# Synthesis of fluorine-containing benzimidazole derivatives*

*T. P. Vasilyeva,* N. M. Karimova, and Yu. V. Slavich*

*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5085. E-mail: d-20@mail.ru*

Various fluorine-containing benzimidazoles were obtained by the reaction of *o*-phenylenediamine, 3,4-diaminotoluene, and 1,2-diamino-4-chlorobenzene with hexafluoropropene or perfluoro(methyl vinyl ether) in DMF. A new efficient method of synthesis of 2-(1,2,2,2-tetrafluoroethyl)benzimidazole by the reaction of *o*-phenylenediamine with hexafluoropropene in the presence of diethylamine or dimethylamine in ethyl acetate is developed.

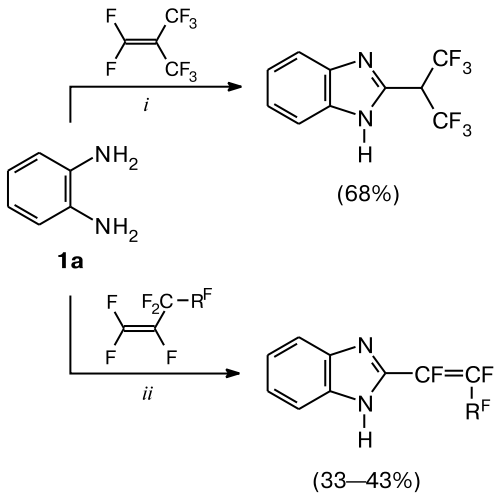
**Key words:** 2-(1,2,2,2-tetrafluoroethyl)-1*H*-benzimidazole, 2-[(fluoro)trifluoromethoxymethyl]-1*H*-benzimidazole, 2-difluoromethyl-1*H*-benzimidazole, 6- or 5-substituted 2-(1,2,2,2-tetrafluoroethyl)- and 2-[(fluoro)trifluoromethoxymethyl]-1*H*-benzimidazoles, *o*-phenylenediamine, 3,4-diaminotoluene, 1,2-diamino-4-chlorobenzene, hexafluoropropene, perfluoro(methyl vinyl ether), heterocyclization, silylation.

Benzimidazoles belong to a very important class of organic compounds and many of them (especially, 2-substituted) are used as drugs. 2-Benzylbenzimidazole (dibazole) is among them, it is used as a hypotensive drug and for flu prevention. Some compounds with high anti-HIV activity were found among fluorine-containing 2-arylsubstituted benzimidazoles.[1] It is known that modification of bioactive compounds by introducing fluorine or fluoroalkyl substituents often leads to enhancement of pharmacokinetic properties. Therefore, the development of new methods of synthesis of 2-fluoroalkyl benzimidazoles is topical.

The purpose of the present work is the development of optimal conditions of synthesis of 2-(α-hydropolyfluoroalkyl)benzimidazoles starting from *o*-phenylenediamines and fluoroolefins, the study of the influence of the olefin structure, catalysts, and the solvent on the heterocyclization reaction .

Despite high bioactivity of fluorine-containing benzimidazoles, their synthesis is studied insufficiently yet. Thus it was reported that 2-difluoromethyl-1*H*-benzimidazole (**2**) was obtained by the reaction of *o*-phenylenediamine (**1a**) with tetrafluoroethylene in an autoclave (135 atm, 136 °C, the yield 50%)[2] or with oxo ester $F_2CHC(O)CBr_2COOMe$ (yield 20—30%).[3] But these methods are not preparative ones. In other papers by Russian[4—8] and Japanese authors[9,10] devoted basically to the study of biological activity[4—6] or crystal structures[7,8] of fluorine-substituted benzimidazoles, no procedures of their synthesis were given, rather only the reactants, *o*-phenylenediamine (**1a**) and hexafluoropropene (in DMF)[4,5,9] or 2-fluoro-2-trifluoromethoxyacetic acid[7], or $Et_2NCF_2CH(F)CF_3$ (in THF)[10] were mentioned. The drawback of the latter procedure is that it requires special preparation of starting *N,N*-diethyl-*N*-(1,1,2,3,3,3-hexafluoroprop-1-yl)amine. The reactions of **1a** with other terminal perfluoroolefins are documented. The reaction with perfluoroisobutylene at room temperature (in an autoclave) resulted in 2-$(CF_3)_2CH$-substituted benzimidazole[11], whereas heterocyclization of **1a** with perfluorinated hept-1-ene or allylbenzene at elevated temperature was complicated by subsequent dehydrofluorination with formation of 2-perfluoroalkenyl benzimidazoles in moderate yields[12] (Scheme 1).

**Scheme 1**




*i*. 20 °C, DMF;
*ii*. 80 °C, MeCN or dioxane; $R^F = C_4F_9, C_6F_5$

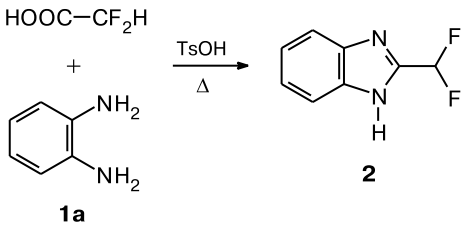
* The present paper is dedicated to the memory of Professor A. F. Kolomiets.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 182—187, January, 2010.

## Results and Discussion

The preparative methods of synthesis of benzimidazoles containing fluoroalkyl substituents in position 2 ($CHF_2$, $CH(F)CF_3$, and $CH(F)OCF_3$) and substituents (Me or Cl) in the aromatic ring are described in the present paper. Our first attempts to obtain 2-difluoromethylbenzimidazole (**2**) by the reaction of **1a** with tetrafluoroethylene in an open system in the presence of $Et_2NH$ as an HF acceptor (in AcOEt) were unsuccessful, probably, because of low reactivity of this olefin. Therefore, **2** was synthesized by a traditional method for benzimidazoles, *i.e.*, by condensation of **1a** with difluoroacetic acid in an organic solvent in the presence of 5 mol.% of *p*-toluenesulfonic acid (Scheme 2).

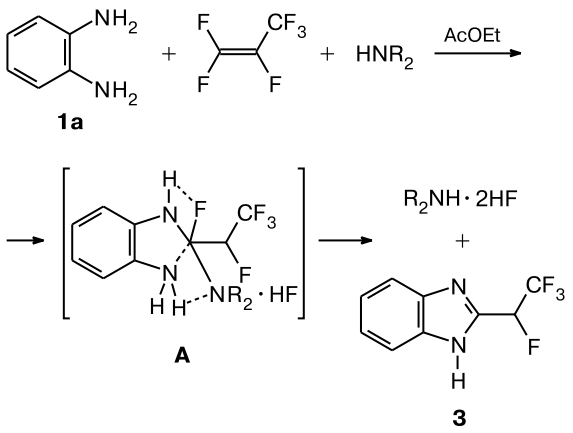
**Scheme 2**




2-(1,2,2,2-Tetrafluoroethyl)benzimidazole (**3**) (drug "fluorasol") can find application in medicine and veterinary due to its high physiological activity,[4—6] therefore we have studied its synthesis in detail. A method for preparation of fluorasol **3**, similar to that shown in scheme 2, is noneconomic because the starting 2,3,3,3-tetrafluoropropionic acid is hardly accessible. The reaction of **1a** with hexafluoropropene in DMF[4,5,9] should be carried out in sealed tubes, which is also unacceptable in case of considerable loads. Therefore, we developed a new method of manufacture of fluorasol **3** in an open system suitable for scaling. It consists of a three-component reaction of **1a**, hexafluoropropene, and a secondary amine in AcOEt as a solvent (Scheme 3). Various amines (dimethylamine or diethylamine), catalysts, and temperature conditions were tested for procedure optimization. Thus entries *1—4* refer to the absence of a catalyst; a crown ether (entry *5*) and a phase-transfer catalyst (entry *6*) were added to the reaction mixtures (0.15—0.24 mol.%), as well as pyridine (entry *7*) and triethylamine (entries *8*, *9*) (10 mol.% with respect to **1a**) (Table 1). It was shown that the presence of a catalyst (as well as its nature) is not of considerable influence on the yield and the purity of product **3**. The temperature regime is more important, because the reaction with hexafluoropropene, unlike that with tetrafluoroethylene, is exothermic (Scheme 3).

The best results were obtained in the temperature range from 7 to 12 °C with $Et_2NH$ (entry *4*) or at 0 °C with $Me_2NH$ (entry *2*). The increase in the reaction temperature to 25 °C resulted in a decrease in the yield of **3** because of the increase in the amount of the side product, *N,N*-dialkyl-2,3,3,3-tetrafluoropropionamide (up to 30%, entry *9*, Table 1). Among the catalysts tested, only tertiary amines ($Et_3N$, Py) deserve attention, since the presence of them prevents the formation of a sediment of intermediate **A** (see Scheme 3); this is important from the technological point of view.

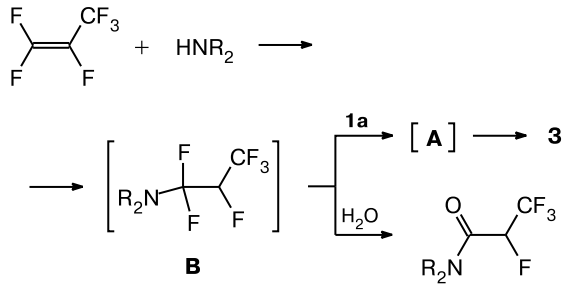
**Scheme 3**




R = Me, Et

We assume that the mechanism of the three-component reaction includes the transient formation of a crystalline complex 1 : 1 : 1 (**A**) insoluble in AcOEt, which then undergoes cyclization to fluorasol **3** upon elimination of dialkylamine dihydrofluoride. Apparently, along with formation of phenylene intermediate **A**, competing reaction of hexafluoropropene with dialkylamines takes place resulting in α,α-difluoroamines **B**. Possibly, the reaction of the latter with **1a** also affords fluorasol **3**, while the side products (dialkylamides) form in the reaction with the atmospheric moisture (Scheme 4).

**Scheme 4**




R = Me, Et

Further, we compared the above-described method with the known methods[4,5,9] by examples of reactions of compound **1a** and its monosubstituted analogs (**1b,c**) with both hexafluoropropene and perfluoro(methyl vinyl ether).

**Table 1.** The influence of the reaction conditions on the yield and purity of fluorasol **3** prepared by coupling of *o*-phenylenediamine (**1a**) with hexafluoropropene

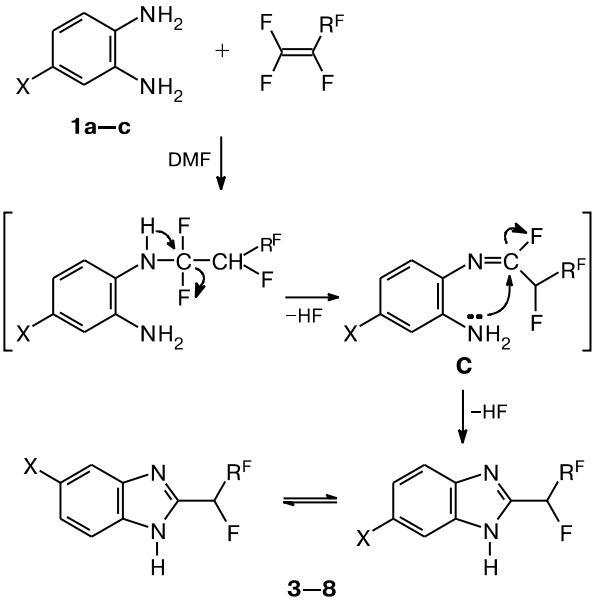
| Entry | **1a**/g (mol) | $R_2NH$ /g (mol) | AcOEt /mL | Catalyst /mg (mmol) | $T^a$/°C | Yield of **3** /g (%) | M.p. of **3** /°C |
|---|---|---|---|---|---|---|---|
| *1* | 5.4 (0.05) | $Me_2NH$ 2.7 (0.06) | 40 | — | −10 | 8.05 (74) | 186—195 |
| *2* | 5.4 (0.05) | $Me_2NH$ 2.7 (0.06) | 40 | — | 0 | 9.5 (87) | 195—197 |
| *3* | 5.4 (0.05) | $Me_2NH$ 2.7 (0.06) | 40 | — | 10 | 7.87—7.93 (72—73)[b] | 195—197 |
| *4* | 5.4 (0.05) | $Et_2NH$ 4.38 (0.06) | 40 | — | 7—12 | 9.3 (85) | 188—192 |
| *5* | 3.51 (0.032) | $Et_2NH$ 2.85 (0.039) | 26 | Dicyclohexano-18-crown-6 17.6 (0.047) | 10 | 5.59 (79)[b] | 190—192 |
| *6* | 3.51 (0.032) | $Et_2NH$ 2.85 (0.039) | 25 | $[PhCH_2NEt_3]^+Cl^-$ 17.6 (0.077) | 10 | 5.25 (74) | 190—191 |
| *7* | 5.4 (0.05) | $Et_2NH$ 4.38 (0.06) | 40 | Py 400 (5.06) | 15—20 | 8.3 (76) | 195—199 |
| *8* | 5.4 (0.05) | $Et_2NH$ 4.38 (0.06) | 40 | $Et_3N$ 510 (5) | 15—20 | 8.88 (81.5) | 185—193 |
| *9* | 16.2 (0.15) | $Et_2NH$ 11.5 (0.16) | 130 | $Et_3N$ 1515 (15) | ≥25 | 22.89 (70)[c] | 188—190 |

[a] Temperature of the reaction.
[b] Two runs.
[c] $CF_3CH(F)CONEt_2$ (9 g, 30%) with b.p. 76 °C (10 Torr) was isolated from the filtrate by distillation.

It is found that, indeed, replacement of the solvent (DMF instead of AcOEt) brings about spontaneous cyclocondensation of different phenylenediamine derivatives with fluoroolefins in the absence of dialkylamines. In this way, both the previously known and novel 2-fluoroalkylbenzimidazoles **3**—**8** were obtained (Scheme 5).

We assume that in this case initial addition of the amino group to the double bond of the olefin takes place; dehydrofluorination of 1 : 1 adducts formed affords the reactive imidoyl fluorides **C**, which undergo cyclization in compounds **3**—**8**. As a result of prototropic tautomerization of benzimidazoles,[13] the cyclization of 4-methyl- or 4-chloro-substituted phenylenediamines with fluoroolefins results in 5- or 6-X-substituted benzimidazoles **5**—**8** in which the positions 5 and 6 are equivalent (see Scheme 5). The process is lengthy, which is a drawback of this method. The reaction is exothermic in the presence of secondary amines (see Scheme 3) and completes in 1—2 h, whereas in DMF (see Scheme 5) reaction with $CF_2{=}CF{-}R^F$ takes from 2—3 ($R^F = CF_3$) to 4—7 days ($R^F = OCF_3$); therefore, the latter reaction was carried out in sealed tubes. In addition, the reactions in DMF were complicated by polymerization (which probably involved the double bond —N=C< of intermediate **C**), which made difficult the isolation and purification of the products. After multiple treatments with activated charcoal and sublimations, the yields

**Scheme 5**




X = H (**1a**), Me (**1b**), Cl (**1c**)

| Compound | **3** | **4** | **5** | **6** | **7** | **8** |
|---|---|---|---|---|---|---|
| X | H | H | Me | Me | Cl | Cl |
| $R^F$ | $CF_3$ | $OCF_3$ | $CF_3$ | $OCF_3$ | $CF_3$ | $OCF_3$ |

of the cyclization products were lower (49—60%) than in the former method (see Scheme 3, 72—87%).

The yields and physicochemical properties of compounds obtained are listed in Table 2, and their spectral characteristics are given in Table 3. Unsubstituted benzimidazoles are water-soluble[13]; in contrast, fluorine-substituted benzimidazoles **2**—**8** are insoluble in water, diethyl ether, and petroleum ether. They are soluble in alcohols, AcOEt, MeCN, DMF, and DMSO and are moderately soluble in $CHCl_3$ and benzene. They are easily sublimed in vacuum at elevated temperatures, which is typical of them. In the IR spectra of fluorine-containing benzimidazole derivatives, ν(C=N) are observed at 1590—1630 $cm^{-1}$ and ν(N—H) at 2600—3200 $cm^{-1}$. The $^1H$ NMR spectra of benzimidazoles with $R^F = CF_3$ (**3**, **5**, **7**) contain a doublet of quartets of the methine proton (CHF) at $\delta \approx 6$; for compounds with $R^F = OCF_3$ (**4**, **6**, **8**), it is a doublet at δ~7 (in $CDCl_3$). In DMSO-$d_6$, the signals for CHF are shifted to the lower field by ~1 ppm (for **3**) and 0.45 ppm (for **4**). On the basis of the NMR spectra of benzimidazoles with substituents in the aromatic ring, $R^F = OCF_3$, X = Me (**6**) and Cl (**8**), it can be assumed that for solutions in $CDCl_3$ these compounds exist in both the free form and the form of a stereoisomer with intra- or intermolecular H-bond >CHF...H—N<, which was revealed by doubling of signals for the CHF groups in the $^{19}F$ NMR spectra and by complication of the signals for aromatic protons in the $^1H$ NMR spectra (see Table 3).

We studied the stability of the fluorine-containing benzimidazole derivatives obtained. In solid state, they all are stable and can be stored without changes at room temperature for no less than 5 years. The stability of compounds **3**, **4**, and **6** in DMF solution with heating was estimated by spectroscopy. No changes in the $^{19}F$ NMR spectra of trifluoromethoxybenzimidazoles **4** and **6** occured upon heating (100±1 °C) for 10 h in DMF (at a concentration of 20%). Under the same conditions, the concentration of fluorasol **3** reduced nearly twofold; at the same time, a new signal at δ > 100 appeared. The increased stability of **4** and **6** toward heating in DMF (as compared with fluoroazol **3**) can be related to the presence of H-bonds in their molecules.

In addition, we began studying the reactivities of compounds obtained. It is known that benzimidazoles are easily alkylated, acylated,[13] and silylated with hexamethyldisilazane.[14,15] However, fluorine-substituted analogs were found to be very stable and inert toward alkyl halides, sulfenyl chlorides, chlorotrimethylsilane, and hexamethyldisilazane because of dramatic decrease in the imine nitrogen basicity. Silylation of fluorasol **3** was succesful only with *N,N*-diethyl-*N*-trimethylsilylamine in the presence of catalytic amounts of ammonium sulfate; *N*-trimethylsilylfluoroazol **9** was obtained in high yield (Scheme 6), which will allow modification of fluorine-containing benzimidazoles at the nitrogen atom in the future.

Thus, the following order of reactivity of fluoroolefins with respect to *o*-phenylenediamine was found in the present study:

$$F_2C{=}CF_2 < F_2C{=}CF{-}OCF_3 < F_2C{=}CF{-}CF_3.$$

**Table 2.** Physicochemical characteristics of fluorine-containing benzimidazole derivatives

| Compound | Yield (%) | M.p./°C (solvent) | Found / Calculated (%) | | | Molecular formula | $R_F$[a] |
|---|---|---|---|---|---|---|---|
| | | | C | H | N | | |
| **2** | 65 | 153[b] ($Pr^i$—$H_2O$) | — | — | — | $C_8H_6F_2N_2$ | 0.26 |
| **3** | 72—87[c] | 191—193; 195—197[c] | 49.44 | 2.70 | 12.77 | $C_9H_6F_4N_2$ | 0.40 |
| | 60[d] | (AcOEt—hexane) | 49.54 | 2.75 | 12.84 | | |
| | | 189—190[d] (PhH) | | | | | |
| **4** | 52 | 140—141 | 46.14 | 2.51 | 11.97 | $C_9H_6F_4N_2O$ | 0.44 |
| | | (PhH—petrol. ether) | 46.15 | 2.56 | 11.97 | | |
| **5** | 49 | 176—177[e] | — | — | — | $C_{10}H_8F_4N_2$ | 0.41 |
| | | ($Pr^iOH$—$H_2O$) | | | | | |
| **6** | 57 | 123—124[f] | 48.21 | 3.24 | 11.28 | $C_{10}H_8F_4N_2O$ | 0.47 |
| | | | 48.39 | 3.23 | 11.29 | | |
| **7** | 59 | 144—146[g,h] | — | — | — | $C_9H_5ClF_4N_2$ | 0.48 |
| | | ($CHCl_3$—hexane) | | | | | |
| **8** | 50 | 124—126[h] | 40.12 | 1.87 | 10.19 | $C_9H_5ClF_4N_2O$[i] | 0.55 |
| | | | 40.22 | 1.86 | 10.43 | | |

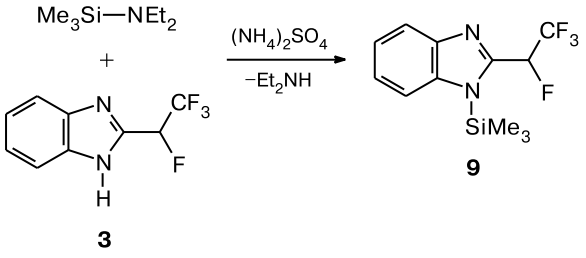
[a] Crimson spot in UV light; system AcOEt—petroleum ether, 1 : 3. [b] M.p. 155—156 °C (see Ref. 2); 146—148 °C (see Ref. 3). [c] Obtained in accordance with Scheme 3 (entries *1—8,* see Table 1); m.p. 184 °C (see Refs 4, 5). [d] Obtained in accordance with Scheme 5. [e] M.p. 176 °C (see Ref. 9); 174—175 °C (see Ref. 10). [f] Purified by sublimation *in vacuo* (1 Torr) at 80 °C. [g] M.p. 143—144 °C (see Ref. 9); 142—143 °C (see Ref. 10). [h] Purified by sublimation *in vacuo* (3 Torr) at 120—154 °C. [i] Found: F, 28.32%, calculated: F, 28.31%.

**Table 3.** Spectral characteristics of fluorine-containing benzimidazole derivatives[a]

| Compound | Solvent | $^1$H NMR, δ (*J*/Hz) | $^{19}$F NMR, δ (*J*/Hz)[b] |
|---|---|---|---|
| **2** | $CDCl_3$ | 6.99 (t, 1 H, $CHF_2$, *J* = 53.9); 7.43 (m, 2 H, H(5)+H(6)); 7.76 (br.s, 2 H, H(4)+H(7)); 10.59 (br.s, 1 H, NH) | 37.45 (s, $CF_2$) |
| **3** | DMSO-$d_6$ | 6.81 (dq, 1 H, CHF, *J* = 42.3, *J* = 6.4); 7.35 (m, 2 H, H(5)+H(6)); 7.70 (br.s, 2 H, H(4)+H(7)); 13.26 (br.s, 1 H, NH) | –2.03 (d, $CF_3$, *J* = 13.9); 119.68 (q, CHF, *J* = 13.9) |
| | $CDCl_3$ | 5.84 (dq, 1 H, CHF, *J* = 46.8, *J* = 8.5); 7.03 (m, 2 H, H(5)+H(6)); 7.58 (m, 2 H, H(4)+H(7)); 9.58 (br.s, 1 H, NH) | — |
| **4** | $CDCl_3$ | 7.05 (d, 1 H, CHF, *J* = 56.2); 7.44 (m, 2 H, H(5)+H(6)); 7.60, 7.88 (both br.s, 1 H each, H(4)+H(7)); 10.44 (br.s, 1 H, NH) | –18.39 (d, $OCF_3$, *J* = 5.05); 45.81 (q, CHF, *J* = 5.05) |
| | DMSO-$d_6$ | 7.50 (d, 1 H, CHF, *J* = 53.9); 7.33 (m, 2 H, H(5)+H(6)); 7.67 (br.s, 2 H, H(4)+H(7)); 13.15 (br.s, 1 H, NH) | — |
| **5** | $CDCl_3$ | 2.56 (s, 3 H, Me); 6.07 (dq, 1 H, CHF, *J* = 43.5, *J* = 5.9); 7.25 (d, 1 H, H(5), *J* = 8.4); 7.50, 7.63 (both br.s, 1 H each, H(4)+H(7)); 10.08 (br.s, 1 H, NH) | –0.06 (d, $CF_3$, *J* = 14.0); 120.02 (q, CHF, *J* = 14.0) |
| **6** | $CDCl_3$ | 2.56 (s, 3 H, Me); 7.01 (d, 1 H, CHF, *J* = 56.3); 7.25 (m, 1 H, H(5)[c,d]; 7.38 (br.s, 1 H, H(7), 43%)[c]; 7.47 (br.d, 1 H, H(7), *J* = 8.1, 57%)[d]; 7.68 (br.s, 1 H, H(4), 43%)[c]; 7.77 (br.d, 1 H, H(4), *J* = 8.1, 57%)[d]; 10.09 (br.s, 1 H, NH) | –18.43 (d, $OCF_3$, *J* = 5.0); 45.62 (q, CHF, *J* = 4.1, 43%)[c]; 45.44 (q, CHF, *J* = 4.6, 57%)[d] |
| **7** | $CDCl_3$ | 6.07 (dq, 1 H, CHF, *J* = 43.7, *J* = 5.8); 7.41 (s, 1 H, H(7)); 7.55 (m, 1 H, H(5)); 7.80 (m, 1 H, H(4)); 10.52 (s, 1 H, NH) | –0.10 (d, $CF_3$, *J* = 13.6); 121.25 (m, CHF) |
| **8** | $CDCl_3$ | 7.02 (d, 1 H, CHF, *J* = 56.2); 7.38 (m, 1 H, H(7)); 7.56 (m, 1 H, H(5)); 7.82 (m, 1 H, H(4)); 10.44 (s, 1 H, NH) | –18.38 (d, $OCF_3$, *J* = 5.0); 46.27 (q, CHF, *J* = 4.5, 44%)[c]; 46.14 (q, CHF, *J* = 5.2, 56%)[d] |

[a] IR spectra (ν/cm$^{-1}$) for **3**: 1600—1630 (C=N), 2600—3200 (NH); for **4**: 1590 (C=N), 2600—3200 (NH); for **6**: 1600 (C=N), 2600—3200 (NH).
[b] Relative TFA, with proton suppression ($^{19}$F{H}).
[c] Free form.
[d] Stereoisomer with the H-bond >CHF...H—N<.

**Scheme 6**




The preparative methods of synthesis were proposed for the known and novel fluorine-substituted benzimidazoles **2**—**8**. Their stabilities were determined. A new method for manufacture of the promising bioactive compound ftorazol (**3**) was developed; this consists of heterocyclization of **1a** with hexafluoropropene in the presence of secondary amines in ethyl acetate. This method has good reproducibility and is suitable for the synthesis of other benzimidazoles containing fluoroalkyl substituents HFC—$R^F$, where $R^F$ = $OCF_3$ or $C_nF_{2n+1}$ (*n* = 2—6), in position 2. Silylated fluorasol (**9**) with high synthetic potential was synthesized for the first time.

## Experimental

NMR spectra were recorded on a Bruker AV-300 spectrometer at frequencies 300 MHz for $^1$H, and 282 MHz for $^{19}$F ($CF_3CO_2H$). All the solvents employed in the reactions were dried with the appropriate drying agents. The reactions were monitored by TLC on silica gel plates (Merck 60 $F_{254}$). Characteristics of the compounds synthesized are given in Tables 2 and 3.

**2-Difluoromethyl-1*H*-benzimidazole (2).** A mixture of *o*-phenylenediamine (**1a**) (10.8 g, 0.1 mol), difluoroacetic acid (10 g, 0.104 mol), and $TsOH \cdot H_2O$ (0.95 g, 0.005 mol) in xylene (60 mL) and benzene (10 mL) was refluxed with a Dean—Stark trap until liberation of water ceased (~6 h) and cooled. The precipitate that formed was filtered off, dissolved in AcOEt (100 mL), and stirred with activated charcoal (2 g) for 5 h. The residue after removal of charcoal and the solvent was purified by precipitation with water from a solution in $Pr^iOH$ to yield 11 g of compound **2**.

When attempted to carry out the reaction of **1a** with tetrafluoroethylene in the presence of $Et_2NH$ in AcOEt (by analogy with the synthesis of **3**), no product **2** was formed (TLC control).

**2-(1,2,2,2-Tetrafluoroethyl)-1*H*-benzimidazole (fluorasol) (3).** To a four-neck flask with a stirrer, thermometer, bubbler, and a reflux condenser connected to the trap cooled to –40 °C, **1a** and a solution of a secondary amine ($Me_2NH$ or $Et_2NH$) in ethyl acetate were placed. Entries *1*—*4* (see Table 1) refer to the

absence of a catalyst. The following catalysts were tested: crown ether (entry *5*), a phase-transfer catalyst (entry *6*) (0.5% mass in respect of **1a**), and tertiary amines (entries *7—9*) (10 mol.% in respect of **1a**). The reaction temperatures are shown in Table 1. Hexafluoropropene was passed at this temperature with vigorous stirring (the reaction is exothermic) until the excess of hexafluoropropene began to condense in the trap (1 h 15 min — 2 h 20 min). During the reaction, a light-colored precipitate of intermediate **A** formed at the beginning, and then dissapeared. In the presence of tertiary amines (entries *7—9*), no formation of a precipitate was observed.

After completion of the reaction (dissapearance of the starting **1a** as judged by TLC in the solvent system acetone—$CCl_4$, 1 : 3), the excess of hexafluoropropene (from the trap) was added to the reaction flask and the mixture was stirred and gradually warmed to 20 °C. The reaction mixture was washed with water (×3), the organic layer was separated, and aqueous layers were extracted with ethyl acetate (×3). The organic layers were combined and discolored by stirring with activated charcoal (10% in respect of the starting **1a**) for 1—1.5 h. After removal of charcoal by filtration, the fitrate was concentrated *in vacuo*, the solid precipitate was washed on a filter with hexane and dried in air.

The loads in the experiments, their conditions, and the results (yields and m.p. of **3**) are presented in Table 1, the physicochemical characteristics and NMR ($^1$H and $^{19}$F) spectra of ftorazol **3** are given in Tables 2 and 3.

**Synthesis of 5- or 6-substituted 2-fluoroalkyl- and 2-fluoroalkoxy-1*H*-benzimidazoles (3—8) (general procedure).** A solution of the corresponding *o*-phenylenediamine (0.073 mol) in DMF (40 mL) was placed in a 250-mL tube, then an excess of hexafluoropropene or perfluoro(methyl vinyl ether) (0.1—0.2 mol) was condensed in the tube at −60—−80 °C. The tube was sealed and gradually warmed to 20 °C. The heterogeneous reaction mixture (consisting of two layers) was kept with periodic shaking until the layer of the fluoroolefin disappeared. The synthesis of compounds with $R^F = CF_3$ (**3**, **5**, **7**) was completed in 2—3 days, but for the preparation of compounds with $R^F = OCF_3$ (**4**, **6**, **8**) longer period (from 4 to 7 days) was needed. After the homogenization was attained, the tube was cooled, opened and the content was poured into ice water (400 ml). If no solidification occurred after mixing with water, water was removed by decantation, and the residue was mixed with fresh portions of water. The precipitate was filtered off, thoroughly washed with water (×3), then with hexane or petroleum ether (×2). The product was discolored by dissolution in ethyl acetate and stirring with activated charcoal for 2—3 h (for 10 g of the raw product, 50 mL of ethyl acetate and 1.5 g of activated charcoal were used). When necessary, the procedure was repeated. After removal of charcoal by filtration, the filtrate was concentrated *in vacuo*, the residue was purified by recrystallization, reprecipitation, or sublimation. The characteristics of compounds **3—8** are given in Tables 2 and 3.

**2-(1,2,2,2-Tetrafluoroethyl)-1-trimethylsilyl-1*H*-benzimidazole (9).** Fluorasol **3** (6.54 g, 0.03 mol) , *N,N*-diethyl-*N*-trimethylsilylamine (13.05 g, 0.09 mol), and catalytic amount (78 mg) of $(NH_4)_2SO_4$ were placed in a Claisen flask with a distillation column, supplied with bubbler and a tube filled with KOH (at the outlet). The mixture was heated in a flow of argon at 120—140 °C (bath) until the distillation of diethylamine ceased (1.5 h). The excess of $Me_3SiNEt_2$ was removed *in vacuo*, the residue was distilled to give compound **9** (7.08 g, 81%) as a viscous light-brown sirup, b.p. 95 °C (0.05 Torr), which is soluble in $CH_2Cl_2$, $CHCl_3$, and MeOH. $^1$H NMR ($CDCl_3$, δ): 0.67 (s, 9 H, $SiMe_3$); 6.08 (dq, 1 H, CHF, $J$ = 44.4 Hz, $J$ = 5.1 Hz); 7.37 (m, 2 H, H(5)+H(6)); 7.65, 7.92 (two m, both 1 H, H(4), H(7)). $^{19}$F NMR ($CDCl_3$, δ): −3.14 (dd, $CF_3$, $J$ = 14.4 Hz, $J$ = 5.1 Hz); 112.35 (dq, CHF, $J$ = 44.4 Hz, $J$ = 14.4 Hz).

Compound **9** is unstable: it is quickly hydrolyzed in air to the initial fluorasol **3** (TLC control).

## References


1. T. Roth, M. Morningstar, P. Boyer, S. Hughes, R. Buckheit, J. Michejda, C. Michejda, *J. Med. Chem.*, 1997, **40**, 4199.
2. D. England, L. Melby, M. Dietrich, R. Lindsey, *J. Am. Chem. Soc.*, 1960, **82**, 5116.
3. K. I. Pashkevich, Z. E. Skryabina, V. I. Saloutin, *Izv. Akad. Nauk USSR, Ser. Khim.*, 1987, 2527 [*Bull. Acad. Sci. SSSR, Div.Chem. Sci.* (*Engl. Transl.*), 1987].
4. A. F. Fokin, E. I. Astashkin, A. Z. Prihod'ko, V. V. Ryabichenko, I. S. Nikolaeva, Yu. V. Slavich, A. F. Kolomiets, *Dokl. Akad. Nauk SSSR*, 1985, **284**, 1492 [*Dokl. Biochem. Phys. Chem* (*Engl. Transl.*), 1985].
5. E. I. Astashkin, A. Z. Prikhod´ko, N. A. Kosheleva, I. G. Pautova, A. F. Kolomiets, Yu. V. Slavich, A. V. Fokin, *Khim.-Farm. Zh.*, 1987, **21**, 265 [*Pharm. Chem. J.* (*Engl. Transl.*), 1987].
6. E. I. Astashkin, A. S. Gukovskaya, A. M. Surin, I. S. Nikolaeva, Yu. V. Slavich, A. F. Kolomiets, A. V. Fokin, *Dokl. Akad. Nauk SSSR*, 1988, **300**, 249 [*Dokl. Biochem. Phys. Chem.* (*Engl. Transl.*), 1988].
7. A. N. Chekhlov, I. V. Martynov, *Dokl. Akad. Nauk SSSR*, 1999, **368**, 639 [*Dokl. Chem.* (*Engl. Transl.*), 1999].
8. A. N. Chekhlov, I. V. Martynov, *Dokl. Akad. Nauk SSSR*, 1999, **365**, 72 [*Dokl. Chem.* (*Engl. Transl.*), 1999].
9. N. Ishikawa, T. Muramatsu, *Nippon Kagaku Kaishi*, 1973, 563.
10. H. Iwakiri, N. Fujiwara, N. Ishikawa, *Nippon Kagaku Kaishi*, 1985, 2161.
11. H. Harada, S. Mizutaki, S. Hayashi, N. Ishikawa, *J. Fluorine Chem.*, 1978, **12**, 211.
12. W. Burger, K. Lunkwitz, *J. Fluorine Chem.*, 1993, **60**, 125.
13. «*Kratkaya khimicheskaya entsyklopediya*» [*Short chemical encyclopaedia*], Sov. Encycl., Moscow, 1961, vol. **1**, p. 399. (in Russian)
14. I. Southon, W. Pfleiderer, *Chem. Ber.*, 1978, **111**, 996.
15. G. Gosselin, H. Loukil, A. Mathieu, A. Mesli, J. Imbach, *J. Heterocycl. Chem.*, 1978, **15**, 657.


*Received September 15, 2009*