Tetrahedron Letters, Vol.30, No.6, pp 655-658, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CYCLIC SULFATES CONTAINING ACID-SENSITIVE GROUPS AND CHEMOSELECTIVE HYDROLYSIS OF SULFATE ESTERS

B. Moon Kim and K. Barry Sharpless*

Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, MA 02139, U.S.A.

Summary: Diols containing acid-sensitive functionalities such as acetonide and silyloxy groups are efficiently converted to the corresponding cyclic sulfates via formation of the cyclic sulfites in the presence of a base and oxidation of the isolated sulfites using catalytic RuO_4. Reactions of these cyclic sulfates with nucleophiles such as azide and benzoate provide sulfates, which can be successfully hydrolyzed by using a catalytic amount of sulfuric acid and 0.5~1.0 eq of water in THF.

Recently we reported on the asymmetric dihydroxylation of olefins using a catalytic amount of osmium tetroxide in the presence of cinchona alkaloids.[1] This methodology, coupled with the preparation and nucleophilic opening of the cyclic sulfates derived from the diols,[2] places homochiral vicinal diols in a new light as synthons for synthetic organic chemistry. In order for this sequence to be useful in multistep organic syntheses it needs to meet the rigorous requirement of protecting groups, many of which are acid-sensitive. We report here a method to prepare cyclic sulfates from diols containing acid-sensitive groups and a mild acid-catalyzed hydrolysis of the resulting sulfate esters by a modification of the literature procedure[3] (Scheme 1).

Scheme 1

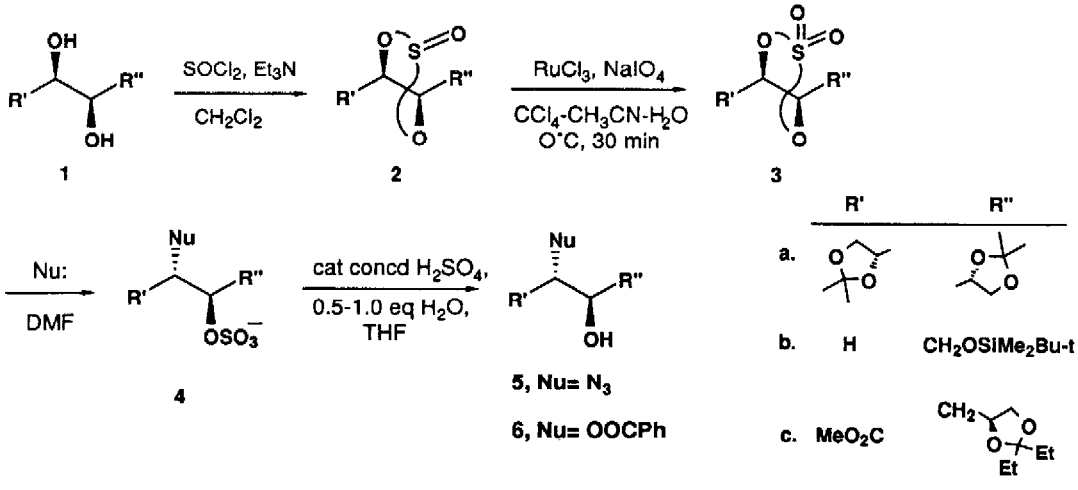

Table 1. Preparation and Opening of Cyclic Sulfates and Hydrolysis of the Resulting Sulfate Esters[a]

Entry	cyclic sulfates[c]	reaction conditions for nucleophilic opening	hydrolysis conditions[b] mol eq of concd H_2SO_4	mol eq of water	reaction time (min)	product	isolated yield (%)
1	**3a** (94)	LiN_3, DMF 60-70°C, 5 h	0.5	1.0	20	**5a**	91[d]
2	**3b**[e] (87)	$PhCO_2NH_4$, DMF RT, 30 min	0.1	-	20	**6b**	85
3	**3b**[e]	LiN_3, DMF RT, 20 min	0.3	0.5	30	**5b**	88[f]
4	**3c**[g](95)	LiN_3, DMF RT, 30 min	0.4	0.5	25	**5c**	73
5	**3c**[h] (96)	LiN_3, DMF RT, 30 min	0.2	0.5	10	**5c**	81

[a]For a representative procedure, see reference 5. [b]All the hydrolyses were carried out at room temperature (22-23°C). [c]Numbers in parentheses are yields from the corresponding diols. [d]The azidoalcohol was converted to a known compound, 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-altritol (H_2, Pd/C, EtOAc, rt, 2 h, 94% yield). mp 113.5-114.5°C, $[\alpha]^{24}_D$ 2.1° (*c* 1.0, $CHCl_3$), lit. mp 115-116°C, $[\alpha]^{26}_D$ 2.5±0.7° (*c* 1.0, $CHCl_3$), B. R. Baker and A. H. Haines, *J. Org. Chem.* **1963**, *28*, 442. [e]prepared by catalytic dihydroxylation of 1-*t*-butyldimethylsilyloxy-2-propene.[6] [f]A separable 10:1 mixture of 3-*t*-butyldimethylsilyloxy-1-azido-2-propanol and 3-*t*-butyldimethylsilyloxy-2-azido-1-propanol. [g]Prepared from the corresponding α,β-unsaturated ester[7] by the asymmetric dihydroxylation (52% de).[1] [h]A diastereomeric mixture (1.1/1) of 2,3-syn, 3,5-anti and 2,3-syn, 3,5-syn compound obtained from catalytic dihydroxylation[6] of the corresponding α,β-unsaturated ester[7].

First we examined the preparation of cyclic sulfates in the presence of acid-labile functionalities such as ketals and a silyl-protected alcohol. When 1,2:5,6-di-*O*-isopropylidene-*D*-mannitol (**1a**) was treated with thionyl chloride in the presence of triethylamine in dichloromethane, almost quantitative formation of the corresponding cyclic sulfite **2a** was observed. Treatment of the crude reaction mixture under the usual catalytic oxidation conditions[2] did not provide the corresponding cyclic sulfate **3a**, presumably due to inactivation of the ruthenium catalyst by the amine.[4] However when the cyclic sulfite **2a** was isolated and then oxidized with catalytic RuO_4, it was converted to the cyclic sulfate **3a** in excellent yield (94% from the diol **1a**). Similarly, 3-*t*-butyldimethylsilyloxy-1,2-propanediol (**1b**) and ketal diol **1c**[7] were smoothly converted to the corresponding cyclic sulfates **3b** and **3c** in 87% and 95% yield, respectively.

Nucleophilic opening of the cyclic sulfates in DMF was facile and even an electronically deactivated and hindered cyclic sulfate **3a** was opened in 5 h at 70°C.[8] Nucleophilic opening of cyclic sulfates which are unhindered or activated by an adjacent carbonyl group occurs at room temperature in usually less than 30 min. In order to effect a selective hydrolysis of the sulfate esters in the presence of acid-labile groups, we

investigated the known mild hydrolysis of sulfates using a catalytic amount of acid in moist ethereal solvents.[3] In fact, the direct adaptation of the literature procedure which employs a minimal amount of dilute sulfuric acid resulted in hydrolysis of both the sulfate and the alcohol protecting groups. However, as can be seen in Table 1, hydrolysis of sulfates in THF using a catalytic amount of *concd sulfuric acid*[9] *in the presence of 0.5-1.0 equivalent of water* proved to be very selective - all the alcohol protecting groups examined were found intact after the hydrolyses of the sulfate esters were complete.[10] *We find that the use of this minimum amount of water is crucial to achieve the desired chemoselectivity.*

Table 2. Reactive Cyclic Sulfates Enable a One-Pot Opening/Hydrolysis Sequence in THF.[a]

Entry	cyclic sulfates	reaction condns for nucleophilic opening	hydrolysis condns: mol eq of conc H_2SO_4	hydrolysis condns: mol eq of water	hydrolysis condns: reaction time (min)	product	isolated yield (%)
1	**3b**	$PhCO_2NH_4$, 60°C, 12 h	0.1[b]	-	10	**6b**	71
2	**3b**	LiN_3 RT, 2 h	0.3	1.0	30	**5b**	85[c]
3	**3c**	LiN_3 RT, 2 h	0.4	0.5	30	**5c**	92

[a]A nucleophile (2 eq) was added to a solution (0.1-0.25 M) of a cyclic sulfate in THF and the mixture was stirred under the given reaction conditions. Concd sulfuric acid and water were added and the reaction was followed by TLC. When hydrolysis was complete the reaction mixture was worked up as described in ref 5. [b]Hydrolysis of sulfate had already begun before adding the acid. [c]A separable 10:1 mixture of 3-*t*-butyldimethylsilyloxy-1-azido-2-propanol and 3-*t*-butyldimethylsilyloxy-2-azido-1-propanol.

Since the nucleophilic opening of cyclic sulfates can be very fast, especially in the case of terminal diols or diols with α-carbonyl groups, we examined the possibility of using THF for both the opening and hydrolysis steps. Indeed, although the opening of sulfates **3b** and **3c** was much slower in THF than in DMF, one-pot hydrolysis of the resulting sulfate esters furnished the desired alcohols in high yields (Table 2).

Acknowledgments: We are grateful to the National Institutes of Health (GM 28384) for financial support.

References and Notes

1. (a) E. N. Jacobson, I. Markó, W. S. Mungall, G. Schröder, and K. B. Sharpless, *J. Am. Chem. Soc.*, **110**, 1968, (1988). (b) E. N. Jacobson, I. Markó, M. B. France, J. S. Svendsen, and K. B. Sharpless, *Ibid.*, in press. (c) J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobson, and K. B. Sharpless, *Ibid.*, in press.
2. Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.* **110**, 7538 (1988).
3. M. B. Goren and M. E. Kochansky, *J. Org. Chem.*, **38**, 3510 (1973) and references cited therein.
4. We found that the presence of pyridine also inactivates the ruthenium catalyst.
5. A typical experimental procedure is as follows: To a cooled (ice-water), magnetically stirred solution of 1,2:5,6-diisopropylidene *D*-mannitol (5.35 g, 20.0 mmol) and triethylamine (11.15 mL, 8.095 g, 80.0 mmol) in

dichloromethane (60 mL) was added a dichloromethane solution (5 mL) of thionyl chloride (2.18 mL, 3.569 g, 30.0 mmol) dropwise over a period of 10 min. Stirring was continued for 5 min at 0 °C (the reaction was followed by TLC). The reaction mixture was diluted with cold ether (100 mL) and washed with cold water (2 x 100 mL) and brine (100 mL). The organic solution was dried over $MgSO_4$ and filtered. The filtrate was concentrated by rotary evaporation, the residue was pumped under reduced pressure (0.2 mmHg, 1 h), and to this residue was added a cold solution of CCl_4 (60 mL) and CH_3CN (60 mL). The flask was cooled in an ice bath and cold water (90 mL) was added. $RuCl_3 \cdot H_2O$ (23 mg, 0.1 mmol) and $NaIO_4$ (8.56 g, 40.0 mmol) were added at once and the reaction mixture was stirred vigorously at 0 °C. The reaction was followed by TLC. After 45 min stirring, ether (120 mL) was added and the layers were separated. The aqueous layer was extracted with ether (50 mL) and the combined organic layers were washed with brine (60 mL). Drying ($MgSO_4$), followed by concentration of the filtrate, furnished 6.46 g of a pale yellow solid. This crude product was recrystallized in a minimum amount of acetone (10 mL) and petroleum ether (35-60 °C, 150 mL) to yield 5.59 g as a first crop and 0.55 g from the mother liquor (overall 94% yield). $[\alpha]^{23}_D$ +28.7° (*c* 2.9, $CHCl_3$). mp 124.0-126.0 °C (118.5 °C deform). IR (cm^{-1}, KBr) 2993, 2937, 2907, 1560, 1457, 1396, 1372, 1260, 1241, 1208, 1146, 1080, 1055, 952, 914, 830, 786, 670, 644. ^1H NMR($CDCl_3$) 1.35 (6H, s), 1.45 (6H, s), 4.06 (2H, ABX, J_{AB}=9.6 Hz, J_{AX}=3.5 Hz), 4.19 (2H, ABX, J_{AB}=9.6 Hz, J_{BX}=6.1 Hz), 4.45 (2H, m), 4.68-4.72 (2H, m). ^{13}C NMR ($CDCl_3$) 24.79, 26.65, 66.16, 73.50, 82.48, 110.99. Anal. Calcd for $C_{12}H_{20}O_8S$: C, 44.43; H, 6.22; S, 9.87. Found: C, 44.07; H, 6.10; S, 9.83.

A mixture of *D*-mannitol 1,2:5,6-diacetonide 2,3-cyclic sulfate (162 mg, 0.500 mmol) and LiN_3 (49 mg, 1.00 mmol) in dry DMF (2.5 mL) was stirred under nitrogen for 3 h at 70-80 °C. The solvent was then removed under reduced pressure (0.2 mmHg, T_b ~40 °C). The residue was suspended in dry THF (5 mL), and concd H_2SO_4 (25 μL) and water (9 μL) were added to the stirred suspension. The hydrolysis was followed by TLC (Hex-EtOAc = 2:1). After 20 min excess sodium bicarbonate (~100 mg) was added and the reaction mixture was stirred for 20 min. Filtration through a Celite and silica gel bed and concentration of the filtrate under reduced pressure provided a viscous, pale yellow oil. Column chromatography (silica gel, Hex-EtOAc = 5:1 v/v) of the crude product gave 131 mg (91% yield) of 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol as a colorless oil. IR (cm^{-1}, film) 3454(br), 2987, 2963, 2936, 2111, 1456, 1372, 1215, 1179, 1157, 1062. ^1H NMR ($CDCl_3$) 1.34 (3H, s), 1.37(3H, s), 1.40 (3H, s), 1.48 (3H, s), 2.82 (-OH, d, *J*=6.2 Hz), 3.32 (1H, t, *J*=5.3 Hz), 3.77-4.21 (6H, m), 4.47 (1H, dt, *J*=5.1, 6.5 Hz). ^{13}C NMR ($CDCl_3$) 25.13, 25.23, 26.15, 26.53, 63.43, 66.04, 66.65, 72.54, 75.82, 76.04, 109.57, 109.97. Anal. Calcd for $C_{12}H_{21}N_3O_5$: C, 50.15; H, 7.37; N, 14.63. Found: C, 50.26; H, 7.15; N, 14.42.

6. (a) V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.* 1973 (1976). (b) V. VanRheenen, D. Y. Cha, and W. M. Hartley, *Org. Synth.* **58**, 43 (1980).
7. (a) S. Masamune, P. Ma, H. Okumoto, J. W. Ellingboe, and Y. Ito, *J. Org. Chem.*, **49**, 2834 (1984). (b) M. J. Huggins and D. G. Kubler, *Ibid.*, **40**, 2813, (1975).
8. In our previous report we used solvents other than DMF, e.g. acetone-water, acetone or THF. We have since found that DMF is the best solvent for nucleophilic substitutions involving unactivated cyclic sulfates.
9. The amount of acid needed to initiate the hydrolysis varies according to the nature (basicity) of the reaction mixture.
10. In a control experiment, **4a** (Nu=N_3) was stirred under the hydrolysis condition for 24 h and the alcohol **5a** was obtained in ~60% yield.

(Received in USA 11 November 1988)