secondary alcohols 2 that were prepared from cyclic sulfate 1 are summarized in Table 1. Reaction conditions generally involved the addition of 1 to a slight excess of the nucleophile in THF at −78 °C, allowing the reaction mixture to warm to room temperature, and eventual acid-catalyzed hydrolysis.[7a] The anions derived from acetonitrile, *tert*-butyl acetate, ethyl cyclohexanecarboxylate, *N,N*-diethylpropionamide, dimethyl methylphosphonate, and phenyl methyl sulfone react with 1 to give the corresponding alcohols 2 in moderate to good yields. Entry 1: Lithioacetonitrile addition [see typical experimental procedure (vide infra)] cleanly gave the expected alcohol. The hydrolysis conditions of the intermediate sulfate salt are sufficiently mild to prevent γ-lactone formation. Entry 2: The cyclic byproduct in the case of *tert*-butyl acetate is believed to arise from the β-keto ester formed by a Claisen condensation between the initial product and excess nucleophile present in the reaction mixture. Notice that the *tert*-butyl ester also survived the hydrolysis treatment. The geometry of the double bond has not been confirmed; however it is a single isomer. Entry 3: Opening of 1 by the enolate of ethyl cyclohexanecarboxylate was not accompanied by the incorporation of a second molecule of the enolate. Partial lactonization of the γ-hydroxyester

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(13) Cyclic sulfate 1 was easily purified by MPLC on SiO_2 with 6:1 hex/EtOAc as the eluent. Solvents were removed at or below rt. Samples of 1 have been stored for over 1 year at ~−20 °C with no obvious decomposition.

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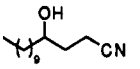
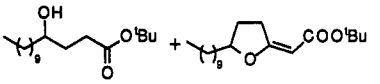
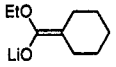
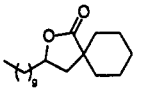
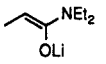
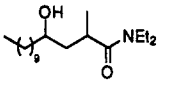
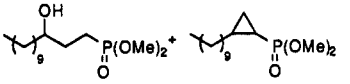
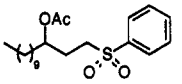
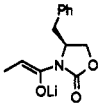
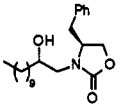
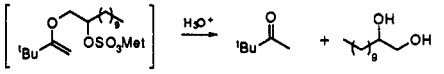
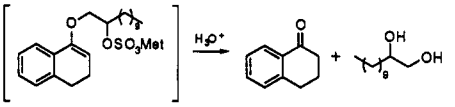
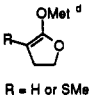
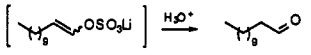
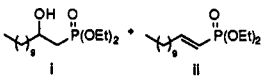
Table 1. C–C Bond-Forming Reactions of Cyclic Sulfate 1 with Various Carbon Nucleophiles

entry	nucleophile	(equiv)	product(s)	yield[a] (%)
1	$LiCH_2CN$	(1.1)		73
2		(1.4)		59 + 30
3		(1.4)		92
4		(1.4)		72[b]
5	$(MeO)_2P(O)CH_2Li$	(1.4)		82 + 7[b]
6	$PhSO_2CH_2Li$	(1.3)		42[c]

[a] Yields represent product(s) purified by MPLC on silica gel. [b] An ~2:1 mixture of diastereomers. [c] Purified after acetylation since the alcohol product and $PhSO_2Me$ coelute.

Table 2. Anomalous (Non-C–C Bond-Forming) Reactions of Cyclic Sulfate 1 with Various Nucleophiles

entry	nucleophile	(equiv)	product(s)	yield[a] (%)
1		(1.3)		45[b]
2		(1–2)		
3		(1–2)		
4		(1–2)	complex mixture of products	
5	^nBuLi	(1.03)		99
6		(1.6)		28 + 36

[a] Yields represent product(s) purified by MPLC on silica gel. [b] A ~1:1 mixture of diastereomers. [c] Metals tried were Li, K, Mg, Ti, and Zn. [d] Metals tried were Li and K.

accompanied the sulfate hydrolysis and proceeded to completion when the hydrolysis period was extended. Entry 4: The amide enolate opening resulted in an ~2:1 mixture of diastereomers. Entry 5: Double displacement explains the cyclopropyl product seen in the case of lithiated dimethyl methylphosphonate. Entry 6: The intermediate γ-hydroxysulfone arising from lithiomethyl phenyl sulfone was not readily separable from the recovered phenyl methyl sulfone. Conversion to the acetate derivative facilitated its isolation. In general, these successful C–C bond-forming reactions proceed quite cleanly; no byproducts other than those shown in Table 1 were observed, and the acidic hydrolysis conditions are sufficiently mild to tolerate a variety of other functionalities.

Some limitations have been identified and are indicated in Table 2. Entry 1: The Evans' enolate derived from the *N*-propionyl-4-benzyl-2-oxazolidinone was not sufficiently reactive to open 1. Prior fragmentation of the enolate and cyclic sulfate opening by the resultant anionic carbamate provided an approximately 1:1 ratio of diastereomeric alcohols. Lithium and potassium versions of this enolate gave similar results. Entries 2 and 3: We have been unable to C-alkylate ketone enolates. For both ketones studied (pinacolone and α-tetralone), the only products isolated were the starting ketone and 1,2-dodecanediol. We believe that the enolates are being alkylated on oxygen. The following observations support this conclusion: (a) the disappearance of the cyclic sulfate can be followed by TLC; (b) there is a change in the color of the solution of the K-enolate of α-tetralone (green to pale yellow) when the cyclic sulfate 1 is added; and (c) O-alkylation of similar enolates by dimethyl sulfate is known.[14] This O-alkylated product, when subjected to

the acidic hydrolysis conditions, should fragment to the starting ketone and 1,2-dodecanediol. Entry 4: lactone enolates consume the cyclic sulfate. However, we have been unable to isolate any identifiable products from the complex product mixture. Entry 5: reaction of *n*-butyllithium with **1** failed to generate a new C–C bond. Instead, dodecanal was isolated in 99% yield. This presumably arises by eliminative opening to an enol sulfate salt.[15] The scope of this reaction is being investigated.

Typical Experimental Procedure. Preparation of 4-Hydroxytetradecanenitrile (2a). To a stirred solution of acetonitrile (0.08 mL, 1.53 mmol, 1.55 equiv) in 2.0 mL of THF in a flame-dried round-bottom flask under a blanket of N_2 gas at −78 °C was added a solution of *n*-BuLi (2.5 M in hexanes, 0.45 mL, 1.13 mmol, 1.14 equiv). The resulting solution was stirred at −78 °C for 2 h. A solution of cyclic sulfate **1** (262 mg, 0.99 mmol) in 3.0 mL of THF was cannulated into the reaction mixture dropwise at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and then warmed to room temperature and stirred for approximately 14 h. The volatile components of the mixture were removed under reduced pressure, and the brownish-yellow residue was dissolved in 10 mL of THF to which 100 μL of water had been added. The clear solution was carefully acidified to pH 2–3 with a small quantity of concentrated sulfuric acid (30 μL in this case) and stirred for ~1 h (until TLC analysis indicated all salt had been hydrolyzed). The cloudy mixture was diluted with 50 mL of ether, washed once with 25 mL of saturated $NaHCO_3$ solution, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure to afford a deep yellow oil (228 mg, 102%) in which only **2a** was observed by ^1H NMR and GC–MS analysis. This crude product was subjected to MPLC on silica gel using hexanes:ethyl acetate = 3:1 to give 163 mg of the hydroxy nitrile **2a** (73%): ^1H-NMR ($CDCl_3$, 500 MHz) δ 3.68–3.76 (m, 1H, C*H*OH), 2.51 (t, 2H, J = 7.3 Hz, CH_2CN), 1.85 (dddd; 1H, *J* = 3.5, 8.0, 9.5, and 14.0 Hz; $CH_aH_bCH_2CN$), 1.69 (dddd; 1H, *J* = 6.5, 6.5, 9.0, and 13.5 Hz; $CH_aH_bCH_2CN$), 1.44–1.49 (m, 2H, $CH(OH)CH_2CH_2$), 1.26 (s, 16H, CH_2), and 0.88 (t, 3H, *J* = 6.8 Hz, CH_3); ^{13}C-NMR ($CDCl_3$ 125 MHz) δ 120.0, 70.0, 37.5, 32.5, 31.9, 29.6, 29.5, 29.4, 29.3, 25.5, 22.7, and 14.1; IR (thin film) 3447, 2925, 2854, 2239, and 1466 cm^{-1}; GC/LRMS (EI, 70 eV): *m/e* (rel intens) 225 (M^+, <1), 206 (1), 178 (5), 171 (10), 164 (6), 126 (14), 97 (52), 84 (71), 69 (56), 57 (55), 55 (100), 43 (68), 41 (93). Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08. Found: C, 74.80; H, 12.21.

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Supplementary Material Available: Procedures for preparation of and spectral and characterization data for **1** and all products in Tables 1 and 2 (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) House, H. O.; *Modern Synthetic Reactions*, 2nd ed.; Benjamin/Cummings: Reading, MA, 1972; Chapter 9.

(15) One other experiment that involved elimination to generate an alkene was the reaction of **1** with potassium diethyl phosphite. A mixture of the β-hydroxy phosphonate **i** and the vinyl phosphonate **ii** was obtained (See Table 2, entry 6).