Tandem Intermolecular–Intramolecular Michael Addition of Bifunctional Hetero Nucleophiles to Polyfluoro-2-alkynoic Acids. Facile Synthesis of Polyfluoroalkylated Azaheterocycles

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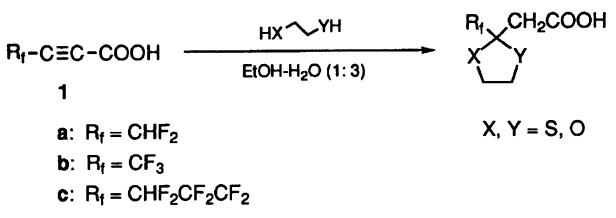
Polyfluoro-2-alkynoic acids, R_f–C≡C–COOH (**1a**—**c**: **a**, R_f=CHF_2; **b**, R_f=CF_3; **c**, R_f=$CHF_2CF_2CF_2$), readily underwent an intermolecular–intramolecular Michael addition reaction with a variety of bifunctional azanucleophiles, such as $RNHCH_2CH_2XH$ (R=H, Me; X=NH, S, O, NMe) and *o*-phenylenediamine, to give the corresponding carboxylated and/or decarboxylated 2-(polyfluoroalkyl)imidazolidine, thiazolidine, and oxazolidine derivatives in moderate to good yields.

Much attention has been paid to the development of new methodologies for the synthesis of polyfluoroalkyl-substituted heterocycles,[1] which are an important class of biologically active compounds.[2] Inspection of many recent reports on this subject has demonstrated the high versatility of polyfluoroacetylenic compounds in the synthesis of polyfluoroalkylated heterocyclic compounds. Thus, per- and polyfluoroalkylacetylenic esters,[3] ketones,[4] aldehydes,[5] and nitriles[6] are utilized not only as good electrophiles in nucleophilic addition reactions but also as potent dipolarophiles in 1,3-dipolar cycloaddition reactions, leading to per- or polyfluoroalkylated heterocycles. In the literature, however, there have scarecely been found the reports on synthetic applications of polyfluoro-2-alkynoic acids,[7] probably because of difficulty in their accessibility.[8] Recently, we developed an efficient and simple method for the preparation of per- or polyfluorinated 2-alkynoic acids (**1**)[9] and applied them to the synthesis of fluorine-containing heterocyclic compounds through the Michael addition reactions with bifunctional hetero nucleophiles, such as 1,2-ethanedithiol, 2-mercaptoethanol, and ethylene glycol, in which the corresponding polyfluoroalkylated 1,3-dithiolanes, 1,3-oxothiolanes, and 1,3-dioxolanes carrying the carboxymethyl group at the 2-position were obtained in good yields, as shown in the following scheme (Scheme 1).[10]

As part of our studies on the chemistry and synthetic utilizations of these polyfluoroalkynoic acids,[11] we have examined tandem Michael reactions between **1** and bifunctional nitrogen nucleophiles of the type of $RNHCH_2CH_2XH$ (where R=H and Me; X=NR, S, and O), taking into account the synthesis of various polyfluoroalkylated azaheterocyclic compounds that should be of biological interest. In this paper, we would like to report the results of these reactions, which can serve as a convenient and efficient route to such polyfluoroalkyl-containing compounds.



Scheme 1.

Results and Discussion

Reaction with Ethylenediamine. 4,4-Difluoro-2-butynoic acid (**1a**) was allowed to react with ethylenediamine (hereinafter symbolized as EN) in ethanol–water (1:3) at room temperature. The reaction with equimolar amount of EN was very sluggish, whereas the reaction with 5 equimolar amounts of EN smoothly occurred to go essentially to completion within 0.5 h, giving a 1:2 salt of EN and 2-(difluoromethyl)imidazolidine-2-acetic acid (**2a**) in 97% yield (Entry 1 in Table 1). Similarly, when 4,4,4-trifluoro-2-butynoic acid (**1b**) or 4,4,5,5,6,6-hexafluoro-2-hexynoic acid (**1c**) was treated with 5 equimolar amounts of EN at room temperature for 1 or 3 h, the corresponding EN salts of 2-(trifluoromethyl)- (**2b**) and 2-(1,1,2,2,3,3-hexafluoropropyl)imidazolidine-2-acetic acid (**2c**) were obtained in 92 and 82% yields, respectively (Entries 3 and 5). To be remarked is that the analogous reaction of fluorine-free 2-butynoic acid with EN did not take place at all either at room temperature or even at reflux temperature (87 °C, 1 h), the starting acid being recovered quantitatively (89—98%). These observations suggest that the presence of the polyfluoroalkyl substituent in

Table 1. Reaction of Polyfluoroalkynoic Acids **1** with Ethylenediamine

Entry	Acid	Temp	Time h	Yield[a]/% **2**	**3**
1	**1a**	R.T.	0.5	97	0
2	**1a**	Reflux	1	0	88
3	**1b**	R.T.	1	92	0
4	**1b**	Reflux	32	0	80
5	**1c**	R.T.	3	82	0
6	**1c**	Reflux	1	0	77

a) Yields refer to pure isolated products.

1 facilitates the reaction with EN.

Monitoring the reactions by ^{19}F NMR revealed that two kinds of intermediates were formed in an early stage of the reaction and both were gradually converted into a single product, the EN salt of **2**, as the reaction proceeded. All attempts to determine the structures of these intermediates failed; they were too labile to isolate even with any careful manipulations, thereupon being very easily transformed into the EN salts of **2**. As depicted in Scheme 2, however, such unstable intermediates are expected to be enamine (**A**) and imine (**B**) tautomers of the 1:1 Michael adducts between **1** and EN in view of the relative fluorine chemical shifts for the starting acid, intermediates, and EN salts of **2**. For example, ^{19}F NMR analysis of the reaction of **1c**, whose resonance due to the difluoromethylene γ to the carboxyl group occurred at $\delta=-22.0$, indicated that the corresponding resonances appeared at $\delta=-33.7$ and -37.4 for the intermediates and at a higher field of $\delta=-41.0$ for the EN salt of **2c**. A trend observed in the chemical shifts would be consistent with the present assignment for the intermediates. More significant is here that the chemical shifts ($\delta=-33.7$ and -37.4) for the intermediates are in good accord with those ($\delta=-30.9$ for the enamine and -35.9 for the imine) reported for the 1:1 Michael adducts between ethyl 4,4,5,5,6,6,7,7-nonafluoro-2-heptynoate and aniline.[3a]

The EN salts of **2** obtained above were stable in aqueous basic solutions, but were easily decarboxylated on exposure to nearly neutral to acidic conditions or on silica-gel column chromatography to furnish the corresponding 2-methyl-2-(polyfluoroalkyl)imidazolidines (**3**) in quantitative yields.

On the other hand, when the reaction of **1** with 5 equimolar amounts of EN was conducted at reflux temperature (87 °C), the decarboxylated derivatives **3** were produced as a sole product in high yields (Entries 2, 4, and 6). These results are in sharp contrast to those obtained previously from the reactions between **1** and bifunctional nucleophiles bearing no nitrogen atom, where 2-carboxymethylated heterocycles are exclusively afforded but any decarboxylated products not formed at all (Scheme 1).[10] On heating the EN salt of **2a** generated in situ by the reaction of **1a** with EN at room temperature, facile decarboxylation took place to give **3a** quantitatively. Similar results were obtained with **2b** and **2c**. These facts strongly suggest that 2-carboxymethylated compounds **2** are initially formed in the reaction and then decarboxylated to give **3**. The decarboxylation of **2b** required a longer period (Entry 4) but its reason is unclear at the present time. It should be noted that this decarboxylation reaction can be regarded, to our knowledge, as a reaction characteristic of **2** and that high susceptibility of **2** to the decarboxylation may be ascribed to the presence of nitrogen atoms, since the analogous 2-carboxymethylated heterocyclic compounds carrying no nitrogen atom do not favor such decarboxylation reaction under heating to reflux as well as acidic or basic conditions.[10]

A plausible mechanism for the formation of **3** from **2** is considered as shown in Scheme 3. 1,3-Diheterocyclic systems involving at least one nitrogen atom are known to undergo a ring–chain tautomerism, which the nitrogen atom is capable of facilitating more effectively than any other hetero atoms such as oxygen and sulfur.[12] Thus, the compounds **2** could take part in this tautomerism to exist in equilibrium with open-chain tautomers **B**. The resulting imine derivatives **B**, equilibrated in part with **A**, are subject to the decarboxylation to yield enamines **C**. The resulting enamines **C** are also in equilibrium with imine tautomers **D**. The enamines **C** and imines **D** may cyclize intramolecularly via "allowed 5-exo-trig" and "disallowed 5-endo-trig" reactions[12c] in Baldwin's rules,[13] respectively, to give rise to the decarboxylated products **3**. With the reaction at reflux temperature, however, it is possible that **3** is generated merely through **B**(**A**) and **C**(**D**) without formation of **2** if the decarboxylation of **B** might occur more rapidly than its cyclization. This possibility can not be ruled out at present.

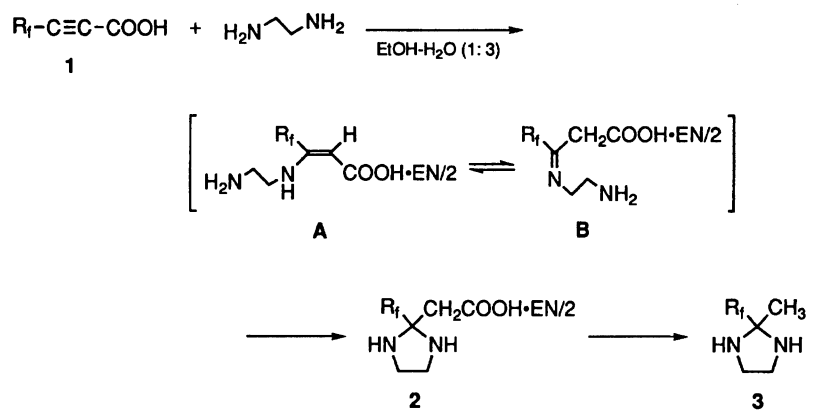
Reaction with *o*-Phenylenediamine. When the acid **1a** was allowed to react with 5 equimolar amounts of *o*-phenylenediamine at room temperature for 7 h, only a decarboxylated product, 2-(difluoromethyl)-2-methyl-2,3-dihydro-1*H*-benzimidazole (**4a**), was provided in 78% yield, as shown in Table 2. Treatment of **1b** with *o*-phenylenediamine at room temperature for 2 h and then at reflux temperature for 5 h gave rise to 52% yield of 2-(trifluoromethyl)-2-methyl-2,3-dihydro-1*H*-benzimidazole (**4b**) (Entry 2). In these reactions were not afforded 2-(polyfluoromethyl)-2,3-dihydro-1*H*-benzimidazole-2-acetic acids which correspond to **2a** or **2b** obtained from the reaction of **1a** or **1b** with EN at room temperature; ^{19}F NMR analysis of the reactions also showed no formation of such compounds even in an early stage of the reaction. These facts may permit us to consider that **4a** and **4b** are produced through the decarboxylation of initially formed 1:1 Michael adducts, such as **B** in Scheme 3, followed by cyclization of the resultant imines **5** corresponding to **D** (Scheme 4).

In contrast, the reaction of **1c** with *o*-phenylenediamine at room temperature for 20 h gave 56% yield of the corresponding decarboxylated imine derivative

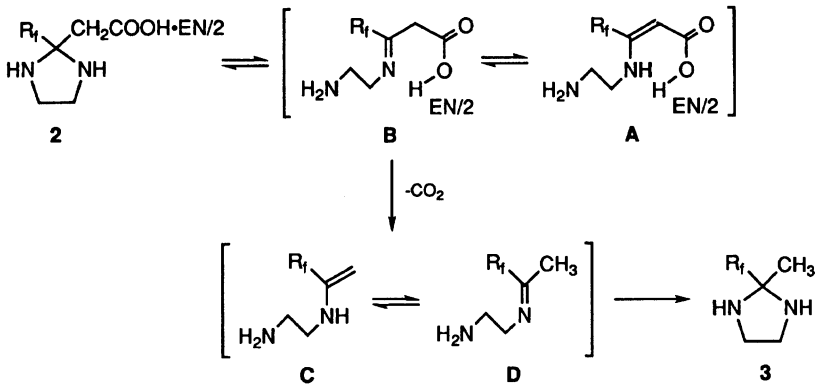
Table 2. Reaction of Polyfluoroalkynoic Acids **1** with *o*-Phenylenediamine

Entry	Acid	Temp	Time h	Yield[a]/% **4**	**5**
1	**1a**	R.T.	7	78	0
2	**1b**	R.T./reflux	2/5	52	0
3	**1c**	R.T.	20	0	56

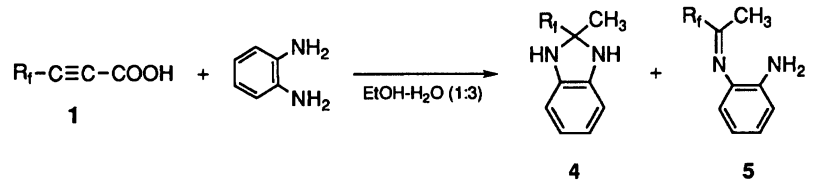
a) Yields refer to pure isolated products.



Scheme 2.



Scheme 3.

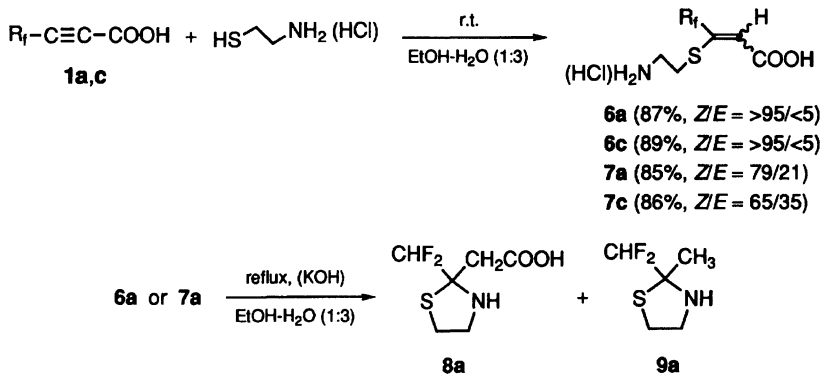


Scheme 4.

5c. (Entry 3), which did not entirely cyclize to **4c** in spite of forced reaction conditions (87 °C, 24 h) being employed. Probably, failure in cyclization of **5c** is attributable to steric effects exerted by the bulky hexafluoropropyl group as well as to low nucleophilicity of the attacking aromatic amino group.

Reaction with 2-Aminoethanethiol. The reaction of **1a** with 1.2 equimolar amounts of 2-aminoethanethiol at room temperature for 0.5 h in ethanol–water (1 : 3) gave a 1 : 1 Michael adduct, 3-(2-aminoethylthio)-4,4-difluoro-2-butenoic acid (**6a**), in 87% yield (Scheme 5). The addition proceeded with high stereoselectivity to afford the *Z*-isomer of **6a** without the formation of a detectable amount of the *E*-isomer (less than 5% yield). The stereochemistry of the adduct was determined on the basis of comparisons of the chemical shift and long-range coupling for its vinylic hydrogen with those for the *E*- and *Z*-isomers of the Michael adduct between **1a** and 2-mercaptoethanol, whose geometrical assignment was made unambiguously by the lactonization experiment on the adduct.[10] Neither adduct of the amino group of 2-aminoethanethiol nor *anti*-Michael adduct[4] of its mercapto group to **1a** was produced in the present reaction. Similarly, the reaction of **1c** with 2-aminoethanethiol gave the corresponding 1 : 1 Michael adduct, 3-(2-aminoethyl)-4,4,5,5,6,6-hexafluoro-2-hexenoic acid (**6c**), in 89% yield.

2-Aminoethanethiol hydrochloride also participated in the reaction with **1a,c** at room temperature in the same solvent giving a mixture of *Z*- and *E*-isomers of hydrochloric acid salts (**7a,c**) of **6a,c**. The addition of 2-aminoethanethiol hydrochloride was appreciably slower and less stereoselective than that of 2-aminoethanethiol (Scheme 5). It is well-documented that the additions of thiols to acetylenic compounds activated by electron-withdrawing groups are accelerated by a base and occur mainly in a *trans* fashion in protic media.[14] In the present reactions, the free amino group of 2-aminoethanethiol can be considered to serve as a base to increase nucleophilicity of its mercapto group (acceleration of re-



Scheme 5.

action) and to furnish exclusively the *Z*-isomers of the Michael adducts **6a,c** (*trans* addition).

Both **6a** and **7a** were recovered unchanged even on keeping stirred in ethanol–water (1 : 3) at room temperature for a long period (72 h). At reflux temperature, **6a** cyclized smoothly followed by decarboxylation to give 2-(difluoromethyl)-2-methylthiazolidine (**9a**) in 74% yield while **7a** (a mixture of *Z*- and *E*-isomers) did not at all. On the other hand, when **6a** or **7a** was heated at reflux temperature for 9 h in the presence of 1.2- or 2.0 equimolar amounts of potassium hydroxide, potassium salt of 2-(difluoromethyl)thiazolidine-2-acetic acid (**8a**) was obtained in 66 or 65% yield, along with 14 or 17% yield of decarboxylated thiazolidine **9a**, respectively (Scheme 5). Either of **6c** and **7c** having a long polyfluoroalkyl group did not produce any cyclization products in spite of prolonged heating (18 h).

Reaction with 2-Aminoethanol. A mixture of **1a** and 5 equimolar amounts of 2-aminoethanol was stirred in ethanol–water (1 : 3) at room temperature for 5 h to afford crude 2-aminoethanol salt of 2-(difluoromethyl)oxazolidine-2-acetic acid (**10a**), which could not be purified by conventional means. Hence, on treating the reaction mixture with an equimolar amount of sodium hydroxide at room temperature for 0.5 h, analytically pure sodium of **10a** was isolated in 75% yield, as shown in Entry 1 of Table 3. Two intermediates, which could not be isolated, were observed by ^{19}F NMR spectra of the reaction mixture. It is probable that such intermediates are enamine and imine tautomers of a 1 : 1 Michael adduct resulting from the addition of not the hydroxyl but the amino group of 2-aminoethanol to **1a**.

Table 3. Reaction of Polyfluoroalkynoic Acids **1** with 2-Aminoethanol

Entry	Acid	Temp	Time h	Yield[a]/% 10	11	12
1	**1a**	R.T.	5	75	0	0
2	**1a**	Reflux	0.5	0	74	0
3	**1c**	R.T.	96	0	6	65
4	**1c**	Reflux	18	0	52	22

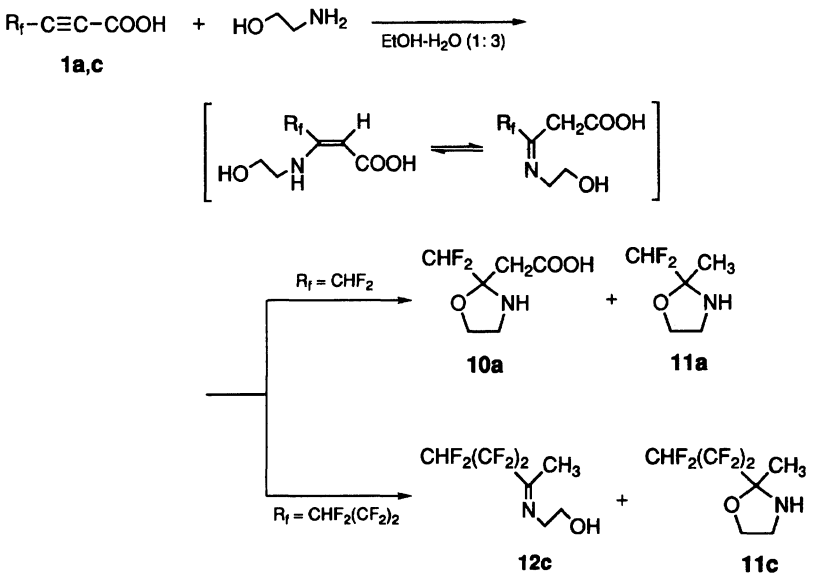
a) Yields refer to pure isolated products.

This expectation comes from the observations that the chemical shifts ($\delta = -38.4$ and -43.2) for their difluoromethyl group are very close to those ($\delta = -37.8$ and -42.8) for the above-described intermediates from **1a** and ethylenediamine, and not to that ($\delta = -40.9$) for the 1 : 1 adduct with ethylene glycol.[10] The reaction carried out at reflux temperature was completed within 0.5 h to give a decarboxylated product, 2-(difluoromethyl)-2-methyloxazolidine (**11a**), in 74% yield (Entry 2).

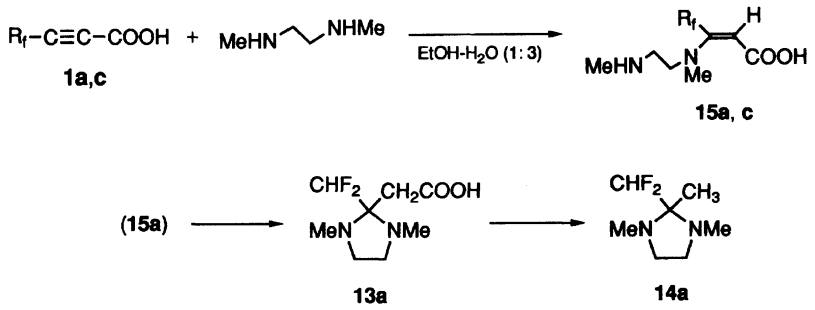
On the other hand, when **1c** was allowed to react with 2-aminoethanol at room temperature for 4 d, 3,3,4,4,5,5-hexafluoro-*N*-(2-hydroxyethyl)-2-pentanimine (**12c**) and 2-(1,1,2,2,3,3-hexafluoropropyl)-2-methyloxazolidine (**11c**) were obtained in 65 and 6% yields, respectively, 2-(1,1,2,2,3,3-hexafluoropropyl)oxazolidine-2-acetic acid (**10c**) being not formed in a detectable amount (Entry 3)(Scheme 6). As pointed out previously in the reaction between **1c** and *o*-phenylenediamine, steric hindrance due to the hexafluoropropyl group would retard intramolecular cyclization of the initially formed 1 : 1 adduct yielding **10c** to result in preferential formation of the decarboxylated imine **12c**. When the reaction was carried out at reflux temperature for 18 h, **11c** and **12c** were isolated in 52 and 22% yields, respectively (Entry 4). A 1 : 11 mixture of **11c** and **12c** was heated at reflux temperature for 18 h in the same solvent, a ratio of **11c** and **12c** being changed into nearly 1 : 2.

Reaction with *N,N'*-Dimethylethylenediamine. *N,N'*-Dimethylethylenediamine smoothly reacted with **1a** in ethanol–water (1 : 3) at room temperature for 0.5 h to afford the cyclization product, 2-(difluoromethyl)-1,3-dimethylimidazolidine-2-acetic acid (**13a**), which was isolated in 74% yield as its sodium salt via treatment of the reaction mixture with aqueous sodium hydroxide. When the reaction was conducted at reflux temperature for 0.5 h, the decarboxylated cyclization product, 2-(difluoromethyl)-1,2,3-trimethylimidazolidine (**14a**) was obtained in 74% yield (Scheme 7). The formation of **14a** may be interpreted by the previously noted ring–chain tautomerism involving an iminium species.[12a,12c]

Similar treatment of **1c** with *N,N'*-dimethylethylene-



Scheme 6.



Scheme 7.

diamine at room temperature gave the 1:1 Michael adduct **15c**, which was also isolated as its sodium salt in 76% yield. However, the cyclization products corresponding to **13c** or **14c** were not formed even when the reaction was conducted for long reaction times at room or reflux temperature. These results can also be explained on the same ground of large steric hindrance between the bulky hexafluoropropyl and the attacking secondary amino groups.

In summary, we have demonstrated that per- or polyfluoro-2-alkynoic acids (**1**) have high reactivities towards a variety of bifunctional nitrogen nucleophiles and that the reactions of **1** proceed through the characteristic processes, particularly ring–chain tautomerism, of nitrogen nucleophiles to lead to unique types of azaheterocycles. Several advantages, such as simple manipulations, mild reaction conditions, and good yields of the products, should allow the present reactions to serve as a general and convenient method for the synthesis of various azaheterocycles carrying per- or polyfluoroalkyl groups.

Experimental

Melting points were obtained on a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrophotometer. ^{1}H NMR spectra were measured with Hitachi R-24B (60 MHz), Varian Gemini-200 (200 MHz), and/or General Electric QE-300 (300 MHz) FT-NMR spectrometers in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference or in a deuterium oxide (D_2O) solution with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. A Hitachi R-24F (56.466 MHz) spectrometer was used for determining ^{19}F NMR spectra in a $CDCl_3$ or D_2O solution with external trifluoroacetic acid. ^{13}C NMR spectra were recorded on a General Electric QE-300 (75.61 MHz) FT-NMR spectrometer in a $CDCl_3$ or D_2O solution with internal Me_4Si or DSS. Mass spectra (MS) were taken on a Hitachi M-80B or a Shimadzu QP1000 GC mass spectrometer operating at an ionization potential of 70 eV.

Polyfluoro-2-alkynoic acids **1a**—**c** were prepared according to the method reported recently by us.[9] All chemicals are of reagent grade and, if necessary, were purified in the conventional manner prior to use.

Reaction of 1 with Ethylenediamine at Room Temperature. To a solution of ethylenediamine (1.503 g, 25 mmol) in 20 mL of ethanol–water (1:3 v/v) was gradually added the acid **1** (5 mmol) at 0 °C and then the mixture was stirred at room temperature for a specific period (0.5—3 h). After removal of the solvents under reduced pressure, the residue was washed successively with chloroform and

acetone to afford analytically pure ethylenediamine salt of 2-(polyfluoroalkyl)imidazolidine-2-acetic acid **2** in 82—97% yields (see Table 1).

Ethylenediammonium Bis[2-(difluoromethyl)imidazolidine-2-acetate] (2a): Mp 128—130 °C; IR (KBr) 3600—2000, 1610, 1394, 1350, 1330, 1050 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ=2.43 (s, 4H), 2.7—3.1 (m, 12H), 5.64 (t, J=55.7 Hz, 2H); ^{13}C NMR (D_2O) δ=39.91, 40.60, 45.55, 78.38 (t, J=21.2 Hz), 116.06 (t, J=246.2 Hz), 177.13; ^{19}F NMR (D_2O) δ=−50.8 (d, J=55.7 Hz, 2F×2); MS (SIMS) m/z (rel intensity) no parent to 420, 241 (4), 181 (26), 137 (66), 61 (100). Found: C, 39.90; H, 6.95; N, 20.08%. Calcd for $C_{14}H_{28}F_4N_6O_4$: C, 40.00; H, 6.71; N, 19.99%.

Ethylenediammonium Bis[2-(trifluoromethyl)imidazolidine-2-acetate] (2b): Mp 134—136 °C; IR (KBr) 3600—2000, 1608, 1382, 1330, 1150, 1122 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=2.55 (s, 4H), 2.8—3.3 (m, 12H); ^{13}C NMR (D_2O) δ=37.67, 39.43, 45.80, 79.32 (q, J=30.0 Hz), 125.58 (q, J=284.6 Hz), 176.19; ^{19}F NMR (D_2O) δ=−2.3 (s, 3F×2); MS(SIMS) m/z (rel intensity) no parent to 456, 259 (2), 199 (37), 155 (37), 61 (100). Found: C, 36.71; H, 6.04; N, 18.44%. Calcd for $C_{14}H_{26}F_6N_6O_4$: C, 36.84; H, 5.74; N, 18.41%.

Ethylenediammonium Bis[2-(1,1,2,2,3,3-hexafluoropropyl)imidazolidine-2-acetate] (2c): Mp 86—88 °C; IR (KBr) 3600—2000, 1580, 1372, 1128, 788 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=2.52 (s, 4H), 2.7—3.3 (s, 12H), 6.44 (tt, J=51.4, 5.6 Hz, 2H); ^{19}F NMR (D_2O) δ=−40.7 (m, 2F×2), −48.7 (m, 2F×2), −58.2 (dm, J=51.4 Hz, 2F×2); MS (SIMS) m/z (rel intensity) no parent to 620, 341 (0.4), 281 (7), 237 (11), 61(100). Found: C, 34.64; H, 4.50; N, 13.42%. Calcd for $C_{18}H_{28}F_{12}N_6O_4$: C, 34.85; H, 4.55; N, 13.55%.

Reaction of 1 with Ethylenediamine at Reflux Temperature. To an ice-cold solution of ethylenediamine (1.503 g, 25 mmol) in 20 mL of ethanol–water (1:3 v/v) was added dropwise 5 mmol of **1**. The mixture was stirred at room temperature for 0.5 h and then heated at reflux temperature (87 °C) for 1—32 h. The mixture was extracted with chloroform or ethyl acetate (30 mL×3) and the combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using chloroform as eluent to give 2-methyl-2-(polyfluoroalkyl)imidazolidine **3** in 77—88% yields (see Table 1).

2-(Difluoromethyl)-2-methylimidazolidine (3a): Mp 31—32 °C; IR (KBr) 3260, 2920, 1562, 1072, 1052 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.28 (br s, 3H), 1.93 (br s, 2H), 3.02 (s, 4H), 5.41 (t, J=56.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=18.99 (t, J=3.0 Hz), 45.63, 77.64 (t, J=21.4 Hz), 116.35 (t, J=246.7 Hz); ^{19}F NMR ($CDCl_3$) δ=−50.0 (d, J=56.1 Hz, 2F); MS m/z (rel intensity) 136 (M^+, 3), 120 (27), 106 (82), 85 (100). Found: C, 44.37; H, 7.48; N, 20.36%. Calcd for $C_5H_{10}F_2N_2$: C, 44.11; H, 7.40; N, 20.58%.

2-Methyl-2-(trifluoromethyl)imidazolidine (3b): Mp 74—75 °C; IR (KBr) 3305, 1130, 1168, 1130, 1108, 1084 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.47 (br s, 3H), 1.87 (br s, 2H), 3.14 (s, 4H); ^{19}F NMR ($CDCl_3$) δ=−3.63 (s, 3F), MS m/z (rel intensity) 154 (M^+, 3), 138 (36), 124 (51), 85 (100). HRMS (CI) Found: m/z 155.0791. Calcd for $C_5H_{10}F_3N_2$: M+H, 155.0797.

2-(1,1,2,2,3,3-Hexafluoropropyl)-2-methylimidazolidine (3c): Mp 38—41 °C; IR (KBr) 3375, 3252, 2950, 2900, 1260, 1118, 1052, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.37 (t, J=1.7 Hz, 3H), 1.89 (br s, 2H), 2.8—3.1 (m, 4H), 6.45 (tt, J=52.7, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=22.79, 46.85, 79.57 (t, J=22.6 Hz), 108.99 (tt, J=252.4, 28.7 Hz), 112.18 (tt, J=261.1, 31.8 Hz), 117.81 (tt, J=261.2, 26.8 Hz); ^{19}F NMR ($CDCl_3$) δ=−42.2 (m, 2F), −50.4 (m, 2F), −57.6 (dtt, J=52.7, 7.1, 7.1 Hz, 2F); MS m/z (rel intensity) 236 (M^+, 12), 220 (30), 206 (44), 84 (100). HRMS (CI) Found: m/z 237.0823. Calcd for $C_7H_{11}F_6N_2$: M+H, 237.0827.

Reaction of 1 with *o*-Phenylenediamine. The acid **1a** (0.600 g, 5 mmol) was slowly added to a solution of *o*-phenylenediamine (2.704 g, 25 mmol) in 30 mL of ethanol–water (1:3 v/v) at room temperature. After being stirred at room temperature for 7 h, the mixture was extracted with dichloromethane (30 mL×3). The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to leave a residue, which was chromatographed on silica gel with benzene to afford 2-(difluoromethyl)-2-methyl-2,3-dihydro-1*H*-benzimidazole (**4a**) in 78% yield.

A solution of **1b** (0.693 g, 5 mmol) and *o*-phenylenediamine (2.704 g, 25 mmol) in 30 mL of ethanol–water (1:3 v/v) was stirred at room temperature for 2 h and then heated at reflux temperature for 5 h. After the same workup as cited above, silica-gel column chromatography (benzene) of the crude products gave 2-methyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-benzimidazole (**4b**) in 52% yield.

Similar treatment of **1c** with *o*-phenylenediamine at room temperature for 20 h provided *N*-(2-aminophenyl)-3,3,4,4,5,5-hexafluoro-2-pentanimine (**5c**) in 56% yield. Even on exposure to heating at reflux temperature in the same solvent, **5c** was not cyclized at all to result in mere decomposition (see Table 2).

2-(Difluoromethyl)-2-methyl-2,3-dihydro-1*H*-benzimidazole (4a): Mp 76—78 °C; IR (KBr) 3380, 3330, 1248, 1072, 1035, 955, 730 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.46 (br s, 3H), 3.72 (br s, 2H), 5.56 (t, J=57.0 Hz, 1H), 6.2—6.8 (m, 4H); ^{19}F NMR ($CDCl_3$) δ=−52.9 (d, J=57.0 Hz, 2F); MS m/z (rel intensity) 184 (M^+, 21), 169 (3), 134 (100). Found: C, 58.84; H, 5.47; N, 15.19%. Calcd for $C_9H_{10}F_2N_2$: C, 58.69; H, 5.47; N, 15.21%.

2-Methyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-benzimidazole (4b): Mp 118—120 °C; IR (KBr) 3320, 1600, 1564, 1420, 1370, 1100, 900, 740 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.54 (br s, 3H), 3.82 (br s, 2H), 6.3—6.8 (m, 4H); ^{19}F NMR ($CDCl_3$) δ=−7.40 (s, 3F); MS m/z (rel intensity) 202 (M^+, 23), 187 (4), 134 (100). Found: C, 53.64; H, 4.58; N, 13.84%. Calcd for $C_9H_9F_3N_2$: C, 53.47; H, 4.48; N, 13.86%.

***N*-(2-Aminophenyl)-3,3,4,4,5,5-hexafluoro-2-pentanimine (5c):** IR (film) 3470, 3370, 3020, 1668, 1608, 1488, 1250, 1108, 795, 740 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=2.13 (s, 3H), 3.62 (br s, 2H), 6.37 (tt, J=52.1, 5.8 Hz, 1H), 6.4—7.2 (m, 4H); ^{19}F NMR ($CDCl_3$) δ=−36.8 (m, 2F), −51.7 (m, 2F), −58.0 (dm, J=52.1, 6.4, 6.4 Hz, 2F); MS m/z (rel intensity) 284 (M^+, 7), 132 (100), 91 (51). Found: C, 46.69; H, 3.60; N, 10.02%. Calcd for $C_{11}H_{10}F_6N_2$: C, 46.49; H, 3.55; N, 9.86%.

Reaction of 1a,c with 2-Aminoethanethiol at Room Temperature. To a solution of 2-aminoethanethiol (0.463 g, 6 mmol) in 20 mL of ethanol–water (1 : 3 v/v) was added dropwise 5 mmol (0.600 g) of **1a**. The whole mixture was stirred at ambient temperature for 0.5 h and then was concentrated in vacuo. The residue was subjected to reprecipitation with chloroform and ethanol to afford *Z*-isomer of 3-[(2-aminoethyl)thio]-4,4-difluoro-2-butenoic acid (**6a**) in 87% yield.

The reaction of **1c** was performed in a similar manner to produce (*Z*)-3-[(2-aminoethyl)thio]-4,4,5,5,6,6-hexafluoro-2-hexenoic acid (**6c**) in 89% yield.

(*Z*)-3-[(2-Aminoethyl)thio]-4,4-difluoro-2-butenoic Acid (6a): Mp 177—179 °C; IR (KBr) 3600—2000, 2170, 1630, 1605, 1552, 1400, 1264, 1248, 1015 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ=3.03 (t, J=5.9 Hz, 2H), 3.14 (t, J=5.9 Hz, 2H), 6.30 (t, J=55.5 Hz, 1H), 6.88 (t, J=1.8 Hz, 1H); ^{13}C NMR (D_2O) δ=29.86, 38.52, 115.54 (t, J=238.4 Hz), 126.08 (t, J=23.8 Hz), 140.43 (t, J=7.7 Hz), 172.76; ^{19}F NMR (D_2O) δ=−32.8 (d, J=55.5 Hz, 2F); MS m/z (rel intensity) 197 (M^+, 0.4), 181 (1), 153 (5), 146 (39), 61 (100). Found: C, 36.71; H, 4.69; N, 6.98%. Calcd for $C_6H_9F_2NO_2S$: C, 36.54; H, 4.60; N, 7.10%.

(*Z*)-3-[(2-Aminoethyl)thio]-4,4,5,5,6,6-hexafluoro-2-hexenoic Acid (6c): Mp 191—193 °C; IR (KBr) 3300—2000, 2200, 1625, 1572, 1520, 1388, 1128, 1100 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=2.8—3.4 (br s, 4H), 6.38 (tt, J=53.0, 6.0 Hz, 1H), 7.18 (br s, 1H); ^{19}F NMR (D_2O) δ=−30.3 (m, 2F), −49.7 (m, 2F), −57.9 (dm, J=53.0 Hz, 2F); MS m/z (rel intensity) 297 (M^+, 1), 280 (22), 253 (25), 232 (100), 146 (37). Found: C, 32.25; H, 3.00; N, 4.79%. Calcd for $C_8H_9F_6NO_2S$: C, 32.33; H, 3.05; N, 4.71%.

Reaction of 1a,c with 2-Aminoethanethiol at Reflux Temperature. The acid **1a** (0.600 g, 5 mmol) was gradually added to a stirred solution of 2-aminoethanethiol (0.463 g, 6 mmol) in ethanol–water (1 : 3 v/v) at room temperature. After being refluxed with stirring for 5 h, the mixture was extracted with chloroform (50 mL×3) followed by drying over anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure and column chromatography on silica gel (chloroform) afforded 2-(difluoromethyl)-2-methylthiazolidine (**9a**) in 74% yield.

Similar treatment of **1c** with 2-aminoethanethiol at reflux temperature for 10 h gave no cyclization product.

2-(Difluoromethyl)-2-methylthiazolidine (9a): IR (film) 3360, 3025, 2980, 2925, 1116, 1092, 1072 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.56 (br s, 3H), 2.98 (br s, 1H), 3.8—4.7 (m, 4H), 5.59 (t, J=56.1 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ=−42.4 (dd, J=277.2, 56.1 Hz, 1F), −47.3 (dd, J=277.2, 56.1 Hz, 1F); MS m/z (rel intensity) 153 (M^+, 4), 138 (5), 102 (27), 57 (100). HRMS Found: m/z 153.0423. Calcd for $C_5H_9F_2NS$: M, 153.0425.

Reaction of 1a,c with 2-Aminoethanethiol Hydrochloride at Room Temperature. To a solution of 2-aminoethanethiol hydrochloride (0.682 g, 6 mmol) in 20 mL of ethanol–water (1 : 3 v/v) was added **1a** or **1c** (5 mmol) at room temperature. The mixture was stirred for a specified period (**1a**, 12 h; **1c**, 24 h) and then concentrated under vacuum. The residue was submitted to reprecipitation with chloroform and ethanol giving a mixture of *E*- and *Z*-isomers of 3-[(2-aminoethyl)thio]polyfluoro-2-alkenoic acid (**7**) in high yield (**7a**, 85%; **7c**, 86%). The ratios of *E*- and *Z*-isomers (**7a**, E/Z=79 : 21; **7c**, E/Z=65 : 35) were measured by ^{19}F NMR spectra of the crude products. Although the *E*- and *Z*-isomers of **7a** and **7c** could not be separated by column chromatography, only *Z*-isomers were isolated by recrystallization from ethanol.

3-[(2-Aminoethyl)thio]-4,4-difluoro-2-butenoic Acid Hydrochloride (7a): *Z*-Isomer: Mp 184—186 °C; IR (KBr) 3600—2000, 1688, 1590, 1472, 1170, 1020, 840 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ=3.31 (s, 4H), 6.54 (t, J=54.4 Hz, 1H), 6.64 (t, J=1.6 Hz, 1H); ^{19}F NMR (D_2O) δ=−32.9 (d, J=54.4 Hz, 2F); MS (CI) m/z (rel intensity) no parent to 234, 198 (60), 154 (100), 102 (77).

E-Isomer: ^1H NMR (200 MHz, D_2O) δ=3.31 (s, 4H), 6.10 (s, 1H), 6.45 (t, J=55.8 Hz, 1H); ^{19}F NMR (D_2O) δ=−36.5 (d, J=55.8 Hz, 2F). Found: C, 30.88; H, 4.42 ; N, 5.91%. Calcd for $C_6H_{10}ClF_2NO_2S$: C, 30.84; H, 4.31; N, 5.99%.

3-[(2-Aminoethyl)thio]-4,4,5,5,6,6-hexafluoro-2-hexenoic Acid Hydrochloride (7c): *Z*-Isomer: Mp 174—176 °C; IR (KBr) 3600—2200, 1700, 1588, 1170, 1142, 1112 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=3.17 (br s, 4H), 6.44 (tt, J=51.0, 5.4 Hz, 1H), 7.13 (s, 1H); ^{19}F NMR (D_2O) δ=−30.1 (m, 2F), −49.3 (m, 2F), −57.9 (dm, J=51.0 Hz, 2F); MS (CI) m/z (rel intensity) no parent to 334, 298 (3), 254 (67), 102 (100).

E-Isomer: ^1H NMR (60 MHz, D_2O) δ=3.17 (br s, 4H), 6.44 (tt, J=51.0, 5.4 Hz, 1H), 6.56 (s, 1H); ^{19}F NMR (D_2O) δ=−27.6 (m, 2F), −48.3 (m, 2F), −57.9 (dm, J=51.0 Hz, 2F). Found: C, 28.91; H, 3.20; N, 4.26%. Calcd for $C_8H_{10}ClF_6NO_2S$: C, 28.80; H, 3.02; N, 4.20%.

Treatment of 6a,c and 7a,c at Reflux Temperature in the Presence of KOH. Isolated **6a** (0.579 g, 2.94 mmol) was heated to reflux for 9 h in the presence of KOH (0.198 g, 3.53 mmol) in 12 mL of ethanol–water (1 : 3 v/v). This mixture was extracted with chloroform (30 mL×3) and the organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica-gel column with chloroform to give 2-(difluoromethyl)-2-methylthiazolidine (**9a**) in 14% yield. The aqueous layer was concentrated to leave a residual solid, which was subjected to reprecipitation with acetone and diethyl ether to furnish potassium 2-(difluoromethyl)thiazolidine-2-acetate (**8a**) in 66% yield.

Treatment of an isomeric mixture of **7a** at reflux temperature for 9 h in the presence of 2 equimolar amounts of KOH gave **8a** and **9a** in 65 and 17% yields, respectively. However, **6c** and **7c** did not any cyclization products even on refluxing for 18 h.

Potassium 2-(Difluorometyl)thiazolidine-2-acetate (8a): Mp 180—182 °C; IR (KBr) 1580, 1388, 1122, 1046, 990, 820 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=2.75 (s, 2H), 2.7—3.9 (m, 4H), 5.92 (t, J=57.1 Hz, 1H); ^{19}F NMR (D_2O) δ=−44.9 (dd, J=123.7, 57.1 Hz, 1F), −47.7 (dd, J=123.7, 57.1 Hz, 1F); MS (SIMS) m/z (rel intensity) 274 ($2M^+$−196, 3), 97 (100).

Reaction of 1a,c with 2-Aminoethanol at Room Temperature. The acid **1a** (0.600 g, 5 mmol) was dropwise added to a solution of 2-aminoethanol (1.528 g, 25 mmol) in 20 mL of ethanol–water (3 : 1 v/v) and the mixture was stirred for 5 h at room temperature. To this mixture was added NaOH (0.200 g, 5 mmol) in one portion. After stirring for 0.5 h at room temperature, the reaction mixture was concentrated under reduced pressure. The re-

sulting residue was submitted to reprecipitation with acetone and diethyl ether to give analytically pure sodium 2-(difluoromethyl)oxazolidine-2-acetate (**10a**) in 75% yield.

A mixture of **1c** (1.100 g, 5 mmol), 2-aminoethanol (1.528 g, 25 mmol), and 20 mL of ethanol–water (1 : 3 v/v) was stirred at room temperature for 4 d. The mixture was extracted with dichloromethane (50 mL×3), followed by drying over anhydrous sodium sulfate, filtered, and concentrated under vaccum. The residue was chromatographed on silica gel with diethyl ether–dichloromethane (1 : 1) to give 3,3,4,4,5,5-hexafluoro-*N*-(2-hydroxyethyl)-2-pentanimine (**12c**) in 65% yield and 2-(1,1,2,2,3,3-hexafluoropropyl)-2-methyloxazolidine (**11c**) in 6% yield (see Table 3).

Sodium 2-(Difluoromethyl)oxazolidine-2-acetate (10a): Mp 178—180 °C; IR (KBr) 1556, 1405, 1368, 1048, 998 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=2.57 (s, 2H), 2.7—4.2 (m, 4H), 5.68 (t, J=54.5 Hz, 1H); ^{19}F NMR (D_2O) δ=−51.5 (dd, J=97.7, 54.5 Hz, 1F), −53.3 (dd, J=97.7, 54.5 Hz, 1F); MS (SIMS) m/z (rel intensity) 226 ($2M^+-180$, 13), 65 (100).

3,3,4,4,5,5-Hexafluoro-*N*-(2-hydroxyethyl)-2-pentanimine (12c): IR (film) 3700—3000, 2930, 2875, 1680, 1260, 1144, 1118, 1064 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=2.00 (s, 3H), 2.78 (s, 1H), 3.1—4.1 (m, 4H), 6.30 (tt, J=51.9, 5.9 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ=−37.4 (m, 2F), −52.1 (m, 2F), −58.3 (dm, J=51.9 Hz, 2F); MS m/z (rel intensity) 237 (M^+, 15), 205 (66), 85 (98), 55 (100). Found: C, 35.71; H, 3.94; N, 6.07%. Calcd for $C_7H_9F_6NO$: C, 35.45; H, 3.83; N, 5.91%.

2-(1,1,2,2,3,3-Hexafluoropropyl)-2-methyloxazolidine (11c): IR (film) 3340, 2980, 2890, 1224, 1118, 1060, 1018, 960, 800 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ= 1.51 (br s, 3H), 2.15 (br s, 1H), 2.7—4.3 (m, 4H), 6.27 (tt, J=52.1, 6.0 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ=−44.1 (m, 2F), −51.0 (m, 2F), −57.9 (dm, J=52.1 Hz, 2F); MS m/z (rel intensity) no parent to 237, 222 (7), 207 (17), 86 (100). HRMS (CI) Found: m/z 238.0668. Calcd for $C_7H_{10}F_6ON$: M+H, 238.0667.

Reaction of 1a,c with 2-Aminoethanol at Reflux Temperature. To a solution of 2-aminoethanol (1.527 g, 25 mmol) in 20 mL of ethanol–water (1 : 3 v/v) was added gradually **1a** (0.600 g, 3 mmol) at room temperature, and the mixture was refluxed for 0.5 h. This mixture was extracted with dichloromethane (50 mL×3) and the extracts were dried, filtered, and concentrated. Chromatography of the residue on silica gel with diethyl ether furnished 2-(difluoromethyl)-2-methyloxazolidine (**11a**) in 74% yield.

The reaction of **1c** with 2-aminoethanol was similarly conducted at reflux temperature for 18 h to give **11c** in 52% yield, together with 22% yield of **12c** (see Table 3).

2-(Difluoromethyl)-2-methyloxazolidine (11a): IR (film) 3320, 2970, 2875, 1060, 1020, 798 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.38 (br s, 3H), 2.18 (br s, 1H), 2.8—4.2 (m, 4H), 5.44 (t, J=54.8 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ=−50.6 (dd, J=96.0, 54.8 Hz, 1F), −52.3 (dd, J=96.0, 54.8 Hz, 1F); MS m/z (rel intensity) 137 (M^+, 1), 121 (2), 106 (72), 86 (100). Found: C, 43.70; H, 6.67; N, 10.02%. Calcd for $C_5H_9F_2NO$: C, 43.79; H, 6.62; N, 10.21%.

Reaction of 1a,c with *N,N′*-Dimethylethylenediamine at Room Temperature. To a stirred solution of *N,N′*-dimethylethylenediamine (1.058 g, 12 mmol) and **1a** (0.360 g, 3 mmol) in ethanol–water (1 : 3 v/v) was added in one portion NaOH (0.120 g, 3 mmol) at room temperature. After stirring at room temperature for 0.5 h, the solvents were removed under reduced pressure. The residue was subjected to reprecipitation with acetone and diethyl ether to give sodium 2-(difluoromethyl)-1,3-dimethylimidazolidine-2-acetate (**13a**) in 74% yield.

When the reaction of **1c** with *N,N′*-dimethylethylenediamine was carried out in the same manner as described above, 3-(1,1,2,2,3,3-hexafluoropropyl)-4-methyl-4,7-diaza-2-octenoic acid (**15c**) was obtained (silica-gel column/methanol) in 76% yield.

Sodium 2-(Difluoromethyl)-1,3-dimethylimidazolidine-2-acetate (13a): Mp 208—210 °C; IR (KBr) 1555, 1386, 1108, 1020, 980, 814, 698 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=2.46 (s, 6H), 2.52 (s, 2H), 2.87 (s, 4H), 6.31 (t, J=54.8 Hz, 1H); ^{19}F NMR (D_2O) δ=−51.7 (d, J=54.8 Hz, 2F); MS (SIMS) m/z (rel intensity) 253 ($2M^+-207$, 0.5), 65 (100).

Sodium 3-(1,1,2,2,3,3-Hexafluoropropyl)-4-methyl-4,7-diaza-2-octenoate (15c): Mp 111—113 °C; IR (KBr) 1630, 1540, 1410, 1210, 1112 cm^{-1}; ^1H NMR (60 MHz, D_2O) δ=2.68 (s, 3H), 2.78 (s, 3H), 2.9—3.5 (m, 4H), 6.12 (s, 1H), 6.30 (tt, J=51.5, 5.2 Hz, 1H); ^{19}F NMR (D_2O) δ=−33.0 (m, 2F), −51.7 (m, 2F), −58.7 (dm, J=51.5 Hz, 2F); MS (SIMS) m/z (rel intensity) 353 ($2M^+-307$, 1), 65 (100).

Reaction of 1a,c with *N,N′*-Dimethylethylenediamine at Reflux Temperature. To a solution of *N,N′*-dimethylethylenediamine (1.058 g, 12 mmol) in 12 mL of ethanol–water (1 : 3 v/v) was added **1a** (0.360 g, 3 mmol) and the mixture was stirred at room temperature. After the formation of **13a** was confirmed by ^{19}F NMR spectra, the mixture was heated to reflux for 0.5 h. Extraction with dichloromethane (30 mL×3), drying over anhydrous sodium sulfate, concentration in vacuo, and chromatography on silica-gel column with diethyl ether gave 2-(difluoromethyl)-1,2,3-trimethylimidazolidine (**14a**) in 74% yield.

With the reaction between **1c** and *N,N′*-dimethylethylenediamine at reflux temperature for 1 h, ^{19}F NMR analysis of the reaction mixture showed only a strong peak due to fluoride ion, neither 1 : 1 Michael adduct nor cyclization products being formed.

2-(Difluoromethyl)-1,2,3-trimethylimidazolidine (14a): IR (film) 2975, 2930, 2902, 2850, 2790, 1460, 1450, 1276, 1225, 1070, 1035 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ=1.18 (br s, 3H), 2.40 (br s, 6H), 2.5—3.1 (m, 4H), 5.36 (t, J=56.2 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ=−47.6 (d, J=56.2 Hz, 2F); MS m/z (rel intensity) no parent to 164, 149 (10), 113 (100). HRMS (CI) Found: m/z 165.1206. Calcd for $C_7H_{15}F_2N_2$: M+H, 165.1204. Found: C, 50.92; H, 8.77; N, 16.79%. Calcd for $C_7H_{14}F_2N_2$: C, 51.20; H, 8.59; N, 17.06%.

References

1) For a recent review, see: K. Tanaka, *Yuki Gosei Kagaku Kyokai Shi*, **48**, 16 (1990), and references cited therein.

2) R. Filler and Y. Kobayashi, "Biomedicinal Aspects of Fluorine Chemistry," Kodansha and Elsevier Biomedical, Tokyo and New York (1982); J. T. Welch, *Tetrahedron*, **43**, 3123 (1987); J. T. Welch and S. Eswarakrishnan, "Fluorine in Bioorganic Chemistry," Wiley, New York (1991).

3) a) J. Froissard, J. Greiner, R. Pastor, and A. Cambon, *J. Fluorine Chem.*, **17**, 249 (1981); b) **26**, 47 (1984); c) A. Chauvin, J. Greiner, R. Pastor, and A. Cambon, *J. Fluorine Chem.*, **27**, 385 (1985); d) Y. Shen, J. Zheng, and Y. Huang, *Synthesis*, **1985**, 970; e) A. Chauvin, J. Greiner, R. Pastor, and A. Cambon, *Tetrahedron*, **42**, 663 (1986); f) J. Fayn, A. Nezis, and A. Cambon, *J. Fluorine Chem.*, **36**, 479 (1987); g) W. Ding, P. Zhang, and W. Cao, *Tetrahedron Lett.*, **28**, 81 (1987); h) B. C. Hamper, *J. Fluorine Chem.*, **48**, 123 (1990); i) M. Haddach, R. Pastor, and J. G. Riess, *J. Fluorine Chem.*, **51**, 197 (1991); j) A. Nezis, J. Fayn, and A. Cambon, *J. Fluorine Chem.*, **53**, 285 (1991); k) **53**, 297 (1991); l) B. C. Hamper, M. L. Kurtzweil, and J. P. Beck, *J. Org. Chem.*, **57**, 5680 (1992); m) W. Ding, J. Pu, and C. Zhang, *Synthesis*, **1992**, 635; n) M. Haddach, R. Pastor, and J. G. Riess, *Tetrahedron*, **49**, 4627 (1993); o) J. Zheng, Z. Wang, and Y. Shen, *J. Fluorine Chem.*, **61**, 17 (1993).

4) C. L. Bumgardner, J. E. Bunch, and M. -H. Whangbo, *J. Org. Chem.*, **51**, 4082 (1986).

5) A. Khanous, A. Gorgues, and J. Cousseau, *J. Fluorine Chem.*, **49**, 401 (1990).

6) J. Fabron, R. Pastor, and A. Cambon, *J. Fluorine Chem.*, **37**, 371 (1987); J. Zheng, Z. Wang, and Y. Shien, *J. Fluorine Chem.*, **61**, 17 (1993).

7) S. Tajammal and A. E. Tipping, *J. Fluorine Chem.*, **47**, 45 (1990).

8) It has been reported that the hydrolysis of perfluoro-2-alkynoates with aqueous sodium hydroxide followed by acidification affords the corresponding 3-alkoxy-substituted perfluoro-2-alkenoic acids, no acetylenic acids being formed. See: Y. Huang, Y. Shen, Y. Xin, Q. Wang, and W. Wu, *Sci. Sin. (Engl. Ed.), Ser. B*, **25**, 21 (1982); Y. Huang, Y. Shen, Y. Xin, G. Fu, and Y. Xu, *Sci. Sin. (Engl. Ed.), Ser. B*, **25**, 587 (1982).

9) H. Yamanaka, T. Araki, M. Kuwabara, K. Fukunishi, and M. Nomura, *Nippon Kagaku Kaishi*, **1986**, 1321.

10) H. Yamanaka, K. Tamura, K. Funabiki, K. Fukunishi, and T. Ishihara, *J. Fluorine Chem.*, **57**, 177 (1992).

11) M. Kuwabara, K. Fukunishi, M. Nomura, and H. Yamanaka, *J. Fluorine Chem.*, **41**, 227 (1988); K. Tamura, T. Ishihara, and H. Yamanaka, *J. Fluorine Chem.*, in press.

12) a) J. B. Lambert, G. -T. Wang, D. E. Huseland, and L. C. Takiff, *J. Org. Chem.*, **52**, 68 (1987); b) F. Fülöp, J. Mattinen, and K. Pihlaja, *Tetrahedron*, **46**, 6545 (1990); c) C. D. Johnson, *Acc. Chem. Res.*, **26**, 476 (1993), and references cited therein.

13) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

14) W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, **37**, 2391 (1972), and references cited therein.