ELSEVIER

Journal of Fluorine Chemistry 105 (2000) 149–157

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Electrochemical fluorination of hexahydroazepine, methylpiperidines and methyl 1-hexahydroazepine-acetate: the preparation of *F*-(1-hexahydroazepine-acetyl fluoride) and its derivatives☆

Takashi Abe[a,*], Sushil K. Pandey[b], Hajime Baba[a]

[a]*Department of Chemistry, National Industrial Research Institute of Nagoya, Hirate-cho 1-1, Kita-ku, Nagoya 462-8510, Japan*
[b]*Department of Chemistry, University of Jammu, Jammu 180006, J&K, India*

Received 1 February 2000; received in revised form 5 April 2000; accepted 12 May 2000

Abstract

The electrochemical fluorination of hexahydroazepine (**1**), methylpiperidines (**2**) [2-methylpiperidine (**2a**), 3-methylpiperidine (**2b**), 4-methylpiperidine (**2c**)] and methyl 1-hexahydroazepine-acetate (**3**) was examined. An extensive cleavage of the C–N bond occurred in the fluorination of *secondary* cyclic amines (**1**, **2a–c**) resulting in only a small yield of the corresponding *F*-(*N*-fluoro cyclic amines). *F*-(1-hexahydroazepine-acetyl fluoride) (**4**) was obtained in a fair yield from the fluorination of **3** along with *F*-[(methylpiperidino)-acetylfluoride] which was formed as a result of the isomerization of **3** during fluorination. In addition, several derivatives of **4** were synthesized. *F*-(1-iodomethyl-hexahydroazepine) (**4a**) was prepared by the reaction of **4** with anhydrous LiI. The compound **4** was converted into its potassium salt (**4c**) via methyl *F*-(1-hexahydroazepine-acetate) (**4b**), which upon pyrolysis in the presence or absence of ethylene glycol resulted in the formation of 1-difluoromethyl-dodecafluoro(hexahydroazepine) (**4d**) and *F*-(3,4,5,6-tetrahydroazepine) (**4e**), respectively. *F*-(1-hexahydroazepine-acetoamide) (**4f**), *F*-(1-hexahydroazepine-acetonitrile) (**4g**) and corresponding *p*-methoxyanilide (**4h**) were also derived from **4**. © 2000 Published by Elsevier Science S.A.

Keywords: Electrochemical fluorination; *F*-carboxylic acid fluorides; Hexahydroazepine; *F*-(1-hexahydroazepine-acetic acid); *F*-(*N*-fluoro-hexahydroazepine)

1. Introduction

Studies on polyfluoro compounds with heteroatom(s), such as oxygen, nitrogen and sulfur, have received an increasing amount of attention from scientists due to their versatility in both the fields of industry and academia [1–6]. They are of particular interest in connection with global environmental problems, such as ozone depletion by CFCs and the greenhouse effect [7,8]. F^1-carboxylic acids with a nitrogen atom in the *F*-alkyl group are regarded as soft (degradable) materials compared with *F*-carboxylic acids without a heteroatom. Hence, they are potentially key intermediates that will help protect the environment through the production of soft fluorochemicals [9,10]. We have reported on the synthesis of many *N*-containing *F*-carboxylic acids by electrochemical fluorination (ECF) which revealed that the incorporation of a cyclic amino group into the substrate (methyl esters of carboxylic acids) positively affects the formation of an uncleaved product compared with that of the acyclic dialkyl amino group [11]. In the present paper, we report on the ECF of 1-hexahydroazepine (**1**), methylpiperidines (**2**) [2-methylpiperidine (**2a**), 3-methylpiperidine (**2b**), 4-methylpiperidine (**2c**)] and methyl (1-hexahydroazepine)-acetate (**3**). Furthermore, by using *F*-(1-hexahydroazepine-acetyl fluoride) (**4**) as the starting material which was obtained from the product of ECF of **3**, several of its derivatives, such as *F*-(1-iodomethyl-hexahydroazepine) (**4a**), *F*-(1-hexahydroazepine-acetic acid) methyl ester (**4b**), potassium salt (**4c**), 1-difluoromethyl-dodecafluoro(hexahydroazepine) (**4d**), *F*-(3,4,5,6-tetrahydroazepine) (**4e**), *F*-(1-hexahydroazepine-acetoamide) (**4f**), *F*-(1-hexahydroazepine-acetonitrile) (**4g**) and *p*-methoxyanilide (**4h**) were prepared and characterized.

2. Results and discussion

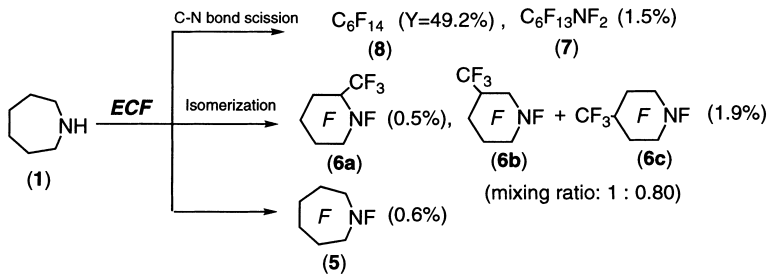
It has been known that the ECF of *secondary* cyclic amines results in fair to low yields of the corresponding

☆ Electrochemical fluorination of *N*-containing carboxylic acids, Part 6.

* Corresponding author. Tel.: +81-52-911-2998; fax: +81-52-916-2802.
E-mail address: abe@nirin.go.jp (T. Abe).

[1] The prefix of *F*- shows that all C–H bonds are replaced with C–F bonds in the molecule.

0022-1139/00/$ – see front matter © 2000 Published by Elsevier Science S.A.
PII: S0022-1139(00)00302-X

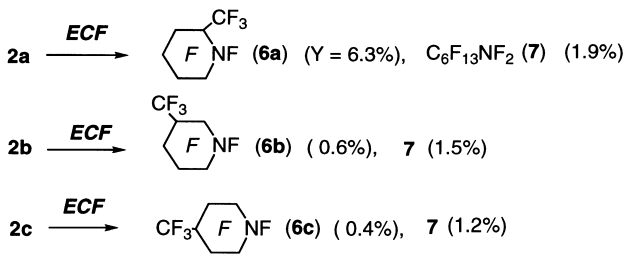


Scheme 1

F-(*N*-fluoro cyclic amines) [12–16]. When hexahydroazepine (**1**) was subjected to ECF, the cleavage of the C–N bond and the isomerization of the seven-membered ring of **1** to the six-membered ring occurred extensively resulting in a small quantity of *F*-(*N*-fluoro-hexahydroazepine) (**5**) along with a mixture of *F*-(*N*-fluoro-methylpiperidines) (**6a–c**), *F*-(*N*,*N*-difuoroamino-hexane) (**7**), *F*-hexane (**8**) (major product), etc. (Scheme 1).

The preparation of compound **5** is not unprecedented. Compound **5** has been prepared in a 60% yield by the fluorination of **1** with F_2 using a cryogenic reactor by Lin and Largow [17]. Though the extensive cleavage of the C–N bond is inevitable in the case of the ECF of cyclic and/or acyclic *secondary* amines [12–16,18], the target compound (**5**) was obtained at a low yield (<1%) by the ECF of **1**. The preferential formation of ring-contracted compounds, such as the six-membered *F*-(*N*-fluoro-methylpiperidines) (**6a–c**) over the targeted seven-membered *F*-(*N*-fluoro-hexahydroazepine) (**5**) was observed. The structure of these isomers (**6a–c**) was determined on the basis of their spectroscopic data by comparing it with those of authenticated samples which were prepared by the ECF of 2-methylpiperidine (**2a**), 3-methylpiperidine (**2b**) and 4-methylpiperidine (**2c**), respectively (Scheme 2). Previously, these *F*-(*N*-fluoro-methylpiperidines) (**6a–c**) have been prepared by the ECF of the corresponding methyl-substituted pyridines [19].

We adopted ^{19}F NMR spectroscopy for the determination of the mixing ratio of **6b** and **6c** obtained as an inseparable mixture after the preparative GC of products mixture from **1**. In the ^{19}F NMR spectra of **6a**, **6b** and **6c**, peaks assigned to CF of the piperidine ring shifted characteristically to a higher field from −158.4 ppm at the 2-position of **6a** to −184.4 ppm at the 3-position of **6b** and to −189.3 ppm at the 4-position of **6c** as the number of bonds separating the nitrogen and carbon increased [20]. Thus, the mixing ratio of **6b**:**6c** could be determined by the integration of CF peaks of **6b** and **6c** to be equal to 1:0.80. No apparent correlation was observed between the CF_3 chemical shifts and their isomeric positions (−72.5 ppm at the 2-position of **6a**, −70.1 ppm at the 3-position of **6b** and −70.2 ppm at the 4-position of **6c**, respectively). The NF chemical shifts of these isomers were −102.0 ppm (**6a**), −111.7 ppm (**6b**) and −111.3 ppm (**6c**).

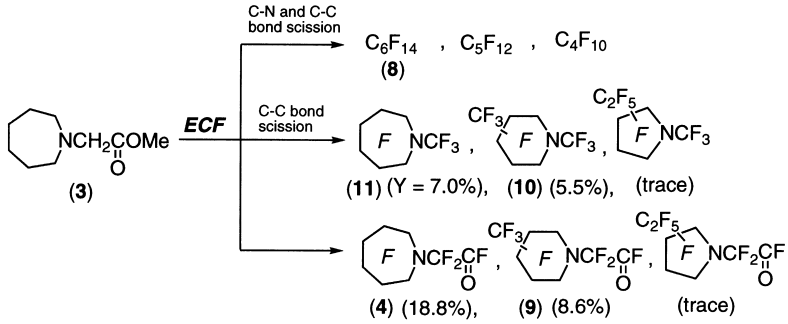


Scheme 2

A relatively higher yield of the corresponding **6a** (GC yield=6.3%) was obtained by the ECF of **2a** when compared with those of **2b** and **2c** (yields were 0.6 and 0.4%, respectively). Such variance in yields depends on the structure of the starting material and has been reported with the fluorination of α-alkyl substituted pyridines. It has been reported that a 2-fluoro and/or a 2-methyl substituent in the pyridine ring inhibit the cleavage of the C–N bonds during ECF, which results in the enhancement of the ECF yield of piridines with a substituent at the 2-position compared with that of piridine [21,22]. The reason for this reduction in cleavage in the case of a 2-methyl substituent is explained by the blocking effect on the C–N bond scission due to the presence of methyl group(s) which sterically protects it.

On the other hand, the ECF of methyl 1-hexahydroazepine-acetate (**3**), which is a *tertiary* amine having a cyclic amino group, proceeded smoothly resulting in fair yields of *N*-containing *F*-carboxylic acid fluorides consisting of not only seven-membered *F*-(1-hexahydroazepine-acetyl fluoride) (**4**) but also six-membered *F*-(methylpiperidino-acetyl fluoride) (**9**). The formation of ring-contracted compounds as a by-product, such as **9** is usually observed in the ECF of cyclic compounds with six-and/or seven-membered rings [23–26]. Other cyclic compounds like *F*-(1-methyl-methylpiperidine) (**10**) and *F*-(*N*-methyl-hexahydroazepine) (**11**) were also formed as a result of the α-bond cleavage of the carboxylic acid during fluorination. However, the isomerization of the ring size of **3** stopped almost at the same stage as the six-membered ring as was indicated by the presence of small peaks due to the five-membered ring compounds in the product gas chromatogram [2] (Scheme 3).

[2] The existence of the isomeric five-membered compounds in the product mixture is easily identified, because the order of their GC retention times is dependent on the ring size, a longer retention time being slow with a characteristic increase in the ring size, viz. five-membered<six-membered<seven-membered (see [23]).



Scheme 3

Thus, the targeted *F*-(1-hexahydroazepine-acetyl fluoride) (**4**) was formed as the principal fluorination product (GC yield=18.8%). The identification of products (**4**, **9**, **10** and **11**) was done by studying their IR, mass and NMR for each of the compounds separated by semi-preparative GC from the reaction mixture.

It has been reported that the ECF of *N*-(ω-chloroalkyl)-hexahydroazepines yields a mixture of corresponding *F*-(*N*-alkyl-hexahydroazepines) together with *F*-(1-alkyl-methyl-piperidines) and trace amounts of isomeric *F*-(*N*-alkyl-pyrrolidines) [23]. Furthermore, it has been shown that *F*-(*N*-alkyl-methylpiperidines) [R_F=$(CF_2)_nCl$ and C_nF_{2n+1}, where n=2, 3], which were formed as a result of the ring isomerization of the starting material, were a mixture of three positional isomers arising from the existence of a CF_3-group on the piperidine ring by ^{19}F NMR spectroscopy (Scheme 4).

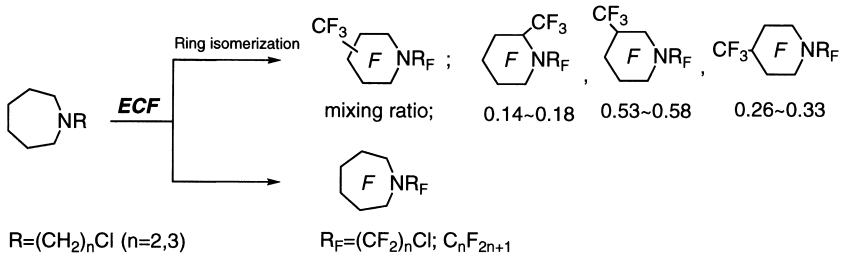
The mixing ratio (2-CF_3–:3-CF_3–:4-CF_3–=0.14–0.18:0.53–0.58:0.26–0.33) of isomers of *F*-(1-alkyl-methyl-piperidines) was determined by means of ^{19}F NMR spectroscopy. Since the three CF absorption peaks of the *F*-piperidine ring exhibit different chemical shifts from each other (151–152 ppm for the 2-CF_3 isomer, 181–182 ppm for the 3-CF_3 isomer and 189–190 ppm for the 4-CF_3 isomer, respectively), these peaks were used for the determination of the isomers.

Similar ^{19}F NMR studies were conducted for the determination of the mixing ratio of isomers by integrating the absorption peaks due to CF on the ring onto carbon CF_3-group bonded in the analysis of both the **9** and **10** compounds (see Section 3). It was found that compounds **9** and **10** consisted of a mixture of *F*-(3-methylpiperidino-acetyl fluoride) (**9b**) and *F*-(4-methylpiperidino-acetyl fluoride) (**9c**) in a ratio of 1:0.52 for the former, and *F*-(1-methyl-3-methylpiperidine) (**10b**) and *F*-(1-methyl-4-methylpiperidine) (**10c**) in a ratio of 1:0.51 for the latter, respectively. The absence of 2-CF_3 substituted isomers (**10a** and **9a**) in both **10** and **9** was rather unexpected (Scheme 5).

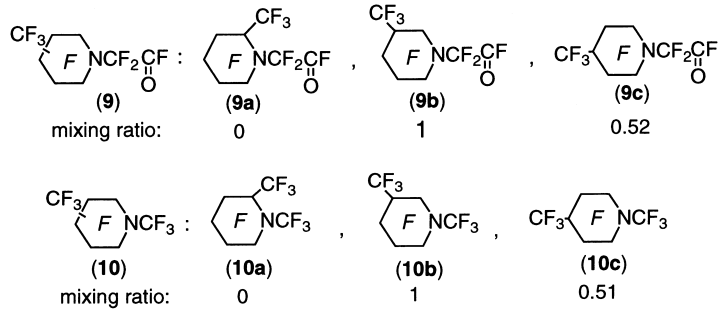
Next, several derivatives were prepared using compound **4** in order to obtain a series of new compounds with a seven-membered *F*-cyclic amino group. The reaction schemes for the preparation of these derivatives are depicted in Scheme 6.

All reactions were conducted in a similar manner as was the case for those with standard *F*-acid fluorides. The compound **4** was reacted with anhydrous LiI at 180°C for 24 h to give *N*-iododifluoromethyl-dodecafluoro(hexahydroazepine) (**4a**) as a pink-colored liquid at a 25% yield which was done according to the reaction described in the literature [27,28].

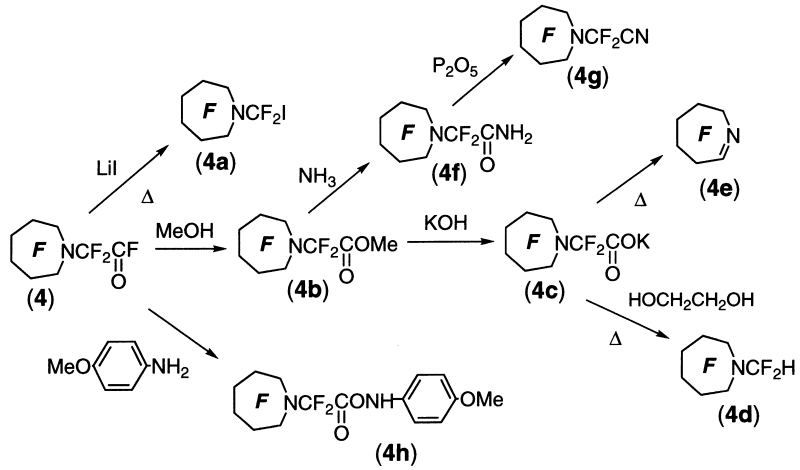
Several methods have been known for the formation of *F*-cyclic imines, such as the defluorination reaction of *F*-(*N*-fluoro cyclic imines) with triphenylphosphine [21] and the reaction of cyclic *F-tertiary* amines with SbF_5 [29]. Recently, we have found an alternative method for the formation of *F*-cyclic imines which consists of the pyrolysis of alkali metal salts of *F*-(cyclic amino-substituted acetic acids) [30]. Therefore, we have extended this reaction to that of compound **4c** for the preparation of a new seven-membered *F*-cyclic imine. The pyrolysis of potassium salt (**4c**) of **4**, which was prepared by the reaction of methyl ester (**4b**) of **4** with powdered KOH in methanol, was done at 245–255°C under the reduced pressure of 95 mmHg to give *F*-(3,4,5,6-tetrahydroazepine) (**4e**) (yield=94%). A similar pyrolytic reaction of **4c** in the presence of ethyleneglycol resulted



Scheme 4



Scheme 5



Scheme 6

in *N*-difluoromethyl-dodecafluoro(hexahydroazepine) (**6d**) (yield=99%). *F*-(1-hexahydroazepine-acetonitrile) (**4g**) was prepared by the dehydration of an amide (**4f**) of **4** with P_2O_5 (yield=46%) using the standard method [31]. The reaction of **4** with *p*-anisidine resulted in the corresponding *p*-methoxyanilide (**4h**) (yield=26%).

A study on the preparation of *F*-cyclic amines with a carboxyl group by ECF is currently in progress.

3. Experimental methods

The apparatus and method of ECF used have been described in the literature [13]. Anhydrous hydrogen fluoride (AHF) (Daikin Industries) was purer than 99.8%. Hexahydroazepine, methylpiperidines, methanol, dichloromethane, acetonitrile, anhydrous LiI, ethylene glycol and *p*-anisidine were used as received. Diethylether was dried over CaH_2 for several days before use. Boiling points were uncorrected. A Shimadzu GC-14B chromatograph with stainless columns (3 mm diameter) packed with 25% Fomblin YR on Chromsorb PAW(6.4 m) was used for the analytical GC work. A GASKURO LL 75 modified gas chromatograph employing a stainless column (10 mm diameter) packed with KelF Wax on Chromosorb PAW and a Varian model 920 GC employing an aluminium column (3/8 in diameter) packed with 20% Fluolube Grease H on Chromosorb PAW (20 ft) were used for the semi-preparative work. The carrier gas was helium in all cases. Infrared spectra were recorded on a Shimadzu FTIR-8000PC spectrometer and 6 cm gas cell with KBr windows was used. ^1H and ^{19}F NMR were measured on a Varian Unity Inova 300 spectrometer (282.238 MHz for ^{19}F and 299.95 MHz for ^1H, respectively). The chemical shifts were reported with respect to $CFCl_3$ for ^{19}F and TMS for ^1H, and the positive shifts are downfield from the reference. Mass spectra were measured on a Shimadzu GC/MS-QP5000 instrument fitted with a capillary column (Neutra Bond-1, 30 m long, 0.25 μm i.d., 1.5 μm thick) at 70 eV.

3.1. Synthesis of methyl 1-hexahydroazepine-acetate (3)

Methyl 1-hexahydroazepine-acetate (**3**) was prepared in accordance with the method reported in the literature [32]. Hexahydroazepine (218.2 g, 2.2 mol) was added using a dropping funnel while cooling with ice-water over 2 h to a solution of methyl chloroacetate (108.5 g, 1.0 mol) dissolved in 200 ml dried ether in a 1 l flask fitted with a mechanical stirrer. After removing the HCl salt from the reaction mixture by filtration, the filtrate was subjected to

distillation resulting in compound **3** (95–97°C/10 mmHg) as a colorless liquid (171.0 g, *Y*=82%). IR (capillary film) (cm^{-1}): 2925 (vs), 2850 (s), 1751 *v*(C=O) (vs), 1450 (m), 1197 (s), 1174 (s), 1143 (s), 1014 (m) and 958 (ms).

3.2. Fluorination of hexahydroazepine (1)

Compound **1** (31.7 g, 0.320 mol) was charged into an electrolytic cell containing 420 ml electrically purified AHF and the solution was subjected to fluorination with an anodic current density of 2.9 A/dm^2, a cell voltage of 6.2–6.4 V, and a cell temperature of 7–8°C over a period of 601 min (227 Ah). The voltage reached 6.8 V at the final stage of the fluorination.

The effluent gases from the cell were passed over NaF pellets and then condensed in a trap cooled to −78°C. The gaseous products which did not condense in the −78°C trap were then bubbled through a fluoropolymer bottle containing water and a gas washing bottle containing an aqueous solution of a mixture of K_2CO_3, KOH and KI. All products except new ones were identified by comparison with their IR spectra and GC retention times with those of authenticated samples. When unknown compounds were found among the fluorination products with IR data which were not available in our laboratory, they were separated from other products by use of semi-preparative GC, and their structures were determined on the basis of ^{19}F NMR and mass spectra.

The products (19.5 g) condensed in the −78°C trap consisted of C_4F_{10} (**12**) (trace), C_5F_{12} (**13**) (2.3 g), C_6F_{14} (**8**) (16.2 g), and unidentified products (1.0 g) (products were arranged in order of the elution time on GC). Cell drainings (42.6 g) consisted of **13** (0.3 g), **8** (37.0 g), *F*-(1-fluoro-2-methylpiperidine) (**6a**) (0.5 g), a mixture of *F*-(1-fluoro-3-methylpiperidine) (**6b**) and *F*-(1-fluoro-4-methylpiperidine) (**6c**) (mixing ratio; **6b**:**6c**=1:0.80) (2.0 g), *F*-(*N*-fluoro-hexahydroazepine) (**5**) (0.6 g), *F*-(*N*,*N*-difluoroamino-hexane) (**7**) (1.8 g), and unidentified products (0.4 g). The GC yield of *F*-(*N*-fluoro-hexahydroazepine) (**5**) was 0.6%. The assignment of the structure of compounds **6a–c** was done by a comparison with spectroscopic data (IR, mass and ^{19}F NMR) from those of authenticated samples which were prepared by ECF of methylpiperidines (**2a–c**). The spectral data of **5** were identical with those published in the literature [17]. The mixing ratio of **6b** and **6c**, which could not be separated by GC, was determined to be **6b**:**6c**=1:0.8 by the integration of the CF-absorption peaks of the piperidine ring in their ^{19}F NMR spectra. Their CF absorption peaks exhibited chemical shifts at −184.4 ppm for **6b** and −189.4 ppm for **6c**, respectively.

F-(*N*,*N*-difluoroamino-hexane) (**7**) had bp 82–83°C, d_4^{20} 1.7749 and n_D^{20}<1.28. It consisted of a mixture of several structural isomers with a molecular formula of $C_6F_{13}NF_2$ by studying the ^{19}F NMR. No further analysis to determine its structure was conducted. IR (gas): 1348 (ms), 1300–1261(s to vs, broad), 1155 (m), 1220 (w), 1989 (w), 954 (ms), 899 (w), 822 (w), 780 (m), 725 (ms), 531 (w). Mass: 319 $[M–NF_2]^+$ (1.1), 231 $C_5F_9^+$ (1.6), 181 $C_4F_7^+$ (4.4), 169 $C_3F_7^+$ (4.6), 131 $C_3F_5^+$ (6.7), 119 $C_2F_5^+$ (16.8), 100 $C_2F_4^+$ (4.8), 69 CF_3^+ (100), 50 CF_2^+ (2.0). ^{19}F NMR ($CDCl_3$): δ 20.9–17.4 (m, NF_2), δ −80.3 to 80.7 (m, CF_3), δ −108.0 to 126.7 (m, CF_2), δ −185.5 to 185.9 (m, CF).

3.3. Fluorination of 2-methylpiperidines (2a)

Sample **2** (30.8 g, 0.311 mol) was similarly fluorinated under the following conditions: 2.9 A/dm^2, 5.5–5.6 V, 7–8°C, 256 Ah (671 min). The work-up resulted in the following products in the −78°C trap (15.7 g): **12** (0.7 g), **13** (2.2 g), **8** (12.1 g), *F*-(1-fluoro-2-methylpiperidine) (**6a**) (0.3 g), and unidentified products (0.4 g). Cell drainings (45.4 g): **13** (0.4 g), **8** (36.5 g), *F*-(1-fluoro-2-methylpiperidine) (**6a**) (6.3 g), *F*-(*N*,*N*-difluoroamino-hexane) (**7a**) (1.6 g), and unidentified products (0.6 g). The GC yield for **6a** and **7a** were 6.3 and 1.4%, respectively. The ^{19}F NMR data for **6a** were the same as which has been reported [20]. The physico-chemical properties and spectral data (IR and mass) for **6a** are shown.

F-(1-fluoro-2-methylpiperidine) (**6a**) [19] had bp 70.5–71.0°C (reported: bp 71.7°C), d_4^{20} 1.7927 and n_D^{20} 1.2840 (reported: 1.3167). IR (gas): 1343 (ms), 1324 (w), 1290 (s), 1275 (s), 1258 (vs), 1225 (vs), 1200 (m), 1181 (s), 1161 (m), 1103 (m), 1052 (m), 1007 (m), 958 (s), 876 (s), 740 (m), 665 (w), 628 (w). Mass: 333 M^+ (0.1), 314 $[M–F]^+$ (10.5), 295 $[M–F_2]$ (3.9), 264 $[M–CF_3]^+$ (30.2), 245 $C_6F_9N^+$ (11.4), 195 $C_4F_7N^+$ (3.0), 181 $C_4F_7^+$ (4.0), 176 $C_4F_6N^+$ (3.1), 169 $C_3F_7^+$ (3.0), 164 $C_3F_6N^+$ (7.2), 145 $C_3F_5N^+$ (6.4), 131 $C_3F_5^+$ (17.0), 119 $C_2F_5^+$ (18.5), 114 $C_2F_4N^+$ (16.4), 100 $C_2F_4^+$ (47.6), 95 $C_2F_3N^+$ (3.0), 93 $C_3F_3^+$ (4.8), 76 $C_2F_2N^+$ (8.4), 69 CF_3^+ (100), 50 CF_2^+ (9.4).

F-(*N*,*N*-difluoroamino-hexane) (**7a**) consisted of a mixture of several structural isomers with a molecular formula of $C_6F_{13}NF_2$ by ^{19}F NMR. No further analysis to determine its structure was conducted. IR (gas): 1340–1255 (m to vs, broad), 1217 (m, sh), 1173 (m), 1151 (m), 1105 (w), 1074 (w), 1109 (w), 988 (w), 953 (w), 934 (w), 830 (w), 817 (w), 794 (w), 726 (m). Mass: 231 $C_5F_9^+$ (1.3), 181 $C_4F_7^+$ (2.2), 169 $C_3F_7^+$ (6.7), 131 $C_3F_5^+$ (7.8), 119 $C_2F_5^+$ (17.3), 100 $C_2F_4^+$ (4.5), 69 CF_3^+ (100), 50 CF_2^+ (2.2). ^{19}F NMR ($CDCl_3$): δ 23.9–23.5 (m, NF_2), δ −80.7 to 81.3 (m, CF_3), δ −117.1 to 127.6 (m, CF_2), δ −163.8 (m, CF).

3.4. Fluorination of 3-methylpiperidine (2b)

Sample **3** (30.9 g, 0.311 mol) was similarly fluorinated under the following conditions: 2.9 A/dm^2, 5.5–5.6 V, 7–8°C, 256 Ah (670 min). The work-up gave the following products in the −78°C trap (15.9 g): **12** (0.5 g), **13** (2.9 g), **8** (12.4 g), and unidentified products (0.1 g). Cell drainings (38.6 g): **13** (0.5 g), **8** (35.6 g), *F*-(1-fluoro-3-methylpiperidine) (**6b**) (0.6 g), *F*-(*N*,*N*-difluoroamino-hexane) (**7b**) (1.4 g), and unidentified products (0.5 g).

The GC yield for **6b** and **7b** were 0.6 and 1.5%, respectively. The ^{19}F NMR data for **6b** were the same as that reported [20]. Spectral data (IR and mass) for **6b** and **7b** are shown as follows.

F-(1-fluoro-3-methylpiperidine) (**6b**): IR (gas): 1331 (m), 1302 (vs), 1275 (vs), 1260 (s), 1235 (s), 1219 (m), 1195 (m), 1173 (s), 1158 (m), 1134 (w), 1027 (m), 1017 (m), 958 (s), 869 (s), 732 (ms). Mass: 333 M^+ (2.1), 314 $[M–F]^+$ (9.2), 295 $[M–F_2]$ (10.1), 231 $C_5F_9^+$ (1.9), 226 $C_5F_8N^+$ (1.2), 195 $C_4F_7N^+$ (4.4), 181 $C_4F_7^+$ (15.5), 164 $C_3F_6N^+$ (1.8), 152 $C_2F_6N^+$ (4.1), 150 $C_3F_6^+$ (3.0), 145 $C_3F_5N^+$ (8.7), 131 $C_3F_5^+$ (18.4), 114 $C_2F_4N^+$ (21.7), 100 $C_2F_4^+$ (87.16), 95 $C_2F_3N^+$ (2.7), 93 $C_3F_3^+$ (6.7), 81 $C_2F_3^+$ (2.4), 76 $C_2F_2N^+$ (3.8), 69 CF_3^+ (100), 50 CF_2^+ (9.1).

F-(*N*,*N*-difluoroamino-hexane) (**7b**) had bp 81–82°C, d_4^{20} 1.7912 and n_D^{20}<1.28. It consisted of a mixture of several structural isomers having a molecular formula of $C_6F_{13}NF_2$ by ^{19}F NMR. No further analysis for the determination of its structure was conducted. IR (gas): 1348 (w), 1320–1261 (m to vs), 1237 (s, sh), 1221 (m), 1193 (w), 1175 (w), 1157 (w), 1138 (w), 1121 (w), 1031 (w), 994 (w), 954 (m), 895 (w), 831 (w), 821 (w), 780 (w), 734 (m), 723 (m). Mass: 319 $[M–NF_2]^+$ (0.6), 231 $C_5F_9^+$ (1.2), 181 $C_4F_7^+$ (2.9), 169 $C_3F_7^+$ (5.1), 131 $C_3F_5^+$ (6.2), 119 $C_2F_5^+$ (15.3), 100 $C_2F_4^+$ (3.6), 93 $C_3F_3^+$ (1.7), 69 CF_3^+ (100), 50 CF_2^+ (1.5). ^{19}F NMR ($CDCl_3$): δ 23.2–17.5 (m, NF_2), δ −80.2, −80.8 (m, CF_3), δ −108.0 to 125.6 (m, CF_2), δ −184.4, −185.9 (m, CF).

3.5. Fluorination of 4-methylpiperidine (2c)

Sample **4** (31.5 g, 0.318 mol) was similarly fluorinated under the following conditions: 2.9 A/dm^2, 5.6–5.7 V, 7–8°C, 255 Ah (664 min). The work-up gave the following products in the −78°C trap (17.3 g): **12** (1.3 g), **13** (2.3 g), **8** (13.3 g), and unidentified products (0.4 g). Cell drainings (40.6 g): **13** (0.5 g), **8** (38.1 g), *F*-(1-fluoro-4-methylpiperidine) (**6c**) (0.4 g), *F*-(1-*N*,*N*-difluoroamino-hexane) (**7c**) (1.4 g), and unidentified products (0.2 g).

The GC yield for **6c** and **7c** were 0.4 and 1.2%, respectively. The ^{19}F NMR data for **6c** were the same as that which has been reported [20]. Spectral data (IR and mass) for **6c** and **7c** are shown as follows.

F-(1-fluoro-4-methylpiperidine) (**6c**): IR (gas): 1313 (s), 1293 (m), 1276 (s), 1256 (vs), 1207 (vs), 1193 (s), 1169 (s), 1125 (w), 1068 (w), 974 (w), 956 (s), 873 (ms), 729 (w), 665 (w), 630 (w). Mass: 333 M^+ (0.7), 314 $[M–F]^+$ (12.8), 295 $[M–F_2]$ (3.7), 264 $[M–CF_3]^+$ (1.7), 181 $C_4F_7^+$ (9.4), 176 $C_4F_6N^+$ (1.4), 164 $C_3F_6N^+$ (1.3), 152 $C_2F_6N^+$ (2.5), 150 $C_3F_6^+$ (2.2), 145 $C_3F_5N^+$ (8.9), 131 $C_3F_5^+$ (16.1), 119 $C_2F_5^+$ (11.5), 114 $C_2F_4N^+$ (31.8), 100 $C_2F_4^+$ (93.0), 95 $C_2F_3N^+$ (2.5), 93 $C_3F_3^+$ (9.1), 76 $C_2F_2N^+$ (3.8), 69 CF_3^+ (100), 50 CF_2^+ (8.4).

F-(*N*,*N*-difluoroamino-hexane) (**7c**) had bp 81.0–82.5°C, d_4^{20} 1.7897 and n_D^{20}<1.28. It consisted of a mixture of several structural isomers with a molecular formula of $C_6F_{13}NF_2$ by ^{19}F NMR. No further analysis to determine its structure was conducted. IR (gas): 1384 (w), 1348 (w), 1300–1251 (m to vs, broad), 1156 (w), 1106 (w), 989 (w), 949 (w), 903 (w), 856 (w), 820 (w), 782 (w), 746 (w). Mass: 319 $[M–NF_2]^+$ (0.3), 231 $C_5F_9^+$ (1.2), 181 $C_4F_7^+$ (5.1), 169 $C_3F_7^+$ (1.2), 131 $C_3F_5^+$ (6.8), 119 $C_2F_5^+$ (25.8), 100 $C_2F_4^+$ (5.0), 93 $C_3F_3^+$ (2.6), 69 CF_3^+ (100), 50 CF_2^+ (2.2). ^{19}F NMR ($CDCl_3$): δ 21.2–18.1 (m, NF_2), δ −80.3, −80.5, −80.9 (m, CF_3), δ −108.4 to 126.6 (m, CF_2), δ −184.4, −185.4, −185.9 (m, CF).

3.6. Fluorination of methyl 1-hexahydroazepine-acetate (3)

Sample **3** (40.0 g, 0.234 mol) was similarly fluorinated under the following conditions: 2.9 A/dm^2, 5.9–6.4 V, 7–8°C, 230 Ah (694 min). The products in the −78°C trap (11.8 g) and the cell drained products (40.1 g) were similarly analyzed by GC. The products in the −78°C trap consisted of **12** (1.5 g), **13** (3.1 g), **8** (5.2 g), *F*-(1-methyl-methylpiperidines) (**10**) [29] (0.7 g), *F*-(1-methyl-hexahydroazepine) (**11**) (0.6 g) and unidentified products (0.7 g). Cell drainings (40.1 g) consisted of **8** (1.0 g), **10** (4.2 g), **11** (5.7 g), *F*-(methylpiperidino-acetyl fluoride) (**9**) (8.2 g), *F*-(1-hexahydroazepine-acetyl fluoride) (**4**) (18.1) and unidentified products (2.9 g). The GC yield of *F*-(methylpiperidino-acetyl fluoride) (**9**) and *F*-(1-hexahyrdoazepine-acetyl fluoride) (**4**) were 8.6 and 18.8%, respectively.

Spectral data (IR and ^{19}F NMR) for **9** and **4** are shown as follows.

F-(methylpiperidino-acetyl fluoride) (**9**) (nc): IR (gas): 1895 ν(C=O) (m), 1329 (m), 1303 (m), 1240 (vs), 1192 (m), 1158 (m), 1135 (w), 1097 (w), 1057 (w), 1030 (w), 1000 (m), 950 (m), 861 (w), 818 (w). Compound **9** showed complex absorption peaks comprised of many AB-type multiplets in the ^{19}F NMR spectrum due to the mixture of *F*-(3-methylpiperidino-acetyl fluoride) and *F*-(4-methylpiperidino-acetyl fluoride) which was present in a ratio of 1:0.53. ^{19}F NMR ($CDCl_3$): δ 14.0 (m), −51.5 (m, CF_3–), δ −73.8 to 100.6 (m, CF_2), δ −119.6 to 138.4 (m, CF_2), δ −182.4 (m, CF), δ −189.4 (m, CF).

F-(1-hexahydroazepine-acetyl fluoride) (**4**) (nc): IR (gas): 1896 ν(C=O) (s), 1334 (s), 1306 (m), 1262 (sh, m), 1231–1239 (vs), 1190 (m), 1161 (m), 1107 (w), 1058 (ms), 1047 (sh, w), 993 (ms), 950 (ms), 936 (sh, m), 846 (w), 817 (w), 769 (w), 699 (w), 665 (w). ^{19}F NMR ($CDCl_3$): δ 13.2 (m, 1F, –C(O)F), δ −82.9 (quintet, NCF_2), δ −86.6 (m, 4F, α-CF_2 of the ring), δ −124.7 (m, 4F, β-CF_2 of the ring), δ −128.8 (m, 4F, γ-CF_2 of the ring).

Further analysis of **9** and **4** was conducted on a form of their methyl esters. Methyl esters of **9** and **4** were prepared by mixing about 10 g of cell drainings with 5 ml of methanol. The reaction was completed within a few minutes. The lower layer of the reaction mixture was separated by means of semi-preparative GC to give the corresponding *F*-cyclic amines [*F*-(*N*-methyl-methylpiperidine) (**10**) and *F*-(*N*-methyl-hexahydroazepine) (**11**)] and two methyl esters of

F-carboxylic acids (**9** and **4**). The separation of the methyl ester (**4b**) of **4** was conducted repeatedly until a sufficient amount of **4b** for the studies on the preparation of its derivatives was obtained.

F-(*N*-methyl-methylpiperidine) (**10**) [28] had bp 108.0–108.5°C, d_4^{20} 1.8327 and n_D^{20} 1.2860. IR (gas): 1353 (vs), 1308 (ms), 1284 (m), 1260–1230 (vs), 1179 (m), 1161 (m), 1149 (m), 1124 (w), 1106 (w), 1023 (w), 1002 (w), 963 (w), 919 (m), 870 (w), 736 (w), 716 (w), 665 (w), 683 (w). Mass: 364 $[M–F]^+$ (14.4), 314 $[M–CF_3]^+$ (3.1), 276 $C_6F_8N^+$ (13.1), 214 $C_4F_8N^+$ (1.7), 188 $C_5F_6N^+$ (2.1), 181 $C_4F_7^+$ (9.6), 164 $C_3F_6N^+$ (7.8), 150 $C_3F_6^+$ (1.7), 145 $C_3F_5N^+$ (1.8), 131 $C_3F_5^+$ (11.1), 119 $C_2F_5^+$ (80.8), 114 $C_2F_4N^+$ (18.8), 100 $C_2F_4^+$ (54.9), 95 $C_2F_3N^+$ (1.7), 93 $C_3F_3^+$ (5.3), 76 $C_2F_2N^+$ (2.0), 69 CF_3^+ (100), 50 CF_2^+ (4.9). ^{19}F NMR: δ −70.0 (m, NCF_3), δ −70.2 (m, NCF_3), δ −86.6 (t, CF_3, J=15.5 Hz), δ −86.9 (t, CF_3, J=15.5 Hz), δ −95.3 to 140.7 (m, CF_2), δ −182.8 (m, CF), δ −190.6 (m, CF). The mixing ratio of two isomers was determined by the integration of two CF peaks on the piperidine ring to be *F*-(1-methyl-3-methylpiperidine):*F*-(1-methyl-4-methylpiperidine)=1:0.51.

F-(*N*-methyl-hexahydroazepine) (**11**) (nc) had bp 111.5–112.5°C, d_4^{20} 1.8741 and n_D^{20} 1.2928. IR (gas): 1347 (vs), 1297 (m), 1242 (vs), 1206 (m), 1174 (m), 1163 (m), 1142 (m), 1098 (w), 1047 (w), 1003 (ms), 955 (m), 936 (m), 917 (m), 886 (m), 745 (w), 730 (w). Mass: 364 $[M–F]^+$ (4.1), 314 $[M–CF_3]^+$ (0.7), 276 $C_6F_8N^+$ (6.5), 226 $C_5F_8N^+$ (1.5), 181 $C_4F_7^+$ (2.7), 176 $C_4F_6N^+$ (1.8), 169 $C_3F_7^+$ (3.2), 164 $C_3F_6N^+$ (1.9), 145 $C_3F_5N^+$ (1.7), 131 $C_3F_5^+$ (67.3), 119 $C_2F_5^+$ (11.1), 114 $C_2F_4N^+$ (12.0), 100 $C_2F_4^+$ (20.3), 93 $C_3F_3^+$ (3.3), 76 $C_2F_2N^+$ (1.4), 69 CF_3^+ (100), 50 CF_2^+ (3.4). ^{19}F NMR ($CDCl_3$): δ −50.2 (quintet, 3F, CF_3, J=18.9 Hz), δ −88.6 (m, 4F, α-CF_2), δ −124.7 (m, 4F, β-CF_2), δ −129.0 (m, 4F, γ-CF_2).

Methyl *F*-(methylpiperidino-acetate) (nc) had bp 160–162°C, d_4^{20} 1.7520 and n_D^{20} 1.3237. IR (capillary film): 2968 *v*(CH) (m), 1788 *v*(C=O) (vs), 1444 (m), 1314 (vs, broad), 1250–1139 (vs, broad), 1029 (s), 1017 (s), 958 (s), 931 (w), 893 (s), 876 (ms), 845 (w), 820 (ms), 740 (s), 707 (s), 692 (m), 643 (ms), 630 (m), 583 (m), 555 (w). Mass: 364 $[M–C(O)OMe]^+$ (9.4), 181 $C_4F_7^+$ (1.4), 159 $C_3F_7^+$ (6.0), 145 $C_3F_5N^+$ (1.8), 131 $C_3F_5^+$ (14.8), 119 $C_2F_5^+$ (11.7), 100 $C_2F_4^+$ (21.2), 97, 2.4, 81 $C_2F_3^+$ (8.4), 69 CF_3^+ (32.5), 59 $C(O)OMe^+$ (100), 50 CF_2^+ (1.2). ^{19}F NMR ($CDCl_3$): δ −70.1 (m, CF_3), δ −70.4 (m, CF_3), δ −91.4 (m, $NCF_2C(O)O$), δ −92.2 (m, $NCF_2C(O)O$), δ −182.6 (m, 2F, CF), δ −190.5 (m, CF). ^{1}H NMR: δ 3.98 (s, CH_3), δ 3.96 (s, CH_3). The mixing ratio of two isomers was determined to be methyl *F*-(3-methylpiperido-acetate):methyl *F*-(4-methylpiperido-acetate)=1:0.52 by the integration of two CF peaks on the piperidine ring.

Methyl *F*-(1-hexahydroazepine-acetate) (**4b**) (nc) had bp 163–165°C, d_4^{20} 1.7749 and n_D^{20} 1.3278. IR (capillary film): 2968 *v*(CH) (m), 1794 *v*(C=O) (vs), 1445 (m), 1334–1275 (vs), 1220 (vs), 1186 (s), 1159 (vs), 1119 (s), 1072 (s), 1042 (s), 933 (s), 944–930 (s), 876 (w), 863 (m), 846 (ms), 834 (m, sh), 793 (ms), 743 (s), 665 (ms), 685 (m), 638–648 (m). Mass: 404 $[M–F]^+$ (0.8), 364 $[M–C(O)OMe]^+$ (6.1), 314 $C_5F_{12}N^+$ (0.6), 176 $C_4F_6N^+$ (1.4), 169 $C_3F_7^+$ (2.6), 145 $C_3F_5N^+$ (1.7), 131 $C_3F_5^+$ (7.8), 119 $C_2F_5^+$ (2.7), 114 $C_2F_4N^+$ (9.1), 109 $CF_2C(O)OMe^+$ (11.6), 100 $C_2F_4^+$ (4.2), 93 $C_3F_3^+$ (1.0), 81 $C_2F_3^+$ (5.7), 78 $FC(O)OMe^+$ (1.9), 76 $C_2F_2N^+$ (1.0), 69 CF_3^+ (21.4), 59 $C(O)OMe^+$ (100), 50 CF_2^+ (2.6). ^{19}F NMR ($CDCl_3$): δ −86.6 (m, 2F, –NCF_2), δ −117.3 (quintet, 4F, α-CF_2 J=11.3 Hz), δ −123.5 (s, 4F, β-CF_2), δ −128.7 ppm (s, 4F, γ-CF_2). ^{1}H NMR: δ 3.98 (s, CH_3).

*3.7. Preparation of F-(N-iododifluoromethyl-hexahydroazepine) (***4e***)*

A total of 5.0 g of the cell drained product from the fluorination of **3** (containing 1.0 g of *F*-(methylpiperidino-acetyl fluoride) (**9**) and 2.3 g of *F*-(1-hexahydroazepine-acetyl fluoride) (**4**) by GC) and 0.88 g (6.5 mmol) anhydrous LiI was placed in a 75 ml stainless steel container equipped with a Hoke miniature valve, evacuated while cooling at −78°C, and heated at 180°C for 16 h. The volatile compounds were removed via a vacuum line after cooling the cylinder at −78°C, the pressure in the cylinder was removed by filling it with Ar and finally the product was collected with a syringe. The pink-colored liquid (3.42 g) was found to contain 0.37 g of *F*-(*N*-iodomethyl-hexahydroazepine) (**4e**) and 0.71 g of *F*-(*N*-iodomethyl-methylpiperidine) (**13**) in addition to the unreacted **9** and **4** by GC analysis. The yields of *F*-(*N*-iodomethyl-hexahydroazepine) (**4e**) and *F*-(*N*-iodomethyl-methylpiperidine) (**13**) were 42 and 36%, respectively, based on the sample consumed.

F-(*N*-iodomethyl-hexahydroazepine) (**4e**) (nc) had bp 113–114°C, d_4^{20} 2.1407 and n_D^{20} 1.3556. IR (gas): 1329 (ms), 1290 (s), 1236 (vs), 1210 (w), 1188 (w), 1162 (m), 1131 (w), 1116 (w), 1098 (m), 1079 (w), 1045 (w), 1011 (s), 965 (m), 933 (ms), 839 (w), 965 (m), 934 (ms), 839 (w), 794 (ms), 768 (m), 752 (w). Mass: 364 $[M–I]^+$ (4.2), 177 CF_2I^+ (8.5), 145 $C_3F_5N^+$ (2.7), 131 $C_3F_5^+$ (13.4), 127 I^+ (100), 119 $C_2F_5^+$ (2.1), 114 $C_2F_4^+$ (20.3), 100 $C_2F_4^+$ (42.3), 95 $C_2F_3N^+$ (2.6), 93 $C_3F_3^+$ (4.9), 81 $C_2F_3^+$ (2.0), 76 $C_2F_2N^+$ (3.2), 69 CF_3^+ (53.9), 50 CF_2^+ (27.0). ^{19}F NMR ($CDCl_3$): δ −15.8 ppm (quintet, 2F, NCF_2I, J=25.9 Hz), δ −89.0 ppm (t, 4F, α-CF_2, J=24.2 Hz), δ −124.3 (s, 4F, β-CF_2), δ −128.7 (s, 4F, γ-CF_2).

F-(*N*-iodomethyl-methylpiperidine) (**13**) (nc): IR (gas): 1343 (m), 1313 (vs), 1284 (m), 1262 (s), 1231 (ms), 1213 (ms), 1184 (ms), 1173 (ms), 1153 (m), 1138 (w), 1102 (m), 1030 (ms), 998 (m), 975 (m), 961 (m), 889 (ms), 877 (w), 763 (ms), 703 (w). Mass: 364 $[M–I]^+$ (3.1), 195 CF_3I^+ (1.3), 177 CF_2I^+ (7.0), 131 $C_3F_5^+$ (8.3), 127 I^+ (52.2), 119 $C_2F_5^+$ (2.6), 114 $C_2F_4N^+$ (10.3), 100 $C_2F_4^+$ (10.4), 95 $C_2F_3N^+$ (2.1), 93 $C_3F_3^+$ (2.6), 69 CF_3^+ (100). 50 CF_2^+ (16.1). ^{19}F NMR ($CDCl_3$): δ −17.8 to 18.2 ppm (m, –NCF_2I), δ −70.9 to 138.0 ppm (m, CF_2), δ −182.7 (m, CF), δ −189.9 (m,

CF). The mixing ratio of the two isomers was determined to be *F*-(1-iodomethyl-3-methylpiperidine):*F*-(1-iodomethyl-4-methylpiperidine)=1:0.48 by the integration of the two CF-peaks on the piperidine ring.

3.8. Preparation of potassium salt (**4c**) of **4**

Powdered KOH (0.46 g, 8.2 mmol) was charged into a 100 ml flask containing 3.2 g (7.5 mmol) of **4b** in 5 ml of methanol. After stirring with a magnetic stirrer at room temperature for 3 h, the volatile compounds were evaporated under reduced pressure and thoroughly dried in a vacuum to give a white solid (3.2 g, *Y*=95%). IR (KBr disk): 1697 *v*(C=O) (vs), 1664 (vs), 1290 (s), 1271 (vs), 1161 (s), 1060 (m), 991 (s), 941 (s) and 750 (m).

3.9. Preparation of N-difluoromethyl-dodecafluoro(hexahydroazepine)(**4d**)

A total of 1.0 g (2.2 mmol) of compound **4c** and 1.0 g of ethylene glycol was introduced into a 30 ml stainless steel cylinder. After evacuating the cylinder while cooling at −78°C, the contents were heated at 170°C for 6 h. The CO_2 was removed on vacuum line while cooling the cylinder at −78°C, and then the compound was finally collected at −196°C trap as a colorless liquid (0.81 g, *Y*=99%).

N-difluoromethyl-dodecafluoro(hexahydroazepine) (**4d**) (nc) had bp 96–97°C, d_4^{20} 1.8378 and n_D^{20} 1.3006. Mass: 346 $[M–F]^+$ (0.7), 276 $C_6F_{11}N^+$ (1.3), 176 $C_4F_6N^+$ (0.9), 145 $C_3F_5N^+$ (1.8), 131 $C_3F_5^+$ (9.4), 114 $C_2F_4N^+$ (2.8), 100 $C_2F_4^+$ (12.4), 96 $C_2F_3NH^+$ (2.8), 93 $C_3F_3^+$ (1.9), 76 $C_2F_2N^+$ (1.3), 69 CF_3^+ (18.7), 51 CF_2H^+ (100). IR (gas): 1449 (m), 1352 (ms), 1339 (ms), 1286 (vs), 1239 (vs), 1222 (s), 1185 (m), 1162 (ms), 1130 (s), 1097 (m), 1035 (s), 988 (s), 970 (s), 930 (s), 948 (m), 716 (s), 700 (w), 665 (w). ^{19}F NMR: δ −90.1 ppm (m, 4F, α-CF_2), δ −95.0 (d, quartet, 2F, *J*=57.0, 11.9 Hz, NCF_2), δ −125.7 (m, 4F, β-CF_2) and δ −129.2 ppm (m, 4F, γ-CF_2).

3.10. Preparation of F-(3,4,5,6-tetrahydroazepine) (**4e**)

Compound **4c** (1.5 g, 3.3 mmol) was placed in a 50 ml flask which was connected to a trap at −78°C and the vacuum pump. The contents were heated at 245–255°C under a reduced pressure of 95 mmHg to give *F*-(3,4,5,6-tetrahydroazepine) (**4e**) as a colorless liquid with a pungent order in the trap cooled at −78°C (0.99 g, *Y*=84%).

F-(3,4,5,6-tetrahydroazepine) (**4e**) (nc) had bp 65–66°C, d_4^{20} 1.7608 and n_D^{20} 1.3007. Mass: 276 $[M–F]^+$ (8.1), 226 $C_5F_8N^+$ (10.9), 176 $C_4F_6N^+$ (19.1), 131 $C_3F_5^+$ (83.6), 114 $C_2F_4N^+$ (7.7), 100 $C_2F_4^+$ (20.1), 69 CF_3^+ (100). IR (cm^{-1}): 1766 (vs), 1298 (s), 1217 (vs), 1174 (vs), 1159 (vs), 1097 (ms), 981 (s), 937 (s) and 952 (m). ^{19}F NMR ($CDCl_3$): δ −23.8 (s, 1F, CF), δ −88.3 (t, 2F, CF_2, *J*=8.7 Hz), δ −116.5 (s, 2F, CF_2), δ −126.6 (m, 2F, CF_2), δ −127.4 (s, 2F, CF_2), δ −130.2 (s, 2F, CF_2).

3.11. Preparation of F-(1-hexahydroazepine-acetoamide) (**4f**)

In a 100 ml round bottom flask containing 2.96 g (7.0 mmol) of **4b** dissolved in 2 ml dry ether, 12 mmol of NH_3 was condensed at −196°C. After allowing the preparation to stand for approximately 6 h at room temperature, the volatile materials were pumped away leaving behind a pale yellow solid (approximately 2.68 g). The yield was almost quantitative.

F-(1-hexahydroazepine-acetoamide) (**4f**) (nc) had mp 47–48°C. IR (KBr disk): 1707 *v*(C=O) (s), 1350 (ms), 1304 (s), 1231 (vs), 1190 (ms), 1161 (ms), 1132 (w), 1098 (ms), 1017 (s), 968 (ms), 929 (s), 832 (ms). ^{19}F NMR ($CD_3C(O)CD_3$): δ −86.1 (s, α-CF_2), δ −117.9 ppm (s, 2F, $NCF_2C(O)$), δ −122.7 (s, 4F, β-CF_2), δ −128.0 ppm (s, 4F, γ-CF_2).

3.12. Preparation of F-(1-hexahydroazepine-acetonitrile) (**4g**)

A total of 1.26 g (3.2 mmol) of **4f** and 2 g of P_2O_5 were placed in a 100 ml round bottom flask. After heating the reaction mixture at 146°C for 2.5 h, the compound was collected in −78°C trap as a colorless liquid (1.26 g, *Y*=46%). *F*-(1-hexahydroazepine-acetonitrile)(**4g**) (nc) had bp 134.5–135.5°C, d_4^{20} 1.8060 and n_D^{20} 1.3106. IR (gas): 2267 *v*(CN) (s), 1238 (ms), 1316 (s), 1304–1296 (s), 1271 (m), 1239 (vs), 1187 (m), 1168 (m), 1151 (m, sh), 1133 (m), 1105 (w), 1046 (w), 1028 (s), 978 (m), 934 (s), 842 (w), 828 (ms), 665 (m). Mass: 364 $[M–CN]^+$ (0.8), 214 $C_4F_8N^+$ (0.8), 150 $C_3F_6^+$ (1.0), 145 $C_3F_5N^+$ (1.5), 131 $C_3F_5^+$ (17.2), 126 $C_3F_4N^+$ (10.1), 119 $C_2F_5^+$ (3.0), 107 $C_3F_3N^+$ (5.9), 100 $C_2F_4^+$ (55.2), 93 $C_3F_3^+$ (2.2), 81 $C_2F_3^+$ (1.4), 76 $C_2F_2N^+$ (100), 69 CF_3^+ (51.7), 50 CF_2^+ (27.1). ^{19}F NMR: δ −86.4 (s, 4F, α-CF_2), δ −104.2 ppm (m, 2F, NCF_2CN), δ −123.4 (s, 4F, β-CF_2), δ −128.6 ppm (s, 4F, γ-CF_2).

3.13. Preparation of p-methoxyanilide (**4h**) of **4**

A total of 10.1 g (0.1 mol) triethylamine and 3.6 g (30 mmol) of *p*-anisidine, 3.1 g (10 mmol) of compound **2** (cell drain obtained from the fluorination of **3** was used) was added to a 50 ml Teflon vessel containing 20 ml of dichloromethane, and the mixture was allowed to stand in a draft overnight to give a white solid. The crude product was purified by column chromatography (eluent: a mixture of hexane and acetonitrile) to give *F*-(1-hexahydroazepine-acetyl)-*p*-methoxyanilide as a white crystal (1.07 g, *Y*=25.8%).

F-(1-hexahydroazepine-acetyl)-*p*-methoxyanilide (**4h**) (nc): mp 114–115°C. ^{1}H NMR ($CDCl_3$): δ −83.1 ppm (quintet, 2F, –NCF_2–C(O)O–), δ −86.3 (s, 4F, α-NCF_2, ring), δ −124.4 (s, 4F, β-CF_2), δ −128.8 (s, 4F, γ-CF_2). ^{1}H NMR: δ 3.8 (s, 3H, OCH_3), δ 6.9 (d, 2H, Ph), δ 7.4 (d, 2H, Ph).

Acknowledgements

This investigation was supported by the New Energy and Industrial Technology Development Organization (NEDO). One of the authors, S.K. Pandey, would like to thank the Research Institute of Innovative Technology for the Earth, Japan, for providing a visiting scientist fellowship. The authors also wish to thank Ms. I. Soloshonok and Ms. J. Tachibana for performing the NMR, mass and IR spectra.

References

[1] R.E. Banks, Fluorocarbons and their Derivatives, Macdonalds, London, 1970, pp. 70–101.
[2] M. Howe-Grant (Ed.), Fluorine Chemistry: A Comprehensive Treatment, Encyclopedia Preprint Series, Wiley, 1995, pp. 304–318, and reference therein.
[3] R.F. Anderson, J.O. Punderson, in: R.E. Banks (Ed.), Organofluorine Chemicals and their Industrial Applications, Ellis Horwood, Chichester, 1982, pp. 235–457.
[4] D.S.L. Slinn, S.W. Green, in: R.E. Banks (Ed.), Preparation, Properties and Industrial Applications of Organofluorine Compounds, Ellis Harwood, Chichester, 1982, pp. 45–82.
[5] R.D. Chambers, Fluorine in Organic Chemistry, Wiley, New York, 1973, pp. 3–4.
[6] R.E. Bank, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry: Principles and Commercial Applications, Plenum Press, New York, 1994.
[7] A.R. Ravishankara, S. Solomon, A.A. Turnipseed, R.F. Warren, Science 259 (1993) 194.
[8] M.J. Molina, F.S. Rowland, Nature 249 (1974) 810.
[9] A. Sekiya, N. Ishikawa, Kikan Kagaku Sousetu, No. 11, 1991, Chem. Soc. Jpn., Gakkai Shyuppan Center, 1991, pp. 81–98.
[10] A. Sekiya, S. Misaki, J. Fluor. Chem. 101 (2000) 215.
[11] T. Abe, E. Hayashi, H. Fukaya, H. Baba, J. Fluor. Chem. 50 (1990) 173.
[12] T.C. Simmons, F.W. Hoffmann, R.B. Beck, H.V. Holler, T. Katz, R.J. Koshar, E.R. Larsen, J.E. Mulvaney, K.E. Paulson, F.E. Rogers, B. Singleton, R.E. Sparks, J. Am. Chem. Soc. 79 (1957) 3429.
[13] T. Abe, H. Fukaya, T. Ono, E. Hayashi, I. Soloshonok, K. Okuhara, J. Fluor. Chem. 87 (1998) 193.
[14] J.H. Simons, US Patent 2,490,098 (1949).
[15] J.H. Simons, Chem. Abstr. 44 (1950) 6443.
[16] R.E. Banks, P.A. Carson, R.N. Haszeldine, J. Chem. Soc., Perkin Trans. 1 (1973) 1111.
[17] W.H. Lin, R.J. Largow, J. Fluor. Chem. 50 (1990) 15.
[18] T. Abe, E. Hayashi, H. Baba, J. Fluor. Chem., in press.
[19] R. E. Banks, J.E. Burgers, R.N. Haszeldine, J. Chem. Soc. (1965) 2720.
[20] J. Lee, K.G. Orrell, Trans. Faraday Soc. 63 (1967) 16.
[21] V.J. Davis, R.N. Haszeldine, A.E. Tipping, J. Chem. Soc. (1975) 1263.
[22] P. Sartori, D. Valayutham, N. Ignatev, M. Noel, J. Fluor. Chem. 87 (1998) 31.
[23] E. Hayashi, T. Abe, H. Baba, S. Nagase, J. Fluor. Chem. 26 (1984) 417.
[24] T. Abe, E. Hayashi, H. Fukaya, H. Baba, J. Fluor. Chem. 50 (1990) 173.
[25] T. Abe, E. Hayashi, H. Fukaya, Y. Hayakawa, H. Baba, J. Fluor. Chem. 57 (1992) 101.
[26] T. Abe, H. Fukaya, E. Hayashi, Y. Hayakawa, M. Nishida, H. Baba, J. Fluor. Chem. 66 (1994) 193.
[27] H. Fukaya, T. Abe, E. Hayashi, Chem. Lett. (1990) 813.
[28] H. Fukaya, T. Matsumoto, E. Hayashi, Y. Hayakawa, T. Abe, J. Chem. Soc., Perkin Trans. 1 (1996) 915.
[29] V.A. Petrov, V.K. Grinevskaya, K.N. Makarov, G.G. Belen'kii, L.S. German, Izv. Akad. Nauk SSSR, Ser. Khim. (1990) 1616.
[30] M. Nishida, H. Fukaya, T. Abe, J. Fluor. Chem. 76 (1996) 3.
[31] H. Gilman, R.J. Jones, J. Am. Chem. Soc. 65 (1943) 1458.
[32] R.B. Mofett, J. Org. Chem. 14 (1949) 862.