A route to fluorocontaining 1,3-thiazolines *via* internal polyfluorooxiranes

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The reaction of internal fluoroolefin oxides with thiourea results in 2-amino-5-fluoro-4-hydroxy-4,5-di(polyfluoroalkyl)-1,3-thiazolines, providing a route to an unknown type of fluorine-containing thiazolines with two fluoroalkyl substituents.

Recently, we have shown that oxides of internal fluoroolefins, in contrast with hexafluoropropylene oxide,[1] give heterocyclic compounds, polyfluoroalkylated diazinols and oxazinols, when they are treated with ethylenediamine or 2-aminoethanol, respectively.[2] However, other reactions of the former compounds with nucleophiles containing more than one functional group, are unknown.

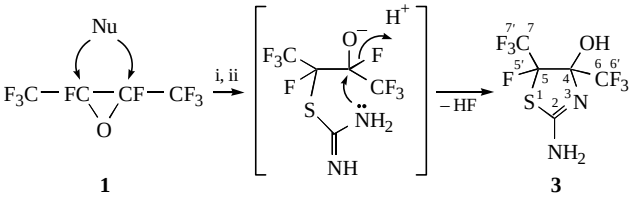
We describe here the interaction of polyfluoro-2,3-epoxyalkanes **1** and **2a**,**b**[3] with thiourea. We found that the reaction does not occur under mild conditions reported for terminal fluorooxiranes, which easily interact with thiourea resulting in 5-fluoroalkyl-4-oxothiazolines.[4] The interaction of **1** and **2a**,**b** with thiourea was carried out at elevated temperature (70–90 °C, sealed tubes in the case of **1**, **2a**) at the molar ratio oxirane:thiourea = 1:3 using MeOH, DMSO or DMF as a solvent. As a result, 2-amino-5-fluoro-4-hydroxy-4,5-di(polyfluoroalkyl)-1,3-thiazolines **3**,[†,‡] **4a**, **5a**, **4b** and **5b**[§] were obtained.

Symmetrical octafluoro-2,3-epoxybutane **1** (*E*:*Z* ~ 90:10) reacting with thiourea gave one regioisomer, 2-amino-5-fluoro-4-hydroxy-4,5-bis(trifluoromethyl)-1,3-thiazoline **3**. We found stereoisomer (*E*)-**3** to be the principal product along with 2–8% of (*Z*)-**3** when the reaction was carried out both in DMF and in MeOH (Scheme 1, Table 1).

The reaction of unsymmetrical oxiranes **2a** (*E*:*Z* ~ 90:10) and **2b** (*E*:*Z* ~ 85:15) with thiourea afforded mixtures of regioisomers **4a**, **5a** and **4b**, **5b** in the *E*-form as major products and those in the *Z*-form as minor products (Scheme 2, Table 1).

The structural assignment for (*E*)-**3** and (*Z*)-**3** was made on the basis of their ^{19}F NMR spectra[¶] by comparison of the coupling constants $^4J(F^{5'},F^{6'})$ and $^5J(F^{6'},F^{7'})$ of the formers. Thus, the coupling constant $^4J(F^{5'},F^{6'})$ in (*E*)-**3** is considerably greater (21.5 Hz) than that in (*Z*)-**3** (3.9 Hz). In contrast, compound (*Z*)-**3** exhibited a greater coupling constant $^5J(F^{6'},F^{7'})$ (11.7 Hz) than that in (*E*)-**3** (5.4 Hz). This fact can be explained by the geometrical vicinity of the interacting nuclei [$CF^{5'}$ and $CF_3^{7'}$ in (*E*)-**3**; $CF_3^{6'}$ and $CF_3^{7'}$ in (*Z*)-**3**] resulting in a rise of through-space scalar coupling along with the through-bond transmitted coupling between the latters. Analogous regularities were reported for the coupling constants $^4J_{F,F}$ and $^5J_{F,F}$ of (*E*)- and (*Z*)-isomers of internal fluorooxiranes.[5]

The assignment of the ^{19}F NMR spectra for (*E*)- and (*Z*)-isomers of **4a**,**b** and **5a**,**b** was made by comparison with those of (*E*)-**3**, (*Z*)-**3**. The (*E*)-configuration of **4a**,**b** was determined from the greater coupling constant $^4J(F^{5'},F^{9'})$ (21 Hz) as compared with that in **4a**,**b** having the (*Z*)-configuration (3.9 Hz). The (*E*)-configuration of **5a**,**b** was inferred from the large coupling constant $^4J(F^{5'},F_A^{6'})$ (41–41.5 Hz). The coupling between these



1 **3**

Scheme 1 *Reagents and conditions*: i, MeOH, NH_2CSNH_2 (a three-fold excess), sealed tube, 70–75 °C, 2 h; ii, DMF, NH_2CSNH_2 (a three-fold excess), sealed tube, 70–75 °C, 2 h.

† All new compounds (*E*)-**3**, (*E*)-**4a**,**b** and (*E*)-**5a** gave satisfactory elemental analyses and were characterised by IR (Vazeline oil), ^{19}F NMR (75.3 MHz, [$^2H_6$]acetone, C_6F_6) and ^{1}H NMR (100 MHz, [$^2H_6$]acetone, Me_4Si) spectroscopy and mass spectrometry; compound (*E*)-**3**, additionally, by ^{13}C NMR spectroscopy (20.1 MHz, [$^2H_6$]acetone, Me_4Si).

‡ *2-Amino-5-fluoro-4-hydroxy-4,5-bis(trifluoromethyl)-1,3-thiazoline* (*E*)-**3** (*typical procedure*). A mixture of oxirane **1** (*E*:*Z* ~ 90:10) (4.1 g, 19 mmol), thiourea (4.3 g, 56.6 mmol) and DMF (10 ml) was heated in a sealed tube for 2 h at 70–75 °C (water bath) with intermittent shaking. After cooling, the tube was opened and the reaction mixture was poured into water (50 ml). The resulting precipitate was collected by filtration and washed with a small amount of water. The solid residue was dissolved in water (120 ml) and filtered to remove an insoluble material. The filtrate was extracted with diethyl ether; the organic layer was dried over $MgSO_4$ and evaporated. The solid residue was recrystallised from benzene to give (*E*)-**3**.

§ (*E*)-**3**: yield 64% (MeOH), 37% (DMF); mp 158–159 °C (from benzene). ^{1}H NMR, δ: 7.38 (br. s, 2H, NH_2), 6.83 (s, 1H, OH). ^{19}F NMR, δ: 93.1 (dq, 3F, $CF_3^{7'}$), 86.4 (dq, 3F, $CF_3^{6'}$), 20.1 (qq, 1F, $CF^{5'}$); $^4J_{5',6'}$ 21.5 Hz, $^3J_{5',7'}$ 10.3 Hz, $^5J_{6',7'}$ 5.4 Hz. ^{13}C NMR, δ: 161.4 (C^2), 123.7 (C^6, ^1J 287.5 Hz), 122.7 (C^7, ^1J 283.2 Hz, $^2J_{7,5'}$ 34.8 Hz), 116.9 (C^5, ^1J 143.2 Hz, $^2J_{5,7'}$ 30.8 Hz), 104.7 (C^4, $^2J_{4,6'}$ 30.5 Hz, $^2J_{4,5'}$ 23.8 Hz). IR, ν/cm^{-1}: 3470, 3370 (NH), 3050 (br., OH, NH), 1640 (C=N), 1625, 1575 (NH). MS, *m*/*z*: 272 (M^+).

2-Amino-5-fluoro-5-heptafluoropropyl-4-hydroxy-4-trifluoromethyl-1,3-thiazoline (*E*)-**4a**: yield 35% (MeOH), 17% (DMSO); mp 157–158 °C (from benzene). ^{1}H NMR, δ: 7.35 (br. s, 2H, NH_2), 6.72 (s, 1H, OH). ^{19}F NMR, δ: 87.2 (t, 3F, $CF_3^{9'}$), 83.1 (ddd, 3F, $CF_3^{8'}$), 57.2 (tq, 1F, $CF_A^{6'}$), 45.2 (m, 1F, $CF_B^{6'}$), 42.2 (dd, 1F, $CF_A^{7'}$), 40.1 (t, 1F, $CF_B^{7'}$), 20.7 (m, 1F, $CF^{5'}$); $J_{6'A,6'B}$ 289.1 Hz, $J_{7'A,7'B}$ 288.1 Hz; $^4J_{5',7'A}$ 24.4 Hz, $^4J_{5',9'}$ = $^5J_{6'B,9'}$ = 21.0 Hz, $^4J_{6'A,8'}$ 13.7 Hz, $^4J_{6'B,8'}$ 9.8 Hz. IR, ν/cm^{-1}: 3470, 3370 (NH), 3010 (br., OH, NH), 1645 (C=N), 1625, 1585 (NH). MS, *m*/*z*: 372 (M^+).

2-Amino-5-fluoro-5-(1,1,2,2,3,3-hexafluoropropyl)-4-hydroxy-4-trifluoromethyl-1,3-thiazoline (*E*)-**4b**: yield 23% (DMSO), mp 122–123 °C (from benzene). ^{1}H NMR, δ: 7.18 (br. s, 2H, NH_2), 6.60 (tt, 1H, HCF_2), 6.51 (s, 1H, OH). ^{19}F NMR δ: 87.2 (t, 3F, $CF_3^{9'}$), 56.2 (tt, 1F, $CF_A^{6'}$), 44.0 (m, 1F, $CF_B^{6'}$), 37.4 (ddq, 1F, $CF_A^{7'}$), 35.2 (ddq, 1F, $CF_B^{7'}$), 26.0 (dm, 2F, $CF_2^{8'}$), 21.4 (m, 1F, $CF^{5'}$); $J_{6'A,6'B}$ 289.6 Hz, $J_{7'A,7'B}$ 284.4 Hz; $^2J_{8',H}$ 51.6 Hz, $^5J_{6'B,9'}$ = $^4J_{5',9'}$ = $^4J_{5',7'A}$ = 21.0 Hz, $^3J_{7',8'}$ = $^3J_{7',H}$ = 5.9 Hz. IR, ν/cm^{-1}: 3465, 3370 (NH), 3050 (br., OH, NH), 1645 (C=N), 1625, 1585 (NH). MS, *m*/*z*: 354 (M^+).

2-Amino-5-fluoro-4-heptafluoropropyl-4-hydroxy-5-trifluoromethyl-1,3-thiazoline (*E*)-**5a**: yield 16% (MeOH), 105–107 °C (obtained by reprecipitation from MeOH by water). ^{1}H NMR, δ: 7.22 (br. s, 2H, NH_2), 6.65 (s, 1H, OH). ^{19}F NMR, δ: 93.6 (ddd, 3F, $CF_3^{9'}$), 83.0 (t, 3F, $CF_3^{8'}$), 48.8 (dm, 1F, $CF_A^{6'}$), 44.9 (m, 1F, $CF_B^{6'}$), 43.0 (t, 1F, $CF_A^{7'}$), 40.6 (t, 1F, $CF_B^{7'}$); 20.0 (m, 1F, $CF^{5'}$), $J_{7'A,7'B}$ 285.6 Hz, $J_{6'A,6'B}$ 282.2 Hz, $^4J_{5',6'A}$ 41.0 Hz, $^5J_{6'B,9'}$ 13.7 Hz, $^3J_{5',9'}$ = $^4J_{6',8'}$ = 9.8 Hz, $^5J_{6'A,9'}$ 3.9 Hz. IR, ν/cm^{-1}: 3510–3150 (OH, NH), 1670, 1650, 1600 (NH, C=N).

¶ (*Z*)-**3**: ^{19}F NMR, δ: 92.2 (dq, 3F, $CF_3^{7'}$), 85.0 (qd, 3F, $CF_3^{6'}$), 26.3 (qq, 1F, $CF^{5'}$); $^3J_{5',7'}$ = $^5J_{6',7'}$ = 11.7 Hz, $^4J_{5',6'}$ 3.9 Hz.

(*Z*)-**4a**: ^{19}F NMR, δ: 86.3 (td, 3F, $CF_3^{9'}$), 83.2 (m, 3F, $CF_3^{8'}$), 51.5 (m, 1F, $CF_A^{6'}$), 42.9 (m, 1F, $CF_B^{6'}$), 40.9 (dt, 2F, $CF_2^{7'}$), 27.7 (m, 1F, $CF^{5'}$); $J_{6'A,6'B}$ 287.1 Hz, $^4J_{5',7'}$ 20.5 Hz, $^5J_{6',9'}$ 18.6 Hz, $^5J_{5',8'}$ = $^4J_{5',9'}$ = $^3J_{6',7'}$ = = 3.9 Hz.

(*Z*)-**5a**: ^{19}F NMR, δ: 93.6 (ddd, 3F, $CF_3^{9'}$), 83.0 (t, 3F, $CF_3^{8'}$), 43.4 (m, $\delta_{6'A6'B}$), 41.9 (t, 2F, $CF_2^{7'}$), 29.3 (q, 1F, $CF^{5'}$); $^5J_{6'B,9'}$ 20.5 Hz, $^5J_{6'A,9'}$ 16.6 Hz, $^3J_{5',9'}$ 12.7 Hz, $^3J_{6',7'}$ 2.9 Hz.

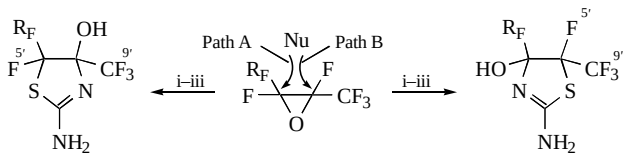
(*E*)-**5b**: ^{19}F NMR, δ: 93.2 (dd, 3F, $CF_3^{9'}$), 45.6 (dm, 1F, $CF_A^{6'}$), 39.3 (m, 1F, $CF_B^{6'}$), 38.1 (m, 1F, $CF_A^{7'}$), 35.0 (m, 1F, $CF_B^{7'}$), 26.0 (dm, 2F, $CF_2^{8'}$), 19.2 (m, 1F, $CF^{5'}$); $J_{7'A,7'B}$ 277.5 Hz, $J_{6'A,6'B}$ 275.2 Hz, $^2J_{8',H}$ 51.6 Hz, $^4J_{5',6'A}$ 41.5 Hz, $^3J_{7',H}$ 5.9 Hz.

Table 1 Composition and molar ratios of the products of the reaction of oxiranes **1** and **2a**,**b** with thiourea at the molar ratio oxirane:thiourea = 1:3 (from ^{19}F NMR data).

Starting oxirane (*E*:*Z*)	Solvent	Reaction products (molar ratio)
1 (90:10)	DMF	(*E*)-**3**, (*Z*)-**3** (92:8)
1 (90:10)	MeOH	(*E*)-**3**, (*Z*)-**3** (98:2)
2a (90:10)	DMSO	(*E*)-**4a**, (*Z*)-**4a**, (*E*)-**5a**, (*Z*)-**5a** (51: 7:39: 3)
2a (90:10)	MeOH	(*E*)-**4a**, (*Z*)-**4a**, (*E*)-**5a**, (*Z*)-**5a** (59: 2:39: 1)
2a (60:40)	MeOH	(*E*)-**4a**, (*Z*)-**4a**, (*E*)-**5a**, (*Z*)-**5a** (43:16:33: 8)
2a (60:40)	DMSO	(*E*)-**4a**, (*Z*)-**4a**, (*E*)-**5a**, (*Z*)-**5a** (36:26:27:11)
2a (85:15)	DMSO	(*E*)-**4b**, (*Z*)-**4b**, (*E*)-**5b**, (*Z*)-**5b** (76: 9:13: 2)

atoms in (*Z*)-**5a**,**b** was not observed.

As can be seen in Table 1, the fraction of the reaction products in the (*Z*)-form increases with increasing fraction of the (*Z*)-isomer in the starting oxirane. Note that the nature of the solvent influences the relative amounts of the resulting stereoisomers. When the reaction of **2a** [(*E*):(*Z*) ~ 60:40] was performed in DMSO, the total molar ratio (*E*):(*Z*) of **4a** and **5a** had nearly the same value as in the starting oxirane: [(*E*)-**4a**+(*E*)-**5a**]:[(*Z*)-**4a**+(*Z*)-**5a**] ~ 63:37. At the same time, in MeOH, the relative quantity of (*Z*)-thiazolines decreased: [(*E*)-**4a**+(*E*)-**5a**]:[(*Z*)-**4a**+ +(*Z*)-**5a**] ~ 76:24. It is evident that the reaction is stereospecific for both (*E*)- and (*Z*)-oxiranes when it is carried out in DMSO, and the predominant formation of (*E*)-thiazolines is observed in the presence of MeOH.



a $R_F = CF_2^{6'}CF_2^{7'}CF_3^{8'}$
b $R_F = CF_2^{6'}CF_2^{7'}CF_2^{8'}H$

Scheme 2 *Reagents and conditions*: i, **2a**, NH_2CSNH_2 (a three-fold excess), MeOH, sealed tube, 85–90 °C, 3 h; ii, **2a**, NH_2CSNH_2 (a three-fold excess), DMSO, sealed tube, 85–90 °C, 10 h; iii, **2b**, NH_2CSNH_2 (a three-fold excess), DMSO, 60–65 °C, 1.5 h.

Individual thiazolines (*E*)-**3**, (*E*)-**4a**,**b** and (*E*)-**5a** were isolated as stable colourless crystals by recrystallization or reprecipitation from corresponding isomer mixtures.

Thus, we have developed an approach to the synthesis of functionalised 1,3-thiazolines with two fluoroalkyl substituents, which are of interest as biologically active compounds[6] and new convenient building blocks for complex heterocyclic systems.

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