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A Convenient Preparation of 2-Substituted (*S*)-Aziridines[1]

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Abstract: 2-Monosubstituted (*S*)-aziridines (*S*)-**3** were obtained by hydrogenation of (*R*)-2-sulfonyloxynitriles (*R*)-**2** with $LiAlH_4$ in good chemical yields and high enantiomeric excess.

In a recent review D. Tanner reported comprehensively on the syntheses and reactions of chiral aziridines.[3] One of the most important methods for the preparation of 2-substituted (*S*)-aziridines starts from natural L-α-amino acids. By hydrogenation the corresponding optically active 1,2-amino alcohols are obtained which cyclize to the chiral aziridines after activation of the primary hydroxyl group.[3] The disadvantage of this procedure, however, is the limited number of available homochiral amino acids.

K. Ichimura et al. have described the synthesis of racemic 2-monosubstituted aziridines starting from α-chloro-, α-bromo- and α-sulfonyloxynitriles by hydrogenation with $LiAlH_4$.[4] α-Chloronitriles of bicyclic heptene and heptane had been already reduced with $LiAlH_4$ yielding spiro aziridines.[5a] For the preparation of 2-isobutylaziridines it was proved[4b] that the hydrogenation of (*S*)-α-chloroisocapronitrile occurs without racemization and the cyclization occurs with inversion of configuration. The optically active 2-chloro-4-methyl-pentanenitrile had to be prepared in a multi step synthesis from L-leucine.[4a] It was shown earlier that optically active 2-halogenonitriles can easily racemize; this is a great disadvantage for stereoselective follow-up reactions.[5b]

Optically active cyanohydrins such as (*R*)-**1a-e** became easily accessible by enzyme-catalyzed addition of HCN to aldehydes.[6] Particularly by using organic solvents high enantiomeric excesses were achieved.[6] Since chiral cyanohydrins could be sulfonylated nearly without racemization,[3c] a general and convenient route to chiral 2-substituted aziridines should be practicable by hydrogenation of the sulfonylated chiral cyanohydrins.

The 2-sulfonyloxynitriles (*R*)-**2a-e** were obtained in high enantiomeric excess (Table 1) starting from cyanohydrins (*R*)-**1a-e** prepared by (*R*)-oxynitrilase [EC 4.1.2.10] catalyzed addition of HCN to the corresponding aldehydes in diisopropyl ether as described in Ref.[3c] The best reaction conditions for the hydrogenation of compounds (*R*)-**2a-e** are the following: diethyl ether as solvent, a temperature of -80°C to room temperature, reaction times of 4 to 5 hours and an 1.5 fold excess of $LiAlH_4$.

Under the optimized reaction conditions the (*R*)-sulfonyloxynitriles (*R*)-**2a-e** were hydrogenated to give primarily the amines **A**,[4b] which could not be isolated since they react immediately in an intramolecular S_N2 reaction under inversion of configuration to yield the (*S*)-aziridines (*S*)-**3a-e** as outlined in the Scheme. The data are summarized in Table 1.

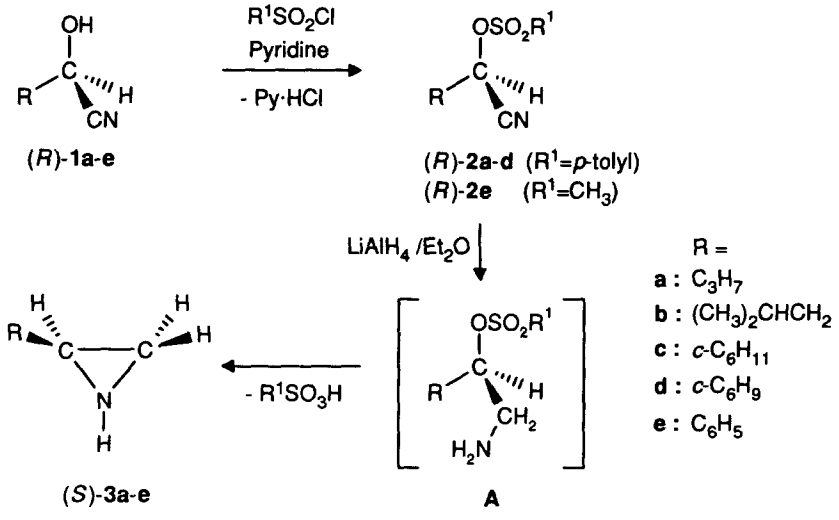

Table 1. Hydrogenation of (*R*)-2-Sulfonyloxynitriles (*R*)-**2a-e** with $LiAlH_4$ (150 mol%) to the Aziridines (*S*)-**3a-e** in Diethyl Ether at -80°C to Room Temperature[7]

Educts (*R*)-**2**		Reaction	Aziridines (*S*)-**3**					
	ee %[a]	time [h]		Yield [%]	$[\alpha]_D^{20}$ (c, solvent)	bp[°C/Torr]	Ref. $[\alpha]_D^{20}$ (c, solv.)	Ref.
a	96.3	4	**a**	56.1	-18.75 (0.96,heptane)	67-68/140	-19.2 (0.5,heptane)	8
b	96.2	4-5	**b**	58.3	-16.80 (5.4,ethanol)	59-61/50	-15.6 (10,ethanol)	9
					-24.0 (1.0,benzene)		-26.4 (1.83,benzene)	4a,10
c	96.1	4-5	**c**	64.6	-13.5 (1.0,$CHCl_3$)	70/12	-11.58 (0.9, $CHCl_3$) (>96%ee, (*S*)-conf.)	11
d	94.1	5	**d**	65.9	-20.1 (1.9,ethanol)	69/12	-	
e	99.5	5	**e**	56.1[b]	+31.3 (1.4,$CHCl_3$)	84/15	+29.4 (1.53, $CHCl_3$)	12,13
e	99.5	5	**e**	12.9[b,c]	-	-	-	

[a] Values of the starting cyanohydrins (*R*)-**1**, determined by gas chromatography on β-cyclodextrin phases. [b] Product mixture (*S*)-**3e** and phenethylamine in a ratio of 2:1 (determined by ^1H NMR spectroscopy). [c] 105 mol% $LiAlH_4$.

The aliphatic (*S*)-aziridines (*S*)-**3a-d** were obtained in chemical yields comparable to those in Ref.[4a] The optical yields were determined by comparison of specific rotation values with those of aziridines obtained from optically active amino acids[9,10,12,14] confirming also the (*S*)-configuration of the aziridines obtained.

Ichimura et al. have already described that racemic 2-bromopropio- and 2-bromoisobutyronitrile were hydrogenated with $LiAlH_4$ to give the desired aziridine and the corresponding dehalogenated primary amine as the by-product.[4a] In the hydrogenation of the aliphatic compounds (*R*)-**2a-d** with $LiAlH_4$ no trace of primary amine could be detected, but in the hydrogenation of the mandelonitrile derivative (*R*)-**2e** besides (*S*)-2-phenylaziridine (*S*)-**3e** phenethylamine is formed in a ratio of (*S*)-**3e** : phenethylamine = 2:1, determined by ^1H NMR spectroscopy. Neither by distillation nor by chromatography could both components be separated. By a decrease of the amount of $LiAlH_4$ only the total yield of (*S*)-**3e** and phenethylamine was diminished to 12.9%.

With the reaction sequence described in this article optically active (*S*)-aziridines can be easily obtained in good chemical yields and high optical purity.

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7. *Preparation of aziridines* (*S*)-**3**; *general procedure*: At -80°C a solution of (*R*)-**2**[3c] in diethyl ether (20 ml) is dropped to a suspension of $LiAlH_4$ in diethyl ether (60 ml). The reaction mixture is warmed up to room temperature within 1-2 h and after cooling again to -80°C hydrolyzed with 1 M K_2HPO_4/KH_2PO_4 buffer (pH 7) and stirred at room temperature for 1 h. The precipitate is filtered off and extracted with diethyl ether (20 ml). The aqueous phase is extracted twice with diethyl ether and the com-

bined ether solutions are dried with K_2CO_3/Na_2SO_4 (1:1). The solvent is removed and the residue is distilled *in vacuo* to give (*S*)-**3**.

Educts (*R*)-**2**		$LiAlH_4$	Products		Elemental Analysis or MS [70 eV, *m/z*(%)]				
	g (mmol)	g (mmol)	(*S*)-**3**	yield g	Molecular Formula	Calcd. Found	C	H	N
a	9.0 (35.5)	2.30 (60.5)	**a**	1.69	$C_5H_{11}N$	84 (11) [M], 70 (75), 56			
					(85.1)	(100), 42 (16), 28 (58)			
b	8.1 (30.3)	1.98 (52.1)	**b**	1.62	$C_6H_{13}N$	98 (3) [M], 84 (35), 56 (100),			
					(99.1)	41 (13), 42 (9), 28 (27)			
c	7.9 (26.9)	1.74 (45.8)	**c**	2.18	$C_8H_{15}N$		76.74	12.07	11.19
					(125.2)		76.82	11.79	11.18
d	7.8 (26.8)	1.67 (44.0)	**d**	2.17	$C_8H_{13}N$		77.99	10.64	11.37
					(123.2)		77.84	10.75	11.24
e	7.0 (33.1)	2.13 (56.1)	**e**[a]	1.71					
e	4.0 (18.9)	0.75 (19.8)	**e**[a]	0.29					

	^1H NMR (250 MHz, $CDCl_3$, δ)
(*S*)-**3a**	0.41 (s, 1 H, NH), 0.96 (t, 3 H, CH_3), 1.21-1.57 (m, 4 H, CH_2), 1.32 (d, ^3J=3.5 Hz, 1 H, CH_{az}), 1.74 (d, ^3J=6.0 Hz, 1 H, CH_{az}), 1.89-1.97 (m, 1 H, CH_{az})
(*S*)-**3b**	0.46 (s, 1 H, NH), 0.89 (d, 6 H, CH_3), 1.13-1.30 (m, 2 H, CH_2), 1.25 (d,^3J=3.7 Hz, 1 H, CH_{az}), 1.64-1.78 (m, 1 H, CH), 1.68 (d, ^3J=5.8 Hz, 1 H, CH_{az}), 1.83-1.91 (m, 1 H, CH_{az})
(*S*)-**3c**	0.31 (s, 1 H, NH), 0.66-0.79 (m, 1 H, $CH_{cycloh.}$), 0.96-1.25 (m, 5 H, C_6H_{11}), 1.29 (dd, ^3J=2.5 Hz, 1 H, CH_{az}), 1.55-1.71 (m, 6 H, C_6H_{11}, CH_{az}), 1.80-1.86 (m, 1 H, CH_{az})
(*S*)-**3d**	0.47 (s, 1 H, NH), 1.00-1.18 (m, 1 H, $CH_{cycloh.}$), 1.35 (d, ^3J=4.3 Hz, 1 H, CH_{az}), 1.29-1.49 (m, 1 H, CH), 1.70-2.22 (m, 7 H, C_6H_9, CH_{az}), 5.57-5.67 (m, 2 H, CH=CH)
(*S*)-**3e**[a)]	1.07 (s, 3 H, NH, NH_2), 1.80 (d, *J*=3.3 Hz, 1 H, CH_{az}), 2.20 (d, *J*=6.0 Hz, 1 H, CH_{az}), 2.73-3.03 (m, 5 H, 2 CH_2, CH_{az}), 7.19-7.36 (m, 5 H, Ph)

[a] Mixture of (*S*)-**3e** and phenethylamine in a ratio of 2:1.

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