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ONE POT SYNTHESIS OF HOMOCHIRAL AZIRIDINES AND AMINOALCOHOLS FROM HOMOCHIRAL 1,2-CYCLIC SULFATES

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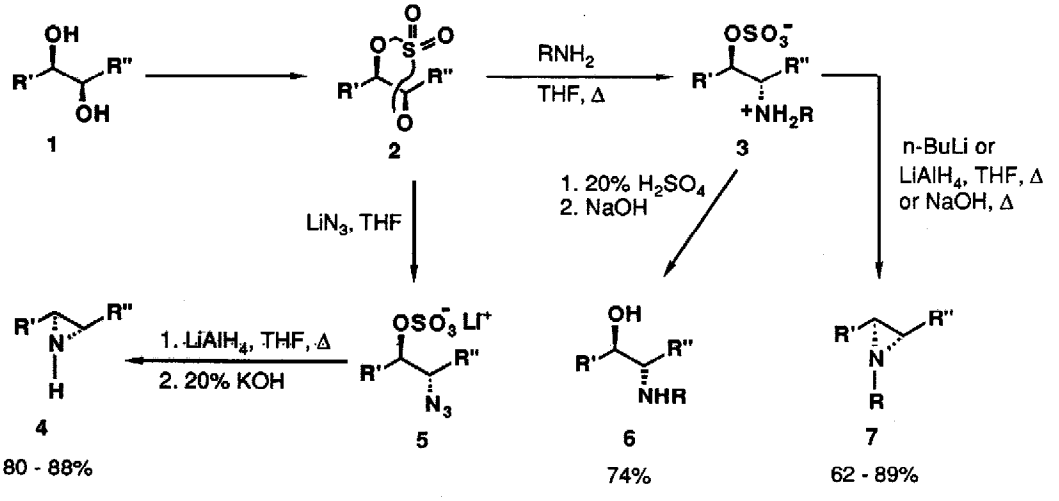
Abstract: Preparations of homochiral *N*-substituted aziridines and aminoalcohols from 1,2-cyclic sulfates are reported. Primary amines react with cyclic sulfates to give β-aminosulfates which can be converted either to aziridines or to aminoalcohols by treatment with base or aqueous acid, respectively. Reaction of cyclic sulfates with azide followed by $LiAlH_4$ reduction/cyclization yields *N*-unsubstituted aziridines.

The growing importance of functionalized aziridines in organic synthesis[1] and their presence in bioactive molecules[2-7] has created a need for synthesizing optically active aziridines. To date the only general route to homochiral aziridines has been through the amino alcohols obtained from optically pure amino acids.[8]

Scheme 1



The availability of homochiral diols (1) from the catalytic asymmetric dihydroxylation of olefins,[9] coupled with the facile electrophilic behavior of the derived cyclic sulfates (2),[10] has enabled us to develop efficient routes to homochiral aziridines (Scheme 1).

Treatment of the cyclic sulfates (2) with an excess of a primary amine in dry THF at reflux afforded β-aminosulfates (3) which, following deprotonation by n-BuLi at room temperature, cyclized to the aziridines (7) in good to excellent yield (Table 1).[11] The β-aminosulfates (3) could also be transformed into the aziridines by treatment with $LiAlH_4$ in refluxing THF.[11]

Table 1 Cyclic Sulfate Route to *N*-Substituted Aziridines

	Cyclic Sulfates			Aziridines			
Entry	R'	R"	RNH_2	Overall yield 2->7[a]	$[\alpha]^{22}D$ (*c* in $CHCl_3$)	%ee/de[b]	(abs. config.)[b]
1	(*R*)-Cyclohexyl	H	$PhCH_2NH_2$	78 (77)	-1.85° (0.92)	>96	(*S*)
2	(*R*)-Cyclohexyl	H	$Ph(CH_2)_3NH_2$	81 (79)	+3.21° (1.71)	>96	(*S*)
3	(*R*)-Cyclohexyl	H	(*S*)-2-aminobutane	(79)	+25.16° (1.57)	>96	(*SS*)
4	(*R*)-Cyclohexyl	H	(*S*)-2-methylbenzyl amine	79	-49.6° (1.2)	>96	(*SS*)
5	(*R*)-n-Butyl	(*R*)-n-Butyl	$PhCH_2NH_2$	62	-20° (0.86)	67[c]	(*SS*)
6	(*R*)-Phenyl	(*R*)-Phenyl	$PhCH_2NH_2$	73 (70)	-104.78° (1.41)	>96	(*SS*)
7	(*R*)-Phenyl	(*R*)-Phenyl	(*S*)-2-aminobutane	(82)	-108.0° (2.0)	>96	(*SSS*)
8	(*R*)-Benzyl	H	$PhCH_2NH_2$	(81)	-2.60° (1.38)	20[d]	(*S*)
9	(*R*)-Benzyl	H	(*S*)-2-aminobutane	(89)	+13.84° (1.82)	19[d,e]	(*SS*)

a. The value in parentheses indicates the yield of aziridine obtained using $LiAlH_4$.
b. The %de was determined by NMR spectroscopy. The % ee is assumed based on the optical purity of the starting diol used and has in one case been correlated by comparison with an authentic sample prepared from optically pure aminoacid [entry 8; $[\alpha]^{22}D$= -13.58°(*c* 1.59, $CHCl_3$)][8]. The other absolute configurations are assigned on the assumption of stereospecific inversion at the stereogenic center(s) of the cyclic sulfates.
c. The cyclic sulfate was derived from diol of 67% enantiomeric excess.
d. The cyclic sulfate was derived from diol of 20% enantiomeric excess.
e. The ^{13}C NMR indicates 19% de which is consistent with the 20% ee of the starting diol.

Hydrolysis of the β-aminosulfates (3) with 20% aq. H_2SO_4 followed by adjustment of the pH to 10 with 20% NaOH gave aminoalcohols (6) in good yield. Interestingly, the aziridines themselves are stable to the above described hydrolytic conditions. The β-aminosulfates (3) are not cyclized to the aziridines by treatment with 20% NaOH at room temperature; however, they do cyclize upon refluxing with 20% NaOH followed by steam distillation (Wenker Procedure).[1a] The formation of aziridines (7) by deprotonation of the β-aminosulfates (3) either with n-BuLi or $LiAlH_4$ proceeds via S_N2 displacement of sulfate by the adjacent amino group. Formation of aziridines from cyclic sulfates is therefore assumed to occur with inversion at the stereogenic center(s) (Tables 1 & 2). This assumption was proved in one case by independent synthesis of the aziridine from phenylalanine of known configuration (Table 1, entry 8).

We have also developed a route to homochiral *N*-unsubstituted aziridines by simple alteration of the nucleophile. Thus, treatment of the cyclic sulfates (**2**) with LiN_3 in THF gave the desired azidosulfates (**5**),[12] which upon reduction with $LiAlH_4$ in refluxing THF followed by 20% KOH, afforded the *N*-unsubstituted homochiral aziridines (**4**) in good yield (Table 2).[13]

Table 2 Cyclic Sulfate Route to *N*-Unsubstituted Aziridines

	Cyclic Sulfates		Aziridines			
Entry	R'	R"	Overall yield 2–>4	$[\alpha]^{22}_D$ (*c* in $CHCl_3$)	% ee[a]	(abs.config.)[b]
1	(*R*)-Cyclohexyl	H	80	-11.76°(0.91)	>96	(*S*)
2	(*R*)-n-Butyl	(*R*)-n-Butyl	88	-23.43°(0.96)	67[c]	(*SS*)

a. The % ee is based on ^1H and ^{13}C NMR of Mosher amide derivatives.
b. The absolute configuration has been assigned on the basis of assumed stereospecific inversion at the stereogenic center(s).
c. The cyclic sulfate was derived from diol of 67% enantiomeric excess.

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(11) *Typical procedure for the preparation of N-substituted aziridines:* To a solution of (*R*)-1-cyclohexyl-1,2-ethanediol cyclic sulfate (1.03g, 5 mmol) in dry THF (50 mL) is added benzylamine (1.07g, 10 mmol). After refluxing for 8 h at ca. 60°C (TLC reveals disappearance of the cyclic sulfate), the reaction mixture is cooled to room temperature and n-BuLi (6 mL, 12 mmol, 2M in hexane) is slowly added. The resultant pale yellow solution is stirred at room temperature for 2 h and then diluted with ether (50 mL), washed with water (2 X 20 mL), brine (20 mL) and dried over Na_2SO_4. Removal of the solvent gave 2(*S*)-cyclohexyl-1-benzylaziridine (0.837g, 78%) as a pale yellow oil. Alternatively, after refluxing a mixture of *R*)-1-cyclohexyl-1,2-ethanediol cyclic sulfate (1.03 g, 5 mmol) and benzylamine (1.07g, 10 mmol) in dry THF (50 mL) for 8h, the reaction mixture is cooled to room temperature and $LiAlH_4$ (0.28g, 7.5 mmol) is added slowly and the reaction mixture is further refluxed for 8 h. Excess $LiAlH_4$ is quenched with 20% aq. KOH (*ca* 2-3 mL). The reaction mixture is filtered and the filtrand is washed with hot THF (3 X 20-30 mL). The combined filtrates are concentrated under reduced pressure and the residual oil is dissolved in ether (50 mL) and washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Removal of the solvent gave almost pure 2(*S*)-cyclohexyl-1-benzylaziridine (0.827g, 77%) as a pale yellow oil, ^1H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 3.45 (d, *J* 12 Hz, 1 H), 3.18 (d, *J* 12 Hz, 1 H), 1.7-0.8 (br m, 4 H). The product could be further purified by chromatography on silica gel.

Typical procedure for the preparation of N-substituted aminoalcohols: Following removal of the solvent under reduced pressure, the β-aminosulfate 3 from the reaction of (*R*)-1-cyclohexyl-1,2-ethanediol cyclic sulfate (0.206g, 1 mmol) and benzylamine (0.214g, 2 mmol) is stirred with 20% H_2SO_4 (5 mL) and ether (5 mL) at room temperature (refluxing of the two phase mixture expedites the hydrolysis) for 12 h. The organic phase is discarded and the aqueous phase is adjusted to pH 10 with 20% aq. NaOH and extracted with ether (3 X 20 mL). The combined organic phases are washed with brine (20 mL) and dried over Na_2SO_4. Concentration gave 1(*R*)-cyclohexyl-2-benzylaminoethanol (0.117g, 74%), mp. 56-58°C, $[\alpha]^{22}_D$ = -1.2°(*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.3 (S, 5 H), 3.75 (d, *J* 5.77 Hz, 2 H), 3.35 (m, 1 H), 2.75 (dd, *J* 2.5, 9.6 Hz, 2 H), 2.5 (dd, *J* 9.6, 13 Hz, 1 H), 1.9-1.5 (m, 5 H), 1.3-0.9 (m, 7 H) .

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(13) *Typical procedure for the preparation of N-unsubstituted aziridines:* To a solution of 1-(*R*)-cyclohexyl-1,2-ethanediol cyclic sulfate (0.412g, 2 mmol) in dry THF (20 mL) is added LiN_3 (0.196g, 4 mmol, 2 eq.) and the reaction mixture is refluxed for 12 h during which time all the cyclic sulfate is consumed (TLC). The reaction mixture is cooled to room temperature and $LiAlH_4$ (0.11g, 3 mmol, 1.5 eq.) is added slowly and then the reaction mixture is refluxed for another 8 h. Solvent is removed under vacuum and excess $LiAlH_4$ is carefully quenched with 20% aq. KOH (5 mL). The reaction mixture is diluted with water (30 mL) and the aziridine is distilled with water at atmospheric pressure. The distillate is extracted with ether (3 X 20 mL) and the combined extracts washed with brine (10 mL) and dried over Na_2SO_4. Removal of the solvent gave 2-(*S*)-cyclohexylaziridine as an oil in good yield (0.20 g, 80%), ^1H NMR ($CDCl_3$) δ 1.9 (br d, *J* 9 Hz, 1 H), 1.7 (br m, 6 H), 1.35 (m, 1 H), 1.1 (m, 6 H), 0.8 (br s, 1 H).

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