

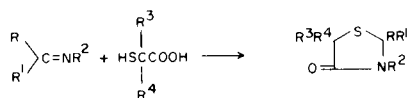
2,2-Bis(polyfluoromethyl)-4-thiazolidinones, -4-oxazolidinones,
and -tetrahydro-4*H*-1,3-thiazin-4-ones

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4-Thiazolidinones have been of considerable interest for investigation of their biological activity and other properties (1). About 2500, exclusive of rhodanine derivatives, are listed by Chemical Abstracts for 1907-1971, and half of these appeared during the decade 1962-1971. However, no examples substituted by fluoroalkyl groups have been recorded. This article reports the accessibility of such derivatives by the reaction of polyfluoroalkylideneimines with α -mercapto acids. This synthe-



sis is an extension of the known reaction of aromatic Schiff bases with α -mercaptoalkanoic acids to form 4-thiazolidinones (2-4).

The fluoroalkyl groups are electron withdrawing and result in an electron-deficient double bond in the imine which is readily susceptible to nucleophilic attack at carbon. With mercaptoacetic acid, addition of the mercapto group to a polyfluoroacetone imine unsubstituted on nitrogen and ring closure to form the thiazolidinone take place at 0-25°. With other α -mercapto acids and with *N*-substituted imines, a temperature of 100° is conveniently employed.

4-Thiazolidinones with an unsubstituted nitrogen atom form salts that can be alkylated. Ir analysis of the alkylated products shows that the carbonyl group is present and that the product is, therefore, an *N*-alkyl derivative and not *O*-alkyl. In Table II, which summarizes the 25 thiazolidinones that have been prepared, compounds **8**, **10**, **12**, **15**, **16**, **17**, **19**, **21**, and **24** were made by *N*-alkylation.

Though the fluoroalkyl groups deactivate the sulfur atom, this atom can still be oxidized to its dioxide by peracetic acid as illustrated by **14** in Table II.

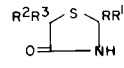
The high reactivity of hexafluoroacetone imine and 1,3-dichlorotetrafluoroacetone imine makes possible their addition to hydroxyacetic acid, in analogy to mercaptoacetic acid, to form 2,2-bis(polyfluoromethyl)-4-oxazoli-

dinones (**26-28**, Table II). This synthesis seems not to have been reported using other imines or Schiff bases. The oxazolidinones can also be *N*-methylated.

2,2-Bis(trifluoromethyl)-4-oxazolidinone (**26**) has been reported previously from the reaction of hexafluoroacetone with formaldehyde cyanohydrin, a reaction also operable with aryl cyanohydrins (5). Other reported polyfluoromethyl derivatives are 2,2,5,5-tetrakis(polyfluoromethyl)-4-oxazolidinones from fluorinated acetones and sodium cyanide (6), and 2,2-bis(chlorodifluoromethyl)-4-methyl-5-oxazolidinone from the reaction of 1,3-dichlorotetrafluoroacetone with alanine (7).

Only about 200 tetrahydro-4*H*-1,3-thiazin-4-ones are known. Surrey introduced the method of synthesis from aromatic Schiff bases and β -mercapto propionic acid (8). Polyfluoroisopropylideneimines have now been shown to react with β -mercapto propionic acid and with cysteine to form 2,2-bis(polyfluoromethyl)tetrahydro-4*H*-1,3-thiazin-4-ones (**29-36**, Table II). Formation of the six-membered

TABLE I

Acid Dissociation Constants						
A		B		C		D
Formula	No.	R	R ¹	R ²	R ³	pK _a
						
A	1	CF ₃	CF ₃	H	H	7.35
A	5	CF ₃	CF ₃	CH ₃	CH ₃	8.37
A	13	CF ₂ Cl	CF ₂ Cl			7.57
B	26	CF ₃	CF ₃			6.42
B	27	CF ₂ Cl	CF ₂ Cl			6.65
C	29	CF ₃	CF ₃			(a)
C	33	CF ₂ Cl	CF ₂ Cl			(a)
D	37	CF ₃	CF ₃			8.83
D	38	CF ₂ Cl	CF ₂ Cl			8.99

(a) Not titratable.

TABLE II
2,2-Bis(polyfluoromethyl)-4-thiazolidinones, 4-oxazolidinones, and tetrahydro-4H-1,3-thiazin-4-ones

No.	Product	Reactants	Solvent	Conditions	Recrystn. Solvent	M.p., °C (B.p.)	% Yield	Formula	Analyses C	Calcd. H	Found N
1		(a) $(CF_3)_2C=NH$ HSCH ₂ COOH	Dichloromethane	0°, 8 hours	Carbon Tetrachloride	114.5-116	67	C ₅ H ₃ F ₆ NOS	25.10 25.13	1.26 1.16	5.86 5.64
2		(c) $(CF_3)_2C=NCH_3$ (d) HSCH ₂ COOH	Dichloromethane	100°, 16 hours Sealed tube	Hexane	47-49	91	C ₆ H ₅ F ₆ NOS	28.47 28.77	1.99 2.11	5.53 5.75
3		(e) $(CF_3)_2C=NPh$ (f) HSCH ₂ COOH	Methanol	100°, 4 hours	Methanol	109-110	32	C ₁₁ H ₇ F ₄ NOS	41.90 41.63	2.24 2.17	4.44 4.52
4		(g) $(CF_3)_2C=NH$ HSCH(CH ₃)COOH	Dichloromethane	0°, 8 hours	Hexane	86.5-88.5	57	C ₆ H ₅ F ₆ NOS	28.47 28.63	1.99 1.88	5.53 5.58
5		(h) $(CF_3)_2C=NH$ HSC(CH ₃) ₂ COOH	Hexane	100°, 20 hours Sealed tube	Hexane	128-129	37	C ₇ H ₇ F ₆ NOS	31.47 31.26	2.64 2.49	5.24 5.17
6		(i) $(CF_3)_2C=NH$ HSCHCOOH CH ₂ COOH	Ether	100°, 20 hours Sealed tube	Nitromethane	203-208	58	C ₇ H ₅ F ₆ NO ₃ S	28.28 28.41	1.70 1.57	4.71 4.95
7		(j) $(CF_3)_2C=NH$ HSCHPhCOOH	Dichloromethane	100°, 5 hours Sealed tube	Carbon Tetrachloride	153-154	68	C ₁₁ H ₇ F ₆ NOS	41.90 41.78	2.24 2.34	4.44 4.47
8		7, KOH, CH ₃ I	Methanol	24°, 16 hours	Methanol	77-78	86	C ₁₂ H ₉ F ₆ NOS	43.77 43.88	2.76 2.91	4.25 4.15

TABLE II (continued)

No.	Product	Reactants	Solvent	Conditions	Recrystn. Solvent	M.p., °C (B.p.)	% Yield	Formula	Analyses C	Calcd. H	Found N
9		$\text{CF}_2\text{Cl}-\text{C}(\text{CF}_3)=\text{NH}(\text{d})$ HSCH_2COOH	Dichloromethane	24°, 16 hours	Hexane	97-98	68	$\text{C}_5\text{H}_3\text{ClF}_5\text{NOS}$	23.50 23.70	1.18 1.38	5.48 5.37
10		9 , KOH, CH_3I	Methanol	Reflux 4 hours	Hexane	45-46	86	$\text{C}_6\text{H}_5\text{ClF}_5\text{NOS}$	26.73 26.57	1.87 1.94	5.20 5.26
11		$\text{CHF}_2-\text{C}(\text{CF}_3)=\text{NH}(\text{k})$ HSCH_2COOH	Dichloromethane	24°, 16 hours	Hexane	97-98	58	$\text{C}_5\text{H}_4\text{F}_5\text{NOS}$	27.15 27.22	1.82 1.87	6.33 6.41
12		11 , KOH, CH_3I	Methanol	Reflux 4 hours		(78/4 mm) $n_D^{25} 1.4302$	75	$\text{C}_6\text{H}_6\text{F}_5\text{NOS}$	30.64 30.78	2.57 2.52	5.96 5.71
13		$(\text{CF}_2\text{Cl})_2\text{C}=\text{NH}(\text{d})$ HSCH_2COOH	Dichloromethane	24°, 1 hour	Hexane	103.5-104.5	62	$\text{C}_5\text{H}_3\text{Cl}_2\text{F}_4\text{NOS}$	22.08 22.06	1.11 1.09	5.12 4.85
14		13 , CH_3COOOH	Acetic Acid	100°, 15 hours	Benzene	112-114	55	$\text{C}_5\text{H}_3\text{Cl}_2\text{F}_4\text{NO}_3\text{S}$	19.75 20.02	0.99 0.77	4.61 4.43
15		13 , NaOH, CH_3I	Aqueous Methanol	24°, 18 hours	Hexane	84-85	62	$\text{C}_6\text{H}_5\text{Cl}_2\text{F}_4\text{NOS}$	25.18 24.86	1.76 1.55	4.90 4.71

TABLE II (continued)

No.	Product	Reactants	Solvent	Conditions	Recrystn. Solvent	M.p., °C (B.p.)	% Yield	Formula	Analyses C	Calcd. H	Found N
16		13, NaOH, PhCH ₂ Br	Aqueous Methanol	Reflux 5 hours	Methanol	43-44 (p)	27	C ₁₂ H ₉ Cl ₂ F ₄ NOS	39.79 39.63	2.51 2.71	3.87 3.84
17		13, KOH, I(CH ₂) ₄ I	Ethanol	Reflux 16 hours	Methanol	134-136	36	C ₁₄ H ₁₂ Cl ₄ F ₈ N ₂ O ₂ S ₂	28.11 28.00	2.02 1.82	4.68 4.39
18		(CF ₂ Cl) ₂ C=NH HSC(CH ₃)COOH		Cooling, then 100°, 0.5 hours	Hexane	82-83	65	C ₆ H ₅ Cl ₂ F ₄ NOS	25.18 25.50	1.76 1.44	4.80 4.67
19		18, KOH, CH ₃ I	Methanol	Reflux 3 hours	Hexane	72-74	80	C ₇ H ₇ Cl ₂ F ₄ NOS	28.01 28.26	2.35 2.46	4.67 4.55
20		(CF ₂ Cl) ₂ C=NH HSC(CH ₃) ₂ COOH (h)		100°, 20 hours Sealed tube	Hexane	74-75	55	C ₇ H ₇ Cl ₂ F ₄ NOS	20.01 27.85	2.35 2.24	4.67 4.49
21		20, KOH, CH ₃ I	Methanol	24°, 16 hours	Hexane	84-86	69	C ₈ H ₉ Cl ₂ F ₄ NOS	30.59 30.62	2.89 2.66	4.46 4.57
22		(CF ₂ Cl) ₂ C=NH HSCPhCOOH CH ₂ COOH	1,2-Dimethoxyethane	100°, 16 hours under reflux	Nitromethane	187-188	66	C ₇ H ₅ Cl ₂ F ₄ NO ₃ S	25.47 25.61	1.53 1.28	4.24 4.12
23		(CF ₂ Cl) ₂ C=NH HSCPhCOOH (j)	Carbon Tetrachloride	100°, 1 hour under reflux	Carbon Tetrachloride	159-160	73	C ₁₁ H ₇ Cl ₂ F ₄ NOS	37.95 37.96	2.03 1.93	4.02 4.04
24		23, KOH, CH ₃ I	Methanol	24°, 16 hours	Methanol	108-109	92	C ₁₂ H ₉ Cl ₂ F ₄ NOS	39.80 39.72	2.50 2.35	3.87 3.86

TABLE II (continued)

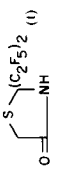
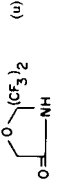
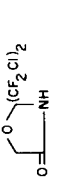
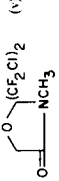
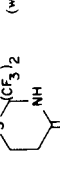
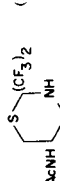
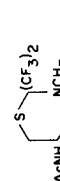
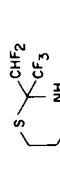
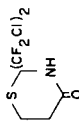
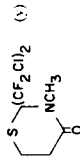
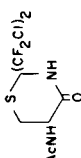
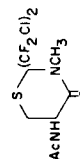

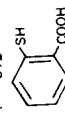
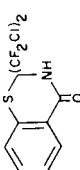
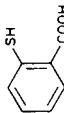
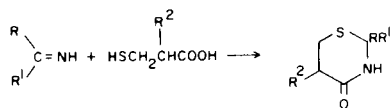
No.	Product	Reactants	Solvent	Conditions	Recrystn. Solvent	M.p., °C (B.p.)	% Yield	Formula	Analyses Calcd. C H N	Found C H N	
25		(C ₂ F ₅) ₂ C=NH (d) HSCH ₂ COOH	Dichloromethane	100°, 16 hours Sealed tube	Hexane	89.5-90.5	72	C ₇ H ₃ F ₁₀ NOS	24.78 24.56	0.89 0.84	4.13 4.00
26		(CF ₃) ₂ C=NH HOCH ₂ COOH		100°, 18 hours Sealed tube	Hexane	77-78	42				
27		(CF ₂ Cl) ₂ C=NH HOCH ₂ COOH		100°, 18 hours Sealed tube	Hexane	76	41	C ₅ H ₃ Cl ₂ F ₄ NO ₂	23.46 23.36	1.18 0.87	5.47 5.37
28		27, KOH, CH ₃ I	Methanol	Reflux 4 hours		(59-63/4 mm) n _D ²⁵ 1.4179	85	C ₆ H ₅ Cl ₂ F ₄ NO ₂	26.68 26.66	1.87 2.11	5.19 5.48
29		(CF ₃) ₂ C=NH HSCH ₂ CH ₂ COOH	Dichloromethane	0°, 18 hours 200°, 2 minutes	Cyclohexane	120-122	31	C ₆ H ₅ F ₆ NOS	28.39 28.31	1.99 2.03	5.52 5.52
30		(CF ₃) ₂ C=NH L-HSCH ₂ CHCOOH NHAc	Dichloromethane	24°, 48 hours Sealed tube	Nitromethane	179-180	17.5	C ₈ H ₈ F ₆ N ₂ O ₂ S ₂	30.96 30.94	2.60 2.52	9.03 8.87
31		30, KOH, CH ₃ I	Methanol	Reflux 3 hours	Nitromethane	144-145	56	C ₉ H ₁₀ F ₈ N ₂ O ₂ S	33.55 33.58	3.13 2.97	8.70 8.43
32		CHF ₂ C=NH (k) CF ₃ HSCH ₂ CH ₂ COOH	Dichloromethane Dichloromethane	100°, 7 hours Sealed tube	Carbon Tetrachloride	87.5-88	50	C ₆ H ₆ F ₅ NOS	30.64 30.69	2.57 2.46	5.95 5.88

TABLE II (continued)

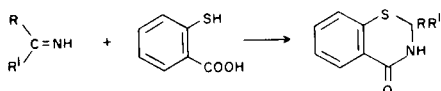
No.	Product	Reactants	Solvents	Conditions	Recrystn. Solvent	M.p., °C (B.p.)	% Yield	Formula	Analyses C	Calcd. H	Found N	Notes
33		(CF ₂ Cl) ₂ C=NH HSCH ₂ CH ₂ COOH		30°, 1 hour 200°, 2 minutes	Carbon Tetrachloride	124-126	42	C ₆ H ₅ Cl ₂ F ₄ NOS	25.18 25.18	1.76 1.83	4.89 4.92	
34		33, MeONa, CH ₃ I	Methanol	Reflux 6 hours	Hexane	84	54	C ₇ H ₇ Cl ₂ F ₄ NOS	28.01 28.18	2.34 2.49	4.67 4.53	
35		(CF ₂ Cl) ₂ C=NH L-HSCH ₂ CHCOOH NHAc	Tetrahydrofuran	24°, 15 hours stirred, 100°, 20 hours, no solvent	Nitromethane	191-193	37	C ₈ H ₈ Cl ₂ F ₄ N ₂ O ₂	27.99 28.00	2.16 2.35	7.79 7.86	
36		35, KOH, MeI	Methanol	24°, 16 hours	Cyclohexane	127-128	52	C ₉ H ₁₀ Cl ₂ F ₄ N ₂ O ₂ S	30.27 30.36	2.82 2.73	7.84 7.61	
37		(CF ₃) ₂ C=NH 	Tetrahydrofuran	24°, 1 hour	Methanol	158-161	70	C ₁₀ H ₅ F ₆ NOS	39.86 39.76	1.67 1.49	4.65 4.73	
38		(CF ₂ Cl) ₂ C=NH 	Tetrahydrofuran	Reflux 16 hours	Methanol	133-135	62	C ₁₀ H ₅ Cl ₂ F ₄ NOS	35.95 35.65	1.51 1.49	4.19 4.02	

(a) ¹H nmr (deuteriochloroform) 3.77 (s, CH₂), 8.90 ppm (NH); ¹⁹F nmr -76.5 ppm (s); ir 3175, 3077 (NH), 2882 (CH), 1706 cm⁻¹ (lactam C=O). (b) Refs. 11-13. (c) Volatile. (d) Ref. 12. (e) ¹H nmr (deuteriochloroform) 3.78 (s, CH₂), 7.4 ppm (m, benzene); ¹⁹F nmr -70.5 ppm (s); (f) Ref. 14. (g) ¹H nmr (deuteriochloroform) 2.57 (d, CH₃), 4.07 (q, CH), 8.92 ppm (broad, NH); ir 3185, 3096 (NH), 2882 (CH), 1718 cm⁻¹ (lactam C=O). (h) Ref. 15. (i) ¹H nmr (acetone-d₆) ABX pattern 1.40 (q, 2 upfield components split to doublets, J = 11 Hz; 2 downfield components split to doublets, J = 4 Hz, CH₂), 2.75 (pair of doublets, J = 4, CH), 7.10 ppm (s, OH+NH, removed by deuterium oxide); ¹⁹F nmr -76.6 ppm (A₃B₃ pattern); ir 3175, 3077 (NH), 2890 (CH), 3330-2500 (background absorption, COOH), 1721, 1709 cm⁻¹ (C=O). (j) Ref. 16. (k) Ref. 17. (l) ¹H nmr (deuteriochloroform) 3.75 (s, CH₂), 9.09 ppm (broad, NH); ¹⁹F nmr -59 ppm (A₂B₂ pattern). (m) ¹H nmr (acetone-d₆) 4.47 (pentet, J = 0.8 Hz, CH₂), ca. 9 ppm (very broad, NH). (n) ¹H nmr (carbon tetrachloride) 3.04 (s, CH₂), 3.63 ppm (s, CH₂); ir 1718 cm⁻¹ (C=O). (o) ¹H nmr (carbon tetrachloride) 1.80 (pentet, CH₂CH₂ in center), 3.55 (t, two CH₂ next to N), 3.73 ppm (s, ring CH₂). (p) Recrystallized after distillation. b.p. 100-119°/0.5 mm. (q) ¹H nmr (deuteriochloroform) 1.60 (s, CH₂), 4.70 (s, CH₂ of benzyl), 7.23 ppm (s, C₆H₅); ir 1718 cm⁻¹ (C=O). (r) ¹H nmr (carbon tetrachloride) 1.60 (d, J = 7 Hz, 5-CH₃), 3.08 (s, NCH₃), 3.94 ppm (q, CH), (s) ¹H nmr (carbon tetrachloride) 1.60 (s, 2 CH₃), 3.07 ppm (pentet, J = 1.5 Hz, NCH₃). (t) ¹H nmr (deuteriochloroform) 3.72 (s, CH₂), 8.92 ppm (broad, NH). (u) ¹H nmr (carbon tetrachloride) 4.49 (s, CH₂), 9.42 ppm (s, NH); ref. 5, m.p. 74-76°. (v) ¹H nmr (neat, external TMS) 2.94 (s, CH₃), 4.44 ppm (s, CH₂); ir 1754 cm⁻¹ (C=O). (w) ir 3185, 3106 (NH), 2950 (CH), 1689 cm⁻¹ (lactam C=O). (x) ¹H nmr (dimethyl sulfoxide-d₆) 1.88 (s, CH₃), 3.17 (d, J = 8 Hz, CH₂), 4.57 (q, J = 8 Hz, CH), 8.32 (d, J = 8 Hz, AcNH), 9.84 ppm (s, ring NH); ¹⁹F nmr (acetone-d₆) -74.9, -76.2 ppm (quartets). (y) ir 1681 cm⁻¹ (C=O).



ring is less facile than the five-membered ring. The compounds undergo *N*-methylation like the thiazolidinones.

By using *o*-mercaptobenzoic acid, 2,2-bis(polyfluoromethyl)-2,3-dihydro-4*H*-1,3-benzothiazin-4-ones are obtained (**37**, **38**, Table II). This type of reaction has been reported for aromatic Schiff bases (9,10).



The 4-oxazolidinones and 4-thiazolidinones are markedly more acidic than the tetrahydro-4*H*-1,3-thiazin-4-ones. The former are soluble in sodium bicarbonate solution whereas the latter are not. This may be the result of a greater relief of torsional strain during anion formation for the five-membered ring compounds than for the six. Approximate pK_a 's were determined by dissolving the compounds in 40% ethanol and measuring the pH's at half neutralization with sodium hydroxide. Values for representative compounds appear in Table I. The thiazinones **29** and **33** were too weak as acids to be titratable, but values could be obtained for their benzo derivatives (**37**, **38**). The greater acidity of trifluoromethyl compounds *vs.* chlorodifluoromethyl in the three comparisons shown can be attributed to the greater inductive effect of the electron-withdrawing trifluoromethyl group. Two methyl groups in the five-position reduce the acidity (**5**). The 4-oxazolidinones (**26**, **27**) are more acidic than the corresponding 4-thiazolidinones. Greater relief of strain from anion formation for the former, with the smaller heteroatom, may contribute to this effect.

EXPERIMENTAL

The ^1H nmr spectra were determined on a Varian A-60 instrument using tetramethylsilane as internal standard. The ^{19}F nmr spectra were measured on a Varian A-56/60 instrument using trichlorofluoromethane as internal standard. Upfield values are recorded with a minus sign. Infrared spectra were measured on a Perkin-Elmer Model 21 spectrometer. Melting and boiling points are uncorrected.

Conditions for preparing the compounds are summarized in

Table II. Where a reaction temperature of 24° or lower is given, the addition of the fluorinated imine to the thio acid is exothermic and cooling may be required during addition. After completion of the reaction, the solvent is evaporated and the residue is washed with water where a water-soluble thio acid was used, or with 5% sodium bicarbonate solution in the case of a water-insoluble acid. In preparation of thiazinones **29** and **33**, solvent was removed before heating to 200° to cause ring closure.

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