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Preparation of (*S*)-2-Fluoronitriles[1]

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Abstract: (*S*)-2-fluoronitriles (*S*)-**4** are obtained in good chemical and high optical yields from (*R*)-cyanohydrins (*R*)-**2** or (*R*)-cyanohydrin trimethylsilylethers (*R*)-**3** by fluorination with DAST or by nucleophilic substitution of α-sulfonyloxynitriles (*R*)-**6**, **7** with fluoride on polymeric supports (Amberlyst A-26 F^-) under inversion of configuration of the starting cyanohydrins.

Whereas chiral 2-fluoronitriles have not yet been described in the literature, for the preparation of racemic 2-fluoronitriles various synthetic routes are available. They were obtained for example starting from *O*-sulfonyl-activated cyanohydrins by nucleophilic substitution with potassium fluoride,[3] by reaction of *O*-trimethylsilyl-protected cyanohydrins with phenyltetrafluorophosphorane in poor yield.[4] In good yields they are formed by reaction of cyanohydrin-*O*-trimethylsilylethers with diethylaminosulfur trifluoride (DAST),[5a] whereas with *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine (FAR) lower yields of 2-fluoronitriles were achieved.[5b] Also the electrochemical oxidation of benzylic nitriles in acetonitrile/triethylamine hydrofluoride was applied for the preparation of 2-fluoro-arylacetonitriles.[6]

Since optically active cyanohydrins are now easily available by enzyme catalyzed reactions,[7] we have investigated their conversion into optically active 2-fluoronitriles by fluorination of free and *O*-trimethylsilyl-protected cyanohydrins with DAST[5a] and by nucleophilic substitution of sulfonyl-activated cyanohydrins[1] with fluoride.

A direct application of optically active 2-fluoronitriles, as pharmaceuticals for example, is not yet described in the literature. But they could be of interest as educts for optically active 2-fluorocarboxylic acids[8] and 2-fluoroamines[9] which are versatile intermediates for the syntheses of biologically active compounds and liquid crystals, respectively.

(*S*)-2-Fluoronitriles (*S*)-4 from (*R*)-Cyanohydrins (*R*)-2 with Diethylaminosulfur trifluoride (DAST)

In recent years DAST has been successfully used for selectively replacing the hydroxyl group by fluorine;[10] optically active hydroxy compounds thereby react under inversion of configuration.[8d,11]

(*R*)-cyanohydrins (*R*)-**2a,d,e**, prepared by (*R*)-Oxynitrilase (EC 4.1.2.10) catalyzed addition of HCN to aldehydes **1**[1], can be converted without racemization to the corresponding *O*-trimethylsilylethers (*R*)-**3a,d,e**.[12] The compounds (*R*)-**3a,d,e** react with DAST under mild conditions to give the (*S*)-2-fluoronitriles (*S*)-**4** (Scheme 1, Table 1).

The *O*-unprotected cyanohydrins (*R*)-**2b-d** can also be directly converted with DAST to give the 2-fluoronitriles (*S*)-**4b-d** in comparable chemical and high optical yields. Compared to the more reactive trimethyl-

silylethers (*R*)-**3** the reaction times had to be longer (Table 1). The enantiomeric excess of the (*S*)-2-fluoronitriles (*S*)-**4** in each case was directly determined by gas chromatography on a β-cyclodextrin phase.

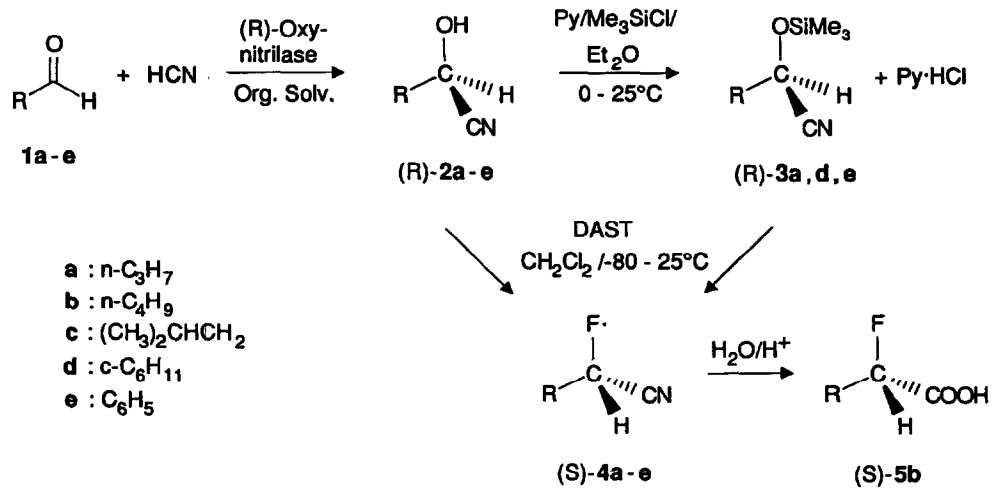

Table 1. Fluorination of Cyanohydrins (*R*)-**2b-d** and of *O*-Trimethylsilyl-cyanohydrins (*R*)-**3a,d,e**[13] with DAST in Dichloromethane at -80°C[14]

educts				reaction	products			
(*R*)-**2**	ee [%]	(*R*)-**3**	yield [%]	time [h]	(*S*)-**4**	yield [%]	ee [%]	$[\alpha]_D^{20}$ (c, CH_2Cl_2)
a	95.7	**a**	60.9	4	**a**	58.1	95.4	-22.5 (1.73)
b	98.1	-	-	18	**b**	66.7	96.9	-21.7 (1.36)
c	96.0	-	-	17	**c**	58.6	93.8	-28.0 (1.00)
d	94.5	**d**	61.1	3.5	**d**	42.0	94.0	-11.8 (1.00)
	96.7	-	-	18	**d**	45.9	96.1	
e	98.2	**e**	72.1	4	**e**	71.3	28.5	
	98.8			4.5[a]	**e**	64.2	35.7	-21.1 (1.09)
	99.3			6[b]	**e**	20.7	46.7	

[a] In n-hexane. - [b] In tetrahydrofurane.

Whereas the reaction of (*R*)-**3a** and (*R*)-**3d** proceeds with almost complete inversion of configuration, the mandelonitrile derivative (*R*)-**3e** reacts under partly racemization (Table 1). In this case, fluorine was probably not introduced in a simple S_N2 manner[10] but via an ion pair mechanism, due to the stabilized benzyl-type carbocation formed,[15] starting from (*R*)-**3e**.

2-Fluoropentanenitrile (*S*)-4a from α-Sulfonyloxynitriles (*R*)-6, 7 with Fluoride

Since racemic 2-sulfonyloxynitriles had already been successfully converted to the respective 2-fluoronitriles by reacting with fluoride,[3] we have now investigated the reaction of the chiral (*R*)-2-(sulfonyloxy)-pentanenitriles (*R*)-6, 7[1] with both, potassium fluoride and fluoride on polymeric supports[16] such as Amberlyst A-26 F^-.

In the reaction of (*R*)-6 or (*R*)-7 with potassium fluoride in the presence of crown ether (dibenzo-18-crown-6) the 2-fluoropentanenitrile (*S*)-4a was obtained in poor chemical yield and partly racemization due to the long reaction times and the comparable high temperatures of 45 to 100°C (Scheme 2, Table 2).

With the anhydrous anion exchange resin Amberlyst A-26 containing fluoride, however, the triflate (*R*)-7 was converted under very mild conditions in a clean S_N2 reaction to yield the 2-fluoropentanenitrile (*S*)-4a in good chemical and high optical yield. The less reactive tosylate (*R/S*)-6 does not react with Amberlyst A-26 F^- even at higher temperature (45°C) (Table 2).

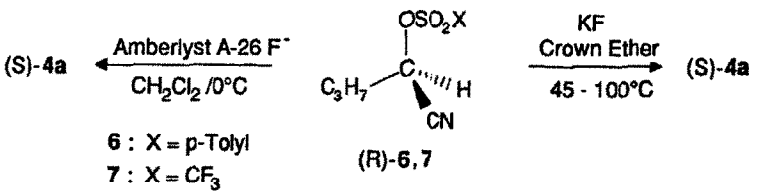

Table 2. Fluorination of 2-(Sulfonyloxy)pentanenitriles (*R*)-6, 7 with Amberlyst A-26 F^-[17] or Potassium Fluoride/Crown Ether[18]

educts		reaction conditions					(*S*)-4a	
(*R*)-2a ee[%]	(*R*)-6,7	Amberlyst A-26 F^-	KF/crown ether	solvent	time [h]	temp. [°C]	yield [%]	ee [%]
0	(R/S)-6	+	-	CH_3CN[a]	156	45	5[b]	0
95	7	+	-	CH_2Cl_2	18	0-25	63.6	91.6
94.5	6	-	+	DMF	144	100	21.7	73.2
96	7	-	+[c]	CH_2Cl_2[d]	168	45	29.3	75.0

[a] Addition of 0.5 ml DMF after 36 h. - [b] Conversion determined by gas chromatography. - [c] Addition of a second portion of KF/crown ether after 48 h. - [d] Addition of 1 ml DMF after 72 h.

The absolute configuration of the 2-fluoronitriles (*S*)-4 prepared and described in this paper, was established by acid catalyzed hydrolysis of (*S*)-4b to the known 2-fluorohexanoic acid (*S*)-5b.[18] Since the hydrolysis occurs without racemization under retention of configuration, proved by comparison of the optical rotation value with literature data,[19] it proves that (*R*)-cyanohydrins (*R*)-2, their *O*-trimethylsilylethers (*R*)-3 and the *O*-sulfonyl-activated derivatives (*R*)-6, 7 were fluorinated under inversion of configuration.

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13. Preparation of (*R*)-**3**; general procedure: At -10°C an equimolar amount of pyridine is added to a solution of (*R*)-**2** in diethyl ether followed by an excess of (trimethylsilyl)chloride (10 - 60 mol%) within 1 h. After 8 - 12 h stirring the reaction mixture is separated from pyridine hydrochloride, concentrated, and the residue is distilled *in vacuo*.
14. Preparation of (*S*)-**4**; general procedure: An excess of DAST (**2**: 10 - 100 mol%; **3**: 10 - 30 mol%) in dichloromethane is dropped to a solution of (*R*)-**2** or (*R*)-**3** in dichloromethane within 0.5 h. The reaction mixture is warmed to room temperature (2 - 6 h), hydrolyzed with icewater and extracted with diethyl ether. The combined extracts are dried with $MgSO_4$, concentrated, and the residue is chromatographed on silica gel with petroleum ether/ethyl acetate (9:1) or fractionally distilled.
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17. Fluorination with Amberlyst A-26 F^-: (*R*)-**7** or (*R/S*)-**6** is dropped to the resin within 0.5 h. With stirring the reaction mixture is warmed to 25°C [(*R*)-**7**] or 45°C [(*R/S*)-**6**], separated from the resin, concentrated, and the residue is distilled.
18. Fluorination with potassium fluoride/dibenzo-18-crown-6: At room temperature a solution of (*R*)-**6** or **7** in 5 ml solvent is dropped to potassium fluoride/crown ether in 50 ml of the same solvent and then warmed to the given temperature (Table 2). After the time given in Table 2, the reaction mixture is hydrolyzed with icewater and extracted four times with diethyl ether. The combined extracts are washed with water, dried with $MgSO_4$ and concentrated. The residue is fractionally distilled.
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