Reactions of polyfluoro-2-alkynoic acids with bifunctional hetero nucleophiles leading to polyfluoroalkylated heterocycles

Hiroki Yamanaka,* Kazushige Tamura, Kazumasa Funabiki, Koushi Fukunishi and Takashi Ishihara

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606 (Japan)

Abstract

Polyfluoro-2-alkynoic acids, R_f–C≡C–COOH ($R_f = HCF_2$, CF_3, $H(CF_2)_3$), readily undergo tandem intermolecular–intramolecular Michael addition with bifunctional hetero nucleophiles, $HX(CH_2)_nYH$ (X, Y = S, O, $n = 2, 3$), to give 2-polyfluoroalkylated 1,3-diheterocyclic compounds in good to excellent yields

Introduction

In view of the high versatility of acetylenic compounds in organic synthesis, alkynes bearing both per- or poly-fluoroalkyl and other electronegative groups, whose acetylenic linkage is very electron-deficient, are extremely useful compounds for the synthesis of a variety of fluorine-containing compounds. Recent reports have demonstrated that per- or polyfluoroalkylacetylenic esters [1], ketones [2], aldehydes [3] and nitriles [4] can serve not only as good electrophiles in nucleophilic addition reactions but also as potent dienophiles and dipolarophiles in Diels–Alder and 1,3-dipolar cycloaddition reactions. For example, Cambon *et al.* investigated the reactions of perfluoro-2-alkynoic acid esters with nucleophiles such as thiols [1d, i], amines [1a, i], diazomethane [1b] and nitrone [1e] to obtain various types of perfluoroalkylated heterocyclic compounds. Hamper reported that the reaction of esters with methylhydrazine proceeded in regioselective manner to give 3-hydroxy-1-methyl-5-(perfluoroalkyl)pyrazoles [1h]. Tajammal and Tipping used methyl 4,4,4-trifluoro-2-butynoate as the dipolarophile for regiospecific, 1,3-dipolar cycloaddition of diazomethane to produce 3-(methoxycarbonyl)-4-(trifluoromethyl)pyrazole [1g]. However, synthetic application of fluorinated 2-alkynoic acids is little known [1g], probably because of their poor accessibility**. We recently developed an efficient method for the prepara-

*Author to whom correspondence should be addressed

**Hydrolysis of perfluoroalkylacetylenic esters with aqueous sodium hydroxide, followed by acidification, afforded vinyl ethers, no acetylenic acids being formed See ref 5

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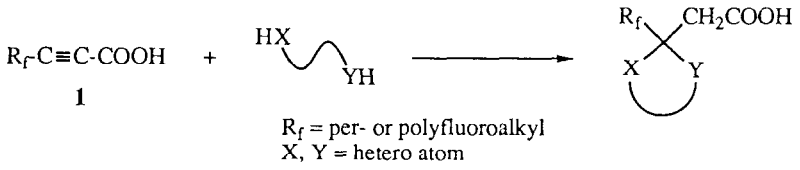
tion of per- or poly-fluorinated 2-alkynoic acids (**1**) [6] and showed that these alkynoic acids are good electrophiles for nucleophilic reactions [7] as well as good dienophiles for Diels–Alder reactions [8]. As part of our studies to extend further the chemistry and synthetic utility of **1**, we have examined the tandem intermolecular–intramolecular Michael reactions between the acids **1** and bifunctional hetero nucleophiles, taking into account that some of these reactions would constitute a promising means for the synthesis of heterocyclic compounds containing a per- or poly-fluoroalkyl group (Scheme 1), which are of interest in medicinal and agricultural fields [9]. In this paper, we would like to report the results of these reactions.



Scheme 1.

Results and discussion

Reaction with 1,2-ethanedithiol

The reactions of polyfluoro-2-alkynoic acids (**1a–c**), R_f–C≡C–COOH, with 1,2-ethanedithiol were investigated under various reaction conditions. The results are summarized in Table 1. These reactions proceeded in the absence of a base at room temperature to give the corresponding Michael adducts, polyfluorinated 3-(2-mercaptoethylthio)-2-alkenoic acids (**2**) as a mixture of the *E*- and *Z*-isomers. The structures of the isomers were determined on the basis of a comparison of the chemical shifts of their vinylic protons with those reported for Michael adducts between ethyl perfluoro-2-alkynoates and methyl mercaptoacetate [1d]. Bumgardner *et al.* have observed that anti-Michael adducts are formed in the reaction of 4,4,4-trifluoro-1-phenyl-2-butyn-1-one with phenoxide and benzenethiolate [2]. The present reactions offered no such anti-Michael adducts as polyfluoro-2-(2-mercaptoethylthio)-2-alkenoic acids. The initially formed Michael adducts **2** hardly underwent the second intramolecu-lar Michael addition reaction yielding cyclization products, 2-(carboxymethyl)-2-(polyfluoroalkyl)-1,3-dithiolanes (**3**), under these nonbasic conditions.

The use of potassium hydroxide (KOH) as base, however, was found to promote efficiently not only the first intermolecular Michael addition providing **2** but also the second intramolecular Michael addition reaction. At the same time, the second intermolecular Michael addition between **2**

TABLE 1

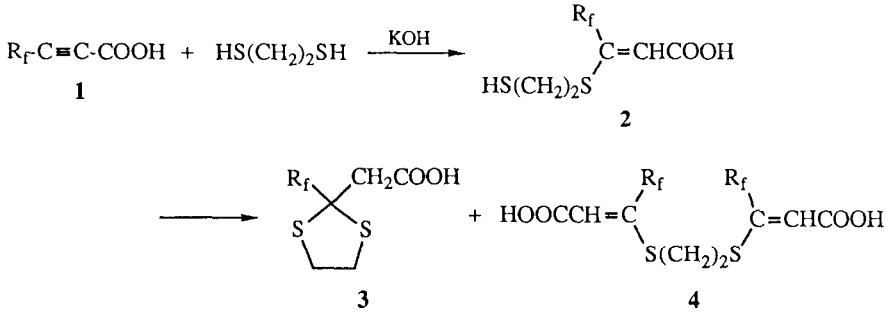
Reactions of polyfluoro-2-alkynoic acids **1** with 1,2-ethanedithiol[a]

Acid 1	Mole ratio		Temp.	Time (h)	Yield[b] (%)		
	Dithiol/**1**	KOH/**1**			**2** (*Z*/*E*)[c]	**3**	**4**
1a	1.2	0	r.t.	48	75 (3.7)	10	0
	1.2	1.2	r.t.	4	35 (*Z* only)	40	15
	1.2	1.2	reflux	24	0	75	15
	1.2	2.0	r.t.	4	0	48	37
	5.0	1.2	reflux	0.5	0	92	0
	5.0	2.0	r.t.	4	0	90	0
1b	5.0	1.2	reflux	2	0	88	0
1c	1.2	0	r.t.	48	85 (3.6)	0	0
	1.2	1.2	r.t.	4	10 (*Z* only)	33	51
	5.0	1.2	reflux	20	0	82	0
	5.0	2.0	r.t.	4	0	90	0

[a]The reactions were performed according to the procedure described in the Experimental section.
[b]Yields refer to pure isolated products.
[c]Determined by ^{19}F NMR.

and dithiol occurred to form appreciable amounts of 2:1 adducts (**4**), as shown in Scheme 2 and Table 1.

Interestingly, controlled experiments indicated that the *E*-isomers of **2** cyclized *via* a second intramolecular Michael addition in preference to the *Z*-isomers (rate constants k_E and k_Z for **2a** were $7.7 \times 10^{-3}\ s^{-1}$ and $3.6 \times 10^{-3}\ s^{-1}$ at 24 °C) and that **2a** could cyclize more readily than **2c** (rate constants k_E and k_Z for **2c** were $1.2 \times 10^{-3}\ s^{-1}$ and $2.1 \times 10^{-4}\ s^{-1}$ at 24 °C). These observations may be interpreted from the following assumption. An intramolecular attack of the thiolate ion on the β-carbon, *i.e.*

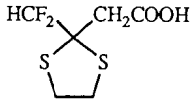
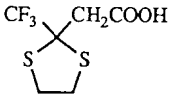
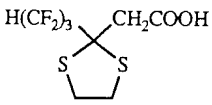
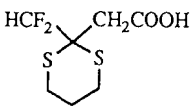


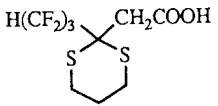
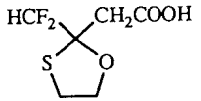
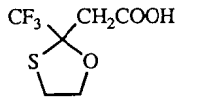
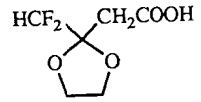
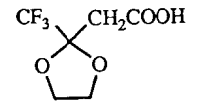
a: $R_f = HCF_2$, **b**: $R_f = CF_3$, **c**: $R_f = H(CF_2)_3$

Scheme 2.

TABLE 2

Physical and spectral data for the cyclization products **3**, **5**, **8** and **10**

Product Yield[a]	IR[b] (cm^{-1})	M.p. (°C)	^1H NMR[c] $\delta(J, Hz)$	^{19}F NMR[c] $\delta(J, Hz)$	Elemental analysis[d] (%)		
					C	H	F
 **(3a)** 92%	1705	84–85	3.21 (2H, s) 3.36 (4H, m) 6.14 (1H, t, $J = 57.0$) 9.95 (1H, br s)	−40.7 (2F, d, $J = 57.0$)	33.50 (33.64)	3.72 (3.76)	17.66 (17.73)
 **(3b)** 88%	1710	137–138	3.15 (2H, s) 3.38 (4H, m) 10.19 (1H, br s)	4.9 (3F, s)	31.24 (31.03)	2.87 (3.04)	24.39 (24.54)
 **(3c)** 82%	1725	83–84	3.26 (2H, s) 3.39 (4H, m) 6.09 (1H, tt, $J = 50.0, 5.6$) 10.22 (1H, br s)	−28.7 (2F, m) −45.1 (2F, m) −58.0 (2F, dm, $J = 50.0$)	30.36 (30.58)	2.50 (2.57)	36.01 (36.27)
 **(5a)** 74%	1695	79–80	1.8–3.5 (6H, m) 2.85 (2H, s) 6.33 (1H, t, $J = 56.4$) 9.04 (1H, br s)	−37.7 (2F, d, $J = 56.4$)	36.98 (36.83)	4.53 (4.42)	16.37 (16.64)

 **(5c)** 26%	1710	114–116	1.2–3.7 (6H, m) 2.94 (2H, s) 6.18 (1H, tt, J = 52.0, 6.0) 8.68 (1H, br s)	−24.3 (2F, m) −45.5 (2F, m) −57.2 (2F, dm, J = 52.0)	33.12 (32.93)	3.15 (3.07)	34.56 (34.72)
 **(8a)** 80%	1720	oil	3.02 (2H, s) 3.04 (2H, t, J = 5.6) 4.21 (2H, t, J = 5.6) 5.92 (1H, t, J = 56.0) 9.11 (1H, br s)	−48.6 (2F, d, J = 56.0)	36.18 (36.37)	3.93 (4.07)	19.07 (19.17)
 **(8b)** 76%	1720	59–61	3.04 (2H, s) 3.16 (2H, t, J = 5.7) 4.31 (2H, t, J = 5.7) 8.67 (1H, br s)	− 0.7 (3F, s)	33.51 (33.34)	3.09 (3.26)	26.22 (26.36)
 **(10a)** 64%	1725	oil	2.85 (2H, t, J = 1.6) 4.10 (4H, m) 5.81 (1H, t, J = 54.6) 10.49 (1H, br s)	−54.7 (2F, dt, J = 54.6, 1.6)	39.31 (39.57)	4.36 (4.43)	20.69 (20.86)
 **(10b)** 63%	1725	102–104	2.88 (2H, s) 4.18 (4H, m) 10.10 (1H, br s)	−5.2 (3F, s)	36.24 (36.01)	3.50 (3.53)	28.35 (28.48)

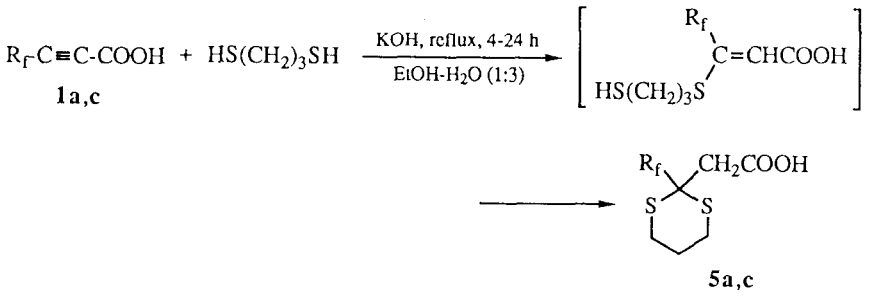
[a]Isolated yields.
[b]The carbonyl (stretching) absorption bands are given.
[c]Measured in chloroform-*d*.
[d]Calcd. values are in parentheses.

cyclization to **3**, is subject to steric hindrance. This effect is more efficiently exerted by the *cis*-carboxylic group in the *Z*-isomer rather than by the *trans*-one in the *E*-isomer and is also caused more strongly by a long R_f chain in **2c** than by a short R_f chain in **2a**, so that the *E*-isomers of **2** cyclize faster than the *Z*-isomers and **2a** does so more readily than **2c**.

As seen from Table 1, the ratios of formation of products **2**, **3** and **4** were varied, depending upon the amounts of KOH and 1,2-ethanedithiol used, as well as the chain length of the R_f group. Eventually, when the reaction was conducted at reflux temperature by using 5 equimolar amounts of 1,2-ethanedithiol and 1.2 equimolar amounts of KOH, the corresponding 1,3-dithiolane derivatives **3** were obtained exclusively in high yields (82 to 92%). Their spectroscopic data, which were in good agreement with the assigned structures, are compiled in Table 2.

Reaction with 1,3-propanedithiol

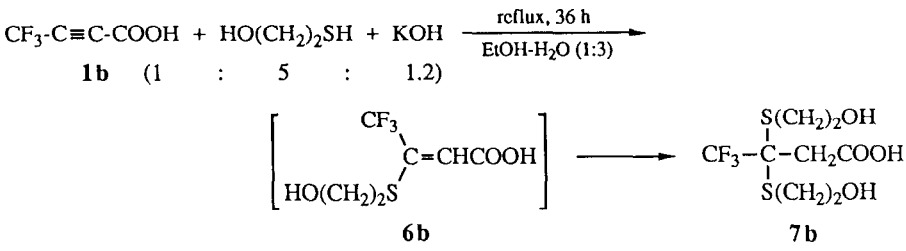
When 4,4-difluoro-2-butynoic acid (**1a**) was allowed to react with 5 equimolar amounts of 1,3-propanedithiol in the presence of 1.2 equimolar amounts of KOH at reflux temperature for 4 h, a 1,3-dithiane derivative **5a** was isolated in 74% yield, as depicted in Scheme 3. Similar treatment (24 h) of **1c** with 1,3-propanedithiol and KOH furnished the cyclization product **5c** (26%) and the 1:1 Michael adduct, 4,4,5,5,6,6-hexafluoro-3-(3-mercaptopropylthio)-2-hexenoic acid (45%). These results present a remarkable contrast to those obtained for the reaction with 1,2-ethanedithiol (see Table 1).



Scheme 3.

Reaction with 2-mercaptoethanol

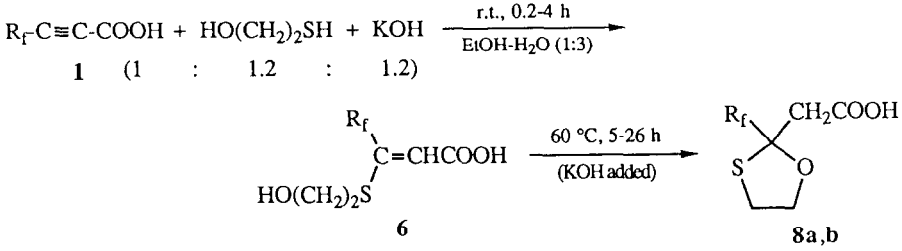
The reactions of **1** with 2-mercaptoethanol in the presence of KOH were examined under similar conditions to those that gave high yields of the cyclization products in the reaction with 1,2-ethanedithiol. Thus, on treating 4,4,4-trifluoro-2-butynoic acid (**1b**) with 5 equimolar amounts of 2-mercaptoethanol and 1.2 equimolar amounts of KOH at reflux temperature, a 1:2 Michael addition product **7b** was obtained in 50% yield, no cyclized product being formed (Scheme 4).



Scheme 4.

The predominant formation of **7b** is rationalized by assuming that an initially formed 1:1 Michael adduct **6b** may be attacked intermolecularly by another thiolate ion from excess 2-mercaptoethanol, before cyclizing through an intramolecular attack of the alcoholate ion in **6b**, because of the high nucleophilicity of the thiolate ion relative to the alcoholate ion [10].

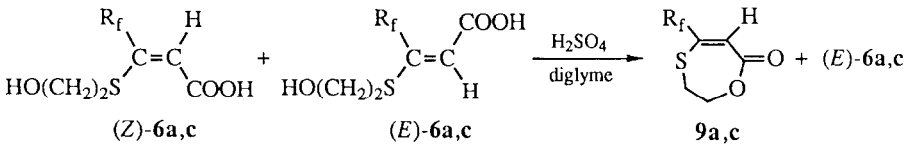
Treatment of **1** with 1.2 equimolar amounts of 2-mercaptoethanol in the presence of 1.2 equimolar amounts of KOH at room temperature in ethanol–water (1:3) gave the 1:1 Michael adducts **6** as a mixture of the *E*- and *Z*-isomers in excellent yields (>85%), without formation either of the 1:2 Michael adducts **7** or of the desired cyclization products **8**. The preferential formation of the *Z*-isomer ($Z/E = 12$ to 16) was also observed in these cases. Out of these 1:1 Michael adducts, **6a** and **6b** were found to undergo the intramolecular cyclization on heating at 60 °C to afford the cyclization products 2-(carboxymethyl)-2-(difluoromethyl)- (**8a**) and -2-(trifluoromethyl)-1,3-oxathiolane (**8b**), as shown in Scheme 5. These products **8a** and **8b** were obtainable in 80% and 76% yields, respectively, by conducting the one-pot reactions of **1a** and **1b** with 1.2 equimolar amounts of 2-mercaptoethanol in the presence of KOH successively at room temperature and at 60 °C, as described in the Experimental section. The *E*-isomer of **6a** cyclized nearly 13 times at 25 °C or 5 times at 60 °C faster than the *Z*-isomer. In contrast, the 1:1 Michael adduct **6c** did not give the cyclization product **8c** even on heating at higher temperatures (reflux) and/or for longer reaction periods (63 h). This may be ascribed to the low



Scheme 5.

nucleophilicity of the alcoholate ion and large steric hindrance effected by the long R_f chain in **6c**.

When a mixture of the *E*- and *Z*-isomers of **6a** or **6c** was heated at 140 °C in diglyme containing a catalytic amount of sulfuric acid, the *Z*-isomer only was transformed into the lactone **9a** or **9c**, respectively, and the *E*-isomer remained unchanged (Scheme 6). These results provide an additional, strong support for the structural assignment of the *E*- and *Z*-isomers of the 1:1 Michael adducts **2** and **6**, though comparison of the chemical shifts of their vinylic protons with those reported for some analogous compounds [1d] make the assignment possible.

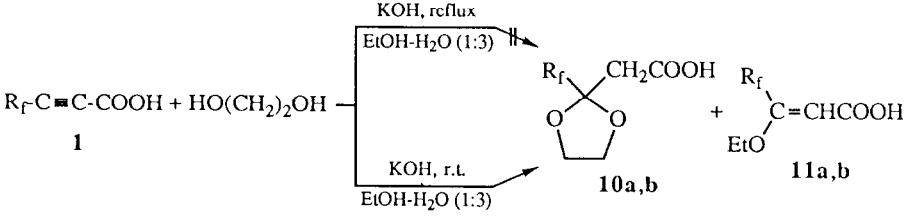


(*Z*)-**6a,c** (*E*)-**6a,c** **9a,c**

Scheme 6.

Reaction with ethylene glycol

When exposed to 5 equimolar amounts of ethylene glycol and 1.2 equimolar amounts of KOH at reflux temperature for 1 h, the acids **1** were merely decomposed and neither Michael adducts nor cyclization products were detected in the reaction mixture. However, the reaction of **1a** was carried out at ambient temperature for 24 h to give 64% yield of 2-(carboxymethyl)-2-(difluoromethyl)-1,3-dioxolane (**10a**), together with a 20% yield of 3-ethoxy-4,4-difluoro-2-butenoic acid (**11a**), as depicted in Scheme 7. The latter compound corresponds to the product arising from the Michael addition of ethanol used as solvent to **1a**. In a similar way, **1b** gave the corresponding cyclization product **10b** and ethanol-adduct **11b** in 63% and 23% yields, respectively. The acid **1c** did not afford any products under the same conditions and was quantitatively recovered unchanged.



Scheme 7.

Experimental

Infrared spectra (IR) were recorded on a Shimadzu IR-400 IR spectrophotometer. ^{1}H NMR spectra were obtained with Hitachi R-24B (60 MHz), Varian XL-200 (200 MHz), and/or GE QE-300 (300 MHz) spectrometers in a chloroform-*d* ($CDCl_3$), dimethyl sulfoxide-d_6 (DMSO-d_6), or acetone-d_6 (CD_3COCD_3) solution with tetramethylsilane as an internal reference. A Hitachi R-24F (56.466 MHz) spectrometer was used to measure ^{19}F NMR spectra in $CDCl_3$, DMSO-d_6 or CD_3COCD_3, with trifluoroacetic acid as an external reference. Mass spectra (MS) were taken on a Hitachi M-80B mass spectrometer or a Shimadzu QP1000 GC mass spectrometer operating at an ionization potential of 70 eV. All melting points are uncorrected.

Polyfluoro-2-alkynoic acids (**1a–c**) were prepared according to the method reported recently by us [6]. Although not isolated in a pure form by fractional distillation and thus containing 10 to 20% tetrahydrofuran which was employed as the solvent during the preparation, the acids were subjected to the reaction without further purification. All chemicals are reagent grade.

The elemental analyses of products gave satisfactory results. Table 2 lists the analytical data of the cyclization products **3a–c, 5a, 5c, 8a, 8b, 10a** and **10b**.

*Reaction of **1a–c** with 1.2 to 5 equimolar amounts of 1,2-ethanedithiol*

To a solution of specified amounts of 1,2-ethanedithiol (12 to 50 mmol) and of KOH (0 to 20 mmol) in 25 ml of ethanol–water (1:3) was gradually added the acid **1** (10 mmol), and the mixture was stirred at room or reflux temperature for 0.5 to 48 h (see Table 1). The reaction mixture was weakly acidified with dilute hydrochloric acid and was extracted with diethyl ether (3 × 50 ml). With the reactions performed in the absence of KOH, the mixture was subjected to extraction without acidification. The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was column-chromatographed on silica gel with benzene to give analytically pure products. The *E*- and *Z*-isomers of **2a** and **2c** could not be separated by column chromatography, but the pure *Z*-isomers were obtained from reactions conducted in the presence of KOH (see Table 1). The results of these reactions are summarized in Table 1.

*4,4-Difluoro-3-(2-mercaptoethylthio)-2-butenoic acid (**2a**)*

Z-isomer: m.p. 65 to 67 °C; IR (KBr) 1670 (C=O), 1585 (C=C) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.73 (1H, t, J = 8.3 Hz), 2.78 (2H, dt, J = 8.3 and 7.2 Hz), 3.27 (2H, t, J = 7.2 Hz), 6.25 (1H, s), 6.27 (1H, t, J = 54.2 Hz), 10.15 (1H, br s); ^{19}F NMR ($CDCl_3$) δ −32.3 (2F, d, J = 54.2 Hz); MS (*m*/*z*) 214 (M^+), 60 (100%).

E-isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.76 (1H, t, $J = 8.3$ Hz), 2.83 (2H, dt, $J = 8.3$ and 7.2 Hz), 3.08 (2H, t, $J = 7.2$ Hz), 5.74 (1H, s), 7.46 (1H, t, $J = 54.2$ Hz), 10.15 (1H, br s); ^{19}F NMR ($CDCl_3$) δ −37.0 (2F, d, $J = 54.2$ Hz).

*4,4,5,5,6,6-Hexafluoro-3-(2-mercaptoethylthio)-2-hexenoic acid (**2c**)*

Z-isomer: m.p. 35 to 36 °C; IR (KBr) 1705 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68 (1H, t, $J = 8.5$ Hz), 2.62 (2H, dt, $J = 8.5$ and 7.4 Hz), 3.18 (2H, t, $J = 7.4$ Hz), 6.10 (1H, tt, $J = 51.9$ and 4.8 Hz), 6.70 (1H, s), 11.00 (1H, br s); ^{19}F NMR ($CDCl_3$) δ −29.8 (2F, m), −49.7 (2F, m), −57.7 (2F, dm, $J = 51.9$ Hz); MS (*m/z*) 314 (M^+), 60 (100%).

E-isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.75 (1H, t, $J = 8.5$ Hz), 2.80 (2H, dt, $J = 8.5$ and 7.4 Hz), 3.16 (2H, t, $J = 7.4$ Hz), 6.04 (1H, s), 6.20 (1H, tt, $J = 51.8$ and 4.8 Hz), 11.00 (1H, br s); ^{19}F NMR ($CDCl_3$) δ −26.7 (2F, m), −48.3 (2F, m), −58.3 (2F, dm, $J = 51.8$ Hz).

*3,8-Bis(difluoromethyl)-4,7-dithia-2,8-decadienedioic acid (**4a**)*

M.p. 138 to 139 °C; IR (KBr) 1675 (C=O), 1590 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, DMSO-d_6) δ 3.16 (4H, s), 6.30 (2H, s), 6.68 (2H, t, $J = 53.6$ Hz), 9.51 (2H, br s); ^{19}F NMR (DMSO-d_6) δ −33.7 (2F, d, $J = 53.6$ Hz); MS (*m/z*) 334 (M^+), 153 (100%).

*3,8-Bis(1,1,2,2,3,3-hexafluoropropyl)-4,7-dithia-2,8-decadienedioic acid (**4c**)*

M.p. 120 to 121 °C; IR (KBr) 1690 (C=O), 1575 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, DMSO-d_6) δ 3.02 (4H, s), 6.83 (2H, tt, $J = 53.6$ and 6.0 Hz), 6.98 (2H, s), 8.93 (2H, br s); ^{19}F NMR (DMSO-d_6) δ −29.5 (2F, m), −49.3 (2F, m), −59.0 (2F, dm, $J = 53.6$ Hz); MS (*m/z*) no parent to 534, 281 ($M^+ - R_fC{=}CHCOOH$, 28%), 254 (100%).

*Reaction of **1a, c** with 5 equimolar amounts of 1,3-propanedithiol*

To a stirred solution of 1,3-propanedithiol (25 mmol) and KOH (6 mmol) in 20 ml of ethanol water (1:3) was added dropwise **1a** (5 mmol) at ambient temperature. After the mixture was refluxed for 4 h, the brown solution was acidified with dilute hydrochloric acid, followed by extraction with diethyl ether (3 × 50 ml). The combined ethereal extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using benzene chloroform as eluent to afford 2-(carboxymethyl)-2-(difluoromethyl)-1,3-dithiane (**5a**) in 74% yield. The reaction of **1c** with 1,3-propanedithiol was performed similarly as described above (reflux time, 24 h), 2-(carboxymethyl)-2-(1,1,2,2,3,3-hexafluoropropyl)-1,3-dithiane (**5c**) being obtained in 26% yield, together with a 45% yield of 4,4,5,5,6,6-hexafluoro-3-(3-mercaptopropylthio)-2-hexenoic acid: IR (film) 1710 (C=O), 1615 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.23 (1H, t, $J = 7.2$ Hz), 1.89 (2H, m), 3.02 (4H, m), 5.96

(1H, tt, $J = 51.4$ and 5.4 Hz), 6.59 (1H, s), 7.49 (1H, br s); ^{19}F NMR ($CDCl_3$) δ −29.3 (2F, m), −48.9 (2F, m), −56.9 (2F, dm, $J = 51.4$ Hz).

Reaction of ***1b*** *with 5 equimolar amounts of 2-mercaptoethanol*

To a stirred solution of 2-mercaptoethanol (25 mmol) and KOH (6 mmol) in 20 ml of ethanol–water (1:3) was gradually added **1b** (5 mmol) at room temperature. After refluxing for 36 h, the reaction mixture was acidified with dilute hydrochloric acid and was extracted with diethyl ether (3 × 50 ml). The combined organic layers were dried, filtered, and concentrated *in vacuo* to leave a residual oil, whose ^{19}F NMR spectrum showed only one singlet peak due to the trifluoromethyl group. This residue was heated under reflux for 20 h in methanol containing a catalytic amount of sulfuric acid. After the usual work-up, column chromatography of the crude product on silica gel with benzene gave methyl 4,4,4-trifluoro-3,3-bis(2-hydroxyethylthio)butanoate (**7b** methyl ester) in 50% yield as a colorless oil: IR (film) 1740 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (2H, s), 2.99 (4H, t, $J = 6.3$ Hz), 3.67 (3H, s), 3.73 (4H, dt, $J = 5.4$ and 6.3 Hz), 3.90 (2H, t, $J = 5.4$ Hz); ^{19}F NMR ($CDCl_3$) δ 8.7 (3F, s); MS (*m/z*) 308 (M^+), 157 (100%).

Reaction of ***1a–c*** *with 1.2 equimolar amounts of 2-mercaptoethanol*

A mixture of **1** (5 mmol), 2-mercaptoethanol (6 mmol), KOH (6 mmol) and 20 ml of ethanol–water (1:3) was stirred at room temperature for 0.2 h (**1a**), 1 h (**1b**) or 4 h (**1c**). After being acidified, the mixture was extracted with diethyl ether (3 × 50 ml). The ethereal extracts were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Chromatography of the residue on silica gel with chloroform or benzene–chloroform furnished the corresponding 1:1 adduct **6a**, **6b** or **6c** in 85%, 92% or 96% yield, respectively, as an isomeric mixture, in which the ratio of the *Z*- to *E*-isomers was 94:6 for **6a**, 93:7 for **6b** and 92:8 for **6c**. The *Z*-isomers of **6a–c** could be separated by silica-gel column chromatography using benzene–chloroform as eluent.

*4,4-Difluoro-3-(2-hydroxyethylthio)-2-butenoic acid (**6a**)*

Z-isomer: m.p. 120 to 121 °C; IR (KBr) 1690 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 3.13 (2H, t, $J = 6.3$ Hz), 3.75 (2H, t, $J = 6.3$ Hz), 6.30 (1H, t, $J = 1.4$ Hz), 6.67 (1H, t, $J = 54.4$ Hz), 7.20 (2H, br s); ^{19}F NMR (CD_3COCD_3) δ −35.7 (2F, dd, $J = 54.4$ and 1.4 Hz); MS (*m/z*) no parent to 198, 180 ($M^+ - H_2O$, 35%), 137 (100%).

E-isomer: ^{1}H NMR (300 MHz, CD_3COCD_3) δ 3.05 (2H, t, $J = 6.3$ Hz), 3.82 (2H, t, $J = 6.3$ Hz), 5.93 (1H, s), 7.20 (2H, br, s), 7.54 (1H, t, $J = 54.1$ Hz); ^{19}F NMR (CD_3COCD_3) δ − 38.3 (2F, d, $J = 54.1$ Hz).

*4,4,4-Trifluoro-3-(2-hydroxyethylthio)-2-butenoic acid (**6b**)*

Z-isomer: m.p. 65 to 66 °C; IR (KBr) 1685 (C=O), 1595 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$–CD_3COCD_3) δ 3.11 (2H, t, $J = 6.0$ Hz), 3.82 (2H,

t, $J = 6.0$ Hz), 6.71 (1H, s), 7.78 (2H, br, s); ^{19}F NMR ($CDCl_3$–CD_3COCD_3) δ 14.3 (3F, s); MS (m/z) 216 (M^+), 155 (100%).

E-isomer: ^{1}H NMR (60 MHz, $CDCl_3$–CD_3COCD_3) δ 3.07 (2H, t, J = 6.0 Hz), 3.83 (2H, t, $J = 6.0$ Hz), 6.10 (1H, s), 7.78 (2H, br s); ^{19}F NMR ($CDCl_3$–CD_3COCD_3) δ 17.6 (3F, s).

*4,4,5,6,6-Hexafluoro-3-(2-hydroxyethylthio)-2-hexenoic acid (**6c**)*

Z-isomer: oil; IR (film) 1720 (C=O), 1615 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.04 (2H, t, $J = 5.0$ Hz), 3.80 (2H, t, $J = 5.0$ Hz), 6.09 (1H, tt, $J = 51.0$ and 5.6 Hz), 6.82 (1H, s), 7.30 (2H, br s); ^{19}F NMR ($CDCl_3$) δ −30.0 (2F, m), −50.0 (2F, m), −57.7 (2F, dm, $J = 51.0$ Hz); MS (m/z) no parent to 298, 280 ($M^+ - H_2O$, 48%), 121 (100%).

E-isomer: ^{1}H NMR (60 MHz, $CDCl_3$), δ 3.08 (2H, t, $J = 5.0$ Hz), 3.85 (2H, t, $J = 5.0$ Hz), 6.09 (1H, tt, $J = 51.0$ and 5.6 Hz), 6.15 (1H, s), 7.30 (2H, br s); ^{19}F NMR ($CDCl_3$) δ −26.7 (2F, m), −48.3 (2F, m), −58.3 (2F, dm, $J = 51.0$ Hz).

A mixture of **1a** (5 mmol), 2-mercaptoethanol (6 mmol), KOH (6 mmol) and 20 ml of ethanol–water (1:3) was stirred at room temperature for 0.2 h. After additional KOH (4 mmol) was added, the whole mixture was heated at 60 °C for 5 h. With **1b**, after stirring at room temperature for 1 h, the reaction mixture was subjected to heating at 60 °C for 26 h, during which 2.5 mmol of KOH was added five times (total 12.5 mmol) to the mixture. Work-up of the reaction mixture and isolation of the products were carried out in an analogous manner to that cited above. The corresponding cyclization products **8a** and **8b** were obtained in 80% and 76% yields, respectively.

A 2:5 mixture of the *E*- and *Z*-isomers of **6a** (5 mmol) was heated at 140 °C for 5 h in diglyme (30 ml) in the presence of a catalytic amount of sulfuric acid. The mixture was poured into water (300 ml) and diethyl ether (50 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 50 ml). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvents by an evaporator followed by silica-gel column chromatography with chloroform gave the lactone **9a** in 61% yield, along with a 26% (90% recovery) yield of the unchanged *E*-isomer. Similarly, **6c** gave the lactone **9c** quantitatively, the *E*-isomer being recovered unreacted.

*3-(Difluoromethyl)-4-thia-2-hexen-6-olide (**9a**)*

Oil; IR (film) 1705 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.38 (2H, m), 4.70 (2H, m), 6.11 (1H, t, $J = 52.6$ Hz), 6.44 (1H, s); ^{19}F NMR ($CDCl_3$) δ −34.3 (2F, d, $J = 52.6$ Hz); MS (m/z) 180 (M^-), 137 (100%).

*3-(1,1,2,2,3,3-Hexafluoropropyl)-4-thia-2-hexen-6-olide (**9c**)*

Oil; IR (film) 1720 (C=O), 1615 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.43 (2H, m), 4.70 (2H, m), 6.00 (1H, tt, $J = 51.0$ and 5.6 Hz), 6.55 (1H, s);

^{19}F NMR ($CDCl_3$) δ −31.5 (2F, m), −50.0 (2F, m), −57.7 (2F, dm, J = 51.0 Hz); MS (m/z) 280 (M^+), 121 (100%).

Controlled cyclization reaction of ***2a*** *or* ***2c*** *and* ***6a***

A mixture of the E- and Z-isomers ($E/Z = 0.6$) of **2a** was stirred at 24 °C in the presence of 1.2 equimolar amounts of KOH in ethanol–water (1:3). The concentrations of the E- and Z-isomers in the mixture were measured by ^{19}F NMR. A plot of the logarithms of the concentrations against reaction times gave a straight line for each isomer, indicating that the reaction is first order. Values of the rate constants k_E and k_Z were calculated as 7.7×10^{-3} s^{-1} and 3.6×10^{-3} s^{-1} from the slopes of these linear rate plots for the E- and Z-isomers, respectively. Similarly, the rate constants k_E and k_Z at 24 °C for the E- and Z-isomers of **2c** were determined as 1.2×10^{-3} s^{-1} and 2.1×10^{-4} s^{-1}, respectively. In the case of **6a**, the rate constants k_E and k_Z were 2.1×10^{-5} s^{-1} and 1.6×10^{-6} s^{-1} at 25 °C, and 2.1×10^{-4} s^{-1} and 4.3×10^{-5} s^{-1} at 60 °C, respectively.

Reaction of ***1a–c*** *with 5 equimolar amounts of ethylene glycol*

A mixture of **1** (5 mmol), ethylene glycol (25 mmol), KOH (6 mmol) and 20 ml of ethanol–water (1:3) was heated at reflux temperature for 1 h. ^{19}F NMR analysis of the reaction mixture showed neither peaks due to the starting acid nor due to any addition products.

A mixture of **1** (5 mmol), ethylene glycol (25 mmol), KOH (6 mmol) and 20 ml of ethanol–water (1:3) was stirred at room temperature for 24 h. The mixture was worked-up similarly to that described above and the crude products were purified by silica-gel column chromatography using benzene–chloroform as eluent. 2-(Carboxymethyl)-2-(difluoromethyl)-1,3-dioxolane (**10a**) (64%) and 3-ethoxy-4,4-difluoro-2-butenoic acid (**11a**) (20%) were isolated from the reaction of **1a**; 2-(carboxymethyl)-2-(trifluoromethyl)-1,3-dioxolane (**10b**) (63%) and 3-ethoxy-4,4,4-trifluoro-2-butenoic acid (**11b**) (23%) were isolated from the reaction of **1b**. The reaction of **1c** resulted in a quantitative recovery of the starting acid.

*3-Ethoxy-4,4-difluoro-2-butenoic acid (**11a**)*

Oil; IR (film) 1705 (C=O), 1665 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.2 Hz), 4.35 (2H, q, J = 7.2 Hz), 5.51 (1H, s), 5.94 (1H, t, J = 54.6 Hz), 10.36 (1H, br s); ^{19}F NMR ($CDCl_3$) δ −41.7 (2F, d, J = 54.6 Hz); MS (m/z) 166 (M^+), 70 (100%).

*3-Ethoxy-4,4,4-trifluoro-2-butenoic acid (**11b**)*

M.p. 49 to 50 °C; IR (Nujol) 1710 (C=O), 1660 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.35 (3H, t, J = 7.2 Hz), 4.29 (2H, q, J = 7.2 Hz), 5.73 (1H, s), 10.90 (1H, br s); ^{19}F NMR ($CDCl_3$) δ 6.3 (3F, s); MS (m/z) 184 (M^+), 87 (100%).

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