ELSEVIER

Journal of Fluorine Chemistry 74 (1995) 9–13

JOURNAL OF FLUORINE CHEMISTRY

Synthesis of per(poly)fluoroalkylisoxazoles

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Received 20 May 1994; accepted 10 January 1995

Abstract

4,5-(1′,4′-Butylene)-3-per(poly)fluoroalkylisoxazoles **2** are synthesized by the reaction of the α-per(poly)fluoroalkyl cyclohexanones **1** with hydroxylamine hydrochloride in the presence of potassium carbonate under reflux in ethanol. The isomeric 3,4-(1′,4′-butylene)-5-per(poly)fluoroalkylisoxazoles **3** can be prepared by a reaction of **1**, first with hydroxylamine hydrochloride to give the corresponding oximes **4**, followed by the treatment of the resultant reaction mixture with potassium carbonate in a one-pot procedure.

Keywords: Synthesis; Per(poly)fluoroalkylisoxazoles; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

Isoxazoles play important roles in medicinal and agricultural chemistry [1]. Moreover, they are useful precursors of several functional groups by ring modification and cleavage [2,3]. Recently, much attention has been paid to the development of synthetic methodologies for heterocyclic compounds bearing a trifluoromethyl or perfluoroalkyl group because of their ability to enhance biological activities and various applications to the material sciences [4]. However, high yielding regiospecific methods for the synthesis of fluoroalkylisoxazoles are still quite limited. They are mainly prepared by the 1,3-dipolar cycloaddition of nitrile oxide to acetylenes or 1,3-dicarbonyl derivatives [5]. However, only the aromatic nitrile oxides are readily available, while the nonaromatic ones are unstable and dimerize to fluoroxanes. Another route to the formation of fluoroalkylisoxazoles is the cyclocondensation of α,β-unsaturated carbonyl derivatives with hydroxylamine, which, however, leads to the formation of a mixture of isomers [6]. We and others proposed recently different methods for preparing α-per(poly)fluoroalkyl ketones **1** [7]. We wish to report in this paper the use of compounds **1** to synthesize the hitherto unknown per(poly)fluoroalkylisoxazoles.

2. Results and discussion

Our method is based on the observation of several groups which reported that amines react with α-per(poly)fluoroalkyl carbonyl derivatives to produce the intermediate, β-*N*-substituted-α,β-unsaturated carbonyl derivatives, which undergo hydrolysis to yield 1,3-dicarbonyl derivatives upon treatment with acid solution (Scheme 1) [8]. On the basis of this, and the known generality of 1,3-dicarbonyl derivatives for the synthesis of isoxazoles by condensation with hydroxylamine [9], it was anticipated that the reaction of α-per(poly)fluoroalkyl carbonyl derivatives with hydroxylamine would lead to the formation of per(poly)fluoroalkylisoxazoles. In fact, it was found that when α-pentafluoroethyl cyclohexanone (**1a**) was allowed to react with hydroxylamine in ethanol under reflux in the presence of potassium carbonate, 4,5-(1′,4′-butylene)-3-trifluoromethylisoxazole (**2a**) was obtained in 90% yield (Scheme 2). The ^{19}F NMR spectrum **2a** revealed a single peak at δ −14.3 ppm and suggested a trifluoromethyl group (other than a pentafluoroethyl group as in the starting material). The ^{13}C NMR spectrum showed a substituted isoxazole ring, δ 110.9 (s, C_4); 153.1 (q, $J_{C-F}=36.2$ Hz, C_3); 171.2 (s, C_5) ppm, and indicated further that the trifluoromethyl group was substituted at the C_3 position of the isoxazole ring [10]. (The spin coupling between the fluorine of the trifluoromethyl group and the carbon of the isoxazole ring, which is linked directly with the trifluoromethyl group, is as much as 36.2 Hz.) The MS spectrum of **2a** showed $m/z=191$ (M^+, 53) (see Experimental details).

A series of α-per(poly)fluoroalkyl cyclohexanones **1a–g**, which were prepared conveniently from per(poly)-fluoroalkyl iodides by the known method [7], were found to react smoothly with hydroxylamine in ethanol under reflux in the presence of potassium carbonate to give 4,5-(1′,4′-

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SSDI 0022-1139(95)03248-7

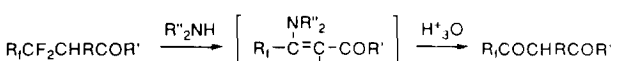
Table 1
Preparation of per(poly)fluoroalkylisoxazoles

Entry No.	Ketones (1)	Method [a]	Time (h) [b]	Product [c]	Yield (%) [d]
1	**1a** [7b]	A	10	**2a**	90
2	**1b** [7a]	A	12	**2b**	80
3	**1c** [7b]	A	12	**2c**	79 [e]
4	**1d** [7a]	A	12	**2d**	75 [e]
5	**1e** [7a]	A	10	**2e**	82
6	**1f** [7a]	A	14	**2f**	81 [e]
7	**1g** [7e]	A	14	**2g**	85 [e]
8	**1c** [7a]	B	12	**3c**	50
9	**1d** [7a]	B	12	**3d**	49
10	**1e** [7a]	B	10	**3e**	52
11	**1f** [7a]	B	12	**3f**	45

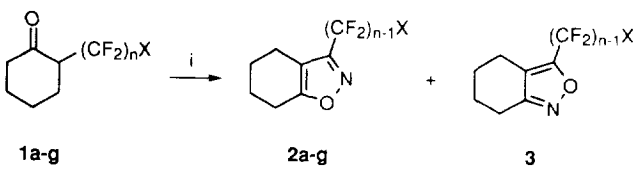
[a] See Experimental details.
[b] All reactions were carried out in $EtOH/H_2O$ under reflux.
[c] All the products are hitherto unknown and are fully characterized by ^1H NMR, ^{19}F NMR, IR spectroscopy, MS and elemental analyses.
[d] Isolated yield.
[e] < 7% of the corresponding isomer **3** was also obtained.

butylene)-3-per(poly)fluoroalkylisoxazoles **2a–g** (Scheme 2) in high yield as listed in Table 1. It should be noted that the per(poly)fluoroalkyl group of the product is one carbon shorter than that of the starting material. In some cases, an isomeric 5-per(poly)fluoroalkylisoxazole (**3**) was also formed, which could be easily separated by column chromatography on silica gel and was shown to be different from **2** by ^{19}F NMR spectroscopy. The spectrum of **3** obtained using these reaction conditions was identical with those from samples made using a variation of this method (see Scheme 4).

Based on known fact [8], the reaction of α-per(poly)-fluoroalkyl ketones with hydroxylamine hydrochloride in the presence of potassium carbonate to give 3-per(poly)-fluoroalkylisoxazoles could be potentially considered to proceed as follows: the α-per(poly)fluoroalkyl ketones release hydrogen fluoride in the presence of K_2CO_3 to give the β-per(poly)fluoroalkyl-α,β-unsaturated ketones, which react with hydroxylamine through an initial Michael reaction, followed by an elimination of another hydrogen fluoride, and subsequent ring-closure and aromatization to provide the 3-per(poly)fluoroalkylpyrazoles **2** (Path I, Scheme 3). β-Per(poly)fluoroalkyl-α,β-unsaturated ketones could also react with hydroxylamine through a 1,2-addition at the carbonyl group, to give an oxime **5**, followed by an intramolecular nucleophilic addition and subsequent elimination of hydrogen fluoride to give the 5-per(poly)fluoroalkyl isoxazoles **3** (Path II, Scheme 3).



Scheme 1.



1a-g **2a-g** **3**

a: X=F, n=2;
b: X=F, n=4;
c: X=F, n=6;
d: X=F, n=8;
e: X=Cl, n=4;
f: X=Cl, n=6;
g: X=Cl, n=8.

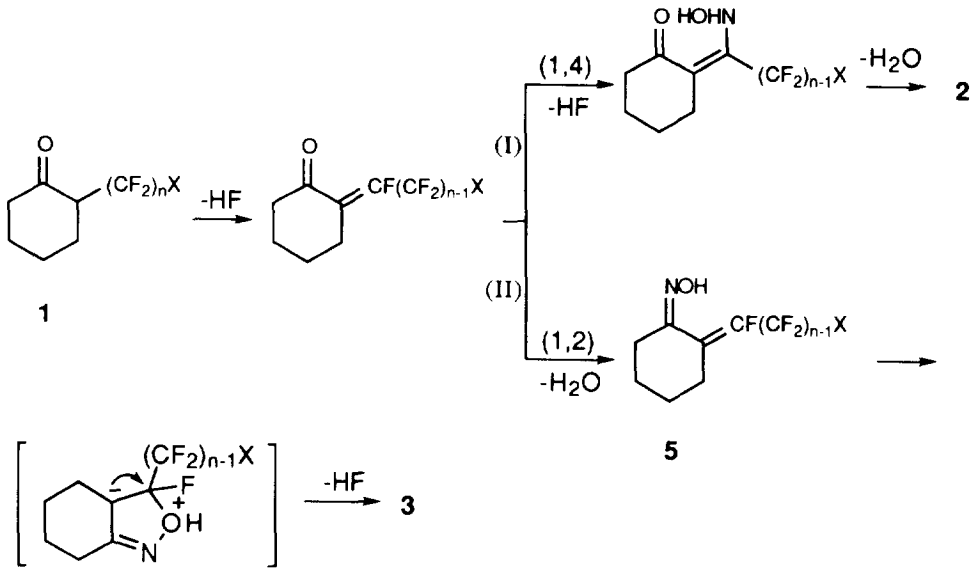
Scheme 2. Reagents and conditions (i) $NH_2OH \cdot HCl$, K_2CO_3, $EtOH/H_2O$, reflux.

Experimentally, α-per(poly)fluoroalkyl ketones **1** reacted with hydroxylamine hydrochloride under reflux in ethanol in the absence of potassium carbonate, leading to the formation of the corresponding oximes **4** alone in almost quantitative yield. The oximes could be separated by distillation under reduced pressure. When compounds **4** were treated with potassium carbonate in ethanol/water under reflux, 5-per(poly)fluoroalkylisoxazoles **3** were obtained. Hence, a tandem reaction of **1**, first with hydroxylamine hydrochloride, followed by the treatment of the resultant reaction mixture with potassium carbonate to give **3** in a one-pot procedure, was developed (Scheme 4). The results are summarized in Table 1.

In summary, reactions of α-per(poly)fluoroalkyl ketones **1** with hydroxylamine hydrochloride under different conditions, leading to the regiospecific formation of 3- and 5-per(poly)fluoroalkylisoxazoles, respectively, have been achieved.

3. Experimental details

^1H NMR spectra were recorded on a Varian EM-360A, JEDL FX-90Q or Bruker AM-300 spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid (δ



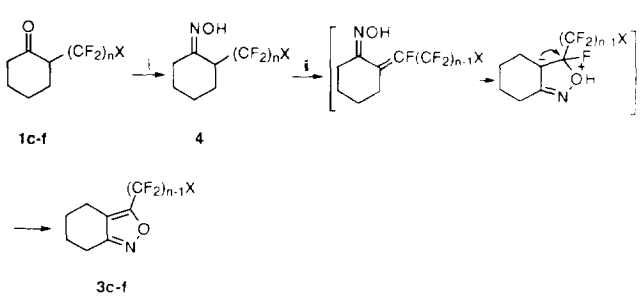
Scheme 3.

0.00) as external standard, downfield shifts being designed as negative. ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. Infrared spectra were taken on a Shimadzu 440-IR spectrometer, and mass spectra were done on a Finnigan 4021 GC/MS/DC instrument. All reactions were monitored routinely with aid of ^{19}F NMR spectroscopy.

All chemicals and reagents were of analytical grade and were used without further purification. Petroleum ether refers to the fraction boiling in the range 30–60 °C. α-Fluoroalkyl ketones **1** were prepared according to Ref. [7].

3.1. General procedure (A) for the preparation of 3-per(poly)fluoroalkylisoxazoles 2

A solution of α-per(poly)fluoroalkyl ketone (**1**) (10 mmol) in ethanol (10 ml) was added to a stirred mixture of hydroxylamine hydrochloride (15 mmol) and potassium carbonate (40 mmol) in ethanol (20 ml) and water (8 ml) at room temperature. The resultant reaction mixture was heated to reflux for several hours, then cooled, diluted with water and extracted with diethyl ether (40 ml × 2). The combined organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography on silica gel column with petroleum ether as solvent, and this solvent was then distilled off.



Scheme 4. Reagents and conditions: (i) $NH_2OH \cdot HCl$, EtOH, reflux. (ii) K_2CO_3, $EtOH/H_2O$, reflux.

4,5-(1′,4′-Butylene)-3-trifluoromethylisoxazole (**2a**): Colourless liquid. IR (cm^{-1}): 3100; 2900; 2840; 1460; 1440; 1250–1100. ^1H NMR ($CDCl_3$) δ: 1.80 (m, 2H); 1.90 (m, 2H); 2.54 (t, J = 6.1 Hz, 2H); 2.75 (t, J = 6.1 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ: 18.9 (s); 21.7 (s); 21.9 (s); 22.5 (s); 110.9 (s, C_4); 120.5 (q, J_{C-F} = 270.3 Hz, CF_3); 153.1 (q, J_{C-F} = 36.2 Hz, C_3); 171.2 (s, C_5) ppm. ^{19}F NMR ($CDCl_3$) δ: −14.3 (s) ppm. MS m/z (relative intensity): 191 (M^+, 53.33); 192 (7.75); 172 (21.67); 163 (50.00); 135 (19.20); 122 (100.00); 94 (68.50); 69 (44.08); 67 (98.33); 55 (35.83); 42 (20.84). Elemental analysis: Calc. for $C_8H_8NF_3O$: C, 50.27; H, 4.22; N, 7.33; F, 29.82%. Found: C, 50.07; H, 4.35; N, 7.82; F, 29.46%.

4,5-(1′,4′-Butylene)-3-heptafluoropropylisoxazole (**2b**): Colourless liquid. IR (cm^{-1}): 2900; 2840; 1460; 1440; 1250–1100. ^1H NMR ($CDCl_3$) δ: 1.8–1.9 (m, 4H); 2.54 (t, J = 6.1 Hz, 2H); 2.76 (t, J = 6.1 Hz, 2H) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.0 (s, 3F); 35.4 (s, 2F); 49.3 (s, 2F) ppm. MS m/z (relative intensity): 291 (M^+, 65.45); 292 (18.24); 263 (49.50); 235 (25.18); 172 (68.17); 122 (100.00); 94 (82.15); 67 (89.17); 55 (43.22). Elemental analysis: Calc. for $C_{10}H_8NF_7O$: C, 41.25; H, 2.77; N, 4.81%. Found: C, 41.42; H, 2.92; N, 4.65%.

4,5-(1′,4′-Butylene)-3-undecafluoropentylisoxazole (**2c**): Colourless liquid. IR (cm^{-1}): 2900; 2845; 1540; 1460; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.81 (m, 2H); 1.90 (m, 2H); 2.56 (t, J = 6.4 Hz, 2H); 2.75 (t, J = 6.4 Hz, 2H) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.7 (s, 3F); 34.0 (s, 2F); 45.1 (m, 4F); 49.0 (s, 2F) ppm. MS mz (relative intensity): 391 (M^+, 93.5); 392 (16.34); 363 (49.50); 335 (17.50); 172 (25.00); 122 (100.00); 94 (71.50); 67 (98.50); 55 (48.42); 42 (28.33). Elemental analysis: Calc. for $C_{12}H_8NF_{11}O$: C,

36.85; H, 2.06; N, 3.58%. Found: C, 37.83; H, 2.16; N, 3.44%.

4,5-(1′,4′-Butylene)-3-pentadecafluoroheptylisoxazole (**2d**): Colourless liquid. IR (cm^{-1}): 2900; 2840; 1540; 1450; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.8–1.9 (m, 4H); 2.55–2.75 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.8 (s, 3F); 34.0 (s, 2F); 45.8 (m, 8F); 49.0 (s, 2F) ppm. MS *m/z* (relative intensity): 491 (M^+, 35.58); 492 (14.58); 463 (15.00); 172 (56.50); 122 (100.00); 94 (62.50); 69 (41.25); 67 (55.75); 55 (27.33); 42 (30.50). Elemental analysis: Calc. for $C_{14}H_8NF_{15}O$: C, 34.23; H, 1.64; N, 2.85%. Found: C, 34.85; H, 1.70; N, 2.58%.

4,5-(1′,4′-Butylene)-3-(3′-chlorohexafluoropropyl)-isoxazole (**2e**): Colourless liquid. IR (cm^{-1}): 2905; 2840; 1545; 1450; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.81 (m, 2H); 1.91 (m, 2H); 2.55 (t, J=6.4 Hz, 2H); 2.75 (t, J=6.4 Hz, 2H) ppm. ^{19}F NMR ($CDCl_3$) δ: −10.3 (s, 2F); 33.4 (s, 2F); 43.5 (s, 2F) ppm. MS *m/z* (relative intensity): 307 (M^+, 34.25); 309 (12.00); 279 (18.33); 281 (5.84); 172 (36.70); 122 (100.00); 94 (61.5); 67 (64.25); 55 ((31.75); 42 (31.58). Elemental analysis: Calc. for $C_{10}H_8NClF_6O$: C, 39.04; H, 2.62; N, 4.55; F, 37.06%. Found: C, 39.05; H, 2.31; N, 4.56; F, 36.83%.

4,5-(1′,4′-Butylene)-3-(5′-chlorodecafluoropentyl)-isoxazole (**2f**): Colourless liquid. IR (cm^{-1}): 2900; 2840; 1620; 1460; 1440; 1250–1100. ^1H NMR ($CDCl_3$) δ: 1.8–1.9 (m, 4H); 2.55 (t, J=6.4 Hz, 2H); 2.75 (t, J=6.4 Hz, 2H) ppm. ^{19}F NMR ($CDCl_3$) δ: −9.8 (s, 2F); 33.7 (s, 2F); 42.8 (m, 4F); 44.6 (s, 2F) ppm. MS *m/z* (relative intensity): 407 (M^+, 50.50); 409 (20.00); 379 (24.17); 381 (8.33); 351 (10.00); 353 (3.08); 172 (94.50); 122 (100.00); 94 (77.33); 67 (89.33); 55 (47.50). Elemental analysis: Calc. for $C_{12}H_8NClF_{10}O$: C, 35.36; H, 1.98; N, 3.44; Cl, 8.70; F, 46.61%. Found: C, 35.48; H, 2.09; N, 3.38; Cl, 8.75; F, 46.31%.

4,5-(1′,4′-Butylene)-3-(7′-chlorotetradecafluoroheptyl)-isoxazole (**2g**): Colourless liquid. IR (cm^{-1}): 2900; 2840; 1625; 1460; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.81 (m, 2H); 1.90 (m, 2H); 2.55 (t, J=6.4 Hz, 2H); 2.76 (t, J=6.4 Hz, 2H) ppm. ^{19}F NMR ($CDCl_3$) δ: −9.5 (s, 2F); 33.8 (s, 2F); 42.8 (s, 2F); 43.9 (m, 6F); 44.4 (s, 2F) ppm. MS *m/z* (relative intensity): 507 (M^+, 32.25); 309 (22.08); 508 (78.33); 510 (26.50); 479 (14.17); 481 (4.17); 172 (100.00); 131 (33.30); 122 (77.20); 94 (64.17); 67 (66.33); 55 (38.33). Elemental analysis: Calc. for $C_{14}H_8NClF_{14}O$: C, 33.12; H, 1.59; N, 2.76; F, 52.39%. Found: C, 33.29; H, 1.67; N, 2.61; F, 52.10%.

α-(6′-Chloroperfluorohexyl)cyclohexanone oxime (**4f**): a solution of hydroxylamine hydrochloride (15 mmol) and α-(6′-chloroperfluorohexyl)cyclohexanone (**1f**) (10 mmol) in ethanol (30 ml) was refluxed for 2 h, then diluted with water (20 ml) and extracted with diethyl ether (40 ml×2). The combined organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was distilled under reduced pressure to give **4f** in 95% yield, b.p. 110 °C/0.8 mmHg. Colourless liquid. IR (cm^{-1}): 3300; 1650; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.3–2.8 (m, 8H); 3.85 (m, 1H); 10.25 (s, 1H) ppm. ^{19}F NMR ($CDCl_3$) δ: −8.4 (s, 2F); 37.0 (s, 2F); 43.8 (m, 6F); 45.8 (s, 2F) ppm. MS *m/z* (relative intensity): 447 (M^+, 6.47); 449 (9.96); 448 (M^++1, 61.41); 450 (20.58); 430 (28.22); 432 (10.79); 412 (10.80); 162 (44.98); 112 (87.14); 85 (100.00); 87 (23.24); 55 (57.59); 41 (41.49). Elemental analysis: Calc. for $C_{12}H_{10}NClF_{12}O$: C, 32.20; H, 2.25; N, 3.13; F, 50.93%. Found: C, 32.53; H, 2.01; N, 3.29; F, 50.74%.

3.2. General procedure (B) for the preparation of 5-per(poly)fluoroalkylisoxazoles **3**

A solution of hydroxylamine hydrochloride (15 mmol) and α-per(poly)fluoroalkyl ketone (**1**) (10 mmol) in ethanol (30 ml) was refluxed for 2 h, then a solution of potassium carbonate (40 mmol) in water (10 ml) was added. The resultant reaction mixture was heated to reflux for several hours, cooled, diluted with water (20 ml) and extracted with diethyl ether (40 ml×2). The combined organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography on silica gel column with petroleum ether as solvent, and this solvent was then distilled off.

3,4-(1′,4′-Butylene)-5-undecafluoropentylisoxazole (**3c**): Colourless liquid. IR (cm^{-1}): 2900; 2840; 1620; 1460; 1440; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.85 (m, 4H); 2.65 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.7 (s, 3F); 35.4 (s, 2F); 49.0 (s, 2F); 45.1 (m, 4F) ppm. MS *m/z* (relative intensity): 391 (M^+, 83.50); 392 (16.25); 363 (15.25); 122 (100.00); 94 (61.50); 67 (88.50); 55 (38.42); 42 (28.17). Elemental analysis: Calc. for $C_{12}H_8NF_{11}O$: C, 36.85; H, 2.06; N, 3.58%. Found: C, 36.83; H, 2.26; N, 3.49%.

3,4-(1′,4′-Butylene)-5-pentadecafluoroheptylisoxazole (**3d**): Colourless liquid. IR (cm^{-1}): 2900; 1620; 1450; 1340; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.85 (m, 4H); 2.65 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.8 (s, 3F); 35.4 (s, 2F); 45.8 (m, 8F); 49.0 (s, 2F) ppm. MS *m/z* (relative intensity): 491 (M^+, 39.58); 492 (12.73); 122 (100.00); 131 (21.25); 94 (81.25); 67 (65.75); 42 (30.33). Elemental analysis: Calc. for $C_{14}H_8NF_{15}O$: C, 34.23; H, 1.64; N, 2.85%. Found: C, 34.74; H, 1.71; N, 2.68%.

3,4-(1′,4′-Butylene)-5-(3′-chlorohexafluoropropyl)-isoxazole (**3e**): Colourless liquid. IR (cm^{-1}): 2900; 1460; 1340; 1200–1100. ^1H NMR ($CDCl_3$) δ: 1.85 (m, 4H); 2.66 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −9.8 (s, 2F); 35.4 (s, 2F); 43.5 (s, 2F) ppm. MA *m/z* (relative intensity): 307 (M^+, 44.25); 309 (16.17); 122 (100.00); 94 (67.50); 67 (68.25); 55 (28.75); 42 (19.58). Elemental analysis: Calc. for $C_{10}H_8NF_6ClO$: C, 39.04; H, 2.62; N, 4.55; F, 37.06%. Found: C, 39.15; H, 2.84; N, 4.56; F, 36.83%.

3,4-(1′,4′-Butylene)-5-(5′-chlorodecafluoropentyl)-isoxazole (**3f**): Colourless liquid. IR (cm^{-1}): 2900; 2840; 1620; 1460; 1450; 1250–1100. ^1H NMR ($CDCl_3$) δ: 1.86 (m, 4H); 2.67 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) δ: −9.8 (s, 2F); 35.3 (s, 2F); 42.8 (m, 4F); 44.6 (s, 2F) ppm. MS *m/z* (relative intensity): 407 (M^+, 52.17); 409 (21.13);

372 (7.17); 122 (100.00); 94 (78.17); 67 (92.43); 55 (48.19); 42 (12.15). Elemental analysis: Calc. for $C_{12}H_8NClF_{10}O$: C, 35.36; H, 1.98; N, 3.44; F, 46.61%. Found: C, 35.47; H, 2.06; N, 3.29; F, 46.45%.

Acknowledgement

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

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