PREPARATION OF (FLUOROMETHYL)- AND (DIFLUOROMETHYL)IMIDAZOLES

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Dedicated to the memory of Professor Miloš Hudlický. He inspired us by his caring for others, his mastery of chemistry and his enthusiasm for life. If chemistry were a tennis match, he would have been a grand slam champion.

2-(Fluoromethyl)- and 2-(difluoromethyl)imidazoles, and 4-(fluoromethyl)- and 4-(difluoromethyl)imidazoles have been prepared by deoxyfluorination of (hydroxymethyl)imidazole or formylimidazole precursors.

Keywords: Fluorinated imidazoles; Deoxyfluorination; Fluorinated heterocycles; Deoxo-Fluor; Fluorinations; Aldehydes; Alcohols.

The imidazole ring plays a crucial role in many aspects of biological structure and function. Accordingly, there has been much interest in the synthesis and biological evaluation of derivatives of imidazole as a strategy to develop biochemical tools and potential medicinal agents. In our own contributions to this research, we developed syntheses of a series of ring-fluorinated imidazoles[1], a class of compounds that provided a large number of useful biochemical tools. As an extension of this work, we also developed new procedures[2] for preparing imidazole derivatives substituted in the 2 or 4 positions with the trifluoromethyl group.

In the inventory of available fluorinated imidazoles, there are only limited examples of imidazoles substituted with a difluoromethyl[3] or fluoromethyl[3a,4] group. In such analogues, fluorine could be present on the carbon that is part of the functionalized side chain of, for example, histidine or histamine. Such is obviously not the case with ring-fluorinated or ring-trifluoromethylated analogues. The greater reactivity[5] of the C–F bond in (difluoromethyl)imidazole relative to the C–F bond in trifluoromethylated or ring-fluorinated imidazoles could also be advantageous in

the design of irreversible enzyme inhibitors or other affinity labels. With these factors in mind, we recently initiated synthetic work to prepare[6] side-chain-fluorinated or -difluorinated derivatives of biologically important imidazoles. As part of this effort, we felt it would be important to study the physical and chemical properties of the parent compounds in this series. In this paper we describe preparation of the hydrochlorides of 2- and 4-(fluoromethyl)-1*H*-imidazoles (**1** and **2**, respectively), and 2- and 4-(difluoromethyl)-1*H*-imidazoles (**3** and **4**, respectively).

RESULTS AND DISCUSSION

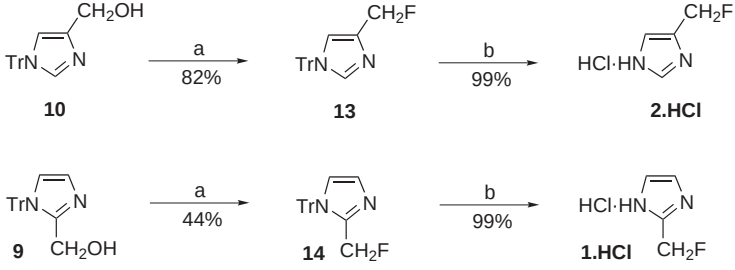
A good method to prepare fluoromethyl and difluoromethyl derivatives is deoxofluorination of their corresponding oxygen counterparts. Therefore, the (hydroxymethyl)- and formylimidazoles **5**–**8** were chosen as precursors to our target compounds. Common deoxofluorination agents include SF_4 in liquid HF (very reactive but inconvenient to use under normal laboratory operations) or the more convenient DAST ((diethylamino)sulfur trifluoride). Recently, Deoxo-Fluor® ([bis(2-methoxyethyl)amino]sulfur trifluoride) was introduced[7] as a more stable and in some respects a more effective alternative to DAST. In the present study, Deoxo-Fluor® was found to be the reagent of choice.

Although there are reports of successful deoxyfluorination reactions in the presence of NH groups (*e.g.* amide[3c]), attempted deoxyfluorination of the parent (hydroxymethyl)imidazoles **5** or formylimidazoles **7** and **8** led to no detectable fluorinated products (based on ^1H and ^{19}F NMR of crude reaction products). Based on the assumption that the free NH group was interfering with deoxyfluorination, we installed the trityl group to protect the NH group.

Deoxyfluorination of 4-(hydroxymethyl)imidazole **10** proceeded smoothly and 4-(fluoromethyl)imidazole **13** was obtained in 82% yield. In contrast, under conditions used for the preparation of **10**, 2-(hydroxymethyl)-imidazole **9** gave only 44% yield of the 2-(fluoromethyl)imidazole **14**. Furthermore, the deoxyfluorination of **9** produced a 10% isolated yield of triphenylmethanol (TrOH) whereas deoxyfluorination of **10** was accompanied by no formation of TrOH. These results reveal a higher lability of the trityl group in **9** or in the fluoromethyl product **14** relative to the 4-substituted series.

The (fluoromethyl)imidazoles **13** and **14** are stable compounds. Test experiments indicate that (fluoromethyl)imidazole **13** is poorly reactive towards nucleophiles. For example, treatment of **13** with 2.5 equivalents of

diethylamine in CH_2Cl_2 at 60 °C for 24 h gave only 5% of substitution of fluorine by amine (based on ^{1}H NMR). Removal of the trityl group gives the much more reactive (fluoromethyl)imidazoles **1** and **2**, wherein the fluorine is subject to rapid substitution by hydroxy group during preparation (detritylation) and isolation. Fortunately, modification of the workup to produce the hydrochlorides of (fluoromethyl)imidazoles **1** and **2** resulted in isolation of these compounds in good purity and in nearly quantitative yields (Scheme 1).



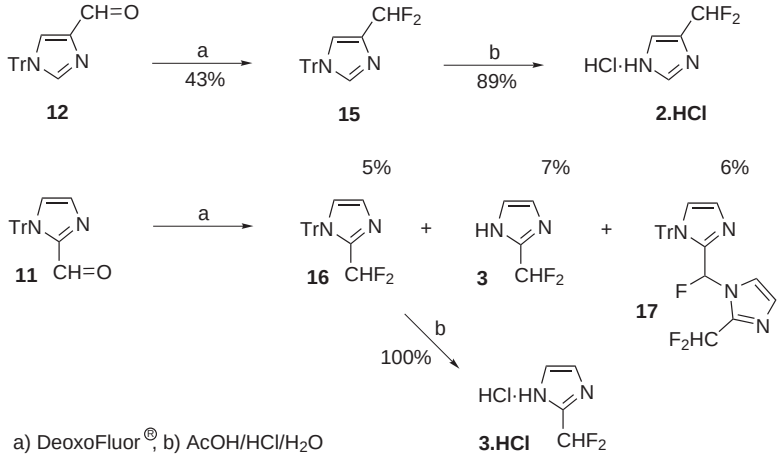
a) DeoxoFluor®, b) AcOH/HCl/H_2O

SCHEME 1

Deoxyfluorination of the aldehydes proved to be significantly more difficult. Reactions of DeoxoFluor® with 4-formylimidazole **12** gave inconsistent results. We tried many variations in which we changed the ratio of substrate/DeoxoFluor®, and addition of NaF [8] or KF with 18-crown-6. Unfortunately, these variations all led to results that were difficult to reproduce, and yields of the target 4-(difluoromethyl)imidazole **15** varied between 10–50%, along with 9–13% of recovered starting aldehyde **12**. In addition, 13–64% of TrOH was obtained as a result of partial detritylation. Since we determined that the subsequent detritylation of **15** proceeded without complications, the low yields and loss of the trityl group are probably a result of side reactions of intermediates formed during deoxofluorination.

Deoxofluorination of 2-formylimidazole **11** proved to be even more problematic. The expected (difluoromethyl)imidazole **16** was formed in 5% yield along with 7% yield of the deprotected 2-(difluoromethyl)imidazole **3**. The dimeric compound **17** was isolated as a third product giving a total product yield of about 20%. This diimidazole **17** is probably the result of the reaction of some deoxofluorination intermediates because no formation of **17** was observed during detritylation of **16** to **3·HCl** (Scheme 2). The diimidazole **17** is unstable in solution and the observed low total product

yield in the reaction of **16** may reflect degradation of **17** and possibly other products. In fact, the isolation of TrOH in high yield (about 80%) demonstrates that the trityl group is readily lost from the products or intermediates during the reaction of **11**.



SCHEME 2

Because of the problems encountered in the preparation of **3**, we explored alternative approaches. These included direct alkylation of 2-lithio-1-tritylimidazole[9] with chlorodifluoromethane[10] or dibromodifluoromethane[10,11]. Unfortunately, despite examining many reaction conditions by varying temperature and/or sequence of addition of reactants, we observed no formation of difluoromethylated or bromodifluoromethylated products, based on ^{1}H and ^{19}F NMR examination of crude products. We note that such procedures were successfully employed for the preparation 1-(difluoromethyl)imidazole[12].

TABLE I
pK_{a1} values of imidazoles

Position	H	CH_3	CH_2F	CHF_2	CF_3
4-	7.00[a]	7.6[a]	6.0[b]	4.1	2.3[a]
2-	7.00[a]	7.9[a]	5.5[b]	3.4	2.1[c]

[a] Ref.[13]; [b] extrapolated; [c] ref.[2c]

The pK_{a1} values of (difluoromethyl)imidazoles **3** and **4** were determined titrimetrically. The high reactivity of (fluoromethyl)imidazoles **1** and **2** precluded direct determination, so these values were estimated by extrapolation from the available values for the corresponding imidazoles substituted with methyl, trifluoromethyl, and difluoromethyl substituents (Table I).

CONCLUSION

We have prepared the target (fluoromethyl)- and (difluoromethyl)imidazoles by deoxyfluorination of trityl-protected (hydroxymethyl)- and formylimidazoles, respectively, followed by deprotection. The lability of the trityl protecting group when the substituent is in the 2 position caused problems in fluorination and in the isolation of products of deoxofluorination. In contrast, formation of 4-(fluoromethyl)imidazole was particularly facile, and 4-(difluoromethyl)imidazole was also readily isolated in reasonable, if modest, yield. The reactivity of fluorine was increased upon removal of the trityl group, presumably due to participation of the nitrogen electron pair in elimination reactions. The pK_{a1}'s of the (difluoromethyl)imidazoles reflect the electronegative effects of fluorine, and are intermediate between trifluoromethyl-substituted and the nonsubstituted imidazoles.

The determination of the rates of fluoride loss from fluorinated imidazoles **1**–**4** will be the subject of subsequent research. To facilitate this study, we plan to examine alternative imidazole protection as a strategy to improve the yields of the key deoxofluorination step.

EXPERIMENTAL

All chemicals were purchased from Aldrich and were used without additional treatment. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 300.1, 75.5 and 282.2 MHz, respectively. Chemical shifts (δ) are given in ppm relatively to TMS in ^{1}H and ^{13}C NMR, and to $CFCl_3$ in ^{19}F NMR. The coupling constants (*J*) are given in Hz. In addition, in the ^{13}C NMR spectra we also give selected coupling constants of carbon by hydrogen where important to prove the signal assignment. Melting points measured in capillaries are not corrected.

Starting Compounds

Starting compounds were prepared by well-known reactions. (1*H*-Imidazol-4-yl)methanol (**5**) was prepared in quantitative yield from the commercially available hydrochloride by addition of an equivalent of NaOH, evaporation to dryness and extraction of the free base from the resulting solid with ethyl acetate. This was oxidized with MnO_2 in dioxane at room temperature to produce 1*H*-imidazole-4-carbaldehyde[14] (**7**). (1-Trityl-1*H*-imidazol-4-yl)methanol (**10**) was prepared from **5**·**HCl** by tritylation[15]. Oxidation of **10** by MnO_2 in dioxane at room temperature gave[15] 1-trityl-1*H*-imidazole-4-carbaldehyde (**12**). 1*H*-Imidazole-2-carbaldehyde

(**8**) is commercially available but direct tritylation of **8** (as in the preparation of **10**) was very slow and proved to be impractical. For this reason, **11** was prepared from 1-trityl-1*H*-imidazole by lithiation and formylation, as reported previously[9]. (1-Trityl-1*H*-imidazol-2-yl)methanol (**9**) was prepared by reduction[16] of **11** with $NaBH_4$; m.p. 241–245 °C. ^{1}H NMR ($CDCl_3$): 7.39–7.30 m, 9 H; 7.16–7.08 m, 6 H; 6.98 d, 1 H, $^3J_{HH}$ = 1.5; 6.77 d, 1 H, $^3J_{HH}$ = 1.5; 3.71 br s, 1 H; 3.67 s, 2 H. For $C_{23}H_{20}N_2O$ (340.4) calculated: 81.15% C, 5.95% H, 8.23% N; found: 81.14% C, 5.94% H, 8.19% N. This compound had been reported in the non-patent literature only as the hemihydrate[17].

2-(Fluoromethyl)imidazole (**1**)

a) A suspension of 196 mg (0.58 mmol) of **9** in 30 ml of dry CH_2Cl_2 was cooled to –65 °C and 125 µl (0.68 mmol) of Deoxo-Fluor® was added. The reaction mixture was allowed to warm to room temperature (2 h) and stirred at room temperature for additional 3 h. The mixture was then extracted with 2 × 20 ml of brine, the organic layer was dried over anhydrous $MgSO_4$, and evaporated to dryness. The resulting solid was separated by preparative TLC (CH_2Cl_2) to obtain 15 mg (10%) of TrOH (as result of detritylation) and 87 mg (44%) of pure (^{1}H NMR) 2-(fluoromethyl)imidazole **14** as a waxy white-off solid.

b) To a solution of 87 mg (0.25 mmol) of **14** in 1 ml of acetic acid was added 0.3 ml of aqueous HCl (1 : 5). The mixture was stirred at room temperature for 1 h and then evaporated to dryness. The resulting solid was triturated with 3 × 10 ml of CH_2Cl_2 and then dried *in vacuo* (0.1 kPa) to give 34 mg (99%) of 2-(fluoromethyl)imidazole hydrochloride (**1·HCl**) as a white solid. The purity based on ^{1}H NMR was above 90%.

2-(Fluoromethyl)-1-trityl-1H-imidazole (**14**). ^{1}H NMR ($CDCl_3$): 7.37–7.32 m, 9 H (Tr); 7.15–7.10 m, 6 H (Tr); 7.08 d, $^3J_{HH}$ = 1.4 (H_{Imi}); 6.80 t, 1 H, $^3J_{HH} \approx {}^5J_{HF} \approx$ 1.5 (H_{Imi}); 4.58 d, 2 H, $^2J_{HF}$ = 48.0 (CH_2F). ^{13}C NMR ($CDCl_3$): 144.57 d, $^2J_{CF}$ = 19.0 ($C2_{imi}$); 142.16, 3 C (Tr); 129.66, 6 CH (Tr); 128.10, 3 CH (Tr); 128.08, 6 CH (Tr); 127.99 d, $^4J_{CF}$ = 2.0, $^1J_{CH}$ = 190.3 d, $^2J_{CH}$ = 9.2 d (CH_{Imi}); 122.66 d, $^4J_{CF}$ = 3.1, $^1J_{CH}$ = 191.7 d, $^2J_{CH}$ = 16.7 d (CH_{Imi}); 76.24 d, $^1J_{CF}$ = 169.8, $^1J_{CH}$ = 154.0 t (CH_2F); 75.45 (Tr). ^{19}F NMR: –208.1 td, $^2J_{FH}$ = 48.1, $^5J_{FH}$ = 1.5 (CH_2F). HRMS (FAB^+; CsI) for $C_{23}H_{19}CsFN_2$ (MCs) calculated: 475.0587; found: 475.0589.

2-(Fluoromethyl)imidazole hydrochloride (**1·HCl**). ^{1}H NMR (DMSO-d_6): 6.75 d, 2 H, $^5J_{HF}$ = 0.6 (H_{Imi}); 5.69 d, 2 H, $^2J_{HF}$ = 47.1 (CH_2F); 4.8–2.4 br s, 2 H (NH·HCl). ^{13}C NMR (DMSO-d_6): 140.06 d, $^2J_{CF}$ = 21.8 ($C2_{Imi}$); 120.25 s ($C2_{Imi}$); 73.07 d, $^1J_{CF}$ = 165.6 (CH_2F). ^{19}F NMR (DMSO-d_6): –213.3 t, $^2J_{FH}$ = 47.1 (CH_2F). HRMS (DEI^+) for $C_4H_5FN_2$ (M) calculated: 100.0437; found: 100.0438. The compound was prepared previously[4a] but there is not given any characteristics.

4-(Fluoromethyl)-1*H*-imidazole (**2**)

a) A suspension of 1.00 g (2.9 mmol) of 4-(hydroxymethyl)imidazole **10** in 100 ml of CH_2Cl_2 was cooled to –65 °C and 0.64 ml (3.5 mmol) of Deoxo-Fluor® was added. The reaction mixture was allowed to warm to room temperature (2 h). After 1.5 h at room temperature, the starting **10** was consumed (TLC) and the reaction mixture was filtered through a pad of 15 g of silica (CH_2Cl_2/Et_2O 4 : 1). The resulting solid (0.87 g) was crystallized from cyclohexane to give 0.83 g (82%) of pure 4-(fluoromethyl)imidazole **13**.

b) To a solution of 0.83 g (0.24 mmol) of **13** in 5 ml of acetic acid was added 0.5 ml of aqueous HCl (1 : 5). The mixture was stirred at room temperature for 1 h and then evaporated to dryness. The resulting solid was partitioned between 10 ml of water and 10 ml of

CH_2Cl_2. The aqueous layer was extracted 2 × 10 ml of CH_2Cl_2 to remove triphenylmethanol and then evaporated to dryness. The resulting waxy solid contained 4-(fluoromethyl)-imidazole **2** and 4-(hydroxymethyl)imidazole **5** (as result of fluorine hydrolysis) in a ratio close to 1 : 1 (both as hydrochlorides).

Using the workup described for preparation of **1·HCl**, the solid produced by evaporation of the crude reaction mixture was triturated with 3 × 10 ml of CH_2Cl_2 and then dried *in vacuo* (0.1 kPa). Under these conditions, 4-(fluoromethyl)imidazole hydrochloride **2·HCl** was obtained in 99% yield with a purity above 90% (based on ^{1}H NMR).

4-(Fluoromethyl)-1-trityl-1H-imidazole (**13**). M.p. 198–199 °C (from cyclohexane/CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 7.46 d, 1 H, $^3J_{HH}$ = 1.2 (H_{Imi}); 7.38–7.30 m, 9 H (Tr); 7.17–7.10 m, 6 H (Tr); 6.73 dd, 1 H, $^4J_{HF}$ = 4.7, $^3J_{HH}$ = 1.2 (H_{Imi}); 5.29 d, 2 H, $^2J_{HF}$ = 49.2 (CH_2F). ^{13}C NMR ($CDCl_3$): 142.08, 3 C, ΣJ_{CH} = 17 (Tr); 139.40, $^1J_{CH}$ = 210.4 d, $^2J_{CH}$ = 7.2 d ($C2_{Imi}$); 136.23 d, $^2J_{CF}$ = 19.8 ($C4_{Imi}$); 129.66, 6 CH (Tr); 128.12, 3 CH (Tr); 128.07, 6 CH (Tr); 121.69 d, $^3J_{CF}$ = 6.3, $^1J_{CH}$ = 191.5 d ($C5_{Imi}$); 78.28 d, $^1J_{CF}$ = 162.3, $^1J_{CH}$ = 151.7 t (CH_2F); 75.50 (Tr). ^{19}F NMR ($CDCl_3$): –202.0 td, $^2J_{FH}$ = 49.1, $^4J_{FH}$ = 4.5 (CH_2F). LRMS (CI^+; NH_3), *m/z* (%, assignment): 343 (6, MH), 279 (2), 262 (15), 244 (7), 243 (30, Tr), 118 (27), 101 (100). For $C_{23}H_{19}FN_2$ (342.4) calculated: 80.68% C, 5.59% H, 8.18% N; found: 80.43% C, 5.73% H, 8.10% N.

4-(Fluoromethyl)-1H-imidazole hydrochloride (**2·HCl**). ^{1}H NMR (DMSO-d_6): 9.16 t, 1 H, $^4J_{HH} \approx {}^5J_{HF} \approx$ 1.3 ($H2_{Imi}$); 6.87 dd, 1 H, $^4J_{HH}$ = 1.3, $^4J_{HF}$ = 4.6 ($H5_{Imi}$); 5.48 d, 2 H, $^2J_{HF}$ = 48.3 (CH_2F); 5.2–1.8 br s, 2 H (NH·HCl). ^{13}C NMR (DMSO-d_6): 135.54 ($C2_{Imi}$); 128.11 d, $^2J_{CF}$ = 20.0 ($C4_{Imi}$); 120.0 d, $^3J_{CF}$ = 6.4 ($C5_{Imi}$); 73.46 d, $^1J_{CF}$ = 161.3 (CH_2F). ^{19}F NMR (DMSO-d_6): –203.5 td, $^2J_{FH}$ = 48.3, $^4J_{FH}$ = 4.4 (CH_2F). HRMS (FAB^+) for $C_4H_6FN_2$ (MH) calculated: 101.0515; found: 101.0515.

2-(Difluoromethyl)imidazole (**3**)

a) A solution of 10.00 g (29.6 mmol) of aldehyde **11** in 400 ml of CH_2Cl_2 was cooled to –65 °C and 8.0 ml (mmol) of Deoxo-Fluor® was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 days. After the mixture was cooled to –65 °C, 16 ml of Et_3N was added (to prevent detritylation) followed by 32 ml of CH_3OH (to quench), and the mixture was allowed to warm to room temperature The mixture was extracted with 3 × 100 ml of a mixture of brine and 10% aqueous citric acid (1 : 1). The organic layer was dried over anhydrous $MgSO_4$ and then evaporated to dryness. The resulting solid was separated by column chromatography (120 g, $CH_2Cl_2 \rightarrow CH_2Cl_2/Et_2O$ 1 : 4) to give 6.34 g (82%) of a mixture TrOH with TrOMe (as result of detritylation by moisture and methanol), 0.55 g (5%) 2-(difluoromethyl)imidazole **16**, 0.37 g (6%) of diimidazole **17** and 0.24 g (7%) of 2-(difluoromethyl)imidazole (**3**).

b) To a solution of 200 mg (0.56 mmol) of **16** in 5 ml of acetic acid, 1 ml of aqueous HCl (1 : 5) was added and the mixture was stirred at room temperature for 45 min, during which time a white precipitate appeared. The mixture was evaporated to dryness and the residue was dissolved in a mixture of 10 ml of water and 20 ml of CH_2Cl_2. The aqueous layer was extracted with 2 × 20 ml of CH_2Cl_2 and evaporated to dryness to give 86 mg (100%) of 2-(difluoromethyl)imidazole hydrochloride (**3·HCl**) as a white solid. This was purified by crystallization from iPrOH/Et_2O to produce colorless needles.

2-(Difluoromethyl)-1-trityl-1H-imidazole (**16**). M.p. 185–188 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): 7.41–7.30 m, 9 H (Tr); 7.16–7.09 m, 7 H (Tr and H_{Imi}); 6.82 d, 1 H, $^3J_{HH}$ = 1.2 (H_{Imi}); 5.79 t, 1 H, $^2J_{HF}$ = 51.9 (CHF_2). ^{13}C NMR ($CDCl_3$): 142.09 t, $^2J_{CF}$ = 27.3 ($C2_{imi}$);

141.60, 3 C (Tr); 129.40, 6 CH (Tr); 128.44, 3 CH, $^1J_{CH}$ = 161.6 d, $^2J_{CH}$ = 7.5 t (Tr); 128.30, 6 CH (Tr); 127.40 t, $^4J_{CF}$ = 1.7, $^1J_{CH}$ = 191.0 d, $^2J_{CH}$ = 9.3 d ($C4_{Imi}$ or $C5_{Imi}$); 122.68 t, $^4J_{CF}$ = 2.6, $^1J_{CH}$ = 192.1 d, $^2J_{CH}$ = 17.5 d ($C4_{Imi}$ or $C5_{Imi}$); 106.40 t, $^1J_{CF}$ = 236.0, $^1J_{CH}$ = 188.2 d (CHF_2); 75.63 (Tr). ^{19}F NMR ($CDCl_3$): –113.5 d, $^2J_{FH}$ = 51.9 (CHF_2). For $C_{23}H_{18}F_2N_2$ (360.4) calculated: 76.65% C, 5.03% H, 7.77% N; found: 76.55% C, 5.15% H, 7.76% N.

[2-(Difluoromethyl)imidazol-1-yl]fluoro(1-trityl-1H-imidazol-2-yl)methane (**17**). M.p. 150–165 °C with decomp. (from diethyl ether). The compound is also unstable in $CDCl_3$ solution if stored at room temperature for extended periods (days). ^{1}H NMR ($CDCl_3$): 7.71 br s, 1 H (H_{Imi}); 7.35– 7.24 m, 9 H (Tr); 7.24 d, 1 H, $^3J_{HH}$ = 1.2 (H_{Imi}); 7.11–7.05 m, 6 H (Tr); 6.95 br s, 1 H (H_{Imi}); 6.88 d, 1 H, $^3J_{HH}$ = 1.2 (H_{Imi}); 6.59 d, 1 H, $^2J_{HF}$ = 47.7 (CHF); 6.29 t, 1 H, $^2J_{HF}$ = 53.0 (CHF_2). ^{13}C NMR ($CDCl_3$): 141.31 d, $^2J_{CF}$ = 28.5 ($C2_{Imi}$-CHF-Imi); 141.27, 3 C (Tr); 139.64 t, $^2J_{CF}$ = 27.7 ($C2_{Imi}$-CHF_2); 129.27, 6 CH, $^1J_{CH}$ = 159.6 d, $^2J_{CH}$ = 6.4 t (Tr); 128.52, 3 CH, $^1J_{CH}$ = 161.8 d, $^2J_{CH}$ = 7.4 t (Tr); 128.34, 6 CH, $^1J_{CH}$ = 162 d, $\Sigma^{<1}J_{CH}$ = 14 m (Tr); 128.25 d, $^4J_{CF}$ = 1.0, $^1J_{CH}$ ≈ 205 d, $^2J_{CH}$ = 10.0 d (CH_{Imi}); 127.51 d, $^4J_{CF}$ = 1.7, $^1J_{CH}$ = 192.1 d, $^2J_{CH}$ = 9.4 d (CH_{Imi}); 129.99 d, $^4J_{CF}$ = 2.7, $^1J_{CH}$ = 192.8 d, $^2J_{CH}$ = 17.1 d (CH_{Imi}); 122.38 dt, J_{CF} = 2.8, 1.0, $^1J_{CH}$ ≈ 196 d, $^2J_{CH}$ ≈ 17 d (CH_{Imi}); 109.18 dd, $^1J_{CF}$ = 237.3, 238.1, $^1J_{CH}$ = 191.7 d (CHF_2); 84.45 ddd, $^1J_{CF}$ = 203.9, $^4J_{CF}$ = 3.7, 2.4, $^1J_{CH}$ = 168.8 d (CHF); 75.89 (Tr). ^{19}F NMR ($CDCl_3$): –112.9 ddd, 1 F, $^2J_{FF}$ = 313.6, $^2J_{FH}$ = 53.0, $^5J_{FF}$ = 7.6 (CHF_2); –116.6 dd, 1 F, $^2J_{FF}$ = 313.6, $^2J_{FH}$ = 53.0 (CHF_2); –122.6 dd, $^2J_{FH}$ = 47.9, $^5J_{FF}$ = 7.6 (CHF). HRMS (FAB^+) for $C_{27}H_{22}F_3N_4$ (MH) calculated: 459.1797; found: 459.1799; daughter fragments of MH, *m/z* (assignment): 243 (Tr), 309 (Tr-Imi), 341 (Tr-Imi-CHF), 118 (H-Imi-CHF_2). For $C_{27}H_{21}F_3N_4$ (458.5) calculated: 70.73% C, 4.62% H, 12.22% N; found: 70.73% C, 4.76% H, 12.16% N.

2-(Difluoromethyl)imidazole (**3**). M.p. 119–120 °C (from $CHCl_3$; decomp. above 165 °C). ^{1}H NMR ($CDCl_3$): 10.1–9.4 br s, 1 H (NH); 7.17 br s, 2 H (H_{Imi}); 6.75 t, 1 H, $^2J_{HF}$ = 54.2 (CHF_2). ^{13}C NMR: 140.27 t, $^2J_{CF}$ = 28.3 ($C2_{Imi}$); 108.72 t, $^1J_{CF}$ = 235.9 (CHF_2); ≈123 very br s ($C4_{Imi}$ and $C5_{Imi}$). ^{19}F NMR ($CDCl_3$): –113.8 d, $^2J_{FH}$ = 54.2 (CHF_2). For $C_4H_4F_2N_2$ (118.1) calculated: 40.69% C, 3.41% H, 23.72% N; found: 40.71% C, 3.40% H, 23.70% N.

2-(Difluoromethyl)imidazole hydrochloride (**3·HCl**). M.p. 162–168 °C (from iPrOH/Et_2O; with decomp.). pK_{a1} = 3.4 at 25 °C. ^{1}H NMR (DMSO-d_6): 10.2–8.2 br s, 2 H (NH·HCl); 7.72 s, 2 H (H_{Imi}); 7.38 t, 1 H, $^2J_{HF}$ = 52.6 (CHF_2). ^{13}C NMR (DMSO-d_6): 137.72 t, $^2J_{CF}$ = 30.5, $\Sigma J_{CF,CH}$ = 90 ($C2_{Imi}$); 121.69 s, $^1J_{CH}$ = 199.8 d, $^2J_{CH}$ = 12.5 d ($C4_{Imi}$ and $C5_{Imi}$); 107.12 t, $^1J_{CF}$ = 237.7, $^1J_{CH}$ = 199.4 d (CHF_2). ^{19}F NMR (DMSO-d_6): –115.4 d, $^2J_{FH}$ = 52.6 (CHF_2). For $C_4H_5ClF_2N_2$ (154.6) calculated: 31.09% C, 3.26% H, 18.13% N; found: 31.33% C, 3.27% H, 17.91% N.

4-(Difluoromethyl)-1*H*-imidazole (**4**)

a) A stirred solution of 1.00 g (3.0 mmol) of aldehyde **12** in 40 ml of dichloromethane was cooled to –65 °C and 1.2 ml of Deoxo-Fluor® (6.5 mmol) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature and was stirred for three days. The mixture was then poured into 100 ml of CH_2Cl_2 and extracted three times with 100 ml of water. The organic phase was dried over anhydrous $MgSO_4$ and evaporated to dryness. The resulting solid (831 mg) was separated by column chromatography (40 g, CH_2Cl_2/Et_2O, 100 : 0 to 8 : 2) to give 271 mg (35%) of TrOH (as a result of partial detritylation), 55 mg (6%) of starting aldehyde **12** and 454 mg (43%) of 4-(difluoromethyl)imidazole **15**.

b) Compound **15** (1.07 g, 2.97 mmol) was dissolved in 25 ml of acetic acid and 8 ml of hydrochloric acid (1:5) was added at room temperature. The mixture was stirred overnight

and then evaporated to dryness. The residue was dissolved in a mixture of 20 ml water, 20 ml of HCl (1 : 5) and 10 ml of CH_2Cl_2 and the aqueous layer was separated. This was extracted three times with 10 ml of CH_2Cl_2, filtered and evaporated to dryness to give 410 mg (89%) of 4-(difluoromethyl)-1*H*-imidazole hydrochloride (**4·HCl**).

4-(Difluoromethyl)-1-trityl-1H-imidazole (**15**). M.p. 183–184 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): 7.39 s, 1 H (H_{Imi}); 7.39–7.32 m, 9 H (Tr); 7.16–7.09 m, 7 H (Tr and H_{Imi}); 6.56 t, 1 H, $^2J_{HF}$ = 56.0 (CHF_2). ^{13}C NMR ($CDCl_3$): 141.94, 3 C (Tr); 139.64 ($C2_{Imi}$); 135.49 t, $^2J_{CF}$ = 27.3 ($C4_{Imi}$); 129.69, 6 CH (Tr); 128.32, 3 CH (Tr); 128.22, 6 CH (Tr); 120.26 t, $^3J_{CF}$ = 4.8 ($C5_{Imi}$); 111.79 t, $^1J_{CF}$ = 234.7 (CHF_2); 75.77 (Tr). ^{19}F NMR ($CDCl_3$): –113.1 d, $^2J_{FH}$ = 56.0 (CHF_2). LRMS (CI^+; NH_3), *m/z* (%, assignment): 378 (1.5, MNH_4), 361 (7, MH), 243 (40, Tr), 153 (38), 136 (100), 119 (65). For $C_{23}H_{18}F_2N_2$ (360.4) calculated: 76.65% C, 5.03% H; 7.77% N; found: 76.66% C, 5.02% H, 7.77% N.

4-(Difluoromethyl)-1H-imidazole hydrochloride (**4·HCl**). M.p. 140–141 °C (from iPrOH; decomp. above 160 °C). pK_{a1} = 4.1 at 25 °C. ^{1}H NMR (DMSO-d_6): 9.04 br s, 1 H (H_{Imi}); 8.00 br s, 1 H (H_{Imi}); 7.23 td, 1 H, $^2J_{HF}$ = 53.4, J_{HH} = 1.2 (CHF_2); 6.5–3.0 very br s, 3 H (NH_2·HCl). ^{13}C NMR (DMSO-d_6): 137.06 s ($C2_{Imi}$); 128.12 t, $^2J_{CF}$ = 28.5 ($C4_{Imi}$); 120.66 t, $^3J_{CF}$ = 7.0 ($C5_{Imi}$); 109.32 t, $^1J_{CF}$ = 234.3 (CHF_2). ^{19}F NMR (DMSO-d_6): –111.7 d, $^2J_{FH}$ = 53.5 (CHF_2). For $C_4H_5ClF_2N_2$ (154.6) calculated: 31.09% C, 3.26% H, 18.13% N; found: 31.39% C, 3.26% H, 17.94% N.

REFERENCES

1. a) Dolensky B., Takeuchi Y., Cohen L. A., Kirk K. L.: *J. Fluorine Chem.* **2001**, *107*, 147; b) Fan J., Dolensky B., Kim I. H., Kirk K. L.: *J. Fluorine Chem.* **2002**, in press; c) Kirk K. L., Cohen L. A.: *J. Am. Chem. Soc.* **1973**, *95*, 4619; d) Kirk K. L., Nagai W., Cohen L. A.: *J. Am. Chem. Soc.* **1973**, *95*, 8389; e) Kirk K. L., Cohen L. A.: *J. Org. Chem.* **1973**, *38*, 3647.
2. a) Hayakawa Y., Kimoto H., Cohen L. A., Kirk K. L.: *J. Org. Chem.* **1998**, *63*, 9448; b) Kimoto H., Cohen L. A.: *J. Org. Chem.* **1979**, *44*, 2902; c) Kimoto H., Kirk K. L., Cohen L. A.: *J. Org. Chem.* **1978**, *43*, 3403.
3. a) Khanna I. K., Weier R. M., Yu Y., Xu X. D., Koszyk F. J., Collins P. W., Koboldt C. M., Veenhuizen A. W., Perkins W. E., Casler J. J., Masferrer J. L., Zhang Y. Y., Gregory S. A., Seibert K., Isakson P. C.: *J. Med. Chem.* **1997**, *40*, 1634; b) Khanna I. K., Yu Y., Huff R. M., Weier R. M., Xu X., Koszyk F. J., Collins P. W., Cogburn J. N., Isakson P. C., Koboldt C. M., Masferrer J. L., Perkins W. E., Seibert K., Veenhuizen A. W., Yuan J., Yang D.-C., Zhang Y. Y.: *J. Med. Chem.* **2000**, *43*, 3168; c) Minakawa N., Kojima N., Sasaki T., Matsuda A.: *Nucleosides Nucleotides* **1996**, *15*, 251.
4. a) Kollonitsch J., Marburg S., Perkins L. M.: *J. Org. Chem.* **1975**, *40*, 3808; b) Kaiser C., Spagnuolo C. J., Adams T. C., Jr., Audia V. H., Dupont A. C., Hatoun H., Lowe V. C., Prosser J. C., Sturm B. L., Noronha-Blob L.: *J. Med. Chem.* **1992**, *35*, 4415.
5. Banks R. E., Smart B. E., Tatlow J. C.: *Organofluorine Chemistry Principles and Commercial Applications*, p. 71. Plenum Press, New York 1994.
6. a) Dolensky B., Kirk K. L.: *J. Org. Chem.* **2002**, *67*, 3468; b) Dolensky B., Kirk K. L.: *J. Org. Chem.* **2001**, *66*, 4687.
7. Lal G. S., Pez G. P., Pesaresi R. J., Prozonic F. M., Cheng H.: *J. Org. Chem.* **1999**, *64*, 7048.
8. Snow K. M., Smith K. M.: *J. Org. Chem.* **1989**, *54*, 3270.
9. Kirk K. L.: *J. Org. Chem.* **1978**, *43*, 4381.

10. McDonald I. A., Lacoste J. M., Bey P., Palfreyman M. G., Zreika M.: *J. Med. Chem.* **1985**, *28*, 186.
11. a) Everett T. S., Purrington S. T., Bumgardner C. L.: *J. Org. Chem.* **1984**, *49*, 3702; b) Iseki K., Asada D., Takahashi M., Nagai T., Kobayashi Y.: *Tetrahedron Lett.* **1995**, *36*, 3711.
12. a) Bissky G., Röschenthaler G.-V., Lork E., Barten J., Médebielle M., Staninets V., Kolomeitsev A. A.: *J. Fluorine Chem.* **2001**, *109*, 173; b) Lyga J. W., Patera R. M.: *J. Fluorine Chem.* **1998**, *92*, 141; c) Poludnenko V. G., Didinskaya O. B., Pozharskii A. F.: *Khim. Geterotsikl. Soedin.* **1984**, *20*, 520; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1984**, *20*, 422; d) Bissky G., Staninets V. I., Kolomeitsev A. A., Röschenthaler G.-V.: *Synlett* **2001**, 374.
13. Akutagawa T., Saito G.: *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1753.
14. a) Battesdy A. R., Nicoletti M., Staunton J., Vleggaar R.: *J. Chem. Soc., Perkin Trans. 1* **1980**, 43; b) Su Q., Wood J. L.: *Synth. Commun.* **2000**, *30*, 3383.
15. Kelley J. L., Miller C. A., McLean E. W.: *J. Med. Chem.* **1977**, *20*, 721.
16. Manoharan T. S., Brown R. S.: *J. Org. Chem.* **1988**, *53*, 1107.
17. Baldwin J. J., Christy M. E., Denny G. H., Habecker C. N., Freedman M. B., Lyle P. A., Ponticello G. S., Varga S. L., Gross D. M., Sweet C. S.: *J. Med. Chem.* **1986**, *29*, 1065.