Fluoroazoles. II. Synthesis and ^1H and ^{19}F Nmr Spectra of 2-, 4-, and 5-Fluoro-1-methylimidazole

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The three possible ring-monofluorinated *N*-methylimidazoles have been prepared by photochemical irradiation of the corresponding diazonium tetrafluoroborates. 5-Fluoro-1-methylimidazole was also obtained by methylation of 1-acetyl-4-fluoroimidazole. The ^1H and ^{19}F nmr spectra of these *N*-methylated fluoroazoles are compared, and the predominance of one tautomeric form in 4(5)-fluoroimidazole is discussed.

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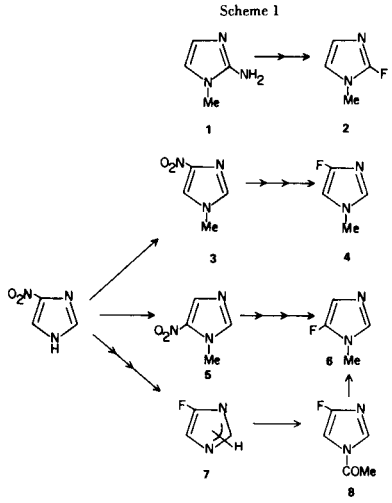
Recently, Kirk and Cohen have successfully synthesized some fluoroimidazoles, outstanding among which are 2- and 4(5)-fluorohistidine, by photochemical irradiation of the corresponding diazonium salts in tetrafluoroboric acid (1a-c). In the first paper of this series (2), we have used this procedure, with slight modifications aimed at improving the yields, to prepare 3(5)-fluoropyrazole, 4-fluoro-3,5-dimethylpyrazole, 4-fluoro-1,3,5-trimethylpyrazole, 3(5)-fluoro-*s*-triazole, and 2-fluorobenzimidazole, which means that this method may be considered as quite general and applicable to any heterocyclic amine capable of being diazotized.

We wish to report here the synthesis and the nmr spectra of the three possible monofluoro derivatives of *N*-methylimidazole (**2**, **4**, and **6**) and the acetyl derivative **8**. The preparation of these compounds was carried out as shown in the following scheme:

Scheme 1



2-Fluoro-1-methylimidazole (**2**) (3) was obtained with an overall yield of 48% by diazotization of **1** in tetrafluoroboric acid and irradiation of the resulting solution. In view of the instability of 4- and 5-amino-1-methylimidazole, **3** and **5** were reduced and quickly treated with nitrous acid, without attempting to isolate the intermediate amines; the overall yields obtained from the nitro derivatives were, respectively, 8% in **4** and 2% in **6**. Reduction was likewise tested on **5** with sodium amalgam and methanol, but we were not able to improve the poor yield in **6** which we obtained by carrying out the reduction with zinc and acid. Acetylation of 4(5)-fluoroimidazole (**7**) (1c) at room temperature gave a single derivative, to which we attributed the structure **8** on the basis of its nmr spectrum; in fact, the assumed H_5 proton of the acetyl derivative is 0.67 ppm shifted downfield with respect to the H_5 proton of **4**, this difference being practically identical to the one existing between the H_5 protons of 1-acetylimidazole and of 1-methylimidazole (4). The reaction of **8** with methyl fluorosulfonate followed by treatment of the resulting imidazolium salt with potassium carbonate and methanol gave a single compound identical to **6**.

The nmr spectra of the fluoro derivatives are shown in Table I (5). Some interesting conclusions may be deduced from these data. First, if the chemical shifts of the aromatic protons of **2**, **4**, and **6** are compared with those of 1-methylimidazole (δ H_2 = 7.37, δ H_4 = 6.98, and δ H_5 = 6.78 ppm) (4), it is obvious that the fluorine is acting in all cases as an electron-donating group, shifting the signals 0.2-0.4 ppm upfield. On the other hand, if the coupling constants measured in **2**, **4**, and **6** are compared, it is seen that $J_{H_2H_5}$ is always greater than $J_{H_2H_4}$. This appears to be a common fact in the *N*-substituted imidazoles (6).

Curiously, the coupling constants measured for **7** coincide fairly well with those measured for 4-fluoro-1-methylimidazole (**4**). Thus, it may well be said that in low polarity solvents and at room temperature, 4-fluoroimidazole is the predominant tautomer in the 4-fluoroimidazole/5-fluoroimidazole equilibrium. The chemical shift of fluorine in **7** is also closer to δ F_4 (**4**) than to δ F_5 (**6**), but this fact is probably of no great value, since it is at present difficult to estimate the influence of the methyl group on the δ F_4 and δ F_5, and the influence of molecular aggregation in **7**.

Table I

Nmr Spectra of Fluoroimidazoles in Deuteriochloroform (a)

	2	4	6	7	8
^1H (b)	H_4 = 6.58, H_5 = 6.63 } (m) Me = 3.48 (s)	H_2 = 6.99 (br. s) H_5 = 6.40 (dd) Me = 3.59 (s)	H_2 = 7.10 (br. s) H_4 = 6.52 (br. d) Me = 3.65 (s)	H_2 = 7.23 (br. s) $H_{5(4)}$ = 6.53 (dd)	H_2 = 7.89 (br. t) H_5 = 7.07 (dd) Me = 2.59 (s)
^{19}F	F_2 = 117.3	F_4 = 134.4	F_5 = 154.8	$F_{4(5)}$ = 139.1	
J	$J_{H_4H_5}$ = 1.5 $J_{F_2H_4} \cong 1.2$ $J_{F_2H_5}$ = 1.6	$J_{H_2H_5}$ = 1.5 $J_{F_4H_5}$ = 8.0	$J_{H_2H_4}$ = 1.1 $J_{H_4F_5}$ = 8.0	$J_{H_2H_{5(4)}}$ = 1.5 $J_{F_{4(5)}H_{5(4)}}$ = 8.0	$J_{H_2H_5}$ = 1.9 $J_{H_2F_4}$ = 1.5 $J_{F_4H_5}$ = 8.2

(a) Chemical shifts in ppm (δ) with TMS as internal reference for ^1H and trichlorofluoromethane as external reference for ^{19}F (ϕ scale, positive values to upfield); coupling constants in Hz. (b) Multiplicities given within parenthesis are the observed at ordinary sweep-range on a 60 MHz apparatus. Assignation of H_4 and H_5 in **2** may be reversed.

EXPERIMENTAL

The magnetic resonance spectra have been recorded on a Perkin-Elmer R-12B spectrometer. Boiling points were determined at the indicated pressure on a Buchi furnace. The photochemical irradiations were carried out with a Philips HPK-125W lamp.

Preparation of **1**, **3**, **5**, and **7**.

2-Amino-1-methylimidazole hydrochloride monohydrate (**1**) was obtained by the method of Storey, *et al.* (7). The nitro derivatives **3** and **5** were prepared from 4(5)-nitroimidazole by known procedures (8a-b). 4(5)-Fluoroimidazole (**7**) was prepared according to the Kirk and Cohen method (1c).

2-Fluoro-1-methylimidazole (**2**).

A solution of 3.04 g. (44 mmoles) of sodium nitrite in 10 ml. of water was slowly added to a stirred solution of 6.06 g. (40 mmoles) of **1** in 250 ml. of 8.5 *M* tetrafluoroboric acid cooled to -20°. Sodium tetrafluoroborate was added until the saturation was achieved. Nitrogen was passed through the reaction mixture, which was then irradiated at -30° until the 2-naphthol test for diazonium compounds was negative (~ 5 hours). The resulting solution was neutralized first with cold sodium hydroxide and then with sodium hydrogencarbonate, vacuum filtered and continuously extracted with dichloromethane for 24 hours. The extract was dried over anhydrous sodium sulfate and the solvent eliminated. The remaining oil was distilled *in vacuo* giving 1.90 g. (48%) of **2**, b.p. 66-69° at 24 mm.

Anal. Calcd. for $C_4H_5FN_2$: C, 47.99; H, 5.03; N, 27.99. Found: C, 48.12; H, 5.21; N, 28.25.

4-Fluoro- and 5-Fluoro-1-methylimidazole.

These fluoro derivatives were obtained according to the procedure described by Kirk and Cohen for the preparation of **7** (1c), but using the modifications described above for **2** (solutions more concentrated in the tetrafluoroborate anion and lower temperatures). 4-Fluoro-1-methylimidazole (**4**), b.p. 75-77° at 24 mm, was obtained with an overall yield of 8% from **3**.

Anal. Calcd. for $C_4H_5FN_2$: C, 47.99; H, 5.03; N, 27.99. Found: C, 47.72; H, 5.24; N, 27.86.

5-Fluoro-1-methylimidazole (**6**), b.p. 71-73° at 24 mm, was obtained with an overall yield of 2% from **5**.

Anal. Calcd. for $C_4H_5FN_2$: C, 47.99; H, 5.03; N, 27.99. Found: C, 48.08; H, 5.17; N, 27.71.

1-Acetyl-4-fluoroimidazole (**8**).

4(5)-Fluoroimidazole (140 mg.) (**7**), 160 μl of acetic anhydride, a small amount of fused sodium acetate, and 1 ml. of dichloromethane were shaken for 24 hours at room temperature. The solvent was removed *in vacuo*, a few ml. of anhydrous benzene were added, and the solvent eliminated again to dryness. The residue was treated with carbon tetrachloride and the resulting solution filtered. Evaporation of the solvent gave 180 mg. of an oil whose nmr spectrum showed the presence of a single product (see Table I).

Anal. Calcd. for $C_5H_5FN_2O$: C, 46.88; H, 3.93; N, 21.87. Found: C, 46.60; H, 4.08; N, 21.53.

Reaction of **8** with Methyl Fluorosulfonate.

One hundred fifty mg. of **8** and 300 mg. of freshly distilled methyl fluorosulfonate in 1 ml. of dichloromethane were refluxed overnight under anhydrous atmosphere. Methanol (2 ml.) and potassium carbonate were then added. After 1 hour, the mixture was treated with 15 ml. of dichloromethane and the resulting solution washed with water. The organic layer was dried and the solvent evaporated *in vacuo*. Distillation of the residue gave 90 mg. of 5-fluoro-1-methylimidazole (**6**).

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