Synthesis of some new *N*-monosubstituted fluoroacetamides

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Abstract

Twenty new *N*-monosubstituted fluoroacetamides with potential toxicological properties have been synthesized by acylation of the corresponding amines with fluoroacetyl chloride. The substituents were cycloalkyl or various alkyl (with straight or branched carbon chain) groups. The yields ranged from 50 to 92%.

Introduction

The toxicity of certain derivatives of fluoroacetic acid to insects and rodents is well known [1, 2]. Due to their physical characteristics and activity as convulsant poisons, sodium fluoroacetate [3, 4] and fluoroacetamide [5, 6] are especially interesting derivatives [7]. Actually, sodium fluoroacetate is a very effective systemic insecticide against *Aphis fabae* Scop [4], but unfortunately its use cannot be recommended since it is a very dangerous poison [6]. Fluoroacetamide is also an active insecticide, but it is less toxic and acts more slowly [9] than sodium fluoroacetate [5, 8]. Although the first paper on fluoroacetamide was by Swarts at the end of the 19th century [10], detailed investigations of its preparation were not attempted until 1943 when this compound was prepared in high yield by treatment of methyl-fluoroacetate with ammonia [11].

Related compounds have been intensively investigated. With the intention of correlating the toxicological properties of various fluorine-containing organic compounds with their chemical structures, *N*-monosubstituted fluoroacetamides have been investigated by several workers [12–15]. The synthetic procedures for *N*-substituted fluoroacetamides, which exhibit significant pesticide activity, have been the subject of numerous patent applications [16]. Various *N*-mono- and *N,N*-disubstituted fluoroacetamides [17] and *N*-methylenefluoroacetamide derivatives [18] have been tested as potential larvicides, contact insecticides and rodenticides.

In this paper the preparations of some new *N*-monosubstituted fluoroacetamides with cycloalkyl or alkyl groups as substituents are described.

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Results and discussion

After examining other procedures, including the preparation of fluoroacetic acid using Ishikawa's reagent [19, 20], we used a standard preparative procedure [14, 21]. Intermediate fluoroacetyl chloride was synthesized from fluoroacetic acid by treatment with phosphorus(V) chloride, the acid being obtained from methylchloroacetate by halogen exchange [21]. An advantage of this procedure is its experimental simplicity providing fluoroacetyl chloride under mild conditions, but with only limited yield.

A number of new *N*-monosubstituted fluoroacetamides have been prepared using the known Schotten–Baumann reaction, acylation of the corresponding amines with fluoroacetyl chloride in the presence of a concentrated aqueous solution of potassium hydroxide:

$$FCH_2COCl + RNH_2 \xrightarrow{KOH} FCH_2\text{–}CONH\text{–}R$$

where R is cycloalkyl or various alkyl as listed in Table 1.

Table 1 lists some characteristics of the various *N*-substituted fluoroacetamides. All compounds synthesized were of very high purity (GC) and gave satisfactory elemental C/H analyses. The infrared and mass spectra of the synthesized *N*-substituted fluoroacetamides (Table 2) confirmed their structures.

From an analysis of the ^1H and ^{13}C NMR spectra (Table 3), it may be concluded that the *N*-monosubstituted 2-fluoroacetamides prepared have characteristic proton and carbon spectra which correspond to their structures.

Experimental

All chemicals used were of p.a. purity grade. IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer, model 580 in the form of KBr pellets or as films. NMR spectra were determined in deuterochloroform ($CDCl_3$) solutions with a Varian FT 80A instrument using tetramethylsilane as the internal standard. Chemical shifts are listed in δ (ppm) values and coupling constants (J) in Hz. Mass spectra were obtained on a Varian Mat 311 A mass spectrometer using a direct probe and 70 eV ionizing energy.

Gas–liquid chromatography was undertaken on a Varian Aerograph instrument series 3700 (FID), equipped with a 200 cm × 2 mm i.d. glass column filled with 4% OV-101 on Chromosorb W-HP 80/100 mesh. Carrier gas: nitrogen, flow rate 30 ml min^{-1}. Programmed temperature: 120–240 °C, 10 °C min^{-1}. Melting points were measured on a Buchi SMP-20 apparatus and are reported uncorrected.

Cyclobutylamine hydrochloride was synthesized in 74% yield from cyclobutanecarboxylic acid, according to the Schmidt procedure [22]. Methyl fluoroacetate was obtained in 42% yield from methyl chloroacetate by treatment with potassium fluoride [21]. An analytical sample was obtained by redistillation, b.p., 104–105 °C/1 kPa. Fluoroacetic acid was obtained in 54%

TABLE 1

Some characteristics of *N*-monosubstituted fluoroacetamides, FCH_2CONHR

Compd. No.	R	Purification[a]	Yield[b] (%)	M.p. (°C) [(b.p. (°C/mbar)]	Analysis			
					Found (%)		Calcd. (%)	
					C	H	C	H
1	n-propyl	B	63	31–33	50.43	8.65	50.42	8.40
2	n-butyl	B	64	31–32	54.18	9.04	54.13	9.02
3	n-pentyl	D	55	33–34	57.30	9.40	57.14	9.52
4	n-hexyl	D	87	34–35	59.60	9.62	59.54	9.93
5	(1-methyl)ethyl	B	72	42–43	50.60	8.66	50.85	8.47
6	(1-methyl)propyl	D	92	64–65	54.18	9.02	54.13	9.02
7	(1,2,2-trimethyl)propyl	M	50	[90–91/23]	59.68	9.71	59.54	9.84
8	(1-methyl)butyl	M	54	31–32	57.39	9.46	57.14	9.52
9	(1,4-dimethyl)pentyl	M	75	61–62	61.65	10.44	61.71	10.29
10	(1,1-dimethyl)ethyl	D	59	[55–56/26]	54.18	9.02	54.13	9.02
11	(2,2-dimethyl)propyl	D	54	72–73	57.20	9.42	57.53	9.59
12	(3-methyl)butyl	M	57	43–44	57.20	9.42	57.14	9.52
13	(1,1,3,3-tetramethyl)butyl	M	52	33–34	64.30	10.58	64.17	10.69
14	(1-methyl)benzyl	D	63	76–77	66.40	6.50	66.50	6.63
15	(2-phenyl)ethyl	D	58	57–58	66.40	6.47	66.30	6.63
16	(2,2-diphenyl)ethyl	D	53	139–140	74.38	6.20	74.71	6.23
17	cyclopropyl	M	60	63–64	51.03	6.77	51.28	6.84
18	cyclobutyl	M	54	46–47	54.92	7.66	54.96	7.63
19	cyclopentyl	M	73	60–61	57.83	8.43	57.93	8.23
20	cycloheptyl	M	69	84–85	62.31	9.17	62.43	9.25

[a]The letters indicate the solvent employed for recrystallization (B = benzene, D = diethyl ether) or a microdistillation procedure (M).
[b]Isolated yields based on fluoroacetyl chloride.

TABLE 2

Summary of IR and MS data for FCH_2CONHR

Compd. No.	R	IR (cm^{-1})	MS, *m/z* (%)[a]
1	n-propyl	3300 (NH); 1665 (C=O); 1040 (C–F)	119 (M^+, 21); 90 (58); 58 (14); 44 (16); 33 (16); 30 (100)
2	n-butyl	3310 (NH); 1665 (C=O); 1045 (C–F)	133 (M^+, 2); 118 (4); 100 (36); 90 (64); 57 (20); 33 (12); 30 (100)
3	n-pentyl	3340 (NH); 1655 (C=O); 1030 (C–F)	147 (M^+, 16); 144 (44); 90 (66); 43 (30); 33 (12); 30 (100)
4	n-hexyl	3310 (NH); 1655 (C=O); 1045 (C–F)	161 (M^+, 2); 128 (96); 104 (44); 90 (100); 90 (100); 78 (50); 58 (30); 30 (70)
5	(1-methyl)ethyl	3310 (NH); 1655 (C=O); 1040 (C–F)	119 (M^+, 21); 104 (44); 78 (6); 58 (18); 44 (100); 33 (12)
6	(1-methyl)propyl	3310 (NH); 1655 (C=O); 1035 (C–F)	133 (M^+, 8); 104 (40); 58 (20); 44 (100); 33 (22)
7	(1,2,2-trimethyl)propyl	3290 (NH); 1645 (C=O); 1035 (C–F)	146 (M^+, 5); 104 (70); 90 (10); 92 (36); 57 (16); 44 (100); 33 (16)
8	(1-methyl)butyl	3300 (NH); 1650 (C=O); 1040 (C–F)	147 (M^+, 2); 118 (20); 114 (28); 104 (100); 90 (34); 78 (20); 44 (54); 33 (6)
9	(1,4-dimethyl)pentyl	3300 (NH); 1650 (C=O); 1040 (C–F)	160 (23); 118 (28); 104 (100); 90 (47); 78 (27); 55 (25); 44 (47); 33 (8)
10	(1,1-dimethyl)ethyl	3320 (NH); 1655 (C=O); 1035 (C–F)	133 (M^+, 7); 118 (30); 78 (18); 58 (100); 41 (32); 33 (14)
11	(2,2-dimethyl)propyl	3310 (NH); 1655 (C=O); 1045 (C–F)	147 (M^+, 6); 132 (18); 91 (92); 72 (16); 58 (64); 41 (100); 33 (44)
12	(3-methyl)butyl	3320 (NH); 1650 (C=O); 1030 (C–F)	147 (M^+, 2); 132 (8); 118 (24); 104 (100); 90 (38); 78 (20); 61 (10); 44 (55); 28 (40)

13	(1,1,3,3-tetramethyl)butyl	3290 (NH); 1685 (C=O); 1075 (C–F)	118 (100); 97 (20); 58 (56); 41 (20); 33 (6)
14	(1-methyl)benzyl	3330 (NH); 1655 (C=O); 1030 (C–F)	181 (M^+, 100); 166 (88); 104 (84); 91 (18); 77 (20); 65 (10); 30 (26)
15	(2-phenyl)ethyl	3310 (NH); 1650 (C=O); 1030 (C–F)	181 (M^+, 23); 104 (100); 91 (26); 77 (8); 65 (10); 30 (26)
16	(2,2-diphenyl)ethyl	3310 (NH); 1665 (C=O); 1040 (C–F)	166 (100); 106 (66); 91 (40); 77 (20); 65 (10); 43 (19); 33 (10); 28 (40)
17	cyclopropyl	3300 (NH); 1655 (C=O); 1045 (C–F)	117 (M^+, 30); 102 (40); 84 (100); 61 (37); 57 (50); 56 (98); 41 (46)
18	cyclobutyl	3300 (NH); 1655 (C=O); 1045 (C–F)	131 (M^{+3}, 18); 103 (80); 70 (23); 61 (174); 43 (100); 33 (22)
19	cyclopentyl	3300 (NH); 1650 (C=O); 1045 (C–F)	145 (M^+, 26); 116 (52); 84 (14); 78 (100); 56 (33); 33 (9)
20	cycloheptyl	3305 (NH); 1650 (C=O); 1040 (C–F)	173 (M^+, 30); 140 (20); 116 (100); 96 (60); 78 (91); 61 (28); 56 (50); 41 (98); 33 (26)

[a]Intensities expressed as percentage of the base peak.

TABLE 3

^{13}C and ^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) of FCH_2CONHR

Compd. No.	R	^{1}H NMR	^{13}C NMR
1	n-propyl	0.94 (3H, t); 1.53 (2H, m); 3.30 (2H, qv); 4.7 (2H, FCH_2, d, $J=47.4$); 6.31 (NH, br.)	11.39 (C-3); 23.02 (C-2); 41.01 (C-1); 80.61 (C=O, d, $J=17.6$); 168.20 (FCH_2, d, $J=184.1$)
2	n-butyl	0.98 (3H, t); 1.44 (4H, m); 3.34 (2H, qv); 4.78 (2H, FCH_2, d, $J=47.4$); 6.16 (NH, br.)	13.75 (C-4); 20.29 (C-3); 31.89 (C-2); 38.97 (C-1); 80.58 (FCH_2, d, $J=184.4$); 167.97 (C=O, d, $J=17.6$)
3	n-pentyl	0.9 (3H, t); 1.43 (6H, m); 3.28 (2H, qv); 4.77 (2H, FCH_2, d, $J=47.5$); 6.64 (NH, br.)	14.02 (C-5); 22.61 (C-4); 20.40 (C-3); 29.46 (C-2); 39.25 (C-1); 80.57 (FCH_2, d, $J=184.5$); 167.97 (C=O, d, $J=17$)
4	n-hexyl	0.88 (3H, t); 1.31–1.62 (8H, m); 3.32 (2H, qv); 4.77 (2H, FCH_2, d, $J=47.5$); 6.38 (NH, br.)	14.02 (C-6); 22.79 (C-5); 29.74 (C-4); 26.86 (C-3); 31.79 (C-2); 39.26 (C-1); 80.54 (FCH_2, d, $J=184.8$); 167.88 (C=O, d, $J=17.4$)
5	(1-methyl)ethyl	1.21 (6H, d, $J=6.6$); 4.75 (2H, FCH_2, d, $J=44.5$); 4.19 (H, m); 6.1 (NH, br)	22.45 (C-2); 41.25 (C-1); 80.49 (FCH_2, d, $J=184.5$); 167.88 (C=O, d, $J=17.4$)
6	(1-methyl)propyl	0.92 (3H, t); 1.17 (3H, d, $J=6.6$); 1.25 (2H, m); 3.99 (1H, kv, $J=6.5$); 4.77(2H, FCH_2, d, $J=17.5$); 6.1 (NH, br.)	20.25 (C-4); 10.39 (C-3); 29.66 (C-2); 46.57 (C-1); 80.46 (FCH_2, d, $J=185.4$); 167.03 (C=O, d, $J=17.3$)
7	(1,2,2-trimethyl)propyl	0.92 (9H, s); 1.11 (3H, d, $J=5.5$); 4.79 (2H, FCH_2, d, $J=47.5$)	15.14 (C-4); 25.61 (C-3); 33.69 (C-2); 51.95 (C-1); 79.82 (FCH_2, d, $J=185.2$); 166.25 (C=), d, $J=17.2$)
8	(1-methyl)butyl	0.92 (2H, A_3B_3); 1.17 (3H, d, $J=6.6$); 4.08 (1H, kv, $J=6.5$); 4.7 (2H, F-CH_2, d, $J=47.52$); 6.1 (NH, br.)	12.63 (C-4); 18.25 (C-3); 37.71 (C-2); 43.77 (C-1); 79.16 (FCH_2, d, $J=184.5$); 165.75 (C=O, d, $J=17.6$)
9	(1,4-dimethyl)pentyl	0.88 (6H, d, $J=5.8$); 1.18 (3H, d, $J=6.5$); 1.0–1.75 (4H, m); 4.12 (1H, septet, $J=6.5$); 4.8 (2H, FCH_2, d, $J=47.52$); 6.15 (NH, br.)	20.31 (C-6); 22.06 (C-5); 27.53 (C-4); 34.17 (C-3); 34.76 (C-2); 44.82 (C-1); 79.88 (FCH_2, d, $J=185.4$); 166.29 (C=O, d, $J=17.6$)
10	(1,1-dimethyl)ethyl	1.40 (9H, s); 4.65 (2H, FCH_2, d, $J=47.7$); 6.1 (NH, br.)	28.80 (C-2); 51.40 (C-1); 80.38 (FCH_2, d, $J=185.8$); 166.74 (C=O, d, $J=17.4$)

11	(2,2-dimethyl)propyl	0.94 (9H, s); 3.14 (2H, d); 4.88 (2H, FCH_2, d, $J=47.5$); 6.31 (NH, br.)	27.27 (C-3); 32.06 (C-2); 50.05 (C-1); 80.42 (FCH_2, d, $J=184.7$); 167.70 (C=O, d, $J=17.2$)
12	(3-methyl)butyl	0.93 (6H, d, $J=6.7$); 1.2–1.9 (3H, m); 3.35 (2H, qv., $J=7.5$); 4.7 (2H, d, $J=47.52$); 6.25 (NH, br.)	21.36 (C-4); 24.89 (C-3); 37.45 (C-2); 36.31 (C-1); 79.31 (FCH_2, d, $J=184.6$); 166.64 (C=O, d, $J=17.5$)
13	(1,1,3,3-tetramethyl)butyl	1.01 (9H, s); 1.46 (6H, s); 1.76 (2H, s); 4.60 (2H, FCH_2, d, $J=47.52$); 6.1 (NH, br.)	28.80 (C-2); 51.40 (C-1); 80.38 (FCH_2, d, $J=185.8$); 166.74 (C=O, d, $J=17.4$)
14	(1-methyl)benzyl	1.42 (3H, d, $J=6.8$); 4.62 (2H, FCH_2, d, $J=47.5$); 5.13 (1H, kv, $J=7.2$); 7.21 (5H, Ar, s)	27.71 (C-2); 21.48 (C-1); 126.19 (C-3′,5′); 128.11 (C-4′); 128.79 (C-2′,6′); 142.52 (C-1′); 80.21 (FCH_2, d, $J=185.4$); 166.65 (C=), d, $J=17.3$)
15	(2-phenyl)ethyl	2.84 (2H, t); 3.58 (2H, qv.); 4.72 (2H, FCH_2, d, $J=47.4$); 6.44 (NH, br.); 7.25 (5H, Ar, s)	35.64 (C-2); 40.19 (C-1); 126.6 (C-3′,5′); 128.74 (C-2′,6′); 128.74 (C-4′); 80.30 (FCH_2, d, $J=175.2$); 168.18 (C=O, d, $J=17.2$)
16	(2,2-diphenyl)ethyl	3.14 (2H, d, $J=7.1$); 4.7 (2H, FCH_2, d, $J=47.4$); 5.33 (1H, qv.); 6.65 (NH, br.); 7.03–7.26 (10H, Ar, m)	42.62 (C-1); 54.08 (C-2); 80.26 (FCH_2, d, $J=187.5$); 127.65 (C-4′); 128.67 (C-3′,5′); 129.32 (C-2′,6′); 166.74 (FCH_2, d, $J=17.2$)
17	cyclopropyl	0.4–1.0 (4H, m); 2.8 (1H, m); 4.75 (2H, FCH_2, d, $J=47.52$); 6.3 (NH, br.)	4.9 (C-β); 21.28 (C-α)
18	cyclobutyl	1.4–2.6 (6H, m); 4.45 (1H, m, $J=8$); 4.7 (2H, FCH_2, d, $J=47.52$); 6.45 (NH, br.)	14.30 (C-γ); 29.78 (C-β); 43.44 (C-α)
19	cyclopentyl	1.2–2.6 (8H, m); 4.3 (1H, m, $J=7.5$); 4.7 (FCH_2, d, $J=47.5$); 6.25 (NH, br.)	22.83 (C-γ); 31.67 (C-β); 49.74 (C-α)
20	cycloheptyl	1.3–2.15 (12H, m); 4.05 (1H, br); 4.75 (2H, FCH_2, d, $J=7.52$); 6.25 (NH, br)	49.74 (C-α); 34.68 (C-β); 27.67 (C-γ); 23.77 (C-δ)

[a]Throughout the specifications listed, values of *c.* 184–187 Hz for coupling constants (J) relate to J_{FCH_2}.

yield by hydrolysis of methyl fluoroacetate, b.p., 167–168/1 kPa. Fluoroacetyl chloride was synthesized in 66% yield from fluoroacetic acid by treatment with phosphorus(V) chloride, b.p., 71–72 °C/1 kPa.

Synthesis of N-*n-propyl 2-fluoroacetamide (typical procedure)*

Fluoroacetyl chloride (4.7 g, 0.05 mol) was dissolved in diethyl ether (25 cm^3) and slowly added dropwise into a solution of n-propylamine (2.9 g, 0.05 mol) in aqueous potassium hydroxide (5.6 g in 2.4 g water). The temperature of the reaction mixture was maintained at 5 °C to 15 °C. When the addition was complete, the reaction mixture was maintained at the same temperature and stirred with a magnetic stirrer for another 5 h. After adding 50 cm^3 water, which was sufficient to dissolve the potassium chloride, the mixture was extracted twice with diethyl ether (50 cm^3). The ether extracts were combined and the crude product obtained by removing the solvent in a rotary evaporator. Recrystallized was effected from benzene when white crystals were obtained, m.p., 31–32 °C. Yield: 63% (3.7 g).

All other new *N*-monosubstituted fluoroacetamides investigated were similarly synthesized.

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