# Fluoroazoles. III. Synthesis and $^1H$ and $^{19}F$ Nmr Spectra of 3-, 4-, and 5-Fluoro-1-methylpyrazole



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The three monofluoro derivatives of *N*-methylpyrazole have been synthesized. 3-Fluoro-1-methylpyrazole and 4-fluoro-1-methylpyrazole were prepared from the appropriate amines by diazotization and photochemical irradiation of the diazonium salts in tetrafluoroboric acid. 5-Fluoro-1-methylpyrazole was obtained from 1-acetyl-3-fluoropyrazole and methyl fluorosulfonate, and also by direct methylation of 3(5)fluoropyrazole with dimethyl sulfate. The $^{19}F$ chemical shifts of these *N*-methylated fluoroazoles cover a great range (*ca.* 50 ppm) and show a good correlation with the chemical shifts of $H_3$, $H_4$, and $H_5$ protons of 1-methylpyrazole. An unexpected long-range coupling $^5J$ (F-$CH_3$) is observed in 3-fluoro-1-methylpyrazole.

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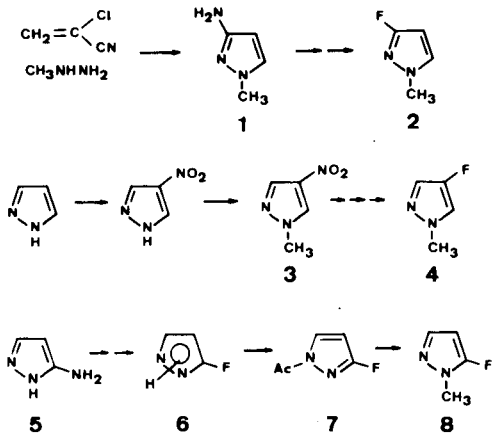
In order to carry out a comparative study, as systematic as possible, on the spectroscopic properties and the reactivity of fluoroazoles, we are presently engaged in the preparation of several fluorinated *N*-methylazoles. Thus, in our former paper (1) we have described the synthesis and nmr spectra of 2-, 4-, and 5-fluoro-1-methylimidazole. *N*-Substitution seemed necessary to avoid ambiguities originated by the presence of tautomeric equilibria.

Few fluorinated pyrazoles are known at present (2). Therefore, we wish to report here the synthesis and nmr spectra of some new fluoropyrazoles, the three monofluoro derivatives of *N*-methylpyrazole (**2**, **4**, and **8**). The preparation of these compounds was accomplished as outlined in the following scheme:

Scheme 1



3-Fluoro-1-methylpyrazole (**2**) was obtained by diazotization of 3-amino-1-methylpyrazole (**1**) in tetrafluoroboric acid and photochemical irradiation of the resulting solution (3). Though we have optimized the method reported by Ege and Arnold for the preparation of **1** (4), only a 10% yield of **2** from methyl hydrazine and chloroacrilonitrile was obtained.

Nitration of commercially available pyrazole and methylation of the nitro derivative afforded 1-methyl-4-nitropyrazole (**3**). Reduction of **3** with zinc and aqueous ethanol, followed by treatment of the reaction mixture with sodium nitrite in tetrafluoroboric acid and irradiation of the diazonium salt solution in the same medium gave 4-fluoro-1-methylpyrazole (**4**) and some 1-methylpyrazole. The overall yield of **4** was 8% from **3**.

Diazotization of 3(5)aminopyrazole (**5**) in tetrafluoroboric acid and irradiation of the solution gave 3(5)fluoropyrazole (**6**) (5). The application of a modified Olofson and Kendall method (6) to **6** allowed a selective alkylation of one nitrogen atom of the pyrazole ring. Thus, treatment of **6** with acetic anhydride in dichloromethane afforded a single acetyl derivative, to which we assigned the structure **7** on the basis of the downfield shift observed for the assumed $H_5$ proton of **7**, with regard to the $H_5$ proton of **2**. The reaction of **7** with methyl fluorosulfonate, followed by addition of aqueous sodium carbonate, gave only a compound (**8**), which showed a $^1H$ nmr spectrum very similar to that of **2**, but which had a shorter retention time and a different $^{19}F$ chemical shift.

We have also explored the direct methylation of 3(5)-fluoropyrazole (**6**). For instance, the reaction of **6** with methyl iodide in potassium *t*-butoxide/*t*-butyl alcohol yielded a mixture of **2** and **8** in a 70:30 ratio (from glc analysis). On the other hand, methylation of **6** with dimethyl sulfate at 50° gave also **2** and **8** but in a 5:95 ratio, approximately; the careful distillation of this mixture allowed us to obtain the major and more volatile **8** in a pure condition.

Nmr spectra of the fluoro derivatives are shown in Table I. Analogously to what has been observed in fluoroimidazoles (1), fluorine acts in all three *N*-methylated fluoropyrazoles as a good electron-donating substituent, as can be deduced by comparing their $^1H$ nmr spectra with

Table I

Nmr Spectra of Fluoropyrazoles in Deuteriochloroform (a)

| | 2 | 4 | 6 | 7 | 8 |
|---|---|---|---|---|---|
| $^1H$ | $H_4$ = 5.76 (dd)<br>$H_5$ = 7.30 (t)<br>Me = 3.75 (d) | $H_3$ = 7.28<br>$H_5$ = 7.28 (br. s)<br>Me = 3.78 (s) | $H_4$ = 5.83 (dd)<br>$H_{5(3)}$ = 7.39 (t) | $H_4$ = 6.16 (dd)<br>$H_5$ = 8.17 (t)<br>COMe = 2.61 (s) | $H_3$ = 7.36 (br. t)<br>$H_4$ = 5.72 (dd)<br>Me = 3.72 (d) |
| $^{19}F$ | $F_3$ = 53.0 | $F_4$ = 99.0 | $F_{3(5)}$ = 55.0 | $F_3$ = 44.0 | $F_5$ = 59.6 |
| J | $J_{H_4H_5}$ = 2.3<br>$J_{F_3H_4}$ = 6.0<br>$J_{F_3H_5}$ = 2.5<br>$J_{F\text{-}Me}$ = 1.1 | $J_{F_4H_3}$ = 4.6<br>$J_{F_4H_5}$ = 4.6 (b) | $J_{H_4H_5}$ = 2.7<br>$J_{F_{3(5)}H_4}$ = 6.0<br>$J_{F_{3(5)}H_{5(3)}}$ = 2.7 | $J_{H_4H_5}$ = 2.8<br>$J_{F_3H_4}$ = 6.0<br>$J_{F_3H_5}$ = 2.8 | $J_{H_3H_4}$ = 2.0<br>$J_{F_5H_4}$ = 6.0<br>$J_{F_5H_3}$ = 2.3<br>$J_{F\text{-}Me}$ = 1.2 |

(a) Chemical shifts in ppm (o) with TMS as internal reference for $^1H$ and trifluoroacetic acid as external reference for $^{19}F$ (positive values upfield); $^{19}F$-$^1H$ coupling constants measured after suitable proton spin decouplings. (b) From the $^{19}F$ spectrum.

that of 1-methylpyrazole ($\delta$ $H_3$ = 7.49, $\delta$ $H_4$ = 6.22, and $\delta$ $H_5$ = 7.35) (7). This effect is more noteworthy on the $H_4$ of **2** and **8**, owing to the presence of a fluorine atom on the positions 3 and 5 of the pyrazole ring, which shifts $H_4$ 0.46 and 0.50 ppm upfield, respectively (8).

The chemical shift of the fluorine nucleus in **2**, **4**, and **8** correlates fairly well with the chemical shift of $H_3$, $H_4$, and $H_5$ protons of 1-methylpyrazole, respectively, $F_3$ (**2**) being the fluorine which appears to be shifted further downfield, whereas the $F_4$ (**4**) is the one shifted further upfield (99 ppm relative to trifluoroacetic acid!).

Regarding to $^{19}F$-$^1H$ coupling constants, it should be noted that $J_{F_3H_4}$ and $J_{F_5H_4}$ have the same value despite that, in view of the corresponding proton-proton coupling constants, the latter would have been expected to be greater than the former. Furthermore, the fluorine nucleus appears in **4** as a triplet, and its coupling constants ($J_{F_4H_3} \cong J_{F_4H_5} \cong 4.6$ Hz) are surprisingly small (9). In summary, interactions between the fluorine atoms and the pyrazole ring are noticeable, particularly in **4**. Although a theoretical study could be required to explain this effect, it seems apparent that the fluorine atom ($F_4$) induces a relative lengthening of $C_3$-$C_4$ and $C_4$-$C_5$ bonds.

Finally, it should be noted that the methyl group appears in **2** (and also in **8**) as a doublet. Since the irradiation of $H_4$ and $H_5$ does not collapse it, a long-range spin coupling through five bonds between the fluorine atom and the *N*-methyl group has to be accepted (10).

## EXPERIMENTAL

Photochemical irradiations were carried out in a cylindrical reactor specially designed to insert the lamp, a Philips HPK-125W, into the solution to be irradiated from the bottom; the reactor was surrounded by a jacket for cooling the solution. Boiling points were determined at the indicated pressure on a Büchi furnace or at atmospheric pressure on a Büchi apparatus. Melting points were also determined on a Büchi apparatus. Magnetic resonance spectra have been recorded on a Perkin-Elmer R-12B spectrometer. Gas-liquid chromatograms were obtained on a Fractovap (Carlo Erba) apparatus equipped with a flame ionization detector, using a 1.5 m x 2 mm column of 15% Carbowax 20M on Chromosorb G (AW-DMCS) and a lineal temperature program going from 60° to 120° with a rate of 6° per minute. Elemental analyses were performed by the "Servicio de Análisis" of the I.Q.O.A. de Catalunya.

Preparation of **1**, **3**, **5**, and **6**.

3-Amino-1-methylpyrazole (**1**) was obtained by the method of Ege and Arnold (4), whose yield was dramatically improved (70%) by extracting the product from the reaction mixture with ethyl acetate (continuous liquid-liquid extraction) instead of diethyl ether. Nitration of pyrazole and methylation of the nitro derivative in alkaline medium by the usual procedures afforded **3** (11). 3(5)Fluoropyrazole (**6**) was prepared from 5 (12) as previously described (5).

3-Fluoro-1-methylpyrazole (**2**).

A solution of 7.59 g. (0.11 mole) of sodium nitrite in 18 ml. of water was slowly added to a stirred solution of 9.70 g. (0.10 mole) of **1** in 250 ml. of 8.5 *M* tetrafluoroboric acid (plus 2 ml. of concentrated sulfuric acid) cooled to -10°. Sodium tetrafluoroborate was added until saturation was achieved. Nitrogen was passed through the solution, which was then irradiated at -30° until the naphthol test for diazonium compounds was negative (*ca.* 8 hours). Sodium carbonate was added to the resulting solution to *p*H 6, and the mixture vacuum filtered and continuously extracted with dichloromethane for 24 hours. The extract was dried and the solvent eliminated by fractional distillation. The remaining oil was distilled at reduced pressure in a Büchi microdistiller giving 1.60 g. (16% crude yield) of 3-fluoro-1-methylpyrazole and some 1-methylpyrazole (*ca.* 5% of the mixture, as detected by glc) (13). The product was again distilled *in vacuo* and the first fraction discarded to obtain pure **2**, b.p. 137-138°; retention time: 13.8 minutes.

*Anal.* Calcd. for $C_4H_5FN_2$: C, 47.99; H, 5.03; N, 27.99. Found: C, 47.74; H, 5.17; N, 27.80.

4-Fluoro-1-methylpyrazole (**4**).

1-Methyl-4-nitropyrazole (8.20 g.) was dissolved in 100 ml. of 78% aqueous ethanol, and 40 g. of zinc powder and 1 g. of calcium chloride were added (14). The mixture was refluxed for 2 hours, filtered, and the ethanol removed *in vacuo*. To the resulting

solution of 4-amino-1-methylpyrazole (15) 100 ml. of 8.5 *M* tetrafluoroboric acid were added, and this new solution was diazotized, irradiated, and extracted as described for **2**. Concentration of the dried extracts gave an oil which was shown by glc and $^1H$ nmr spectroscopy to be composed of 4-fluoro-1-methylpyrazole (70%) and 1-methylpyrazole (30%). The separation was accomplished by column chromatography on silica gel. Elution with a 80:20 mixture of dichloromethane-diethyl ether afforded 510 mg. (8% overall yield) of **4**, b.p. 108-110° (50° at 90 mm); retention time: 11.2 minutes.

*Anal.* Calcd. for $C_4H_5FN_2$: C, 47.99; H, 5.03; N, 27.99. Found: C, 48.04; H, 5.28; N, 27.94.

1-Methylpyrazole was then eluted with ether.

1-Acetyl-3-fluoropyrazole (**7**).

3(5)Fluoropyrazole (1 g.), 1.2 ml. of acetic anhydride, a small amount of fused sodium acetate, and 3 ml. of dichloromethane were stirred for 13 hours at room temperature under anhydrous atmosphere. The mixture was applied to a small silica gel column packed in tetrachloromethane. Elution with dichloromethane provided 900 mg. (70%) of the pure product, m.p. 44-45°.

*Anal.* Calcd. for $C_5H_5FN_2O$: C, 46.87; H, 3.93; N, 21.87. Found: C, 46.98; H, 3.71; N, 21.58.

5-Fluoro-1-methylpyrazole (**8**).

Six hundred mg. of **7** and 1.2 ml. of freshly distilled methyl fluorosulfonate were heated at 70° for 20 hours. Dichloromethane (5 ml.) was added and the mixture washed with 5 ml. portions of 1 *M* aqueous sodium carbonate and, finally, water. The organic layer was dried over anhydrous potassium carbonate and concentrated by fractional distillation. Then, the careful distillation of the residue in a Büchi microdistiller yielded 300 mg. (64%) of chromatographically pure 5-fluoro-1-methylpyrazole, b.p. 25-30° at 70 mm; retention time: 6.2 minutes.

*Anal.* Calcd. for $C_4H_5FN_2$: C, 47.99; H, 5.03; N, 27.99. Found: C, 47.67; H, 5.10; N, 27.72.

Methylation of **6** in Basic Medium.

3(5)Fluoropyrazole (400 mg.) was dissolved in a solution of 0.25 g. of potassium in 15 ml. of *t*-butyl alcohol. Methyl iodide (0.5 ml.) was added and the mixture heated for 18 hours at 40°. Thereafter glc analysis showed the presence of **2** and **8** in a 70:30 ratio.

Reaction of **6** with Dimethyl Sulfate.

3(5)Fluoropyrazole (200 mg.) and dimethyl sulfate (0.25 ml.) were heated at 50° for 15 hours. Five ml. of 5% aqueous sodium bicarbonate were added, and the solution was left overnight and then extracted with three 4 ml. portions of dichloromethane. The organic layer was dried over anhydrous potassium carbonate and the product isolated by distillation in a Büchi microdistiller, giving 120 mg. (52%) of a mixture of **8** (*ca.* 95%) and **2** (5%). A careful redistillation afforded **8** in a pure condition.

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(15) Reduction to the amine was confirmed by the disappearance of the maximum at 278 nm due to the nitro derivative, and by the $^1H$ nmr spectrum of the product (deuteriochloroform, $\delta$): 3.76 (s, 3H, N-Me), 7.00 (s, 1H, $H_5$), and 7.15 (s, 1H, $H_3$).