Multigram Synthesis of 1-(Difluoromethyl)imidazoles and -benzimidazoles

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Abstract: An expedient approach to the difluoromethylation of imidazoles and benzimidazoles has been developed. The key feature of the procedure is the gradual generation of the difluoromethylation reagent in the reaction mixture, which is achieved by the simultaneous addition of chlorodifluoromethane and alkali. The method is applicable to functionalized substrates and allows the corresponding 1-(difluoromethyl)imidazoles and -benzimidazoles to be prepared in 60–95% yield on a hundred-gram scale.

Key words: fluorine compounds, heterocycles, imidazoles, benzimidazoles, difluoromethylation

The introduction of fluorine-containing groups into organic molecules represents an important structure modification owing to the unique properties of the fluorine atom.[1–3] Nearly 20% of pharmaceuticals, including several of the top drugs, and 30–40% of agrichemicals contain fluorine.[4] Among other organofluorine compounds, those possessing a difluoromethyl group (CHF_2) can be delineated. Several examples of difluoromethyl-substituted drugs can be found on the market, including Eflornithine (**1**),[5] Pantoprazole (**2**)[6] and Garenoxacin (**3**)[7] (Figure 1). Heterocyclic compounds containing a difluoromethyl substituent at the nitrogen atom are found among potential drug candidates (e.g., compound **4** which is a neuropeptide Y antagonist[8]) and as agrichemicals [in particular, Sulfentrazone (**5**)[9] and Carfentrazone-ethyl (**6**)[10]] (Figure 2).

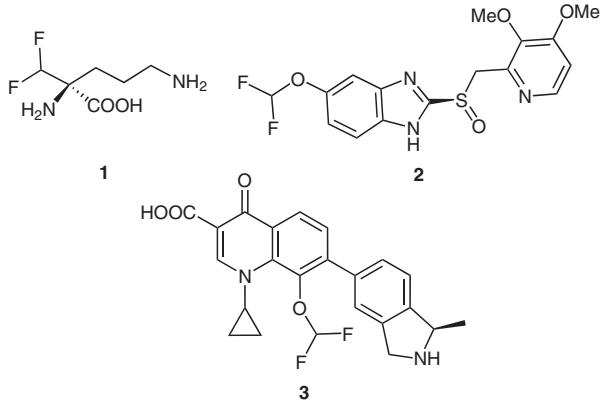

Figure 1 Marketed drugs possessing a difluoromethyl group

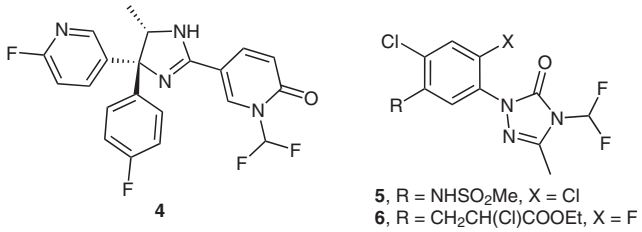

Figure 2

In this work, our results on the N-difluoromethylation of imidazoles and benzimidazoles are described. Several approaches to the synthesis of 1-(difluoromethyl)imidazoles and -benzimidazoles have been reported to date, including either reduction of the corresponding 1-(bromodifluoromethyl)imidazoles and -benzimidazoles,[11,12] or N-difluoromethylation of the parent heterocycles with chlorodifluoromethane,[13–18] sodium trifluoroacetate,[14] methyl chlorodifluoroacetate,[15] chlorodifluoromethyl phenyl sulfone,[19] *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine[20] and other reagents.[21,22] Of these sources of the difluoromethyl group, we turned our attention to chlorodifluoromethane which is readily available commercially. In most of the previous reports, mixed aqueous organic solvent systems were used for the N-difluoromethylation of imidazoles and benzimidazoles with chlorodifluoromethane, including aqueous potassium hydroxide in dioxane,[13,17] acetone,[14] 2-propanol[16] and *N*,*N*-dimethylformamide,[17] as well as tetrahydrofuran or dichloromethane in the presence of benzyltriethylammonium chloride as a phase-transfer catalyst.[18,23] Whereas difluoromethylation of the parent benzimidazole and 2-alkylbenzimidazoles could be performed in moderate to good yields (57–87%), in the case of imidazoles the yield of the corresponding products was diminished significantly (37–44%).[13,14,16,18] Moreover, reactions of functionalized benzimidazoles were complicated by over-difluoromethylation and other side processes.[16–18]

Imidazoles and benzimidazoles **7a–i** considerably varied in their chemical structure were used as model substrates in this study (Table 1). The main idea behind our approach to the difluoromethylation of **7a–i** was to avoid a large excess of strong alkali in the reaction mixture, thus preventing decomposition of chlorodifluoromethane and some of the products.

Three types of reaction conditions were developed for the difluoromethylation of imidazoles and benzimidazoles. The most general procedure involves the gradual addition

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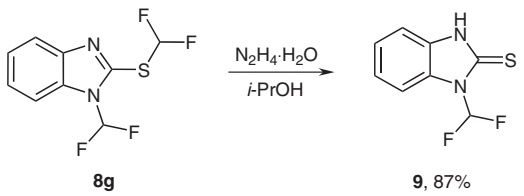
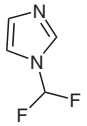
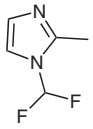
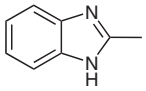
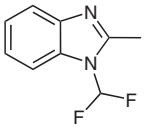
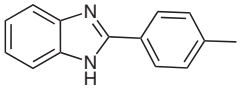
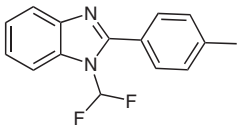
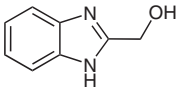
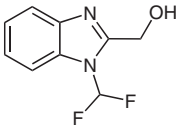
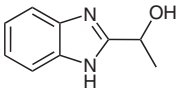
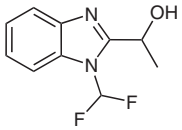
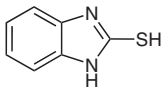
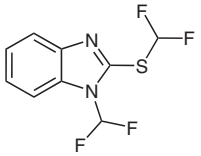
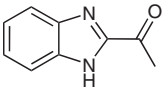
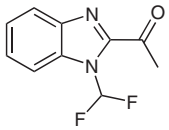
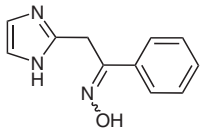
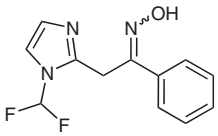
of 35% aqueous potassium hydroxide solution to a solution of the substrate and dibenzo-18-crown-6 (2 mol%) in dioxane, together with constant chlorodifluoromethane bubbling at 70 °C. In particular, difluoromethylation of the functionalized benzimidazoles **7e–h** and imidazole **7i** was performed using this procedure. The corresponding products **8e–i** were obtained in 65–86% yield (Table 1). In the case of substrates **7e** and **7f**, no difluoromethylation at the hydroxy group was observed. On the contrary, only bis(difluoromethylation) product **8g** was obtained from 2-mercapto-1*H*-benzimidazole (**7g**); the mono(difluoromethyl) derivative **9** was obtained by hydrazinolysis of **8g** (Scheme 1). It is interesting to note that the methods reported in the literature afforded mixtures of the corresponding products.[16,18] In fact, the synthesis of pure **9** has not been reported previously; moreover, acetyl-substituted benzimidazole **8h** was isolated in only 13% yield prior to this work.[18]



8g **9**, 87%

Scheme 1

Table 1 Difluoromethylation of Imidazoles and Benzimidazoles **7a–i**

Substrate	Conditions	Product	Yield (%)
7a 	$CHClF_2$, dibenzo-18-crown-6 (2 mol%), 35% aq KOH, DME, 70 °C	**8a** 	75
7b 	$CHClF_2$, dibenzo-18-crown-6 (2 mol%), 35% aq KOH, DME, 70 °C	**8b** 	60
7c 	$CHClF_2$, K_2CO_3, DMF, 90 °C	**8c** 	89
7d 	$CHClF_2$, K_2CO_3, DMF, 90 °C	**8d** 	95
7e 	$CHClF_2$, dibenzo-18-crown-6 (2 mol%), 35% aq KOH, dioxane, 70 °C	**8e** 	69
7f 	$CHClF_2$, dibenzo-18-crown-6 (2 mol%), 35% aq KOH, dioxane, 70 °C	**8f** 	65
7g 	$CHClF_2$, dibenzo-18-crown-6 (2 mol%), 35% aq KOH, dioxane, 70 °C	**8g** 	68
7h 	$CHClF_2$, dibenzo-18-crown-6 (2 mol%), 35% aq KOH, dioxane, 70 °C	**8h** 	70
7i 	$CHClF_2$, dibenzo-18-crown-6 (2 mol%), 35% aq KOH, dioxane, 70 °C	**8i** 	86

We have studied the effect of the phase-transfer catalyst on the difluoromethylation reactions of **7e–i** described above (Table 2). It was found that, at similar catalyst loadings, dibenzo-18-crown-6 gives similar or remarkably higher yields of the products than tetrabutylammonium chloride (TBACl). Increasing the catalyst loading of dibenzo-18-crown-6 from 2% to 5% did not improve the yield significantly.

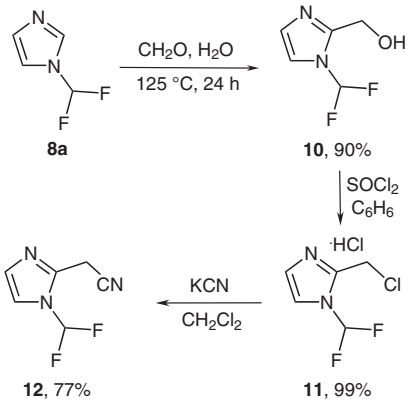
Table 2 Influence of the Phase-Transfer Catalyst on the Difluoromethylation of (Benz)imidazoles **7e–i**

Substrate	Phase-transfer catalyst	Product	Yield (%)
7e	dibenzo-18-crown-6 (2 mol%)	**8e**	69
7e	dibenzo-18-crown-6 (5 mol%)	**8e**	71
7e	TBACl (2 mol%)	**8e**	71
7f	dibenzo-18-crown-6 (2 mol%)	**8f**	65
7f	TBACl (2 mol%)	**8f**	69
7g	dibenzo-18-crown-6 (2 mol%)	**8g**	68
7g	TBACl (2 mol%)	**8g**	57
7h	dibenzo-18-crown-6 (2 mol%)	**8h**	70
7h	TBACl (2 mol%)	**8h**	73
7i	dibenzo-18-crown-6 (2 mol%)	**8i**	86
7i	TBACl (2 mol%)	**8i**	64

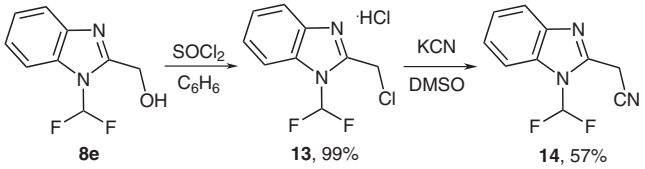
In the case of the difluoromethylation of imidazoles **7a** and **7b**, the choice of solvent for the reaction was limited by the relative volatility of **8a**,**b** which were purified by distillation. Thus, dioxane was replaced by the more expensive and more volatile 1,2-dimethoxyethane (DME). The difluoromethylation products **8a** and **8b** were obtained in 75% and 60% yield, respectively, as colorless liquids (see Table 1).

The reaction of 2-methyl-1*H*-benzimidazole (**7c**) under the conditions described above was much slower; in this case, the product **8c** was obtained in 63% yield. We assume that the higher lipophilicity of **7c** compared to other substrates might be related to that fact. An alternative procedure for the difluoromethylation of **7c** was developed, which included heating a mixture of the substrate and potassium carbonate in *N*,*N*-dimethylformamide at 90 °C for two hours, together with constant chlorodifluoromethane bubbling (see Table 1). Difluoromethylation of benzimidazole **7d** was performed under similar conditions. This procedure allowed the corresponding products **8c** and **8d** to be obtained in excellent yields (89% and 95%, respectively). Application of these conditions to the functionalized benzimidazoles appeared to be fruitless; tar formation was observed in these cases.

The *N*-difluoromethyl group in the molecules of **8a–i** showed remarkable stability: it remained intact upon refluxing these compounds with 40% aqueous potassium hydroxide, concentrated hydrochloric acid or hydrazine hydrate in 2-propanol. Therefore, compounds **8a–i** can be used in further chemical transformations even under rather drastic conditions. In particular, imidazole **8a** underwent hydroxymethylation with formaldehyde at 125 °C to afford alcohol **10** in 90% yield. Reaction of alcohol **10** with thionyl chloride resulted in almost quantitative formation of halide **11**. Compound **11** was introduced into a nucleophilic substitution reaction; thus, reaction with potassium cyanide afforded nitrile **12** which was isolated in 77% yield (Scheme 2). Analogously, nitrile **14** was obtained from 2-(hydroxymethyl)benzimidazole **8e** in two steps via formation of the chloride **13** (Scheme 3).



Scheme 2



Scheme 3

In conclusion, practical procedures for the difluoromethylation of imidazoles and benzimidazoles have been developed. The method opens an entry to the multigram synthesis of the corresponding 1-(difluoromethyl)imidazoles and -benzimidazoles. The most general procedure involves the gradual addition of aqueous alkali to a solution of the substrate and the phase-transfer catalyst in dioxane, together with constant chlorodifluoromethane bubbling. A slightly modified procedure (DME instead of dioxane as the solvent) was used when volatile difluoromethylation products were obtained. Finally, a potassium carbonate–*N*,*N*-dimethylformamide system was fruitful in the case of more lipophilic benzimidazoles containing no additional functional groups.

Solvents were purified according to standard procedures. Compounds **7d**,[24] **7h**[25] and **7i**[26] were prepared according to the methods reported in the literature. Starting materials were purchased from Acros, Merck and Fluka. Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz

for ^{1}H, 124.9 MHz for ^{13}C and 470.3 MHz for ^{19}F). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as an internal standard. Elemental analyses were performed on an Elementar vario MICRO cube CHNS/O analyzer. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument [chemical ionization (CI)]. The ozone depletion potential of chlorodifluoromethane is no longer considered acceptable in many countries. On a large scale, excess of this reagent can be trapped by hot 40% aq KOH.

1-(Difluoromethyl)imidazoles 8a,b; General Procedure

Imidazole **7a** or **7b** (1 mol), dibenzo-18-crown-6 (7.2 g, 0.02 mol) and DME (1 L) were placed into a 2-L flask equipped with a condenser, a mechanical stirrer, a gas bubble inlet and a dropping funnel, and heated to 65–70 °C. $CHClF_2$ was bubbled through and 35% aq KOH soln was gradually added to the reaction mixture until disappearance of the starting imidazole by TLC (approx. 3 mol of the alkali). The consumption of the KOH soln was monitored by pH control (indicator paper, pH = 9–11). After the reaction was complete, the mixture was cooled, the aqueous salt layer was separated and the organic phase was concentrated under reduced pressure at r.t. The residue was distilled under reduced pressure.

1-(Difluoromethyl)-1*H*-imidazole (8a)

Yield: 295 g (75%); colorless liquid; bp 79 °C/12 mmHg.

For spectroscopic and physical data, see ref.[18]

1-(Difluoromethyl)-2-methyl-1*H*-imidazole (8b)

Yield: 79 g (60%); colorless liquid; bp 70 °C/12 mmHg.

^{1}H NMR (DMSO-d_6): δ = 7.00 (t, J = 60.3 Hz, 1 H, CHF_2), 6.92 (s, 1 H), 6.72 (s, 1 H), 2.28 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 143.92 (s), 128.29 (s), 115.45 (s), 108.35 (t, J = 247.5 Hz, CHF_2), 13.08 (s, CH_3).

^{19}F NMR (DMSO-d_6): δ = –93.36 (d, J = 60 Hz, CHF_2).

MS (APCI): m/z = 133 $[M + H]^+$.

Anal. Calcd for $C_5H_6F_2N_2$: C, 45.46; H, 4.58; N, 21.20. Found: C, 45.71; H, 4.23; N, 20.97.

1-(Difluoromethyl)benzimidazoles 8c,d; General Procedure

Benzimidazole **7c** or **7d** (0.1 mol), K_2CO_3 (60 g, 0.43 mol) and DMF (300 mL) were placed into a 1-L flask equipped with a condenser, a stirrer, a gas bubble inlet and a dropping funnel, and heated to 90 °C. $CHClF_2$ was bubbled through the reaction mixture until disappearance of the starting benzimidazole by TLC. After the reaction was complete, the mixture was cooled and poured into H_2O (1.5 L). The product was collected by filtration and washed with H_2O (3 × 150 mL). If no solid product was formed (e.g., for **8c**), the mixture obtained after pouring into H_2O was extracted with hexanes (3 × 300 mL). The combined extracts were concentrated, and the crude product was recrystallized (hexanes with charcoal).

1-(Difluoromethyl)-2-methyl-1*H*-benzimidazole (8c)

Yield: 170 g (89%); colorless solid; mp 84 °C.

For spectroscopic and physical data, see ref.[18]

1-(Difluoromethyl)-2-(4-methylphenyl)-1*H*-benzimidazole (8d)

Yield: 21 g (95%); yellow crystals; mp 116 °C.

^{1}H NMR (DMSO-d_6): δ = 7.87–7.88 (m, 1 H), 7.80–7.81 (m, 1 H), 7.65 (d, J = 8.0 Hz, 2 H), 7.41–7.43 (m, 2 H), 7.39 (d, J = 8.0 Hz, 2 H), 7.32 (t, J = 58.8 Hz, 1 H, CHF_2), 2.48 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 152.1, 143.2, 141.3, 129.9, 129.8, 129.3, 125.8, 124.4, 124.3, 120.3, 112.6, 110.3 (t, J = 252.5 Hz, CHF_2), 21.5 (s, CH_3).

^{19}F NMR (DMSO-d_6): δ = –92.09 (d, J = 60 Hz, CHF_2).

MS (APCI): m/z = 259 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{12}F_2N_2$: C, 69.76; H, 4.68; N, 10.85. Found: C, 69.93; H, 4.38; N, 11.09.

1-(Difluoromethyl)(benz)imidazoles 8e–i; General Procedure

A (benz)imidazole **7e–i** (1 mol), dibenzo-18-crown-6 (7.2 g, 0.02 mol) and dioxane (1 L) were placed into a 2-L flask equipped with a condenser, a mechanical stirrer, a gas bubble inlet and a dropping funnel, and heated to 70 °C. $CHClF_2$ was bubbled through and 35% aq KOH soln was gradually added to the reaction mixture until disappearance of the starting (benz)imidazole by TLC (approx. 3 mol of the alkali). The consumption of the KOH soln was monitored by pH control (indicator paper, pH = 9–11). After the reaction was complete, the mixture was cooled, the aqueous salt layer was separated and the organic phase was concentrated under reduced pressure. The residue was dissolved in benzene (600 mL). The resulting solution was washed with 10% aq KOH (200 mL) and H_2O (200 mL), dried over Na_2SO_4 and concentrated to dryness. The product was recrystallized [benzene (**8e**,**f**,**i**) or hexanes with charcoal (**8g**,**h**)].

[1-(Difluoromethyl)-1*H*-benzimidazol-2-yl]methanol (8e)

Yield: 137 g (69%); yellowish solid; mp 162 °C.

^{1}H NMR (DMSO-d_6): δ = 8.09 (t, J = 58.1 Hz, 1 H, CHF_2), 7.72 (d, J = 9.0 Hz, 1 H), 7.70 (d, J = 9.0 Hz, 1 H), 7.33–7.40 (m, 2 H), 5.99 (t, J = 5.5 Hz, 1 H, OH), 4.87 (d, J = 5.5 Hz, 2 H, CH_2OH).

^{13}C NMR (DMSO-d_6): δ = 153.2, 142.6, 131.9, 124.7, 124.1, 120.4, 112.5, 110.2 (t, J = 245 Hz, CHF_2), 57.2.

^{19}F NMR (DMSO-d_6): δ = –98.2 (d, J = 58 Hz, CHF_2).

MS (APCI): m/z = 199 $[M + H]^+$.

Anal. Calcd for $C_9H_8F_2N_2O$: C, 54.55; H, 4.07; N, 14.14. Found: C, 54.31; H, 3.84; N, 14.12.

1-[1-(Difluoromethyl)-1*H*-benzimidazol-2-yl]ethanol (8f)

Yield: 63 g (65%); colorless solid; mp 66 °C.

For spectroscopic and physical data, see ref.[18]

1-(Difluoromethyl)-2-[(difluoromethyl)sulfanyl]-1*H*-benzimidazole (8g)

Yield: 98 g (68%); colorless solid; mp 60 °C.

For spectroscopic and physical data, see ref.[16]

1-[1-(Difluoromethyl)-1*H*-benzimidazol-2-yl]ethanone (8h)

Yield: 35 g (70%); colorless solid; mp 65 °C.

For spectroscopic and physical data, see ref.[18]

2-[1-(Difluoromethyl)-1*H*-imidazol-2-yl]-1-phenylethanone Oxime (8i)

Yield: 18 g (86%); white crystals; mp 150 °C.

^{1}H NMR (DMSO-d_6): δ = 11.72 (s, 1 H), 7.97 (t, J = 59.1 Hz, 1 H, CHF_2), 7.77 (d, J = 6.4 Hz, 2 H), 7.46 (s, 1 H), 7.35–7.40 (m, 3 H), 6.92 (s, 1 H), 4.33 (s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 152.2, 143.8, 136.2, 129.3, 129.2, 128.7, 126.7, 116.1, 109.1 (t, J = 247 Hz, CHF_2), 24.3.

^{19}F NMR (DMSO-d_6): δ = –91.4 (d, J = 59 Hz, CHF_2).

MS (APCI): m/z = 252 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{11}F_2N_3O$: C, 57.37; H, 4.41; N, 16.73. Found: C, 56.99; H, 4.28; N, 16.70.

1-(Difluoromethyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (9)
A mixture of bis(difluoromethyl) derivative **8g** (250 g, 1 mol), hydrazine hydrate (156 g, 3 mol) and *i*-PrOH (700 mL) was refluxed for 3 h (monitored by TLC), then cooled and concentrated under reduced pressure; the residue was poured into H_2O (2 L). The resulting mixture was acidified to pH 4–5 with concd HCl; the precipitate was collected by filtration and washed with H_2O (3 × 200 mL).

Yield: 174 g (87%); colorless solid; mp 205 °C (*i*-PrOH–H_2O).

^{1}H NMR (DMSO-d_6): δ = 13.17 (br s, 1 H, NH), 8.08 (t, *J* = 58.1 Hz, 1 H, CHF_2), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.26–7.33 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 168.5 (C=S), 131.0, 128.0, 124.7, 123.4, 110.64, 110.62, 110.59 (t, *J* = 246 Hz, CHF_2).

^{19}F NMR (DMSO-d_6): δ = –102.0 (d, *J* = 58 Hz, CHF_2).

MS (APCI): *m*/*z* = 201 $[M + H]^+$.

Anal. Calcd for $C_8H_6F_2N_2S$: C, 47.99; H, 3.02; N, 13.99; S, 16.02. Found: C, 48.16; H, 2.81; N, 14.34; S, 16.15.

[1-(Difluoromethyl)-1*H*-imidazol-2-yl]methanol (10)
Imidazole **8a** (295 g, 2.5 mol) and 40% aq formaldehyde (244 g, 3.25 mol) were heated in an autoclave at 125 °C for 24 h. After the resulting mixture was cooled, the unreacted starting materials were distilled off with water steam. The residue was concentrated, and the crude product was collected by filtration, dried and then recrystallized ($CHCl_3$–hexane).

Yield: 333 g (90%); colorless solid; mp 106 °C.

^{1}H NMR (DMSO-d_6): δ = 7.81 (t, *J* = 59.8 Hz, 1 H, CHF_2), 7.37 (s, 1 H), 6.94 (s, 1 H), 5.74 (br s, 1 H, OH), 4.67 (s, 2 H, CH_2OH).

^{13}C NMR (DMSO-d_6): δ = 147.8, 128.7, 115.8, 108.6 (t, *J* = 248 Hz, CHF_2), 56.6 (CH_2OH).

^{19}F NMR (DMSO-d_6): δ = –91.7 (d, *J* = 60 Hz, CHF_2).

MS (APCI): *m*/*z* = 149 $[M + H]^+$.

Anal. Calcd for $C_5H_6F_2N_2O$: C, 40.55; H, 4.08; N, 18.91. Found: C, 40.82; H, 3.85; N, 19.06.

2-(Chloromethyl)-1-(difluoromethyl)(benz)imidazoles 11 and 13; General Procedure
2-(Hydroxymethyl)-1-(difluoromethyl)(benz)imidazole **10** or **8e** (1 mol) was suspended in benzene (200 mL), and thionyl chloride (238 g, 2 mol) was added slowly over 2 h with vigorous stirring. After the addition was complete, the mixture was heated at 50 °C for 15 min (**10**) or 5 h (**8e**), then cooled and concentrated to dryness. CAUTION! The products (especially **11**) are strong irritants and harmful to the skin.

2-(Chloromethyl)-1-(difluoromethyl)-1*H*-imidazole Hydrochloride (11)
Yield: 139 g (99%); colorless solid; mp >250 °C (dec) (MeOH).

^{1}H NMR (DMSO-d_6): δ = 13.13 (br s, 1 H), 8.26 (t, *J* = 58.0 Hz, 1 H, CHF_2), 7.98 (s, 1 H), 7.54 (s, 1 H), 5.21 (s, 2 H, CH_2Cl).

^{13}C NMR (DMSO-d_6): δ = 143.5, 125.3, 119.2, 108.6 (t, *J* = 253 Hz, CHF_2), 34.0.

^{19}F NMR (DMSO-d_6): δ = –94.3 (d, *J* = 58 Hz, CHF_2).

MS (APCI): *m*/*z* = 167 $[M + H]^+$.

Anal. Calcd for $C_5H_6Cl_2F_2N_2$: C, 29.58; H, 2.98; Cl, 34.93; N, 13.80. Found: C, 29.31; H, 3.25; Cl, 35.32; N, 13.61.

2-(Chloromethyl)-1-(difluoromethyl)-1*H*-benzimidazole Hydrochloride (13)
Yield: 51 g (99%); colorless solid; mp >250 °C (dec) (MeOH).

^{1}H NMR (DMSO-d_6): δ = 14.10 (br s, 1 H), 8.37 (t, *J* = 56.8 Hz, 1 H, CHF_2), 7.69 (m, 2 H), 7.32–7.36 (m, 2 H), 5.30 (s, 2 H, CH_2Cl).

^{13}C NMR (DMSO-d_6): δ = 148.9, 140.9, 131.4, 125.9, 125.0, 120.1, 112.7, 109.8 (t, *J* = 248 Hz, CHF_2), 36.8 (CH_2Cl).

^{19}F NMR (DMSO-d_6): δ = –95.9 (d, *J* = 57 Hz, CHF_2).

MS (APCI): *m*/*z* = 217 $[M + H]^+$.

Anal. Calcd for $C_9H_8Cl_2F_2N_2$: C, 42.71; H, 3.19; Cl, 28.02; N, 11.07. Found: C, 42.86; H, 3.14; Cl, 28.33; N, 10.70.

[1-(Difluoromethyl)-1*H*-imidazol-2-yl]acetonitrile (12)
To a suspension of finely powdered KCN (260 g, 4 mol) in CH_2Cl_2 (4 L), dibenzo-18-crown-6 (24 g, 0.067 mol) was added, followed by chloride **11** (203 g, 1 mol) (CAUTION! HCN is evolved). The mixture was refluxed with vigorous stirring for 8 h. The mixture was filtered, and the filtrate was dried over Na_2SO_4 and then filtered again. HCl was bubbled through the resulting solution until saturation. The precipitate formed was collected by filtration to give **12** as the hydrochloride; yield: 177 g (90%).

The hydrochloride was carefully dissolved in sat. aq $NaHCO_3$ (1.2 L). The product **12** was extracted with CH_2Cl_2 (800 mL, then 2 × 300 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and distilled under reduced pressure.

Yield: 121 g (77%); colorless solid; mp 34 °C; bp 97 °C/1 mmHg.

^{1}H NMR (DMSO-d_6): δ = 7.45 (d, *J* = 1.2 Hz, 1 H), 7.44 (t, *J* = 60.2 Hz, 1 H, CHF_2), 7.29 (s, 1 H), 4.28 (s, 2 H, CH_2CN).

^{13}C NMR (DMSO-d_6): δ = 136.1, 129.5, 118.4, 114.2, 108.4 (t, *J* = 251.3 Hz, CHF_2), 18.2.

^{19}F NMR (DMSO-d_6): δ = –94.97 (d, *J* = 60 Hz, CHF_2).

MS (APCI): *m*/*z* = 158 $[M + H]^+$.

Anal. Calcd for $C_6H_5F_2N_3$: C, 45.87; H, 3.21; N, 26.74. Found: C, 45.94; H, 2.98; N, 26.55.

[1-(Difluoromethyl)-1*H*-benzimidazol-2-yl]acetonitrile (14)
To a soln of KCN (130 g, 2 mol) in anhyd DMSO (600 mL), chloride **13** (126 g, 0.5 mol) was added in portions with stirring (CAUTION! HCN is evolved). After the addition was complete, the resulting mixture was heated at 45–50 °C for 2 h, then cooled, diluted with $CHCl_3$ (2 L) and washed with H_2O (4 × 700 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized (benzene with charcoal).

Yield: 59 g (57%); yellowish crystals; mp 68 °C.

^{1}H NMR ($CDCl_3$): δ = 7.75 (d, *J* = 7.6 Hz, 1 H), 7.34–7.56 (m, 4 H), 4.20 (s, 2 H, CH_2CN).

^{13}C NMR ($CDCl_3$): δ = 141.9, 141.6, 132.7, 125.3, 124.5, 120.8, 113.8, 110.1, 108.3 (t, *J* = 249 Hz, CHF_2), 19.3.

^{19}F NMR ($CDCl_3$): δ = –89.5 (d, *J* = 58 Hz, CHF_2).

MS (APCI): *m*/*z* = 208 $[M + H]^+$.

Anal. Calcd for $C_{10}H_7F_2N_3$: C, 57.97; H, 3.41; N, 20.28. Found: C, 57.73; H, 3.42; N, 19.93.

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