1-Alkyl-2-trifluoromethylaziridines: the bacisity and ring-opening reactions under the action of acids

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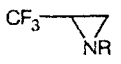
The basicity of 1-alkyl-2-trifluoromethylaziridines is ~two orders of magnitude lower than that of non-fluorinated analogs. Aziridines are stable to H_2S and AcOH, but react with AcSH, HCl, HBr, H_2SO_4, TsOH, and picric acid to give products of ring-opening.

Key words: 1-alkyl-2-trifluoromethylaziridines; reactivity, basicity.

Aziridines have been studied in detail,[1,2] but the properties of their fluorine-containing analogs are almost unknown, despite the large number of publications describing the synthesis of these compounds.[3—12] Most of the compounds of this series are chemically inert. Thus high thermal and chemical stability of 1-acyloxy- and 1-tosyloxy-2,2-bis(trifluoromethyl)aziridines has been reported.[13] Ring-opening reactions have been observed only for ethyl 3-perfluoroalkylaziridine-2-carboxylate refluxed with HCl.[12]

Previously, we developed a convenient preparative method for the synthesis of 1-alkyl-2-trifluoromethylaziridines according to Gabriel, by cyclization of *N*-alkyl-2-bromo-3,3,3-trifluoropropylamines,[14,15] which allows one to study the properties of this class of compounds. For example, it was shown that 2-trifluoromethylaziridines react vigorously with 40% HBr at low temperatures to form solely 2-bromo-1-trifluoromethylethylamines.[16]

In the present work, the basicity of 1-alkyl-2-trifluoromethylaziridines (**1**) was determined and their ring-opening reactions under the action of acids were studied.



1a—d

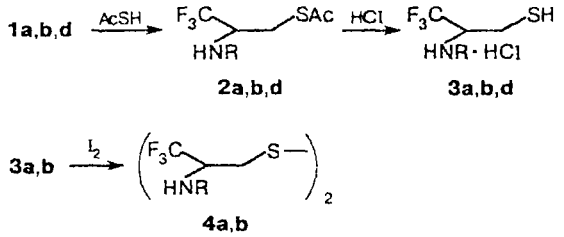
R = Me (**a**), Et (**b**), $PhCH_2$ (**c**), *cyclo*-C_6H_{11} (**d**)

It turned out that the basicity of aziridines **1** measured by potentiometric titration in water is approximately two orders of magnitude lower than that of non-fluorinated aziridines[2] (pK_a and pK_b refer to dissociation of an aziridinium ion and protonation of aziridine, respectively):

Compound	pK_a	pK_b
1a	5.72	8.28
1b	5.84	8.16
1c	5.69	8.31
1d	5.93	8.07

The low basicity of compounds **1a—d** causes them to be less reactive than their non-fluorinated analogs in reactions with acids. Thus, unlike ordinary aziridines,[1,2] 1-alkyl-2-trifluoromethylaziridines **1a—d** do not react with H_2S in MeOH at after 1 day 20 °C even after the addition of acetic or trifluoroacetic acids as protonating agents.

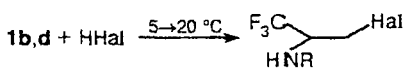
Thioacetic acid, which is much stronger, reacted vigorously with aziridines **1** in the absence of a solvent to give ring-opening products in preparative yields. Thioacetates **2a,b,d** were converted without isolation into aminothiol hydrochlorides **3a,b,d**, and compounds **3a,b** were oxidized with an ethanolic solution of I_2 to disulfides **4a,b**.



2a,b,d **3a,b,d**

4a,b

Under the action of 20% HCl, as in reactions with HBr (*cf.* Ref. 16), aziridines **1** form *N*-(2-chloro(bromo)-1-trifluoromethylethyl)alkylamines (**5,6**) in high yields.



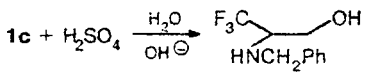
5b,d; 6d

5: Hal = Cl
6: Hal = Br

The aziridine ring also opens easily under the action of other strong acids. Aziridine **1c** reacts vigorously with 50% H_2SO_4 to give 2-benzylamino-3,3,3-trifluoropropyl alcohol (**7c**) following alkaline hydrolysis in 73% yield.

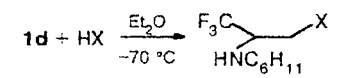
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 6, pp. 1185—1188, June, 1997.

1066-5285/97/4606-1136 $18.00



7c

However, in an attempt to obtain aziridinium salts by the reaction of **1** with weak nucleophiles such as picric or toluene-*p*-sulfonic acids, we obtained only ring-opening products. Thus, in reactions with TsOH and picric acid, aziridine **1d** is transformed into crystalline derivatives, toluenesulfonate **8d** and picrate **9d** in ~80% yields even at −70 °C.



8d, 9d

8d: X = TsO
9d: X = $(NO_2)_3C_6H_2O$

Aziridines **1** react with CF_3CO_2H and perchloric acid with the same ease, but the reaction products could not be isolated. AcOH, a relatively weak acid, does not react with aziridines **1**, even after prolonged storage at 20 °C.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker WP-200 SY spectrometer (200.12 and 188.31 MHz, respectively) with Me_4Si (^1H) as the internal standard and CF_3COOH (^{19}F) as the external standard.

The reaction conditions, yields, and characteristics of compounds **3—9** are given in Table 1. The parameters of the ^1H and ^{19}F NMR spectra are given in Table 2.

The potentiometric titration of aziridines **1a—d** was performed at 298±0.1 K according to a known procedure[17] using a Radelkis OP-211/1 pH-meter with a glass Radiometer G 202 C electrode and a calomel Radiometer K 401 electrode with a contact through porous ceramics. The electrode pair was calibrated with reference to buffer solutions. The concentration of the solution of aziridines studied was 10^{-3} mol L^{-1}, titration was performed with 0.02 *M* HCl, and the accuracy of p*K* determination was 0.03—0.06 units.

2-Cyclohexylamino-3,3,3-trifluoropropanethiol hydrochloride (3d). AcSH (2.28 g, 2.2 mL, 30 mmol) was added dropwise with stirring to aziridine **1d** (5.79 g, 30 mmol). The mixture was kept at 20 °C for 1 h, then 20 mL of 20% HCl was added, and the mixture was refluxed under N_2 for 0.5 h. The solution was concentrated and a dry residue was reprecipitated from ethanol with ether.

Di(2-methylamino-3,3,3-trifluoropropyl) disulfide (4a). AcSH (2.28 g, 2.2 mL, 30 mmol) was added dropwise with stirring to aziridine **1a** (3.75 g, 30 mmol). The mixture was kept at 20 °C for 1 h, treated with 25 mL of 10% HCl, and refluxed for 0.5 h. A 10% solution of I_2 in ethanol was added dropwise to the cooled mixture until negative test for the SH group in a reaction with sodium nitroprusside. The mixture was neutralized with a 10% aqueous solution of $NaHCO_3$, and the organic layer that formed was extracted with $CHCl_3$. The extract was dried with $MgSO_4$, the solvent was removed, and the residue was distilled.

Di(2-ethylamino-3,3,3-trifluoropropyl) disulfide (4b) was obtained analogously from aziridine **1b** (5.56 g, 40 mmol) and AcSH (3.04 g, 3 mL, 40 mmol).

***N*-(2-Chloro-1-trifluoromethylethyl)ethylamine (5b).** 20% HCl (7.3 mL, 40 mmol) was added dropwise with stirring at +5 °C to aziridine **1b** (2.78 g, 20 mmol). After 10 min, an

Table 1. The characteristics of compounds **3—9**

Compound	Yield (%)	B.p./°C (*p*/Torr) [M.p.]	Found / Calculated (%) C	H	N	S	Molecular formula
3d	88	[157—158]	40.72 40.98	6.39 6.45	5.11 5.31	—	$C_9H_{16}F_3NS \cdot HCl$
4a	60	125—127 (8)	30.43 30.38	4.48 4.43	—	19.64 20.25	$C_8H_{14}F_6N_2S_2$
4b	70	132—133 (10)	35.11 34.88	5.32 5.23	—	18.71 18.60	$C_{10}H_{18}F_6N_2S_2$
5b	80	40 (60)	33.85 34.19	5.05 5.12	7.58 7.97	—	$C_5H_9ClF_3N$
5d	83	75 (10)	46.82 47.05	6.50 6.53	5.87 6.10	—	$C_9H_{15}ClF_3N$
6d	85	95 (15)	39.51 39.41	5.46 5.47	5.12 5.11	—	$C_9H_{15}BrF_3N$
7c	73	[96]	54.43 54.79	5.42 5.48	6.21 6.39	—	$C_{10}H_{12}F_3NO$
8d	80	[130]	52.23 52.60	6.06 6.02	4.03 3.83	—	$C_{16}H_{22}F_3NO_3S$
9d	80	[200—202]	36.44 36.39	3.32 3.45	11.52 11.33	—	$C_{15}H_{17}F_3N_4O_7 \cdot 4H_2O$

Table 2. The ^1H and ^{19}F NMR spectra of compounds **3—9**

Compound	Solvent	δ ^1H (*J*/Hz)			δ ^{19}F (*J*/Hz)
		CH (m)	CH_2	Other signals	
3d	CD_3OD	4.4	3.1 (dd, 1 H, *J* = 14.8, 7.4); 3.3 (dd, 1 H, *J* = 14.8, 4.9)	1.0—2.2 (m, 11 H, C_6H_{11}); 3.4 (m, 1 H, NH); 2.6 (br.s, 1 H, SH)	−5.95 (d, 3 F, CF_3, *J* = 6.6)
4a	$CDCl_3$	3.35	2.8 (dd, 1 H, *J* = 13.5, 5.9); 3.2 (dd, 1 H, *J* = 13.5, 2.9)	1.5 (s, 1 H, NH); 2.6 (s, 3 H, CH_3)	−3.4 (d, 3 F, CF_3, *J* = 7.0)
4b	$CDCl_3$	3.35	2.7 (m, 1 H); 3.05 (dd, 1 H, *J* = 13.0, 2.9)	1.0 (t, 3 H, CH_3, *J* = 6.9); 1.5 (br.s, 1 H, NH); 2.7 (m, 2 H, $C\underline{H}_2CH_3$)	−3.3 (d, 3 F, CF_3, *J* = 6.0)
5b	$(CD_3)_2CO$	5.0	4.5 (dd, 1 H, *J* = 12.0, 4.5); 4.55 (dd, 1 H, *J* = 12.0, 3.0)	1.5 (t, 3 H, CH_3, *J* = 7.5); 2.0 (s, 1 H, NH); 3.5 (m, 2 H, $C\underline{H}_2CH_3$)	—
5d	CD_3OD	4.7	3.9 (dd, 1 H, *J* = 13.5, 3.1); 4.0 (dd, 1 H, *J* = 13.5, 4.5)	1.0—2.0 (m, 11 H, C_6H_{11}); 3.0 (m, 1 H, NH)	−6.5 (d, 3 F, CF_3, *J* = 7.5)
6d	$CDCl_3$	3.4	3.4 (m, 1 H); 3.6 (m, 1 H)	1.0—1.9 (m, 11 H, C_6H_{11}); 2.6 (m, 1 H, NH)	—
7c	$CDCl_3$	3.2	3.6 (m)	2.5 (m, 1 H, NH); 3.9 (d, 2 H, CH_2Ph, *J* = 6.45); 5.1 (s, 1 H, OH); 7.3 (m, 5 H, C_6H_5)	−5.0 (d, 3 F, CF_3, *J* = 7.0)
8d	CD_3OD	4.5	3.9 (m)	1.0—2.2 (m, 11 H, C_6H_{11}); 2.4 (s, 3 H, $C\underline{H}_3C_6H_4$); 3.25 (s, 1 H, NH); 7.4 (m, 4 H, C_6H_4)	−5.2 (d, 3 F, CF_3, *J* = 7.0)
9d	CD_3OD	4.9	3.5 (dd, 1 H, *J* = 12.6, 9.3); 3.7 (dd, 1 H, *J* = 12.6, 5.0)	1.1—2.2 (m, 11 H, C_6H_{11}); 3.15 (s, 1 H, NH); 8.7 (s, 2 H, C_6H_2)	—

excess of a 10% aqueous solution of $NaHCO_3$ was added, and the organic layer was separated, dried with $MgSO_4$, and distilled.

***N*-(2-Chloro-1-trifluoromethylethyl)cyclohexylamine (5d)** was obtained analogously from aziridine **1d** (10 mmol) and 20% HCl (20 mmol).

***N*-(2-Bromo-1-trifluoromethylethyl)cyclohexylamine (6d)** was obtained analogously from aziridine **1d** (10 mmol) and 40% HBr (20 mmol).

2-Benzylamino-3,3,3-trifluoropropyl alcohol (7c). 50% H_2SO_4 (3.92 g, 20 mmol) was added dropwise with stirring at 0—5 °C to aziridine **1c** (2.01 g, 10 mmol). The mixture was kept at 20 °C for 15 min, poured into 15 mL of water, and neutralized with $NaHCO_3$ (3.36 g, 40 mmol). The crystals that formed were filtered off, washed with water, and dried in air.

2-Cyclohexylamino-3,3,3-trifluoropropyl toluene-*p*-sulfonate (8d). A solution of $TsOH \cdot H_2O$ (1.9 g, 10 mmol) in 5 mL of ether was added dropwise at −70 °C to aziridine **1d** (1.93 g, 10 mmol). The precipitate that formed was filtered off, washed with ether, and dried.

***O*-(2-Cyclohexylamino-2-trifluoromethylethyl)-2,4,6-trinitrophenol (9d)** was obtained analogously from aziridine **1d** (10 mmol) and picric acid (15 mmol).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-32884).

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Received June 25, 1996;
in revised form February 10, 1997