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Journal of Fluorine Chemistry 128 (2007) 1046–1051
JOURNAL OF FLUORINE CHEMISTRY
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Fluoroalkylation of pent-4-en-1-ols initiated by sodium dithionite to synthesize fluorine-containing tetrahydrofuran derivatives

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Received 19 April 2007; received in revised form 15 May 2007; accepted 15 May 2007
Available online 18 May 2007

Abstract

Fluoroalkylation of pent-4-en-1-ols with RCF_2I initiated by $Na_2S_2O_4$ was carried out at 5–10 °C in aqueous acetonitrile affording corresponding adducts, which were converted to fluoroalkyl tetrahydrofurans by heating in DMF or acetonitrile, providing a convenient method for the synthesis of fluorine-containing tetrahydrofuran derivatives.

Keywords: Addition; Cyclization; Fluorine-containing; Tetrahydrofuran

1. Introduction

The synthesis of fluorine-containing compounds has engendered great interest among scientists owing to their enormous applications in agricultural chemistry, medicinal chemistry, material science and organic synthesis [1]. The addition of fluoroalkyl halide to unsaturated compounds initiated by metal and metal complexes [2], sulfuroxy-acid salts [3], photolysis [4], electrolysis [5], AIBN [6] and others [7] has provided a convenient method for the introduction of fluoroalkyl group into organic molecules. Such method has been used on the reaction of different alkenes, alkynes affording corresponding adducts, which have synthetically useful C–X bond [8]. Fluoroalkylation of unsaturated acids initiated by $Na_2S_2O_4$ was also described in our laboratory giving γ-butyrolactones [9]. The addition reaction of R_FI to allylic alcohol followed by basic treatment was reported to give fluoroalkylmethylepoxides [10]. However limited examples have been reported on the fluoroalkylation of other unsaturated alcohols. The addition of R_FI to pent-4-en-1-ol initiated by AIBN afforded fluorinated tetrahydrofuran [11]. AIBN initiated addition of R_FI to hex-5-en-1-ol gave only adducts, which were treated with strong base to afford polyfluoroalkenyl tetrahydropyran derivatives [12]. In this paper, we describe the fluoroalkylation of pent-4-en-1-ol and its derivatives initiated by $Na_2S_2O_4$ expecting to obtain fluoroalkyl tetrahydrofuran derivatives, which presented a kind of important compounds widespread in synthetic and natural products with various bioactivities [13]. Our study showed that the reaction gave only adducts instead of fluoroalkyl tetrahydrofurans and the adducts could be converted to corresponding tetrahydrofurans by heating in DMF or acetonitrile in the absence of any bases. This provided a convenient method for the synthesis of fluoroalkyl tetrahydrofurans.

2. Results and discussion

In the typical reaction of $ClCF_2CF_2I$ (**1a′**) and 2-methyl-pent-4-en-1-ol (**2a**), the radical addition initiated by $Na_2S_2O_4$ was carried out in aqueous acetonitrile at 0–5 °C for 1 h. Adduct **3aa′** was obtained instead of a cyclization product **5aa′**, even when the reaction lasted for longer time.

Since the presence of C–X bond could be exploited for further cyclization in basic medium [10,12,14], cyclization of the crude adduct **3aa′** was investigated in the presence of

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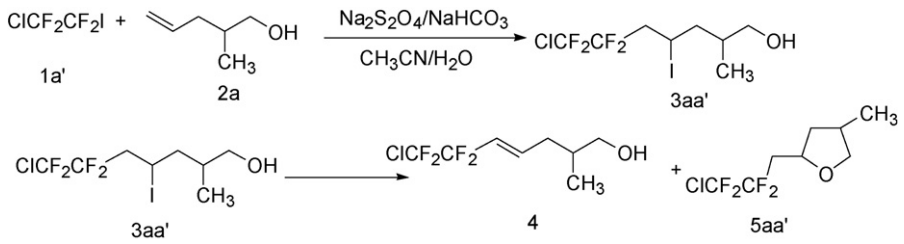
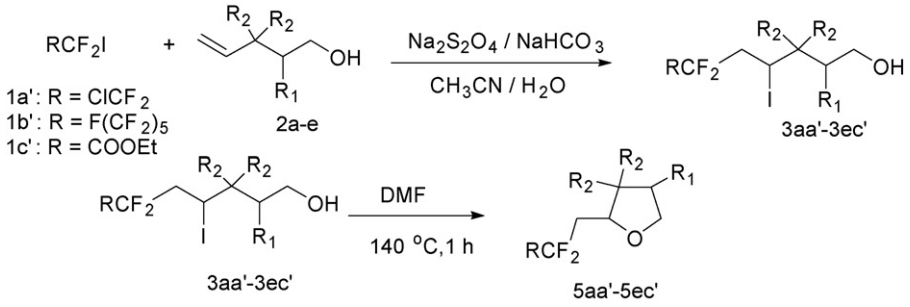
0022-1139/$ – see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.jfluchem.2007.05.013



Scheme 1.



Scheme 2.

different bases and solvents (Scheme 1). The results were listed in Table 1. The results showed that strong base and protic solvent favored the elimination. For example, treatment of **3aa′** with NaOH in methanol or ethyl ether at room temperature gave only elimination product **4** (Table 1, entries 1, 2) [12]. In the presence of K_2CO_3, a base with moderate strength, the reaction proceeded at room temperature in CH_3OH for 10 h to afford a *E*/*Z* mixture of **4** in 15:1 ratio with major *E*-isomer (Table 1, entry 3). When ethyl ether was used as the solvent, K_2CO_3 failed to give any product (Table 1, entries 4, 5), even the reaction was carried out under reflux. In acetonitrile, treatment of **3aa′** with K_2CO_3 at room temperature for 16 h gave a mixture of elimination product **4** and cyclization product **5aa′** in 60:40 ratio with 24% conversion of **3aa′** (Table 1, entry 8). Other moderate or weak bases, such as Et_3N, $NaHCO_3$, also failed to give any product in ethyl ether (Table 1, entries 6, 7).

Since the presence of bases was adverse to cyclization due to the elimination reaction, cyclization of crude **3aa′** in the absence of any bases was investigated. The results showed that heating was necessary for cyclization to occur and no elimination product **4** formed (Table 1, entries 9–12). In acetonitrile longer reaction time was required (10 h). In DMF, higher temperature speeded cyclization. For example, when heating at 90 °C, **3aa′** was converted to **5aa′** completely within 5 h. The reaction time was reduced to 1 h at 140 °C. Heating **3aa′** at 110 °C for 3 h without any solvents also gave **5aa′** in 65% yield.

The crude addition products **3ab′** and **3ac′** obtained from the reaction of alkyl iodide $F(CF_2)_6I$ (**1b′**), ICF_2COOEt (**1c′**) with **2a** initiated by $Na_2S_2O_4$ were also easily converted to corresponding tetrahydrofurans **5ab′** and **5ac′** after heating in DMF at 140 °C for 1 h in 62% and 54% yields (Scheme 2, Table 2, entries 2–3).

When pent-4-en-1-ol **2b** and its derivatives **2c**–**2e** were used as the substrates, the two-step reaction also proceeded smoothly, giving corresponding tetrahydrofurans

Table 1
Reaction of **3aa′** under different conditions

Entry	Base[a]	Solvent	Temperature	Time (h)	Conversion[b] (%)	**5aa′**/**4** ratio[b]	Yield of **5aa′**[b]
1	NaOH	CH_3OH	25 °C	1	100	0/100	–
2	NaOH	Et_2O	25 °C	5	100	0/100	–
3	K_2CO_3	CH_3OH	25 °C	10	100	0/100	–
4	K_2CO_3	Et_2O	25 °C	10	0	–	–
5	K_2CO_3	Et_2O	Reflux	10	0	–	–
6	Et_3N	Et_2O	25 °C	10	0	–	–
7	$NaHCO_3$	Et_2O	25 °C	10	0	–	–
8	K_2CO_3	CH_3CN	25 °C	16	24	40/60	–
9	–	CH_3CN	Reflux	10	100	100/0	68
10	–	DMF	90 °C	5	100	100/0	70
11	–	DMF	140 °C	1	100	100/0	69
12	–	–	110 °C	3	100	100/trace	65

[a] 5 equiv. of K_2CO_3, Et_3N, $NaHCO_3$ or 1.2 equiv. of NaOH.
[b] Based on GC.

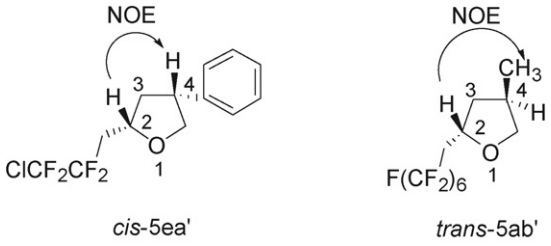


Fig. 1. ^{1}H–^{1}H NOESY of *cis*-**5ea′** and *trans*-**5ab′**.

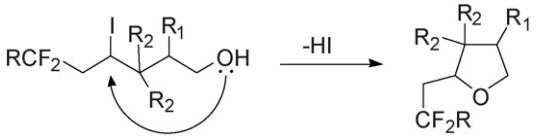


Fig. 2. Intramolecular S_N2 reaction of the adducts.

5bb′, **5ca′**–**5cc′**, **5da′**–**5dc′** and **5ea′**–**5ec′** in 42–71% yields (Scheme 2, Table 2, entries 4–13).

The results indicated that for 2-substituted-pent-4-en-1-ols **2a**, **2d** and **2e**, a mixture of *trans*-/*cis*-isomers was obtained. Analysis of the crude product by ^{1}H NMR spectroscopy and integration of signals attributed to proton on C-2 indicated that the *trans*/*cis* ratio ranged from 1.20:1 to 2.60:1 (Table 2, entries 1–3, 8–13) with major *trans*-isomer. The NMR signal of the proton on C-2 exhibited a multiplet in lower field for *trans*-isomer than for *cis*-isomer.

For *cis*-isomer of **5aa′**–**5ac′**, **5da′**–**5dc′** and **5ea′**–**5ec′**, comparatively large chemical shift differences between the two protons at C-3 ($\Delta\delta$ = 0.7–1.2 ppm) were observed. However, in *trans*-isomer, small differences ($\Delta\delta$ = 0.0–0.2 ppm) were observed. The results were consistent with the established stereochemistry of 2,4-disubstituted tetrahydrofurans [15]. The confirmation of the stereochemistry was based on the ^{1}H–^{1}H NOESY data (Fig. 1). For example, in *cis*-**5ea′** the observed correlated peaks between the proton on C-2 (δ = 4.42–4.36 ppm) and the proton on C-4 (δ = 3.55–3.45 ppm) showed a *cis* orientation of the two protons. However, the absence of the correlated peaks between the corresponding protons indicated a *trans* configuration. The stereochemistry of **5ab′** was obtained by analysis of the correlationship between the proton on C-2 and the three protons on CH_3. In *trans*-**5ab′**, apparent correlated peaks between the corresponding protons were observed. However, in *cis*-**5ab′** the absence of the correlated peaks between the corresponding protons indicated a *cis* orientation of the two protons on C-2 and C-4.

Table 2
Data of the reaction of RCF_2I **1** with pent-4-en-1-ols **2**

Entry	Pent-4-enols	R_1	R_2	RCF_2I	Products	Yield[a]	*Trans*/*cis*[b]
1	**2a**	Me	H	**1a′**	**5aa′**	55	1.22:1
2	**2a**	Me	H	**1b′**	**5ab′**	62	1.26:1
3	**2a**	Me	H	**1c′**	**5ac′**	54	1.30:1
4	**2b**	H	H	**1b′**	**5bb′**	62	–
5	**2c**	H	Me	**1a′**	**5ca′**	69	–
6	**2c**	H	Me	**1b′**	**5cb′**	65	–
7	**2c**	H	Me	**1c′**	**5cc′**	42	–
8	**2d**	*n*-Pr	H	**1a′**	**5da′**	55	1.20:1
9	**2d**	*n*-Pr	H	**1b′**	**5db′**	53	1.20:1
10	**2d**	*n*-Pr	H	**1c′**	**5dc′**	53	1.21:1
11	**2e**	Ph	H	**1a′**	**5ea′**	66	2.60:1
12	**2e**	Ph	H	**1b′**	**5eb′**	71	2.45:1
13	**2e**	Ph	H	**1c′**	**5ec′**	61	2.20:1

[a] Isolated yield based on pent-4-en-1-ols **2**.
[b] Based on ^{1}H NMR.

We attempted to obtain fluoroalkyl tetrahydrofurans in one pot by heating the radical addition mixture under reflux without further treatment. But when the addition reaction mixture of $ClCF_2CF_2I$ (**1a′**) and 3,3-dimethyl-pent-4-en-1-ol (**2c**) was heated under reflux for 6 h, the conversion of **3ca′** was very low (<10%).

The mechanism of the addition of RCF_2I to pent-4-en-1-ols initiated by sodium dithionite was a single electron transfer process [16]. The formation of tetrahydrofurans may proceed by intramolecular S_N2 reaction of the adducts (Fig. 2).

In conclusion, we have developed a two-step practical protocol for the synthesis of fluoroalkyl tetrahydrofurans by fluoroalkylation of pent-4-en-1-ols initiated by sodium dithionite followed by intramolecular cyclization.

3. Experimental

IR spectra were measured on a Nicolet Magna IR-550 spectrometer. High-resolution mass spectra were obtained on a Finnigan GC-MS-4021 spectrometer. NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC-500 spectrometer operating at 500 MHz (^{1}H NMR), 125.8 MHz (^{13}C NMR) and 470.5 MHz (^{19}F NMR). Chemical shifts (δ) are given in ppm relative to TMS for ^{1}H and ^{13}C, and relative to $CFCl_3$ for ^{19}F NMR. Column chromatography was performed using silica gel H, particle size 20–30 μm.

*3.1. General procedure for the reaction of RCF_2I (**1**) with pent-4-en-1-ols (**2**)*

To the mixture of pent-4-en-1-ols (1 mmol), RCF_2I (1 mmol), acetonitrile (3 mL), water (1 mL) at 0–5 °C under stirring was added the mixture of $Na_2S_2O_4$ (260 mg, 1.5 mmol) and $NaHCO_3$ (130 mg, 1.5 mmol) in portions in 20 min. After stirring for 1 h at the same temperature, the reaction mixture was treated with water (5 mL) and then extracted with ethyl ether (3× 10 mL). The combined organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. After removal of ethyl ether, the residue was heated in DMF in 140 °C oil bath for 1 h and then cooled to room temperature. The mixture was treated with 10% Na_2SO_3 (10 mL) and then extracted with ethyl ether (3× 10 mL). The combined organic layer was washed with saturated brine and water and then dried over anhydrous sodium sulfate. After removal of ethyl ether, the residue was purified by column chromatography eluting with PE and EA to give the corresponding tetrahydrofurans.

3.2. Elimination reaction of *3aa′* to give *4*

To the residue obtained from the addition of **1a′** to 2-methyl-pent-4-en-1-ol (**2a**) after removal of ethyl ether was added K_2CO_3 (540 mg, 5 mmol) and methanol (2 mL). After stirring for 10 h at ambient temperature, the reaction mixture was treated with water (3 mL) and then extracted with ethyl ether (3× 10 mL). The combined organic layer was washed with saturated brine and water and then dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by column chromatography eluting with PE and EA (6:1/V) to give a pale yellow oil **4** in a mixture of *E*/*Z* isomer in 51% yield.

3.2.1. 7-Chloro-6,6,7,7-tetrafluoro-4-iodo-2-methyl-heptan-1-ol (*3aa′*)

3aa′ was obtained as an oil by column chromatography eluting with PE and EA (6:1/V). IR (film, υ_{max}, cm^{-1}): 3346 (broad), 2961, 1462, 1381, 1259, 1208, 1152, 1085, 1037, 936. ^1H NMR ($CDCl_3$) δ: (major) 4.27–4.24 (1H, m), 3.52–3.42 (2H, m), 3.00–2.62 (2H, m), 1.89–1.83 (2H, m), 1.79–1.75 (1H, m), 1.63 (1H, br, OH), 0.85 (3H, d, J = 6.7 Hz); (minor) 4.38–4.36 (1H, m), 3.52–3.42 (2H, m), 3.00–2.62 (2H, m), 2.04–1.99 (2H, m), 1.79–1.75 (1H, m), 1.63 (1H, br, OH), 0.94 (3H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: (major) 125.1–118.2 (m), 66.8, 42.9, 41.5 (t, J = 21.0 Hz), 35.9, 18.8, 13.7; (minor) 125.1–118.2 (m), 65.4, 44.0, 41.0 (t, J = 21.1 Hz), 35.0, 18.3, 16.1. ^{19}F NMR ($CDCl_3$) δ: −72.63 (2F, m), −113.29 (2F, m). HRMS (EI): $C_8H_{12}ClF_4IO$ cacld: 361.9558; found: 361.9560.

3.2.2. 7-Chloro-6,6,7,7-tetrafluoro-2-methyl-hept-4-en-1-ol (*4*)

IR (film, υ_{max}, cm^{-1}): 3346 (broad), 2963, 1675 (C=C), 1461, 1385, 1258, 1154, 1090, 1042, 977, 947. ^1H NMR ($CDCl_3$) δ: (*E*) 6.34 (1H, dtt, J_1 = 15.6 Hz, J_2 = 7.5 Hz, J_3 = 2.1 Hz), 5.59 (1H, dt, J_1 = 15.6 Hz, J_2 = 11.7 Hz), 3.46–3.40 (2H, m), 2.33–2.28 (1H, m), 2.03–1.97 (1H, m), 1.79–1.72 (1H, m), 1.54 (1H, br, OH), 0.86 (3H, d, J = 6.8 Hz); (*Z*) 6.12–6.05 (1H, m), 5.60–5.48 (1H, m), 3.46–3.40 (2H, m), 2.42–2.36 (1H, m), 2.20–2.13 (1H, m), 1.79–1.72 (1H, m), 1.54 (1H, br, OH), 0.89 (3H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: (*E*) 140.3 (t, J = 8.5 Hz), 124.8–110.3 (m), 117.4 (t, J = 23.6 Hz), 66.3, 35.0, 34.2, 15.1; (*Z*) 142.5 (t, J = 6.8 Hz), 124.8–110.3 (m), 116.2 (t, J = 23.5 Hz), 66.6, 35.2, 34.8, 15.2. ^{19}F NMR ($CDCl_3$) δ: −72.33 (2F, m), −112.25 (2F, m). HRMS (EI): $C_8H_{10}ClF_4O$ ($M-1$) cacld: 233.0356; found: 233.0356.

3.2.3. 2-(3-Chloro-2,2,3,3-tetrafluoropropyl)-4-methyl-tetrahydrofuran (*5aa′*)

Pale yellow oil; IR (film, υ_{max}, cm^{-1}): 2985, 1461, 1378, 1261, 1156, 1089. ^1H NMR ($CDCl_3$) δ: (*trans*) 4.29–4.23 (1H, m), 3.95 (1H, dd, J_1 = 8.3 Hz, J_2 = 6.9 Hz), 3.24 (1H, dd, J_1 = 8.3 Hz, J_2 = 6.7 Hz), 2.42–2.22 (2H, stack), 2.20–2.01 (1H, m), 1.80–1.67 (2H, m), 0.99 (3H, d, J = 5.2 Hz); (*cis*) 4.19–4.14 (1H, m), 3.85 (1H, t, J = 7.9 Hz), 3.31 (1H, t, J = 7.9 Hz), 2.42–2.22 (3H, stack), 2.20–2.01 (1H, m), 1.20–1.12 (1H, m), 1.00 (3H, d, J = 5.2 Hz). ^{13}C NMR ($CDCl_3$) δ: (*trans*) 126.9–115.2 (m), 75.7, 72.5, 41.0, 37.3 (t, J = 21.1 Hz), 33.7, 15.1; (*cis*) 126.9–115.2 (m), 75.2, 73.7, 42.4, 37.4 (t, J = 21.2 Hz), 35.0, 18.2. ^{19}F NMR ($CDCl_3$) δ: −72.76 (2F, m), −114.13 (2F, t, J = 18.8 Hz); HRMS (EI): $C_8H_{11}OF_4Cl$ cacld: 234.0435; found: 234.0391.

3.2.4. 4-Methyl-2-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-heptyl)-tetrahydro-furan (*5ab′*)

Pale yellow oil; IR (film, υ_{max}, cm^{-1}): 2966, 1365, 1240, 1205, 1145, 1054, 1070. ^1H NMR ($CDCl_3$) δ: (*trans*) 4.37–4.32 (1H, m), 4.03 (1H, dd, J_1 = 8.3 Hz, J_2 = 6.8 Hz), 3.32 (1H, dd, J_1 = 8.3 Hz, J_2 = 6.8 Hz), 2.56–2.28 (2H, stack), 2.26–2.12 (1H, m), 1.88–1.75 (2H, m), 1.06 (3H, d, J = 5.8 Hz); (*cis*) 4.29–4.22 (1H, m), 3.93 (1H, t, J = 7.9 Hz), 3.39 (1H, t, J = 7.9 Hz), 2.56–2.28 (3H, stack), 2.26–2.12 (1H, m), 1.28–1.20 (1H, m), 1.07 (3H, d, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$) δ: (*trans*) 121.7–106.7 (m), 75.7, 72.2, 41.0, 37.6 (t, J = 20.9 Hz), 33.8, 18.4; (*cis*) 121.7–106.7 (m), 75.3, 73.5, 42.4, 37.8 (t, J = 20.9 Hz), 35.0, 18.0. ^{19}F NMR ($CDCl_3$) δ: −82.04 (3F, t, J = 9.4 Hz), −114.27 (2F, m), −123.06 (2F, m), −124.10 (2F, m), −124.91 (2F, m), −127.37 (2F, m). HRMS (EI): $C_{12}H_{11}OF_{13}$ cacld: 418.0602, found: 418.0649.

3.2.5. Ethyl 2,2-difluoro-3-(4-methyl-tetrahydrofuran-2-yl)propanoate (*5ac′*)

Pale yellow oil; IR (film, υ_{max}, cm^{-1}): 2964, 2934, 2874, 1771, 1455, 1333, 1299, 1230, 1191, 1110, 1068. ^1H NMR ($CDCl_3$) δ: (*trans*) 4.34–4.30 (2H, m), 4.26–4.29 (1H, m), 3.92 (1H, dd, J_1 = 8.3 Hz, J_2 = 6.9 Hz), 3.26 (1H, dd, J_1 = 8.3 Hz, J_2 = 6.7 Hz), 2.50–2.28 (2H, stack), 2.26–2.13 (1H, m), 1.82–1.65 (2H, m), 1.25 (3H, t, J = 7.2 Hz), 1.03 (3H, d, J = 6.8 Hz); (*cis*) 4.34–4.30 (2H, m), 4.16–4.07 (1H, m), 3.85 (1H, t, J = 7.8 Hz), 3.30 (1H, t, J = 7.8 Hz), 2.50–2.28 (2H, stack), 2.26–2.13 (2H, stack), 1.25 (3H, t, J = 7.2 Hz), 1.23–1.16 (1H, m), 1.04 (3H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ: (*trans*) 164.7 (t, J = 32.3 Hz), 116.0 (t, J = 250.1 Hz), 75.5, 73.0 (dd, J_1 = 6.7 Hz, J_2 = 2.8 Hz), 63.3, 41.3 (t, J = 22.4 Hz), 40.4, 33.6, 18.4, 14.5; (*cis*) 164.7 (t, J = 32.3 Hz), 115.9 (t, J = 250.2 Hz), 75.1, 74.1 (dd, J_1 = 6.9 Hz, J_2 = 2.7 Hz), 63.3, 41.6, 41.5 (t, J = 22.4 Hz), 34.9, 17.9, 14.5. ^{19}F NMR ($CDCl_3$) δ: (*trans*) −109.16 (1F, ddd, J_{F-F} = 263.5 Hz, J_{1H-F} = 23.5 Hz, J_{2H-F} = 14.4 Hz), −102.90 (1F, ddd, J_{F-F} = 263.5 Hz, J_{1H-F} = 14.4 Hz, J_{2H-F} = 9.4 Hz); (*cis*) −108.77 (1F, ddd, J_{F-F} = 263.5 Hz, J_{1H-F} = 23.5 Hz, J_{2H-F} = 18.8 Hz), −103.11 (1F, ddd, J_{F-F} = 263.5 Hz, J_{1H-F} = 14.4 Hz, J_{2H-F} = 9.4 Hz). HRMS (EI): $C_{10}H_{16}O_3F_2$ cacld: 222.1068, found: 222.1075.

3.2.6. 2-(2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoroheptyl)-tetrahydrofuran (*5bb′*) [6]

Colorless oil; ^1H NMR ($CDCl_3$) δ: 4.16–4.10 (1H, m), 3.85–3.81 (1H, m), 3.73–3.68 (1H, m), 2.45–2.31 (1H, m), 2.20–2.05 (2H, stack), 1.92–1.82 (2H, m), 1.58–1.48 (1H, m). ^{19}F NMR ($CDCl_3$) δ: −82.06 (3F, t, J = 9.4 Hz), −114.25 (2F, m), −123.06 (2F, m), −124.09 (2F, m), −124.9 (2F, m), −127.38 (2F, m).

3.2.7. 2-(3-Chloro-2,2,3,3-tetrafluoro-propyl)-3,3-dimethyl-tetrahydro-furan (*5ca′*)

Pale yellow oil; IR (film, υ_{max}, cm^{-1}): 2965, 1465, 1262, 1213, 1154, 1092, 1066, 938. ^1H NMR ($CDCl_3$) δ: 3.96–3.91

(1H, m), 3.90–3.86 (1H, m), 3.74–3.72 (1H, m), 2.29–2.01 (2H, m), 1.86–1.80 (1H, m), 1.78–1.73 (1H, m), 1.07 (3H, s), 0.93 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 116.4–124.2 (m), 79.8, 66.3, 41.5, 41.0, 31.8 (t, J = 21.7 Hz), 24.9, 21.6. ^{19}F NMR ($CDCl_3$) δ: −72.28 (2F, m), −114.22 (2F, m). HRMS (EI): $C_9H_{13}OF_4Cl$ cacld: 248.0591; found: 248.0595.

3.3. 3,3-Dimethyl-2-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-heptyl)-tetrahydro-furan (**5cb′**)

Colorless oil; IR (film, υ_{max}, cm^{-1}): 2960, 2925, 1367, 1239, 1192, 1145. ^{1}H NMR ($CDCl_3$) δ: 3.94–3.86 (2H, m), 3.75–3.72 (1H, m), 2.17–2.08 (2H, m), 1.86–1.80 (1H, m), 1.78–1.73 (1H, m), 1.07 (3H, s), 0.93 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 108.0–123.0 (m), 79.7, 66.6, 41.9–41.8 (m), 41.3, 32.4 (t, J = 21.4 Hz), 25.1, 21.9. ^{19}F NMR ($CDCl_3$) δ: −81.86 (3F, m), −113.88 (2F, m), −122.81 (2F, m), −123.36 (2F, m), −124.41 (2F, m), −127.16 (2F, m). HRMS (EI): $C_{13}H_{13}F_{13}O$ cacld: 432.0759; found: 432.0735.

3.4. 3-(3,3-Dimethyl-tetrahydro-furan-2-yl)-2,2-difluoro-propionic acid ethyl ester (**5cc′**)

Pale yellow oil; IR (film, υ_{max}, cm^{-1}): 2974, 1772, 1467, 1233, 1194, 1107, 978. ^{1}H NMR ($CDCl_3$) δ: 4.32 (2H, q, J = 7.2 Hz), 3.85–3.75 (2H, stack), 3.60–3.57 (1H, m), 2.28–2.18 (1H, m), 2.12–2.03 (1H, m), 1.77–1.71 (2H, m), 1.35 (3H, t, J = 7.2 Hz), 1.01 (3H, s), 0.93 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 164.8 (t, J = 32.3 Hz), 116.6 (t, J = 250.3 Hz), 80.9, 66.4, 63.3, 41.5, 41.0, 36.6 (t, J = 22.8 Hz), 27.5, 22.2, 14.5. ^{19}F NMR ($CDCl_3$) δ: −101.94 (1F, ddd, $J_{F–F}$ = 249.4 Hz, $J_{1H–F}$ = 23.5 Hz, $J_{2H–F}$ = 9.4 Hz), −108.75 (1F, ddd, $J_{F–F}$ = 249.4 Hz, $J_{1H–F}$ = 14.4 Hz, $J_{2H–F}$ = 9.4 Hz). HRMS: $C_{11}H_{17}O_3F_2$ ($M-1$) cacld: 235.1146 found: 235.1128.

3.4.1. 2-(3-Chloro-2,2,3,3-tetrafluoropropyl)-4-propyl-tetrahydrofuran (**5da′**)

Colorless oil; IR (film, υ_{max}, cm^{-1}): 2961, 1464, 1394, 1261, 1213, 1152, 1085, 1043. ^{1}H NMR ($CDCl_3$) δ: (*trans*) 4.25–4.20 (1H, m), 3.96 (1H, dd, J_1 = 8.5 Hz, J_2 = 7.0 Hz), 3.28 (1H, dd, J_1 = 8.5 Hz, J_2 = 7.4 Hz), 2.46–2.32 (1H, m), 2.28–2.08 (2H, stack), 1.76–1.64 (2H, m), 1.30–1.20 (4H, m), 0.85 (3H, t, J = 7.3 Hz); (*cis*) 4.16–4.11 (1H, m), 3.85 (1H, t, J = 8.0 Hz), 3.38 (1H, t, J = 8.0 Hz), 2.46–2.32 (1H, m), 2.28–2.08 (3H, stack), 1.30–1.20 (4H, m), 1.20–1.12 (1H, m), 0.85 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ: (*trans*) 124.9–113.2 (m), 72.2, 70.8, 38.9, 37.5, 35.6 (t, J = 21.2 Hz), 34.6, 20.7, 13.1; (*cis*) 124.9–113.2 (m), 72.6, 71.8, 38.7, 37.6, 35.6 (t, J = 21.2 Hz), 34.4, 20.5, 13.1. ^{19}F NMR ($CDCl_3$) δ: −72.61 (2F, m), −113.95 (2F, m). HRMS (EI): $C_{10}H_{15}ClF_4O$ cacld: 262.0748; 262.0727.

3.4.2. 4-Propyl-2-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)-tetrahydrofuran (**5db′**)

Colorless oil; IR (film, υ_{max}, cm^{-1}): 2961, 1465, 1394, 1240, 1205, 1145, 1054. ^{1}H NMR ($CDCl_3$) δ: (*trans*) 4.36–4.28 (1H, m), 4.02 (1H, t, J = 8.2 Hz), 3.37 (1H, t, J = 8.2 Hz), 2.57–2.41 (1H, m), 2.36–2.15 (2H, stack), 1.85–1.79 (2H, m), 1.40–1.29 (4H, m), 0.92 (3H, t, J = 7.2 Hz); (*cis*) 4.25–4.22 (1H, m), 3.93 (1H, t, J = 7.9 Hz), 3.44 (1H, t, J = 7.9 Hz), 2.57–2.41 (1H, m), 2.36–2.15 (3H, stack), 1.40–1.29 (4H, m), 1.25–1.19 (1H, m), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ: (*trans*) 124.0–116.0 (m), 73.2, 71.5, 39.9, 38.6, 36.9 (t, J = 20.8 Hz), 35.6, 21.6, 14.1; (*cis*) 124.0–116.0 (m), 73.6, 72.5, 39.7, 38.5, 36.9 (t, J = 20.8 Hz), 35.4, 21.4, 14.1. ^{19}F NMR ($CDCl_3$) δ: −81.75 (3F, t, J = 9.4 Hz), −113.92 (2F, m), −122.77 (2F, m), −123.80 (2F, m), −124.61 (2F, m), −127.06 (2F, m). HRMS (EI): $C_{14}H_{15}F_{13}O$ cacld: 446.0915; found: 446.0911.

3.4.3. Ethyl 2,2-difluoro-3-(4-propyl-tetrahydrofuran-2-yl)propanoate (**5dc′**)

Colorless oil; IR (film, υ_{max}, cm^{-1}): 2961, 1773, 1465, 1233, 1186, 1112, 1003. ^{1}H NMR ($CDCl_3$) δ: (*trans*) 4.34–4.29 (2H, m), 4.24–4.17 (1H, m), 3.92 (1H, dd, J_1 = 8.2 Hz, J_2 = 7.3 Hz), 3.30 (1H, t, J = 8.2 Hz), 2.50–2.36 (1H, m), 2.30–2.12 (2H, stack), 1.76–1.73 (2H, m), 1.40–1.25 (4H, m), 1.35 (3H, t, J = 7.1 Hz), 0.90 (3H, t, J = 7.3 Hz); (*cis*) 4.34–4.29 (2H, m), 4.12–4.07 (1H, m), 3.86 (1H, t, J = 8.0 Hz), 3.35 (1H, t, J = 8.0 Hz), 2.50–2.36 (1H, m), 2.30–2.12 (3H, stack), 1.40–1.25 (4H, m), 1.35 (3H, t, J = 7.1 Hz), 1.22–1.14 (1H, m), 0.90 (3H, t, J = 7.3 Hz). ^{13}C NMR: (*trans*) 164.8 (t, J = 32.3 Hz), 115.2 (t, J = 248.4 Hz), 74.1, 73.1–73.0 (m), 63.4, 41.4 (t, J = 22.4 Hz), 40.4, 39.0, 36.0, 22.2, 14.5, 14.8; (*cis*) 164.8, 115.2 (t, J = 248.4 Hz), 74.0–73.9 (m), 73.8, 63.4, 41.4 (t, J = 22.4 Hz), 39.9, 38.7, 36.1, 22.3, 14.5, 14.8. ^{19}F NMR: (*trans*) −102.89 (1F, dt, $J_{F–F}$ = 258.8 Hz, $J_{H–F}$ = 14.1 Hz), −108.43 (1F, ddd, $J_{F–F}$ = 258.8 Hz, $J_{1H–F}$ = 18.8 Hz, $J_{2H–F}$ = 14.1 Hz); (*cis*) −102.61 (1F, dt, $J_{F–F}$ = 263.5 Hz, $J_{H–F}$ = 14.1 Hz), −109.00 (1F, ddd, $J_{F–F}$ = 263.5 Hz, $J_{1H–F}$ = 23.5 Hz, $J_{2H–F}$ = 14.1 Hz). HRMS (EI): $C_{12}H_{20}F_2O_3$ cacld: 250.1381; found: 250.1384.

3.4.4. 2-(3-Chloro-2,2,3,3-tetrafluoropropyl)-4-phenyl-tetrahydrofuran (**5ea′**)

Colorless oil; IR (film, υ_{max}, cm^{-1}): 3064, 2946, 1604, 1495, 1262, 1213, 1151, 1097, 938, 757, 700. ^{1}H NMR ($CDCl_3$) δ: (*trans*) 7.35–7.25 (5H, m), 4.54–4.50 (1H, m), 4.28 (1H, t, J = 8.0 Hz), 3.77 (1H, t, J = 8.0 Hz), 3.55–3.45 (1H, m), 2.67–2.45 (1H, m), 2.35–2.22 (2H, stack), 2.19–2.13 (1H, m); (*cis*) 7.35–7.25 (5H, m), 4.42–4.36 (1H, m), 4.19 (1H, t, J = 8.3 Hz), 3.85 (1H, t, J = 8.3 Hz), 3.55–3.45 (1H, m), 2.67–2.45 (2H, stack), 2.35–2.22 (1H, m), 1.82–1.79 (1H, m). ^{13}C NMR ($CDCl_3$) δ: (*trans*) 142.4, 129.4, 127.9, 127.4, 126.0–115.0 (m), 75.3, 73.3, 45.0, 41.3, 37.4 (t, J = 35.7 Hz); (*cis*) 142.2, 129.4, 127.8, 127.5, 126.0–115.0 (m), 74.8, 74.0, 46.0, 42.3, 36.7 (t, J = 28.8 Hz). ^{19}F NMR ($CDCl_3$) δ: −72.50 (2F, m), −113.81 (2F, t, J = 28.2 Hz). HRMS (EI): $C_{13}H_{13}ClF_4O$ cacld: 296.0591; found: 296.0591.

3.4.5. 4-Phenyl-2-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)-tetrahydrofuran (**5eb′**)

Colorless oil; IR (film, υ_{max}, cm^{-1}): 3032, 1604, 1495, 1239, 1204, 1144, 1123, 1052, 734, 703. ^{1}H NMR ($CDCl_3$) δ: (*trans*) 7.35–7.29 (5H, m), 4.57–4.52 (1H, m), 4.28 (1H, t, J = 7.8 Hz),

3.78 (1H, t, J = 7.8 Hz), 3.55–3.46 (1H, m), 2.63–2.51 (1H, m), 2.40–2.22 (2H, stack), 2.19–2.13 (1H, m); (*cis*) δ = 7.35–7.29 (5H, m), 4.42–4.39 (1H, m), 4.19 (1H, t, J = 8.3 Hz), 3.86 (1H, t, J = 8.3 Hz), 3.55–3.46 (1H, m), 2.63–2.51 (2H, stack), 2.40–2.22 (1H, m), 1.80–1.76 (1H, m). ^{13}C NMR ($CDCl_3$) δ: (*trans*) 142.4, 129.4, 127.9, 127.4, 122.0–108.0 (m), 75.3, 72.9, 45.0, 41.2, 37.7 (t, J = 20.9 Hz); (*cis*) 142.4, 129.4, 127.8, 127.5, 122.0–108.0 (m), 74.9, 73.7, 46.0, 42.4, 37.4 (t, J = 21.3 Hz); ^{19}F NMR ($CDCl_3$) δ: −82.0 (3F, t, J = 9.4 Hz), −114.11 (2F, m), −122.99 (2F, m), −124.03 (2F, m), −124.80 (2F, m), −127.31 (2F, m). HRMS (EI): $C_{17}H_{13}OF_{13}$ cacld: 480.0759, found: 480.0761.

*3.4.6. Ethyl 2,2-difluoro-3-(4-phenyl-tetrahydrofuran-2-yl)propanoate (**5ec′**)*

White solid; IR (film, υ_{max}, cm^{-1}): 3068, 1771, 1605, 1496, 1227, 1177, 1127, 1098, 1054. ^{1}H NMR ($CDCl_3$) δ: (*trans*) 7.33–7.22 (5H, m), 4.46–3.99 (1H, m), 4.36–4.31 (2H, m), 4.18 (1H, dd, J_1 = 8.5 Hz, J_2 = 7.5 Hz), 3.71 (1H, t, J = 8.5 Hz), 3.49–3.44 (1H, m), 2.62–2.47 (1H, m), 2.28–2.19 (2H, stack), 2.15–2.07 (1H, m), 1.36 (3H, t, J = 7.1 Hz); (*cis*) 7.33–7.22 (5H, m), 4.36–4.31 (2H, m), 4.29–4.23 (1H, m), 4.12 (1H, t, J = 8.2 Hz), 3.76 (1H, t, J = 8.2 Hz), 3.49–3.44 (1H, m), 2.62–2.47 (2H, stack), 2.41–2.28 (1H, m), 1.79–1.73 (1H, m), 1.36 (3H, t, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ: (*trans*) 164.8 (t, J = 32.2 Hz), 142.6, 129.4, 127.8, 127.3, 115.9 (t, J = 250.4 Hz), 75.2, 73.8–73.7 (m), 63.5, 44.9, 40.6, 41.4 (t, J = 22.5 Hz), 14.6; (*cis*) 164.8 (t, J = 32.2 Hz), 142.2, 129.4, 127.8, 127.4, 115.9 (t, J = 250.4 Hz), 74.8, 74.5–74.4 (m), 63.5, 46.0, 41.7, 41.2 (t, J = 24.3 Hz), 14.6. ^{19}F NMR ($CDCl_3$) δ: (*trans*) −102.62 (1F, dt, $J_{F–F}$ = 263.4 Hz, $J_{H–F}$ = 14.1 Hz), −108.82 (1F, ddd, $J_{F–F}$ = 263.4 Hz, $J_{1H–F}$ = 23.5 Hz, $J_{2H–F}$ = 14.1 Hz); (*cis*) −102.83 (1F, dt, $J_{F–F}$ = 263.4 Hz, $J_{H–F}$ = 14.1 Hz), −108.25 (1F, ddd, $J_{F–F}$ = 263.4 Hz, $J_{1H–F}$ = 23.5 Hz, $J_{2H–F}$ = 18.8 Hz). HRMS (EI): $C_{15}H_{18}F_2O_3$ cacld: 284.1224; found: 284.1200.

Acknowledgement

We thank the National Natural Science Foundation of China (20672034) for financial support.

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