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The reaction of fluorine-containing compounds with conjugated dienoic acids initiated by sodium dithionite

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Abstract

The reaction of fluorine-containing halides and acetamides with conjugated dienoic acids initiated by sodium dithionite gave halide-free 1,4-adducts in 40–80% yields, with the *E* configuration as the major products.

Keywords: Sodium dithionite; Conjugated dienoic acids; 1,4-Adducts

1. Introduction

The reaction of polyfluoroalkyl halides with unsaturated compounds, such as alkenes and alkynes, is one of the most important methods for the synthesis of fluorinated compounds [1]. Since the discovery of sulfinatodehalogenation reaction, Huang developed several sulfinatodehalogenation reagent systems for fluoroalkylation [2]. Sodium dithionite is used widely for its efficiency to initiate the reaction under mild conditions [3–7]. In our laboratory, sodium dithionite has been used to initiate the fluoroalkyl-lactonization of per and polyfluoroalkyl halides with 4-pentenoic acids [8]. More recently, the reaction of ethyl iododifluoroacetate with cyclopentene and cyclohexene [9] has been found to be a good method to synthesize fluorine-containing lactones. In order to extend the scope of the reaction, the addition reaction of fluorine-containing halides and acetamides with conjugated dienoic acids was studied in the presence of sodium dithionite.

2. Results and discussion

The addition reaction of halogen or halide-containing compounds to 1,3-butadiene, a typical conjugated diene, could be realized in the presence of copper complexes [10], $Ru(PPh_3)_3Cl_2$ [11], Lewis acid [12,13] or even active Mg [14] with 1,4-addition reaction as the main route, accompanied by the formation of the isomeric 1,2-adduct as a minor product. The ratio of the two adducts was affected by the reaction condition, such as the reaction temperature and time [11]. Previous report by Huang and Zhang [15] documented that the reaction of conjugated dienes with polyfluoroalkyl halides initiated by sodium dithionite gave only dimeric adducts. In this paper, we tried the reaction of (*E*)-2,4-pentadienoic acid and sorbic acid as the substrates, with polyfluoroalkyl halides and bromodifluoromethyl-containing compounds in the presence of sodium dithionite. It was found that halide-free 1,4-adducts with the *E* configuration were the major products.

2.1. The reaction between polyfluoroalkyl iodides and conjugated dienoic acids

The addition reaction of polyfluoroalkyl iodides **1** to conjugated dienoic acids **2** was carried out in the presence of sodium dithionite at room temperature in aqueous acetonitrile solution (CH_3CN/H_2O = 3:1 (v/v)) for 11–16 h (Scheme 1).

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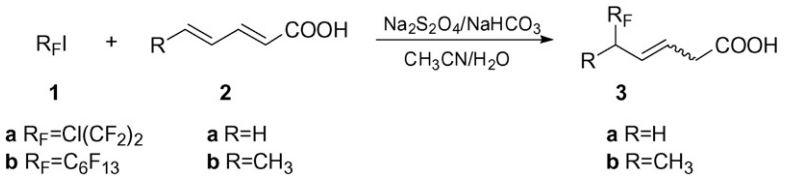


Scheme 1.

Table 1
The addition reaction of polyfluoroalkyl iodides to conjugated dienoic acids

Entry	R_FI	Acid	Temperature (°C)	Time (h)	Yield[a] (%)	Product **3** *E*/*Z*[b]
1	**1a**	**2a**	25	13	64	2.9:1
2	**1a**	**2b**	25	16	71	10.8:1
3	**1b**	**2a**	25	11	57	12.1:1
4	**1b**	**2b**	25	16	65	100:0

[a] Isolated yields.
[b] The isomeric ratio of *E* to *Z* was determined by ^{19}F NMR analysis.

When R_FI **1a** reacted with (*E*)-2,4-pentadienoic acid **2a**, only iodide-free 1,4-adduct was obtained in 64% yield. In the case of sorbic acid **2b**, the yields were 71% and 65% respectively (Table 1, entries 2 and 4). Chen and Hu documented separately that similar halide-free adducts were attained in the reaction of chlorofluorocarbons with unsaturated compounds initiated by $Na_2S_2O_4$ in DMSO [16], or the reaction of CF_2Br_2 with electron-deficient alkenes in the presence of $CrCl_3$ and Fe [17]. And the same result of the reaction between **1b** and **2b** was reported when initiated by Zn [18].

Furthermore, the predominant formation of the *E* isomer was observed in the reaction between R_FI and conjugated dienoic acids. Besides **2a**–**b**, we have also tried the substrate, 5-phenyl-penta-2,4-dienoic acid; however, the product was complicated.

2.2. The reaction between bromodifluoromethyl-containing compounds and conjugated dienoic acids

Huang et al. [19] documented that among the perfluoroalkyl halides, the iodides were more reactive than the corresponding bromides. However the addition reaction of R_FBr, such as CF_2Br_2, with unsaturated compounds initiated by sulfinatode-halogenation reagents also gave good results [20,21].

It was found that CF_2Br_2 could undergo the reaction with conjugated dienoic acids **2** to form the corresponding halide-free 1,4-addition products **5** in the presence of sodium dithionite at 35 °C for 26 h (Scheme 2). For example, the reaction of CF_2Br_2 with **2a** gave **5a** in 85% yield at the isomeric ratio of *E* to *Z* of 7.3. While in the case of **2b**, the yield was lower under similar reaction condition (Table 2, entries 1 and 2).

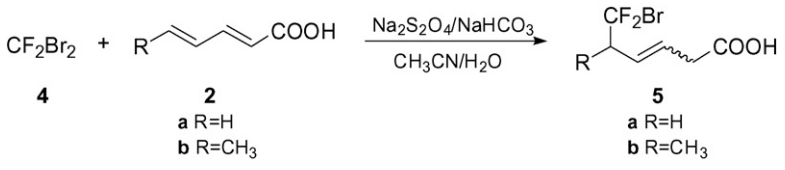
Actually, only a small quantity of adducts were obtained in the reaction of ethyl bromodifluoroactate to **2** at 45 °C for more than 19 h. It was obvious that CF_2Br_2 was more reactive than ethyl bromodifluoroacetate. But it was found surprisedly that we could get good results from the reaction of **7** to **2**, when ethyl bromodifluoroacetate was transformed into bromodifluoroacetamides **7** (Scheme 3).

The corresponding halide-free 1,4-adducts were separated from the reaction of **7b** and **7c** with **2** in the presence of sodium dithionite at 50 °C for 6 h or 23 h in 60–70% yields (Table 2, entries 5–8); while in the case of **7a**, the reaction conversion was lower. Detailed results were summarized in Table 2.

A free radical chain involving a single electron transfer mechanism has been proposed in the addition reaction of perfluoroalkyl iodides to alkenes initiated by sodium dithionite [22]. Accordingly, we proposed that the reaction between fluorine-containing halides or acetamides and conjugated dienoic acids might also involve a single electron transfer (SET) process for the anion radical (Fig. 1).

In the addition, GX accepts one electron from radical anion of sulfur dioxide, produced by decomposition of sodium dithionite; then dissociates to give $G^{\bullet}$ and X^{-}. Owing to the less steric hindrance of R than COOH in **2**, $G^{\bullet}$ reacts at the substituted end R to form the intermediate A. After a series of transformation, A is converted into B, which is more stable with a delocalized allyl type of radical and an electron-withdrawing group COOH. According to Chen and Hu [17], COOH may also attribute to hydrogen abstraction. In Hu's paper, promoted by redox system ($CrCl_3$/Fe) in alcohol or THF, the addition reaction of CF_2Br_2 to electron-deficient alkenes with COOEt, COOMe, $COONH_2$, Ac and CN as the electron-withdrawing group, gave bromine-reduced adducts; while in the case of electron-rich alkenes, the products were the normal adducts. Furthermore, the similar results were described by Huang [1]. So the substituent group COOH on the diene may be the main factor for the reductive adducts.

On the other hand, during the transformation of A to B, C is formed simultaneously. Obviously, the formation of C is



Scheme 2.

Table 2
The reaction between bromodifluoromethyl-containing compounds and **2**

Entry	Compound	Acid	Temperature (°C)	Time (h)	Yield[a] (%)	Product *E*/*Z*[b]
1	**4**	**2a**	35	26	85	7.3:1
2	**4**	**2b**	35	26	40	7.6:1
3	**7a**	**2a**	35	13	12[c]	2.6:1
4	**7a**	**2b**	35	23	10[c]	100:0
5	**7b**	**2a**	50	23	68	2.4:1
6	**7b**	**2b**	50	23	60	26.7:1
7	**7c**	**2a**	50	6	61	2.9:1
8	**7c**	**2b**	50	6	69	10.3:1

[a] Isolated yields.
[b] The isomeric ratio of *E* to *Z* was determined by ^{19}F NMR analysis.
[c] The conversion was 30%, which was determined by GC analysis.

determined by the size of R and G, especially R. In the reaction with **2a** (R=H), the isomeric ratio of *E* to *Z* was approximately 3:1; while in the case of **2b** (R=CH_3), the ratio rose and the *E* isomer predominated in the mixture. Particularly, in the reaction of CF_2Br_2 to **2a**, the ratio of *E* to *Z* isomer was just close to that of **2b**.

In conclusion, the halide-free 1,4-adducts were attained from the reaction of fluorine-containing halides and acetamides with conjugated dienoic acids initiated by sodium dithionite under mild conditions in moderate yields.

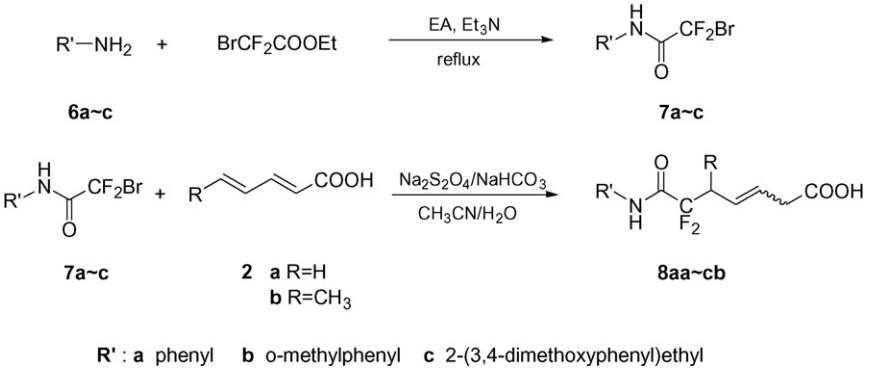
3. Experimental

All melting points were uncorrected, and measured by WRS-1B digital melting point apparatus. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker AC-500 (500 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. ^{19}F NMR spectras were recorded with Bruker AC-500 (470 MHz) spectrometer with $CDCl_3$ as the solvent and TFA as the external standard. Infrared spectras were measured using a Nicolet Magna IR-550 instrument. High-resolution mass spectras were obtained on Finnigan GC–MS-4021 spectrometers. GC was measured by Shimadzu GC-14B instrument.

3.1. Materials

3.1.1. Preparation of (E)-2,4-pentadienoic acid (2a)

The compound **2a** was synthesized employing a modification of a published procedure [23]. Dissolving 30 g (0.288 mol) malonic acid in 42 ml dry pyridine with vigorous stirring; acrolein (freshly distilled) 20.4 g (0.36 mol) was added slowly



Scheme 3.

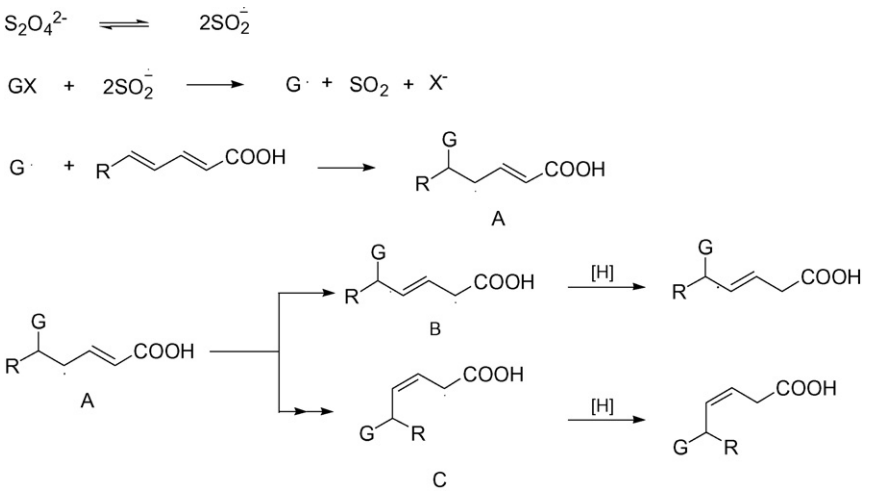


Fig. 1.

with heat evolution. After the addition, the heat of reaction was under control; then the mixture was heated to reflux until no more carbon dioxide was evolved. After cooling, the solution was poured into 150 ml ice and 12 ml 98% sulfuric acid. The yellow precipitate was filtrated quickly from the solution and **2a** was obtained by recrystallization from petroleum ether. mp 70.9–71.8 °C (lit: 73.5 °C).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.26–7.39 (1H, m, CH), 6.46–6.53 (1H, m, CH), 5.92 (1H, d, J = 15.4 Hz, CH–COOH), 5.67 (1H, d, J = 17.0 Hz, CH_2), 5.57 (1H, d, J = 10.1 Hz, CH_2).

3.1.2. General method for the synthesis of acetamides (7)

7 were synthesized according to the analogs as reported [24] with certain changes. After adding **6** 0.1 mol, ethyl bromodifluoroacetate 0.107 mol and triethylamine 0.107 mol in 110 ml ethyl acetate, the solution was heated to reflux for 30 h. Then, the cooling mixture was treated with 15% diluted hydrochloric acid until the pH was up to 3–4. The organic layer was collected and dried over anhydrous Na_2SO_4. After evaporation of ethyl acetate, the residue was purified by recrystallization from petroleum ether to give **7a**–**c**.

3.1.2.1. 2-Bromo-2,2-difluoro-N-phenyl-acetamide (7a).

White needles: mp 88.6–89.1 °C; IR (film), υ (cm^{-1}): 3318, 1700, 755, 688; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.86 (1H, s, NH), 7.57 (2H, d, J = 7.8 Hz, Ph), 7.40 (2H, t, J = 7.8 Hz, Ph), 7.24 (1H, t, J = 7.8 Hz, Ph); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −61.71 (2F, s); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 159.1 (t, J = 28.9 Hz, CO), 136.9, 131.0, 127.9, 122.1, 113.2 (t, J = 316.4 Hz, CF_2Br); EIMS (*m*/*z*): 251 (18.98 (M + 1)$^+$), 249 (19.86 (M − 1)$^+$), 120 (100.0), 92 (35.76), 77 (68.92); HRMS calcd. for $C_8H_6BrF_2NO$ 248.9601 (M − 1), found 248.9597.

3.1.2.2. 2-Bromo-2,2-difluoro-N-(o-toyl)acetamide (7b).

White needles: mp 76.3–76.5 °C; IR (film), υ (cm^{-1}): 3283, 1706, 756; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.75 (1H, d, J = 7.9 Hz, Ph), 7.69 (1H, s, NH), 7.24–7.28 (2H, m, Ph), 7.20 (1H, t, J = 7.4 Hz, Ph), 2.31 (3H, s, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −61.52 (2F, s); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 158.4 (t, J = 26.4 Hz, CO), 133.6, 131.6, 130.8, 127.8, 127.7, 123.9, 112.4 (t, J = 317.0 Hz, CF_2Br), 18.0; EIMS (*m*/*z*): 265 (15.26 (M + 1)$^+$), 263 (15.76 (M − 1)$^+$), 134 (100.0), 106 (24.98), 91 (63.94), 77 (22.25); HRMS calcd. for $C_9H_8BrF_2NO$ 262.9757 (M − 1), found 262.9759.

3.1.2.3. 2-Bromo-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-2,2-difluoro-acetamide (7c).

White needles: mp 62.8–63.1 °C; IR (film), υ (cm^{-1}): 3232, 3084, 1699, 692; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.83 (1H, d, J = 8.1 Hz, Ph), 6.74 (1H, dd, J = 8.1 Hz, J = 1.8 Hz, Ph), 6.71 (1H, d, J = 1.8 Hz, Ph), 6.30 (1H, s, NH), 3.87 (6H, s, OCH_3), 3.60 (2H, q, J = 6.7 Hz, CH_2NH), 2.84 (2H, t, J = 6.7 Hz, CH_2Ph); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −61.64 (2F, s); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 160.6 (t, J = 27.7 Hz, CO), 149.9, 148.7, 130.8, 121.4, 112.6, 112.5 (t, J = 316.4 Hz, CF_2Br), 112.3, 56.6, 56.5, 42.0, 35.3; EIMS (*m*/*z*): 339 (4.43 (M + 1)$^+$), 337 (4.8 (M − 1)$^+$), 164 (59.24), 151.1 (100.0), 149.0 (9.35), 77 (12.81); HRMS calcd. for $C_{12}H_{14}BrF_2NO_3$ 337.0125 (M − 1), found 337.0127.

3.2. General procedure of the addition reaction of polyfluoroalky iodides to 2

Acid **2** (2 mmol) and **1** (3 mmol) were dissolved in 7.2 ml acetonitrile and 2.4 ml water with magnetic stir. Then, $Na_2S_2O_4$ 0.52 g (3 mmol) and $NaHCO_3$ 0.25 g (3 mmol) were added to the solution. The mixture was stirred at room temperature. After the reaction was completed, determined by TLC, the mixture was treated with 8 ml water, extracted with ether of 3× 10 ml. The combined organic layer was washed with saturated brine and dried over anhydrous Na_2SO_4. After evaporation of ether, the crude product was subjected to column chromatograph to give the pure product.

3.2.1. 7-Chloro-6,6,7,7-tetrafluoro-hept-3-enoic acid (3aa)

The product was isolated in 64% yield by column chromatography eluting with petroleum ether and ethyl acetate (10:1). IR (film), υ (cm^{-1}): 3044, 2962, 1717, 1153, 799; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 11.43 (1H, s, COOH), 5.94–5.99 (1H-*Z*, m, CH), 5.82–5.87 (1H-*E*, m, CH), 5.67–5.72 (1H-*Z*, m, CH), 5.58–5.64 (1H-*E*, m, CH), 3.19 (2H, d, J = 6.9 Hz, CH_2–COOH), 2.82–2.91 (2H, td, $J_{H,F}$ = 17.6 Hz, $J_{H,H}$ = 6.9 Hz, CH_2–CF_2); ^{19}F NMR (470 MHz, $CDCl_3$), δ: *Z* −72.08 (2F, s, CF_2Cl), −114.07 (2F, t, J = 18.8 Hz, CF_2CH_2), *E* −72.01 (2F, s, CF_2Cl), −114.34 (2F, t, J = 18.8 Hz, CF_2CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: *Z* 177.7, 127.9, 123.8 (t, J = 298.8 Hz, CF_2Cl), 121.2, 115.2 (t, J = 254.5 Hz, CF_2), 33.4, 30.09 (t, J = 22.8 Hz, CH_2–CF_2); *E* 178.0, 129.6, 124.3 (t, J = 298.8 Hz, CF_2Cl), 122.6, 116.8 (t, J = 254.5 Hz, CF_2), 38.2, 35.1 (t, J = 22.9 Hz, CH_2–CF_2); EIMS (*m*/*z*): 236 (0.36 (M + 1)$^+$), 234 (0.91 (M − 1)$^+$), 214 (68.72), 172 (57.12), 131 (23.81), 99 (12.85), 55 (100.0), 45 (20.47); HRMS calcd. for $C_7H_7ClF_4O_2$ 234.0071 (M − 1), found 234.0096.

3.2.2. 7-Chloro-6,6,7,7-tetrafluoro-5-methyl-hept-3-enoic acid (3ab)

The product was isolated in 71% yield by column chromatography eluting with petroleum ether and ethyl acetate (10:1). IR (KBr), υ (cm^{-1}): 2994, 2950, 1717, 1154, 739; ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.75–5.79 (1H, m, CH), 5.53–5.73 (1H, m, CH), 3.15 (2H, d, J = 5.2 Hz, CH_2COOH), 2.99–3.06 (1H, m, CH–CH_3), 1.27 (3H, d, J = 7.2 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −68.75 to −67.79 (2F, m, CF_2Cl), −117.63 (2F, AB, J = 263.2 Hz, CF_2CH); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 178.5, 130.4, 126.3, 124.8 (t, J = 302.7 Hz, CF_2Cl), 117.5 (t, J = 257.8 Hz, CF_2CH), 40.6 (t, J = 22.9 Hz, CH–CH_3), 38.1, 14.3; EIMS (*m*/*z*): 248 (M^+, 0.49), 208 (12.71), 145 (13.34), 113 (23.58), 71 (100.00), 60 (19.42); HRMS calcd. for $C_8H_9ClF_4O_2$ 248.0227, found 248.0206.

3.2.3. 6,6,7,7,8,8,9,9,10,10,11,11,11-Tridecafluoro-undec-3-enoic acid (3ba)

The product was isolated in 57% yield by column chromatography eluting with petroleum ether and ethyl acetate

(10:1). mp 44.8–45.9 °C. IR (KBr), υ (cm^{-1}): 3032, 1707, 1429, 1236, 1144, 703; ^1H NMR (500 MHz, $CDCl_3$), δ: 5.77–5.83 (1H, m, CH), 5.51–5.57 (1H, m, CH), 3.13 (2H, d, $J = 6.9$ Hz, CH_2COOH), 2.75–2.84 (2H, td, $J_{H,F} = 18.1$ Hz, $J_{H,H} = 7.0$ Hz, CH_2CF_2); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −82.17 (3F, s, CF_3), −114.49 (2F, t, $J = 14.1$ Hz, CF_2CH_2), −123.20 (2F, s, CF_2CF_2), −124.13 (2F, s, CF_2CF_2), −124.40 (2F, s, CF_2CF_2), −127.41 (2F, s, CF_2CF_2); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 177.4, 130.1, 122.0, 119.8, 117.8, 111.7, 111.5, 109.3, 108.8, 38.1, 35.4 (t, $J = 22.6$ Hz, CH_2–C_6F_{13}); EIMS (*m/z*): 418 (0.76, M^+), 398 (59.87), 356 (100.0), 99 (13.5), 55 (78.07), 45 (9.56); HRMS calcd. for $C_{11}H_7F_{13}O_2$ 418.0238, found 418.0237.

3.2.4. 6,6,7,7,8,8,9,9,10,10,11,11,11-Tridecafluoro-5-methyl-undec-3-enoic acid (**3bb**)

The product was isolated in 65% yield by column chromatography eluting with petroleum ether and ethyl acetate (10:1). ^1H NMR (500 MHz, $CDCl_3$), δ: 9.58 (1H, s, COOH), 5.75–5.81 (1H, m, CH), 5.53–5.58 (1H, m, CH), 3.15 (2H, d, $J = 6.2$ Hz, CH_2), 2.99–3.08 (1H, m, CH–CH_3), 1.26 (3H, d, $J = 6.9$ Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −82.09 (3F, t, $J = 7.1$ Hz, CF_3), −118.45 (2F, AB, $J = 275.0$ Hz, CF_2CH), −121.56 (2F, d, $J = 8.3$ Hz, CF_2), −123.31 to −123.22 (2F, m, CF_2), −124.08 (2F, s, CF_2), −127.44 to −127.36 (2F, m, CF_2) in accordance with Ref. [18].

3.3. Procedure of the addition reaction between CF_2Br_2 and **2**

Acid **2** (2 mmol) and CF_2Br_2 **4** (3 mmol) were dissolved in 7.2 ml acetonitrile and 2.4 ml water with magnetic stir. Then, $Na_2S_2O_4$ 0.52 g (3 mmol) and $NaHCO_3$ 0.25 g (3 mmol) were added to the solution. The mixture was stirred at 35 °C with a condenser for 26 h. After the reaction was completed, the mixture was treated with 8 ml water, extracted with ether of 3× 10 ml. The combined organic layer was washed with saturated brine and dried over anhydrous Na_2SO_4. After evaporation of ether, the crude product was subjected to column chromatograph to give the pure product.

3.3.1. 6-Bromo-6,6-difluoro-hex-3-enoic acid (**5a**)

The product was isolated in 85% yield by column chromatography eluting with petroleum ether and ethyl acetate (8:1). IR (film), υ (cm^{-1}): 3041, 2922, 1714, 972, 631; ^1H NMR (500 MHz, $CDCl_3$), δ: 5.92–5.98 (1H-*Z*, m, CH), 5.82–5.88 (1H-*E*, m, CH), 5.65–5.72 (1H-*Z*, m, CH), 5.59–5.65 (1H-*E*, m, CH), 3.19 (2H, d, $J = 6.8$ Hz, CH_2COOH), 3.08–3.15 (2H, td, $J_{H,F} = 13.3$ Hz, $J_{H,H} = 6.9$ Hz, CH_2CF_2Br); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −45.76 (2F-*Z*, t, $J = 13.1$ Hz), −46.14 (2F-*E*, t, $J = 13.1$ Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: *Z* 177.7, 127.6, 123.4, 120.3 (t, $J = 305.7$ Hz, CF_2Br), 43.1 (t, $J = 23.1$ Hz, CH_2–CF_2Br), 33.6; *E* 178.0, 129.6, 124.7, 122.0 (t, $J = 305.7$ Hz, CF_2Br), 48.0 (t, $J = 23.1$ Hz, CH_2–CF_2Br,), 38.2; EIMS (*m/z*): 149 (21.22), 129 (39.50), 101 (100.0), 77 (32.31), 45 (4.82); HRMS calcd. for $C_6H_7BrF_2O_2$ 227.9597 ($M - 1$), found 227.9579.

3.3.2. 6-Bromo-6,6-difluoro-5-methyl-3-hexenoic acid (**5b**)

The product was isolated in 40% yield by column chromatography eluting with petroleum ether and ethyl acetate (8:1). IR (film), υ (cm^{-1}): 2989, 2944, 1714, 1459, 929; ^1H NMR (500 MHz, $CDCl_3$), δ: 5.72–5.80 (1H, m, CH), 5.44–5.52 (1H, m, CH), 3.10 (2H, d, $J = 6.2$ Hz, CH_2COOH), 2.86–2.90 (1H, m, $CHCH_3$), 1.19 (3H, d, $J = 6.8$ Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −50.14 (2F, AB, $J = 155.1$ Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: *E* 179.2, 132.7, 127.9, 127.5 (t, $J = 308.3$ Hz, CF_2Br), 51.2 (t, $J = 20.9$ Hz, $CHCF_2Br$), 39.2, 16.8; *Z* 178.9, 132.2, 127.5 (t, $J = 308.3$ Hz, CF_2Br), 126.6, 46.8 (t, $J = 20.9$ Hz, $CHCF_2Br$), 34.7, 16.8; EIMS (*m/z*): 244 (0.25 ($M + 1$)$^+$), 242 (0.26 ($M - 1$)$^+$), 199 (2.47), 197 (2.18), 71 (100), 45 (12.03); HRMS calcd. for $C_7H_9BrF_2O_2$ 241.9754 ($M - 1$), found 241.9746.

3.4. General procedure of the reaction between bromodifluoro-containing acetamides and **2**

Acid **2** (2 mmol) and **7** (3 mmol) were dissolved in 9 ml acetonitrile and 3 ml water with magnetic stir. Then, $Na_2S_2O_4$ 0.52 g (3 mmol) and $NaHCO_3$ 0.25 g (3 mmol) were added to the solution. The mixture was stirred at 50 °C (**7a** at 35 °C). After the reaction was completed, determined by TLC, the mixture was treated with 9 ml water, extracted with ethyl acetate of 3× 10 ml. The combined organic layer was washed with saturated brine and dried over anhydrous Na_2SO_4. After evaporation of ethyl acetate, the crude product was subjected to column chromatograph to give the pure product.

3.4.1. 6,6-Difluoro-6-phenylcarbamoyl-hex-3-enoic acid (**8aa**)

The product was isolated in 12% yield by column chromatography eluting with petroleum ether and ethyl acetate (3:1). mp *Z* 113.2–114.9 °C, *E* 121.8–124.3 °C. IR (film), υ (cm^{-1}): 3324, 2922, 1686, 744; ^1H NMR (500 MHz, $CDCl_3$), δ: 7.92 (1H, s, NH), 7.56 (2H, d, $J = 7.5$ Hz, Ph), 7.38 (2H, t, $J = 7.5$ Hz, Ph), 7.20 (1H, t, $J = 7.5$ Hz, Ph), 5.81–5.87 (1H, m, CH), 5.58–5.64 (1H, m, CH), 3.23 (2H-*Z*, d, $J = 6.9$ Hz, CH_2COOH), 3.14 (2H-*E*, d, $J = 6.9$ Hz, CH_2COOH), 2.93–3.01 (2H, td, $J_{H,F} = 16.8$ Hz, $J_{H,H} = 7.2$ Hz, CF_2CH_2); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −107.61 (2F-*E*, t, $J = 18.8$ Hz), −107.22 (2F-*Z*, t, $J = 18.8$ Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 177.1, 162.3 (t, $J = 28.3$ Hz, CO), 136.6, 129.9, 129.5, 128.0, 126.4, 124.0, 122.4, 121.0, 117.7 (t, $J = 255.0$ Hz, CF_2), 38.1, 37.8 (t, $J = 24.2$ Hz, CH_2–CF_2); EIMS (*m/z*): 269 (81.35, M^+), 251 (12.36), 120 (100.0), 77 (74.60), 45 (4.75); HRMS calcd. for $C_{13}H_{13}F_2NO_3$ 269.0863, found 269.0836.

3.4.2. 6,6-Difluoro-5-methyo-6-phenylcarbamoyl-hex-3-enoic acid (**8ab**)

The product was isolated in 10% yield by column chromatography eluting with petroleum ether and ethyl acetate (5:1). mp 117.3–118.2 °C. IR (film), υ (cm^{-1}): 3327, 1704, 1686, 1224, 754; ^1H NMR (500 MHz, $CDCl_3$), δ: 7.91 (1H, s, NH), 7.55 (2H, d, $J = 7.7$ Hz, Ph), 7.37 (2H, t, $J = 7.7$ Hz, Ph), 7.19 (1H, t, $J = 7.7$ Hz, Ph), 5.79–5.84 (1H, m, CH), 5.55–5.60

(1H, m, CH), 3.16–3.25 (1H, m, CH–CH_3), 3.11 (2H, d, J = 6.9 Hz, CH_2COOH), 1.23 (3H, d, J = 6.9 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −113.40 (2F, AB, J = 249.1 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 176.2, 162.4 (t, J = 28.3 Hz, CO), 136.6, 130.8, 129.9, 127.1, 126.3, 121.0, 118.8 (t, J = 255.0 Hz, CF_2), 41.5 (t, J = 24.2 Hz, CH–CH_3), 38.0, 13.4; EIMS (m/z): 283 (56.89, M^+), 265 (13.92), 239 (10.74), 120 (95.52), 77 (100.0), 45 (5.5); HRMS calcd. for $C_{14}H_{15}F_2NO_3$ 283.1020, found 283.1021.

3.4.3. 6,6-Difluoro-6-o-tolylcarbamoyl-hex-3-enoic acid (**8ba**)

The product was isolated in 68% yield by column chromatography eluting with ethyl acetate. mp 93.5–95.1 °C. IR (film), υ (cm^{-1}): 3256, 1691, 1531, 973; ^1H NMR (500 MHz, $CDCl_3$), δ: 7.95 (1H, s, NH), 7.67 (1H, d, J = 7.7 Hz, Ph), 7.12 (2H, t, J = 7.0 Hz, Ph), 7.13 (1H, t, J = 7.0 Hz, Ph), 5.87–5.89 (1H, m, CH-Z), 5.78–5.84 (1H, m, CH-E), 5.54–5.63 (1H, m, CH-Z + E), 3.18 (2H, d, J = 6.7 Hz, CH_2COOH-Z), 3.09 (2H, d, J = 6.7 Hz, CH_2COOH-E), 2.89–3.00 (2H, td, $J_{H,F}$ = 16.8 Hz, $J_{H,H}$ = 7.2 Hz, CF_2CH_2), 2.22 (3H, s, $PhCH_3$); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −105.63 (2F-Z, t, J = 16.5 Hz), −106.21 (2F-E, t, J = 16.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 177.6 (E), 177.4 (Z), 162.5 (t, J = 28.3 Hz, CO), 134.2, 131.3, 130.7, 129.5, 128.1, 127.5, 127.1, 124.0, 117.8 (t, J = 254.8 Hz, CF_2-E), 118.0 (t, J = 254.8 Hz, CF_2-Z), 38.6 (E), 37.8 (t, J = 24.2 Hz, CH_2CF_2-E), 33.3 (Z), 33.0 (t, J = 24.2 Hz, CH_2CF_2-Z), 18.02; EIMS (m/z): 283 (37.82, M^+), 204 (11.96), 134 (100.0), 106 (51.18), 91 (75.22), 77 (18.12); HRMS calcd. for $C_{14}H_{15}F_2NO_3$ 283.1020, found 283.1043.

3.4.4. 6,6-Difluoro-5-methyl-6-o-tolylcarbamoyl-hex-3-enoic acid (**8bb**)

The product was isolated in 60% yield by column chromatography eluting with ethyl acetate. IR (film), υ (cm^{-1}): 3289, 2963, 1710, 1261, 753; ^1H NMR (500 MHz, $CDCl_3$), δ: 7.85 (1H, s, NH), 7.61 (1H, d, J = 7.8 Hz, Ph), 7.13 (2H, t, J = 7.5 Hz, Ph), 7.05 (1H, t, J = 7.1 Hz, Ph), 5.68–5.74 (1H, m, CH), 5.46–5.51 (1H, m, CH), 3.07–3.13 (1H, m, CH–CH_3), 3.00 (2H, d, J = 6.7 Hz, CH_2COOH), 2.15 (3H, s, $PhCH_3$), 1.14 (3H, d, J = 6.9 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −113.38 (2F, AB, J = 249.1 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 177.5, 162.6 (t, J = 28.4 Hz, CO), 134.3, 131.3, 130.6, 130.5, 129.4, 128.4, 127.5, 127.1, 118.9 (t, J = 257.3 Hz, CF_2), 41.4 (t, J = 22.7 Hz, CH–CH_3), 38.3, 18.1, 13.3; EIMS (m/z): 297 (57.32, M^+), 252 (4.93), 238 (10.54), 218 (35.01), 134 (100.0), 106 (39.65), 91 (52.64); HRMS calcd. for $C_{15}H_{17}F_2NO_3$ 297.1176, found 297.1167.

3.4.5. 6-[2-(3,4-Dimethoxy-phenyl)-ethylcarbamoyl]-6,6-difluoro-hex-3-enoic acid (**8ca**)

The product was isolated in 61% yield by column chromatography eluting with petroleum ether and ethyl acetate (2:1). IR (film), υ (cm^{-1}): 3306, 2939, 1699, 1516, 1234, 806; ^1H NMR (500 MHz, $CDCl_3$), δ: 6.82 (1H, d, J = 8.1 Hz, Ph), 6.72 (1H, d, J = 8.1 Hz, Ph), 6.71 (1H, s, Ph), 6.36 (1H, s, NH), 5.82–5.87 (1H, m, CH-Z), 5.73–5.79 (1H, m, CH-E), 5.46–5.55 (1H, m, CH-Z + E), 3.87 (6H, s, OCH_3), 3.55 (2H, q, J = 6.5 Hz, $NHCH_2$), 3.18 (2H, d, J = 6.9 Hz, CH_2COOH-Z), 3.10 (2H, d, J = 6.9 Hz, CH_2COOH-E), 2.79–2.87 (4H, m, Ph–$CH_2{}^+CH_2CF_2$); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −106.36 (2F-Z, t, J = 16.5 Hz), −106.95 (2F-E, t, J = 16.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 176.3 (COOH-E), 176.0 (COOH-Z), 164.5 (t, J = 28.6 Hz, CO), 149.5, 148.3, 131.2, 129.1, 123.6, 121.2, 117.3 (t, J = 253.0 Hz, CF_2-E), 117.5 (t, J = 253.0 Hz, CF_2-Z), 112.6, 112.1, 56.3, 56.2, 41.2, 37.9, 37.6 (t, J = 24.3 Hz, CH_2CF_2), 35.1; EIMS (m/z): 357 (4.69, M^+), 164 (100.0), 151 (48.76), 149 (8.79), 77 (2.25); HRMS calcd. for $C_{17}H_{21}F_2NO_5$ 357.1388, found 357.1387.

3.4.6. 6-[2-(3,4-Dimethoxy-phenyl)-ethylcarbamoyl]-6,6-difluoro-5-methyl-hex-3-enoic acid (**8cb**)

The product was isolated in 69% yield by column chromatography eluting with petroleum ether and ethyl acetate (4:1). IR (film), υ (cm^{-1}): 3337, 2940, 1696, 1515, 1262, 1156, 807; ^1H NMR (500 MHz, $CDCl_3$), δ: 6.82 (1H, d, J = 8.5 Hz, Ph), 6.73 (1H, s, Ph), 6.72 (1H, d, J = 8.5 Hz, Ph), 6.39 (1H, s, NH), 5.70–5.76 (1H, m, CH), 5.45–5.50 (1H, m, CH), 3.87 (6H, s, OCH_3), 3.51–3.59 (2H, m, $NHCH_2$), 3.00–3.11 (3H, m, CH_3, CH_2COOH), 2.77–2.80 (2H, td, $J_{H,H}$ = 6.9 Hz, $J_{H,H}$ = 1.9 Hz, Ph–CH_2), 1.11 (3H, d, J = 6.9 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −114.06 (2F, AB, J = 249.1 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 176.3, 164.6 (t, J = 28.9 Hz, CO), 149.6, 148.3, 131.3, 130.3, 126.7, 121.2, 118.5 (t, J = 255.7 Hz, CF_2), 112.6, 112.1, 56.4, 56.3, 41.2 (t, J = 22.8 Hz, CH–CH_3), 38.0, 35.2, 13.1; EIMS (m/z): 371 (5.17, M^+), 164 (100.0), 151 (59.96), 149 (9.88), 121 (2.15); HRMS calcd. for $C_{18}H_{23}F_2NO_5$ 371.1544, found 371.1544.

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References

[1] W.Y. Huang, Organofluorine Chemistry in China (Chinese), Shanghai, 1996, pp. 217–224.
[2] W.Y. Huang, The Reaction and Application of Sulfinatodehalogenation, Hebei, 2003, pp. 107–112.
[3] F.H. Wu, W.Y. Huang, J. Fluorine Chem. 110 (2001) 59–61.
[4] X.T. Huang, Z.Y. Long, Q.Y. Chen, J. Fluorine Chem. 111 (2001) 107–113.
[5] W. Dmowski, K.P. Maciejewska, Z.U. Lipkowska, Synthesis 6 (2003) 841–844.
[6] W. Dmowski, J. Ignatowska, K.P. Maciejewska, J. Fluorine Chem. 125 (2004) 1147–1151.
[7] J. Ignatowska, W. Dmowski, J. Fluorine Chem. 127 (2006) 720–729.
[8] X.W. Zou, F.H. Wu, Y.J. Shen, S. Xu, W.Y. Huang, Tetrahedron 59 (2003) 2555–2560.
[9] F.H. Xiao, F.H. Wu, Y.J. Shen, L.F. Zhou, J. Fluorine Chem. 126 (2005) 63–67.
[10] Z. Vít, M. Hájek, Collec. Czech. Chem. Commun. 52 (1987) 1280–1284.
[11] H. Matsumoto, T. Nakano, T. Nikaido, Y. Nagai, Chem. Lett. 1 (1978) 115–116.
[12] H. Mayr, W. Striepe, J. Org. Chem. 48 (1983) 1159–1165.
[13] G. Kabas, R. Gabler, J. Org. Chem. 30 (1965) 1248–1249.

[14] R.D. Rieke, H.P. Xiong, J. Org. Chem. 56 (1991) 3109–3118.
[15] W.Y. Huang, H.Z. Zhang, Chin. J. Chem. 9 (1999) 76–83.
[16] Z.Y. Long, Q.Y. Chen, J. Org. Chem. 64 (1999) 4775–4782.
[17] J. Chen, C.M. Hu, J. Chem. Soc. Perkin Trans. 1 (8) (1994) 1111–1114.
[18] N. Requirand, A. Andrieu, H. Blancou, A. Commeyras, J. Fluorine Chem. 69 (1994) 57–59.
[19] B.N. Huang, B.H. Huang, W. Wang, W.Y. Huang, Acta Chim. Sin. 43 (1985) 167.
[20] F.H. Wu, W.Y. Huang, J. Fluorine Chem. 110 (2001) 59–61.
[21] F.H. Wu, B.N. Huang, L. Lu, W.Y. Huang, J. Fluorine Chem. 80 (1996) 91–94.
[22] B.N. Huang, F.H. Wu, C.M. Zhou, J. Fluorine Chem. 75 (1995) 1–5.
[23] M.P. Schneider, M. Goldbach, J. Am. Chem. Soc. 102 (1980) 6114–6116.
[24] W.R. D Jr., C.R. Burkholder, M. Médebielle, J. Fluorine Chem. 95 (1999) 127–130.