Reaction of Imidazole Anions with Difluorodiiodomethane and Their Products Conversion in Sulfinatodehalogenation System

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Treatment of difluorodiiodomethane with *N*-sodium salts of imidazoles at −15 ℃ gave *N*-difluoroiodomethylated imidazoles (3) in good yields. The addition of 3 to alkyne or alkenes initiated by sodium dithionate at room temperature resulted in the corresponding adducts in high yields.

Keywords difluorodiiodomethane, imidazole, sulfinatodehalogenation, alkene

Introduction

Compared with dichlorodifluoromethane and dibromodifluoromethane, their analogue, difluorodiiodomethane CF_2I_2(**1**) has been less investigated, probably because this reagent was difficult to prepare. Dolbier *et al*.[1] first reported its photo- or benzoyl-peroxide induced reaction with alkenes. After our finding of a simple, good method to prepare **1**,[2] we were attracted to study its properties as a difluorocarbene or difluoroiodomethyl radical source. It was found that **1** can add to electron-rich olefins in the presence of $[PdCl_2(PPh_3)_2]$,[3] $[Pd(PPh_3)_4]$,[3] $Na_2S_2O_4$,[4] Fe[5] or unactivated Zn.[5] Lead tetraacetate is even able to induce the addition reaction of **1** to poly- or perfluoroalkenes.[6] **1** can also be used as a trifluoromethylating agent for enamines and azo-aromatic compounds when irradiated in dimethyl formamide.[7] Different from CF_2Br_2, diethyl difluoroiodomethylphosphonate $[ICF_2P(O)(OEt)_2]$ could be directly obtained in nearly quantitative yield by simple treatment of **1** with triethylphosphite in diethyl ether.[8]

Unlike CF_2Cl_2, CF_2Br_2, CF_2BrCl, when **1** was suffered from nucleophilic attack by phenoxides, $ArOCF_2I$ was obtained only in 7%—15% yields, the carbonate ($ArOCO_2Ar$) being the major products.[9] While **1** was treated with thiophenoxides, difluoromethylene derivatives ($ArSCF_2I$, $ArSCF_2SAr$ and $ArSCF_2H$) were obtained also in low yields.[9]

The difluoromethylene moiety has attracted much attention over the years because this group is usually regarded as isopolar and isosteric replacement for oxygen.[10] The introduction of difluoromethyl group into heterocycles may enhance the biological properties as compared to the parent compounds.[11] The introduction of the heteroaryl-*N*-difluoromethyl moiety, *e.g.* imidazole-*N*-CF_2- or benzimidazole-*N*-CF_2-, into organic compounds can induce new biological properties[12] and it would be of interest to find more suitable methods for preparing this kind of difluoromethylene-functionalized compounds.

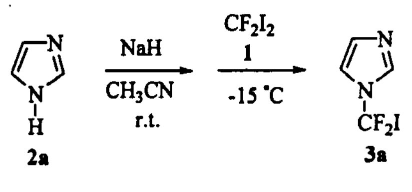
Since the condensation of the sodium salts of pyrazole, imidazole and benzimidazole with CF_2Br_2 gave the corresponding bromodifluoromethylated derivatives,[13] we present here the results of difluorodiiodomethane in the similar fashion and the further conversion of their difluoroiodomethylated products.

Results and discussion

Halophilic reactions of difluorodiiodomethane with N-sodium salts of imidazoles

First, we used imidazolyl-sodium as a nucleophilic reagent. It was found that **1** reacted too vigorously with the imidazolyl-sodium in CH_3CN at room temperature to give the desired product, the reactants becoming a heavy tar. While the temperature was depressed to −15 ℃, 1-difluoroiodomethylimidazole **3a** was obtained in 70% yield after a simple work-up (Scheme 1).

Scheme 1



As the reaction was carried out in a two-phase solution, we tried to add a catalytic amount of 18-crown-6 in the reaction. But the yield could not be improved. Similarly, 2-methylimidazole, benzimidazole and indole gave

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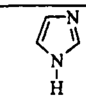
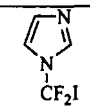
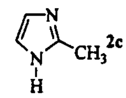
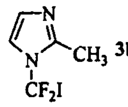
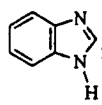
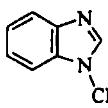
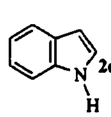
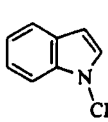
the corresponding 1-difluoroiodomethylated derivatives. The results are summarized in Table 1.

Table 1 Reaction of sodium salts of imidazole, 2-methylimidazole, benzimidazole and indole with CF_2I_2(1)[a]

Entry	Substrate	Product	Yield[b] (%)
1	 2a	 3a	70
2	 2c	 3b	64
3	 2c	 3c	81
4	 2d	 3d	58

[a] 1 : 2 = 1.5 : 1, at − 15 ℃ in CH_3CN for 3 h. [b] Isolated yields based on 2.

However, when sodium salts of benzotriazole, carbazole or pyrrole reacted with CF_2I_2 (1) under similar conditions, no desired products were obtained because of heavy tarring.

Addition reactions of the difluoroiodomethylated compounds with alkyne or alkene in sulfinatodehalogenation system

Sulfinatodehalogenation of perhalocarbons, discovered and developed by Huang and his co-workers since 1983, is a well-known method for initiating the addition of perfluoroalkyl iodides or bromides to alkenes and alkynes.[14] A previous report, however, on the synthesis of bromodifluoromethylated compounds has shown that the bromodifluoromethyl group is not sufficiently reactive to undergo the further addition (Scheme 2).[4,15]

Scheme 2

$$CF_2Br_2 + H_2C{=}CHR \xrightarrow[CH_3CN/H_2O]{Na_2S_2O_4/NaHCO_3} BrCF_2CH_2CHBrR \not\longrightarrow (RCHBrCH_2)_2CF_2$$

Interestingly, the corresponding difluoroiodomethylated compounds were found to proceed further addition to alkene or alkyne smoothly under standard sulfinatodehalogenation conditions (Scheme 3).

The results are summarized in Table 2.

As shown in Scheme 3 and Table 2, **3a**—**3c** reacted with phenylacetylene (**5**), alkenes **7a**—**7d** or **9** to give the corresponding 1:1 adducts in high yields. However, 1-difluoroiodomethylindole (**3d**) was unreactive under the similar conditions.

In order to compare the activity of 1-difluoroiodobenzimidazole versus 1-bromodifluorobenzimidazole,[13] 1-bro-

Scheme 3

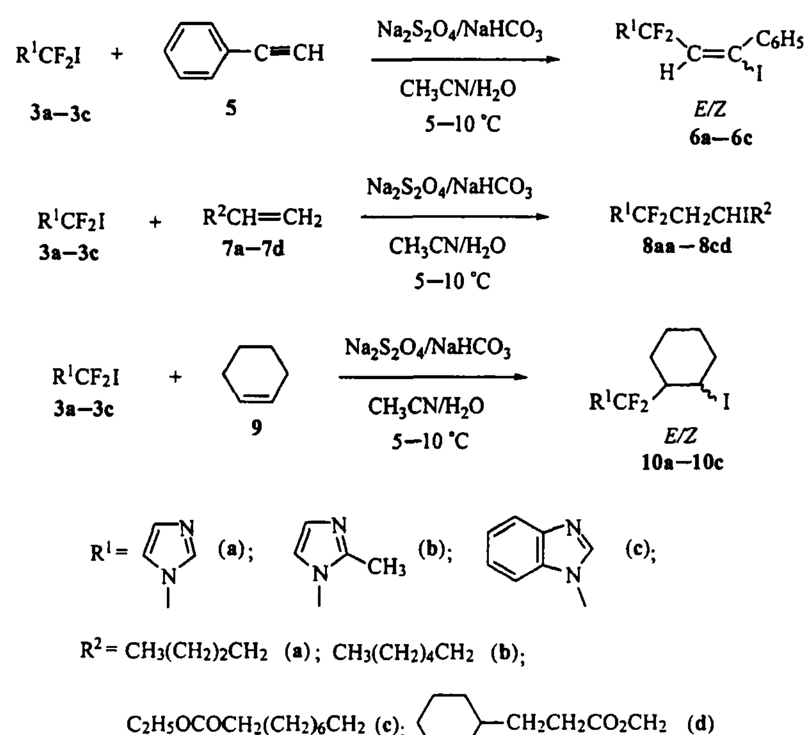


Table 2 Reaction of **3** with phenylacetylene **5**, alkenes **7** or **9** in CH_3CN/H_2O (5 : 1, *V/V*) in the presence of $Na_2S_2O_4/NaHCO_3$[a]

Entry	Iodide	Alkyne or alkene	Product	Yield[b] (%)
1	**3a**	**5**	**6a**	76[c] (1:1)
2	**3b**	**5**	**6b**	71[c] (1:2)
3	**3c**	**5**	**6c**	64[c] (1:2)
4	**3a**	**7a**	**8aa**	80
5	**3a**	**7b**	**8ab**	78
6	**3a**	**7c**	**8ac**	85
7	**3a**	**7d**	**8ad**	82
8	**3b**	**7a**	**8ba**	77
9	**3b**	**7b**	**8bb**	87
10	**3b**	**7c**	**8bc**	81
11	**3b**	**7d**	**8bd**	79
12	**3c**	**7a**	**8ca**	72
13	**3c**	**7b**	**8cb**	78
14	**3c**	**7c**	**8cc**	73
15	**3c**	**7d**	**8cd**	80
16	**3a**	**9**	**10a**	70[c] (1:1)
17	**3b**	**9**	**10b**	67[c] (1:1)
18	**3c**	**9**	**10c**	75[c] (1:1)

[a] **3** : **5** (or **7** or **9**) : $Na_2S_2O_4$: $NaHCO_3$ = 1 : 1.5 : 5 : 5; the reaction temperature was kept at 5—10 ℃. [b] Isolated yields based on **3**. [c] Ratio of *E* : *Z*, based on ^{19}F NMR.

modifluorobenzimidazole was allowed to react with **7c** under the same conditions, but the starting materials remained unchanged. This demonstrated that 1-bromodifluorobenzimidazole is indeed less reactive than 1-difluoroiodobenzimidazole in the sulfinatodehalogenation initiation system. Taking the reaction of **3a** with **7c** as an example, the effects of reaction temperature and solvent on the yields were investigated and shown in Table 3.

From Table 3, it was observed that the complete conversion of **3a** to **8ac** required as long as 24 h at 30 ℃ (Entries 1, 2). However, when the temperature was elevated to 60 ℃, although the conversion time required was shortened, the adduct was obtained in very low yield (Entry 3). The suitable temperature is 5—10 ℃. Meanwhile, the ratio of acetonitrile to water has a significant effect on the yield of **7c**. Water is necessary for this reaction (Entry 8), but too much water may result in the decrease of the yield (Entry 6).

In conclusion, we have provided an efficient way for synthesizing the imidazolyl gem-difluorinated compounds from nucleophilic substitution of imidazole anions on CF_2I_2 followed by addition reaction to alkenes or alkyne in the presence of $Na_2S_2O_4/NaHCO_3/CH_3CN/H_2O$.

Experimental

Melting points were recorded at atmospheric pressure and were uncorrected. ^1H NMR and ^{19}F NMR spectra were recorded on a Varian-360L instrument or Bruker AM-300 spectrometer for solution in $CDCl_3$ or CD_3COCD_3 with TMS and $CFCl_3$ as the internal and external standards respectively, and the upfields are negative. Coupling constants are given in Hz. IR spectra were obtained with a Perkin Elmer 983G spectro-photometer. Lower resolution mass spectra (LRMS) and higher resolution mass spectra (HRMS) were obtained on a HP-5989a and Finnigan MAT-8430 instruments, respectively. Organic solvents were dried by standard methods when necessary. All the commercially available reagents were of analytical grade and were used without further purification. Flash column chromatography was carried out using 300—400 mesh silica gel.

Typical procedure for difluoroiodomethylation of **2**

To a solution of imidazole (1.02 g, 15 mmol) in carefully dried CH_3CN (150 mL) was added sodium hydride (0.60 g, 15 mmol, 60%) in small portions. The reaction mixture was stirred for 1 h at room temperature. After cooling the reactant to −15 ℃, **1** (6.84 g, 22.5 mmol) was added dropwise under nitrogen. After being stirred for 3 h at −15 ℃, the mixture was poured into water, extracted with ether (3 × 50 mL). The combined extracts were washed with water (3 × 50 mL) and dried over sodium sulfate. After evaporation of the ether, the residue was subjected to chromatography on silica gel to give **3a** as a deep brown oil.

Table 3 Reaction of **3a** with **7c** under various conditions in the presence of $Na_2S_2O_4/NaHCO_3$[a]

Entry	Ratio (CH_3CN/H_2O, *V/V*)	Temperature (℃)	Time (h)	Conversion (%)	Yield[b] of **8ac**
1	1:1	30	12	80	61
2	1:1	30	24	100	68
3	1:1	60	16	100	6
4	1:1	0	24	100	73
5	1:1	5	24	100	75
6	2:5	5	24	100	44
7	5:1	10	24	100	85
8	1:0	10	24	0	0
9	2:1	10	24	100	76

[a] **3a** : **7c** : $Na_2S_2O_4$: $NaHCO_3$ = 1 : 1.5 : 5 : 5. [b] Determined by ^{19}F NMR.

1-Difluoroiodomethylimidazole (**3a**) Deep brown oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 7.92 (s, 1H, CH), 7.19—7.25 (m, 2H, CH); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −19.2 (s, CF_2); IR ν_{max}: 3128 (w), 1484 (m), 1368 (m), 1282 (m), 1236 (s), 1097 (vs), 1062 (s), 1010 (m), 857 (s) cm^{-1}; MS (EI) m/z (relative intensity): 244 (M^+, 100), 194 (15), 127 (13), 117 (68), 67 (9). Anal. calcd for $C_4H_3F_2IN_2$: C 19.69, H 1.24, N 11.48, F 15.58; found C 19.90, H 1.37, N 11.43, F 15.62.

1-Difluoroiodomethyl-2-methylimidazole (**3b**) Deep brown oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 7.00—7.10 (m, 2H, CH), 2.49 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −19.7 (s, CF_2); IR ν_{max}: 3160 (w), 1631 (w), 1502 (w), 1405 (m), 1282 (s), 1186 (m), 1111 (m), 1087 (s), 1046 (vs), 875 (s), 742 (s) cm^{-1}; MS (EI) m/z (relative intensity): 258 (M^+, 22), 208 (2), 177 (10), 149 (12), 131 (100), 90 (34), 81 (12); HRMS (EI) calcd for $C_5H_5F_2IN_2$ 257.94656, found 257.94629.

1-Difluoroiodomethylbenzimidazole (**3c**) Pale yellow solid. m.p. 139—141 ℃. ^1H NMR ($CDCl_3$, Me_4Si) δ: 8.18 (s, 1H, CH), 7.46—7.88 (m, 4H, ArH); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −21.0 (s, CF_2); IR (KBr) ν_{max}: 3129 (w), 1612 (w), 1498 (vs), 1479 (m), 1454 (s), 1356 (m), 1317 (s), 1286 (s), 1222 (vs), 1209 (s), 1145 (s), 1109 (m), 1028 (vs), 893 (s), 864 (vs), 780 (s), 745 (s), 509 (m) cm^{-1}; MS (EI) m/z (relative intensity): 294 (M^+, 3), 167 (100), 147 (24), 127 (9), 95 (27). Anal. calcd for $C_8H_5F_2IN_2$: C 32.68, H 1.71, N 9.53, F 12.92; found C 32.62, H 1.88, N 9.40, F 12.50.

1-Difluoroiodomethylindole (**3d**) Pale yellow solid. m.p. 59—61 ℃. ^1H NMR ($CDCl_3$, Me_4Si) δ: 7.03—7.53 (m, ArH); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −23.5 (s, CF_2); IR (KBr) ν_{max}: 3116 (m), 1525 (w), 1456 (vs), 1422 (s), 1363 (s), 1313 (m), 1178 (m), 1104 (s), 1022 (vs), 800 (s), 756 (s), 747 (vs) cm^{-1}; MS (EI) m/z (relative intensity): 293 (M^+, 100), 274 (2), 242 (58), 177 (3), 166 (12), 146 (6), 127 (6), 115 (40). Anal. calcd for $C_9H_6F_2IN$: C 36.89, H 2.06, N 4.78, F 12.97; found C 37.05, H 2.13, N 4.57, F 13.04.

Typical procedure for the reaction of **3** *with* **5**, **7** *or* **9** *initiated by the sulfinatodehalogenation system*

Under N_2 atmosphere, with magnetic stirring, a mixture of $Na_2S_2O_4$ (0.87 g, 5 mmol) and $NaHCO_3$ (0.42 g, 5 mmol) was added to a solution of **3** (1 mmol) and **5** (or **7**, or **9**) (1.5 mmol) in CH_3CN (5 mL) and H_2O (1 mL) at 5—10 ℃. After being stirred for 24 h, the reaction mixture was poured into water, extracted with ether (3 × 20 mL) and washed with water (3 × 20 mL). After removal of the solvent, the residue was chromatographied on a silica gel column to give the product **6** (or **8**, or **10**).

1-(1,1-Difluoro-3-iodo-3-phenylallyl)-1H-imidazole (**6a**) Viscous brown oil. ^1H NMR (CD_3COCD_3, Me_4Si) δ: 6.60—7.90 (m, 8H, ArH), 5.77 (t, J = 10.8 Hz, 1H, CF_2CH); ^{19}F NMR (CD_3COCD_3, $CFCl_3$) δ: −64.2 (d, J = 10.7 Hz, $CF_2CH=C$, E-configuration), −65.7 (d, J = 10.7 Hz, $CF_2CH=C$, Z-configuration); IR ν_{max}: 3059 (w), 1633 (w), 1487 (m), 1444 (w), 1372 (m), 1336 (m), 1283 (s), 1239 (vs), 1091 (s), 950 (m), 696 (s) cm^{-1}; MS (EI) m/z (relative intensity): 346 (M^+, 41), 279 (100), 259 (24), 244 (16), 219 (79), 199 (56), 172 (18), 151 (74), 127 (20), 102 (45), 90 (28), 76 (17); HRMS (EI) calcd for $C_{12}H_9F_2IN_2$ 345.97786, found 345.97755.

1-(1,1-Difluoro-3-iodo-3-phenylallyl)-2-methyl-1H-imidazole (**6b**) Viscous brown oil. ^1H NMR (CD_3COCD_3, Me_4Si) δ: 6.89—7.25 (m, 7H, ArH), 5.77 (t, J = 10.1 Hz, 1H, CF_2CH), 2.40 (s, 3H, CH_3); ^{19}F NMR (CD_3COCD_3, $CFCl_3$) δ: −65.7 (d, J = 10.1 Hz, $CF_2CH=C$, E-configuration), −66.4 (d, J = 10.1 Hz, $CF_2CH=C$, Z-configuration); IR ν_{max}: 3058 (w), 1629 (w), 1541 (m), 1489 (w), 1444 (m), 1400 (s), 1337 (w), 1277 (vs), 1230 (w), 1096 (s), 1071 (s), 986 (m), 695 (s), 675 (m) cm^{-1}; MS (EI) m/z (relative intensity): 360 (M^+, 32), 279 (100), 259 (20), 233 (14), 213 (9), 186 (2), 172 (5), 151 (41), 133 (11), 127 (13), 102 (26), 90 (10), 76 (9); HRMS (EI) calcd for $C_{13}H_{11}F_2IN_2$ 359.99351, found 359.99252.

1-(1,1-Difluoro-3-iodo-3-phenylallyl)-1H-benzoimidazole (**6c**) Viscous brown oil. ^1H NMR (CD_3COCD_3, Me_4Si) δ: 8.23 (s, 1H, CH), 6.79—7.72 (m, 9H, ArH), 5.95 (t, J = 8.1 Hz, 1H, CF_2CH); ^{19}F NMR (CD_3COCD_3, $CFCl_3$) δ: −66.2 (d, J = 8.5 Hz, $CF_2CH=C$, E-configuration), −67.3 (d, J = 8.5 Hz, $CF_2CH=C$, Z-configuration); IR ν_{max}: 3059 (w), 1632 (w), 1614 (w), 1498 (m), 1481 (m), 1455 (s), 1368 (s), 1317 (s), 1286 (vs), 1240 (vs), 1216 (s), 1157 (m), 1067 (s), 989 (m), 956 (m), 745 (s), 697 (s) cm^{-1}; MS (EI) m/z (relative intensity): 396 (M^+, 92), 371 (13), 279 (80), 269 (72), 259 (23), 249 (100), 229 (12), 167 (32), 151 (76), 127 (18), 125 (18), 118 (8), 102 (64), 95 (44), 90 (18), 76 (23); HRMS (EI) calcd for $C_{16}H_{11}F_2IN_2$ 395.99351, found 395.99637.

1-(1,1-Difluoro-3-iodoheptyl)-1H-imidazole (**8aa**) Pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 7.81 (s, 1H, ArH), 7.14—7.17 (m, 2H, ArH), 4.10 (m, 1H, CHI), 2.93—3.25 (m, 2H, CF_2CH_2), 1.26—1.88 (m, 6H, $CH_2CH_2CH_2$), 0.93 (t, J = 7.4 Hz, 3H, CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −73.6 and −77.4 (AB system, J_{AB} = 210.4 Hz, CF_2); IR ν_{max}: 3119 (w), 2960 (s), 2933 (s), 2874 (m), 1517 (w), 1488 (s), 1379 (s), 1338 (s), 1286 (vs), 1243 (vs), 1184 (s), 1124 (s), 905 (s), 733 (m), 656 (s) cm^{-1}; MS (EI) m/z (relative intensity): 328 (M^+, 5), 301 (2), 201 (100), 172 (2), 157 (11), 137 (4), 113 (6), 69

(55), 51 (4), 41 (23). Anal. calcd for $C_{10}H_{15}F_2IN_2$: C 36.60, H 4.61, N 8.54, F 11.58; found C 36.66, H 4.65, N 8.58, F 11.63.

1-(1,1-*Difluoro-3-iodononyl*)-1*H-imidazole* (**8ab**) Pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 7.79 (s, 1H, ArH), 7.12—7.16 (m, 2H, ArH), 4.09 (m, 1H, CHI), 2.91—3.24 (m, 2H, CF_2CH_2), 1.68—1.87 (m, 2H, $CHICH_2$), 1.25—1.63 (m, 8H, $CH_2CH_2CH_2CH_2$), 0.89 (t, J = 7.1 Hz, 3H, CH_2CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −73.3 and −77.1 (AB system, J_{AB} = 207.2 Hz, CF_2); IR ν_{max}: 3119 (w), 2958 (s), 2930 (vs), 2858 (s), 1518 (w), 1488 (s), 1467 (m), 1378 (s), 1337 (m), 1298 (s), 1239 (vs), 1198 (s), 1089 (s), 928 (w), 656 (m) cm^{-1}; MS (EI) m/z (relative intensity): 356 (M$^+$, 3), 341 (1), 229 (100), 157 (9), 90 (10), 77 (7), 69 (71), 55 (12), 41 (20). Anal. calcd for $C_{12}H_{19}F_2IN_2$: C 40.46, H 5.38, N 7.86, F 10.67; found C 40.71, H 5.55, N 7.94, F 10.77.

12,12-*Difluoro-12-imidazol-1-yl-10-iodododecanoic acid ethyl ester* (**8ac**) Viscous pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 7.80 (s, 1H, ArH), 7.13—7.17 (m, 2H, ArH), 4.11 (m, 3H, CHI, OCH_2), 2.92—3.24 (m, 2H, CF_2CH_2), 2.19—2.32 (m, 2H, CH_2CO), 1.60—1.79 (m, 2H, $CHICH_2$), 1.24—1.30 (m, 15H, $CH_2CH_2CH_2CH_2CH_2CH_2$, CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −73.6 and −77.5 (AB system, J_{AB} = 210.6 Hz, CF_2); IR ν_{max}: 3123 (w), 2931 (s), 2857 (s), 1733 (vs), 1487 (m), 1374 (s), 1300 (s), 1243 (s), 1186 (s), 1106 (s), 657 (m) cm^{-1}; MS (EI) m/z (relative intensity): 455 (M$^+$, 1), 411 (25), 369 (6), 329 (100), 309 (5), 283 (42), 263 (4), 159 (12), 90 (6), 69 (64), 55 (15), 41 (14). Anal. calcd for $C_{17}H_{27}F_2IN_2O_2$: C 44.75, H 5.96, N 6.14, F 8.33; found C 44.97, H 6.24, N 6.01, F 8.17.

3-*Cyclohexylpropionic acid* 4,4-*difluoro-4-imidazol-1-yl-2-iodobutyl ester* (**8ad**) Viscous pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 7.81 (s, 1H, ArH), 7.14—7.18 (m, 2H, ArH), 4.17—4.38 (m, 3H, $CHICH_2O$), 2.94—3.23 (m, 2H, CF_2CH_2), 2.39 (t, J = 7.7 Hz, 2H, $COCH_2$), 0.83—1.73 (m, 13H, $CH_2C_6H_{11}$); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −74.5 and −76.9 (AB system, J_{AB} = 209.9 Hz, CF_2); IR ν_{max}: 3125 (w), 2925 (vs), 2852 (s), 1741 (vs), 1488 (m), 1450 (m), 1375 (s), 1338 (s), 1293 (s), 1248 (vs), 1159 (vs), 1082 (s), 967 (m), 656 (m) cm^{-1}; MS (EI) m/z (relative intensity): 440 (M$^+$, 1), 357 (23), 344 (14), 313 (95), 231 (9), 217 (15), 175 (19), 157 (100), 137 (13), 121 (16), 90 (16), 83 (10), 69 (41), 55 (36), 41 (23). Anal. calcd for $C_{16}H_{23}F_2IN_2O_2$: C 43.65, H 5.27, N 6.36, F 8.63; found C 43.78, H 5.52, N 6.18, F 8.67.

1-(1,1-*Difluoro-3-iodoheptyl*)-2-*methyl*-1*H-imidazole* (**8ba**) Pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 6.94—7.01 (m, 2H, ArH), 4.13 (m, 1H, CHI), 2.89—3.22 (m, 2H, CF_2CH_2), 2.53 (s, 3H, $ArCH_3$), 1.25—1.89 (m, 6H, $CH_2CH_2CH_2$), 0.92 (t, J = 7.2 Hz, 3H, CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −73.7 and −77.45 (AB system, J_{AB} = 210.3 Hz, CF_2); IR ν_{max}: 3118 (w), 2960 (s), 2934 (s), 1540 (m), 1503 (m), 1405 (vs), 1302 (m), 1276 (vs), 1222 (m), 1172 (m), 1123 (m), 1066 (m), 990 (m), 731 (m) cm^{-1}; MS (EI) m/z (relative intensity): 342 (M$^+$, 5), 299 (3), 215 (100), 195 (3), 171 (13), 131 (8), 109 (8), 90 (13), 83 (52), 69 (9), 55 (10), 41 (21). Anal. calcd for $C_{11}H_{17}F_2IN_2$: C 38.61, H 5.01, N 8.19, F 11.10; found C 38.95, H 5.18, N 8.32, F 11.07.

1-(1,1-*Difluoro-3-iodononyl*)-2-*methyl*-1*H-imidazole* (**8bb**) Pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 6.94—7.27 (m, 2H, ArH), 4.13 (m, 1H, CHI), 2.88—3.22 (m, 2H, CF_2CH_2), 2.53 (s, 3H, $ArCH_3$), 1.64—1.88 (m, 2H, $CHICH_2$), 1.29—1.55 (m, 8H, $CH_2CH_2CH_2CH_2$), 0.89 (t, J = 6.7 Hz, 3H, CH_2CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −74.0 and −78.0 (AB system, J_{AB} = 210.9 Hz, CF_2); IR ν_{max}: 3118 (w), 2958 (s), 2930 (vs), 2859 (s), 1540 (m), 1502 (w), 1404 (vs), 1308 (w), 1301 (m), 1276 (vs), 1220 (m), 1170 (m), 989 (m), 728 (m) cm^{-1}; MS (EI) m/z (relative intensity): 370 (M$^+$, 1), 258 (3), 243 (100), 223 (2), 185 (3), 171 (9), 131 (3), 109 (2), 90 (4), 83 (27), 55 (10), 43 (11), 41 (17); HRMS (EI) calcd for $C_{13}H_{21}F_2IN_2$ 370.07176, found 370.07571.

12,12-*Difluoro-10-iodo-12-(2-methylimidazol-1-yl) dodecanoic acid ethyl ester* (**8bc**) Viscous pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 6.94—7.01 (m, 2H, ArH), 4.09—4.16 (m, 3H, CHI, OCH_2), 2.88—3.22 (m, 2H, CF_2CH_2), 2.53 (s, 3H, $ArCH_3$), 2.29 (t, J = 7.1 Hz, 2H, CH_2CO), 1.78—1.88 (m, 2H, $CHICH_2$), 1.23—1.30 (m, 15H, $CH_2CH_2CH_2CH_2CH_2$-CH_2, CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −73.7 and −77.5 (AB system, J_{AB} = 208.6 Hz, CF_2); IR ν_{max}: 3119 (w), 2931 (vs), 2857 (m), 1735 (vs), 1465 (w), 1405 (s), 1302 (m), 1276 (s), 1180 (m), 1112 (m), 989 (w), 727 (w) cm^{-1}; MS (EI) m/z (relative intensity): 471 (M$^+$ + 1, 1), 425 (14), 383 (3), 343 (100), 323 (4), 297 (23), 255 (3), 171 (9), 157 (5), 111 (3), 90 (5), 83 (58), 69 (5), 55 (16), 43 (9), 41 (17); HRMS (EI) calcd for $C_{18}H_{29}F_2IN_2O_2$ 470.12419, found 470.12266.

3-*Cyclohexylpropionic acid* 4,4-*difluoro-2-iodo-4-(2-methylimidazol-1-yl) butyl ester* (**8bd**) Viscous pale yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 6.96—7.03 (m, 2H, ArH), 4.19—4.40 (m, 3H, $CHICH_2$), 2.91—3.22 (m, 2H, CF_2CH_2), 2.54 (s, 3H, $ArCH_3$), 2.39 (t, J = 7.4 Hz, 2H, CH_2CO), 0.82—1.70 (m, 13H, $CH_2C_6H_{11}$); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −74.6 and −76.9 (AB system, J_{AB} = 211.2 Hz, CF_2); IR ν_{max}: 2926 (vs), 2853 (s), 1742 (vs), 1540 (w), 1450 (m), 1405 (s), 1277 (s), 1159 (s), 1125 (m), 989 (m), 730 (w) cm^{-1}; MS (EI) m/z (relative intensity):

454 (M^+, 1), 439 (1), 371 (11), 327 (85), 299 (30), 245 (8), 231 (10), 189 (19), 184 (5), 171 (100), 151 (11), 121 (16), 95 (15), 83 (41), 69 (16), 55 (40), 41 (24); HRMS (EI) calcd for $C_{17}H_{25}F_2IN_2O_2$ 454.09289, found 454.09057.

1-(1,1-Difluoro-3-iodoheptyl)-1H-benzoimidazole (**8ca**) Viscous pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 8.11 (s, 1H, ArH), 7.37—7.86 (m, 4H, ArH), 4.14 (m, 1H, CHI), 3.05—3.38 (m, 2H, CF_2CH_2), 1.68—1.89 (m, 2H, $CHICH_2$), 1.22—1.52 (m, 4H, CH_2CH_2), 0.89 (t, J = 6.9 Hz, 3H, CH_3CH_2); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −75.3 and −78.4 (AB system, J_{AB} = 211.3 Hz, CF_2); IR ν_{max}: 2959 (m), 2932 (m), 1614 (w), 1500 (m), 1456 (vs), 1371 (m), 1326 (m), 1290 (s), 1238 (vs), 1168 (w), 943 (w), 765 (m), 744 (vs) cm^{-1}; MS (EI) m/z (relative intensity): 378 (M^+, 46), 251 (100), 231 (4), 207 (14), 193 (6), 167 (20), 147 (10), 131 (8), 119 (61), 95 (12), 77 (8), 69 (10), 41 (16); HRMS (EI) calcd for $C_{14}H_{17}F_2IN_2$ 378.04046, found 378.03843.

1-(1,1-Difluoro-3-iodononyl)-1H-benzoimidazole (**8cb**) Viscous pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 8.11 (s, 1H, ArH), 7.35—7.87 (m, 4H, ArH), 4.14 (m, 1H, CHI), 3.10—3.33 (m, 2H, CF_2CH_2), 1.64—1.83 (m, 2H, $CHICH_2$), 1.26—1.49 (m, 8H, $CH_2CH_2CH_2CH_2$), 0.88 (t, J = 6.4 Hz, 3H, CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −75.8 and −78.8 (AB system, J_{AB} = 209.4 Hz, CF_2); IR ν_{max}: 3061 (w), 2957 (s), 2930 (vs), 2858 (s), 1677 (w), 1614 (w), 1500 (s), 1456 (vs), 1370 (m), 1326 (s), 1290 (s), 1237 (vs), 1191 (m), 942 (m), 744 (vs) cm^{-1}; MS (EI) m/z (relative intensity): 406 (M^+, 5), 344 (2), 279 (71), 258 (11), 207 (7), 167 (11), 157 (2), 147 (6), 119 (100), 95 (9), 77 (6), 55 (4), 43 (9), 41 (15); HRMS (EI) calcd for $C_{16}H_{21}F_2IN_2$ 406.07176, found 406.07626.

12-Benzoimidazol-1-yl-12,12-difluoro-10-iodododecanoic acid ethyl ester (**8cc**) Viscous pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 8.11 (s, 1H, ArH), 7.36—7.86 (m, 4H, ArH), 4.09—4.16 (m, 3H, CHI, OCH_2), 3.10—3.27 (m, 2H, CF_2CH_2), 2.29 (t, J = 7.5 Hz, 2H, CH_2CO), 1.17—1.80 (m, 17H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_2$, CH_2CH_3); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −75.8 and −78.8 (AB system, J_{AB} = 211.4 Hz, CF_2); IR ν_{max}: 2980 (w), 2931 (s), 2856 (m), 1733 (s), 1614 (w), 1500 (m), 1480 (w), 1456 (s), 1372 (m), 1326 (m), 1290 (m), 1237 (s), 1183 (s), 1109 (w), 745 (s) cm^{-1}; MS (EI) m/z (relative intensity): 506 (M^+, 4), 461 (24), 419 (14), 379 (100), 359 (15), 333 (26), 313 (10), 291 (5), 209 (16), 207 (12), 167 (13), 147 (10), 131 (4), 119 (80), 95 (8), 77 (6), 55 (22), 43 (14), 41 (28). Anal. calcd for $C_{21}H_{29}F_2IN_2O_2$: C 49.81, H 5.77, N 5.53, F 7.50; found C 50.22, H 5.82, N 5.76, F 7.26.

3-Cyclohexylpropionic acid 4-benzoimidazol-1-yl-4,4-difluoro-2-iodo-butyl ester (**8cd**) Viscous pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 8.13 (s, 1H, ArH), 7.38—7.88 (m, 4H, ArH), 4.23—4.39 (m, 3H, $CHICH_2O$), 3.19—3.50 (m, 2H, CF_2CH_2), 2.33 (t, J = 8.1 Hz, 2H, CH_2CO), 0.87—1.72 (m, 13H, $CH_2C_6H_{11}$); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −76.7 and −78.3 (AB system, J_{AB} = 210.8 Hz, CF_2); IR ν_{max}: 2925 (vs), 2852 (s), 1741 (vs), 1614 (w), 1500 (m), 1456 (s), 1370 (m), 1327 (s), 1292 (s), 1239 (vs), 1160 (vs), 1048 (m), 984 (m), 744 (s) cm^{-1}; MS (EI) m/z (relative intensity): 490 (M^+, 14), 407 (39), 394 (23), 363 (20), 335 (9), 281 (13), 267 (25), 225 (9), 209 (100), 193 (8), 187 (27), 167 (20), 119 (27), 95 (14), 69 (8), 55 (19), 41 (11). Anal. calcd for $C_{20}H_{25}F_2IN_2O_2$: C 48.99, H 5.14, N 5.71, F 7.75; found C 49.36, H 5.31, N 5.88, F 7.65.

1-[Difluoro-(2-iodocyclohexyl)methyl]-1H-imidazole (**10a**) Viscous pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 7.79 (s, 1H, ArH), 7.11—7.17 (m, 2H, ArH), 4.37 (m, 1H, CHI), 2.73 (m, 1H, CF_2CH), 1.40—2.30 (m, 8H, $CH_2CH_2CH_2CH_2$); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −77.5 (AB system, J_{AB} = 208.1 Hz, *E*-configuration), −80.4 (AB system, J_{AB} = 214.4 Hz, *Z*-configuration); IR ν_{max}: 3117 (m), 2942 (s), 2863 (m), 1515 (m), 1487 (s), 1450 (s), 1363 (s), 1331 (s), 1316 (s), 1283 (vs), 1238 (vs), 1195 (s), 1175 (s), 1132 (s), 1094 (vs), 1062 (s), 1001 (m), 952 (m), 937 (s), 903 (s), 825 (m), 656 (s) cm^{-1}; MS (EI) m/z (relative intensity): 326 (M^+, 14), 244 (2), 199 (100), 173 (5), 111 (8), 90 (14), 81 (17), 77 (11), 69 (21), 51 (5), 41 (12); HRMS (EI) calcd for $C_{10}H_{13}F_2IN_2$ 326.00916, found 326.00535.

1-[Difluoro-(2-iodocyclohexyl)methyl]-2-methyl-1H-imidazole (**10b**) Viscous pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 6.95—7.01 (m, 2H, ArH), 4.52 (m, 1H, CHI), 2.75 (m, 1H, CF_2CH), 2.52 (s, 3H, $ArCH_3$), 0.85—2.25 (m, 8H, $CH_2CH_2CH_2CH_2$); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −74.6 (AB system, J_{AB} = 201.0 Hz, *E*-configuration), −76.9 (AB system, J_{AB} = 213.2 Hz, *Z*-configuration); IR ν_{max}: 3117 (w), 2942 (vs), 2864 (m), 1538 (m), 1501 (m), 1449 (m), 1404 (vs), 1384 (m), 1330 (m), 1316 (s), 1278 (vs), 1213 (s), 1174 (s), 1127 (s), 1101 (s), 1061 (s), 989 (m), 965 (s), 732 (m) cm^{-1}; MS (EI) m/z (relative intensity): 340 (M^+, 18), 213 (100), 193 (3), 173 (3), 131 (19), 127 (2), 111 (13), 95 (19), 90 (13), 83 (36), 81 (16), 67 (9), 55 (8), 41 (17); HRMS (EI) calcd for $C_{11}H_{15}F_2IN_2$ 340.02481, found 340.02686.

1-[Difluoro-(2-iodocyclohexyl)methyl]-1H-benzoimidazole (**10c**) Viscous pale yellow oil. ^1H NMR ($CDCl_3$, Me_4Si) δ: 8.23 (s, 1H, ArH), 7.36—7.87 (m, 4H, ArH), 4.12 (m, 1H, CHI), 0.85—2.12 (m, 9H, CF_2CH, $CH_2CH_2CH_2CH_2$); ^{19}F NMR ($CDCl_3$, $CFCl_3$)

δ: −81.8 (AB system, J_{AB} = 213.6 Hz, *E*-configuration), −90.9 (AB system, J_{AB} = 214.2 Hz, *Z*-configuration); IR ν_{max}: 3060 (w), 2941 (s), 2862 (s), 1613 (w), 1498 (s), 1455 (vs), 1378 (s), 1336 (s), 1320 (s), 1286 (vs), 1250 (vs), 1218 (vs), 1193 (s), 1167 (vs), 1106 (s), 1052 (s), 956 (vs), 744 (vs) cm^{-1}; MS (EI) *m/z* (relative intensity): 376 (M^+, 26), 249 (100), 229 (3), 175 (3), 167 (30), 147 (12), 131 (17), 119 (29), 97 (41), 90 (15), 83 (48), 81 (34), 70 (99), 67 (24), 55 (46), 41 (62); HRMS (EI) calcd for $C_{14}H_{15}F_2IN_2$ 376.02481, found 376.02536.

References

1 Elsheimer, S.; Dolbier, Jr., W. R.; Murla, M.; Seppelt, K.; Paprott, G. *J. Org. Chem*. **1984**, *49*, 205.

2 (a) Chen, Q.-Y.; Zhu, S.-Z. *Sci. China, Ser. B* **1987**, *30*, 561.
(b) Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Chem. Commun*. **1992**, 807.
(c) Xiao, J.-C.; Duan, J.-X.; Li, A.-R.; Guo, Y.; Chen, Q.-Y. *Collect. Czech. Chem. Commun*. **2002**, *67*, 1320.

3 Li, A.-R.; Chen, Q.-Y. *Chin. J. Chem*. **1996**, *14*, 549.

4 Li, A.-R.; Chen, Q.-Y. *J. Fluorine Chem*. **1997**, *82*, 151.

5 Li, A.-R.; Chen, Q.-Y. *J. Fluorine Chem*. **1997**, *81*, 99.

6 Li, A.-R.; Chen, Q.-Y. *Synthesis* **1997**, 1481.

7 Chen, Q.-Y.; Li, Z.-T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 645.

8 Li, A.-R.; Chen, Q.-Y. *Synthesis* **1996**, 606.

9 Guo, Y.; Chen, Q.-Y. *J. Fluorine Chem*. **2000**, *102*, 105.

10 Stremler, K. E.; Poulter, C. D. *J. Am. Chem. Soc*. **1987**, *109*, 5542.

11 (a) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun*. **1981**, 930.
(b) Blackburn, G. M.; Kent, D. E.; Klokmann, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119.

12 Bissky, G.; Staninets, V. I.; Kolomeitsev, A. A.; Röschenthaler, G.-V. *Synlett* **2001**, 374.

13 Yagupolskii, L. M.; Fedyuk, D. V.; Petko, K. I.; Troitskaya, V. I.; Rudyk, V. I.; Rudyuk, V. V. *J. Fluorine Chem*. **2000**, *106*, 181.

14 (a) Huang, W.-Y. *J. Fluorine Chem*. **1992**, *58*, 1.
(b) Huang, W.-Y.; Wu, F.-H. *Israel J. Chem*. **1999**, *39*, 167.

15 Wu, F.-H.; Huang, B.-N. *Chin. Chem. Lett*. **1993**, *4*, 683.

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