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# $^{19}$F-$^{19}$F COUPLING CONSTANTS IN THE AZOLE SERIES. SYNTHESIS OF 3,4-, 4,5-, AND 3,5-DIFLUOROPYRAZOLES[1]

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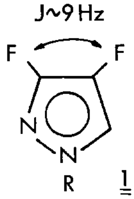
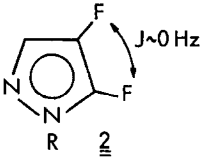
Summary: Stepwise syntheses of difluoroazoles **1**, **2**, and **3** have been performed. The $J_{FF}$ coupling constants are reported for the first time. Surprisingly, no coupling between $F_4$ and $F_5$ is observed.

Since the development of some suitable methods for attaching a fluorine atom to an azole ring,[2,3] several fluoroazoles have been prepared. However, despite the fact that polyfluorinated six-membered nitrogen heterocycles are well known,[4] no ring-di(or tri)fluorinated azole has been reported yet.

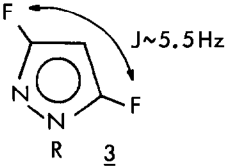
In order to evaluate all the possible $^3J_{FF}$ and $^4J_{FF}$ which may appear in the pyrazole nucleus we have synthesized compounds **1**, **2**, and **3**: their $^{19}$F-$^{19}$F coupling constants and $^{19}$F chemical shifts[5] are summarized below.



**1**



**2**



**3**

a, R = H  b, R = Me  c, R = Ac

| | **1a**[6] | **1b** | **1c** | | **2b** | | **3a** | **3b** | **3c** |
|---|---|---|---|---|---|---|---|---|---|
| $F_3$ | 65.0 | 63.6 | 53.5 | $F_4$ | 108.8 | $F_3$ | 44.5 | 43.4 | 36.4 |
| $F_4$ | 111.0 | 109.1 | 101.0 | $F_5$ | 67.1 | $F_5$ | 44.5 | 48.1 | 36.7 |

Chemical shifts ($^1$H and $^{19}$F) and $^1$H-$^{19}$F coupling constants[7] agree well with those previously observed in *N*-substituted 3-, 4-, and 5-fluoropyrazoles,[1] the most noteworthy effect caused by the introduction of a "new" fluorine atom being an upfield shift of *ca.* 10 ppm of the "first" fluorine, when both are found in an *orto* relative position, and a downfield shift of *ca.* 10 ppm too, when the halogens are found in *meta*, but this general trend could be expected on the basis of the $\pi$-donor and $\sigma$-withdrawing character of the fluorine as substituent. Nevertheless, regarding to $^{19}$F-$^{19}$F coupling constants, it is remarkable that in **2** the fluorine nuclei are not coupled to each other, a fact that is very surprising since in the pyrazole ring: (a) $J_{H_4H_5}$ is always slightly greater than $J_{H_3H_4}$, (b) $J_{H_4F_3} \sim J_{H_4F_5}$ and $J_{H_3F_4} \sim J_{H_5F_4}$, and (c) there is no doubt about the magnetic non-equivalence of the two fluorines (they lie 40 ppm apart!).[8]

3,4-Difluoropyrazole (**1a**)[6] was synthesized in eight steps from 3(5)-aminopyrazole, which was first converted to its 4-nitro derivative by means of the usual acetylation-nitration-deacetylation sequence. The photochemical irradiation (H.P. mercury lamp, without filter, 30 h, r.t.) of the corresponding diazonium salt in $HBF_4$[1,2] afforded 3(5)-fluoro-4-nitropyrazole in 53% yield. The catalytic hydrogenation (Pd/C, 4 atm) of this compound gave almost quantitatively the amine, which yielded **1a** (7%, mp = 67-69º, $M^+$= 104) by diazotization and irradiation in $HBF_4$ at -20º. The treatment of **1a** with $CH_2N_2$ in presence of $BF_3$ gave **1b**.[9] On the other hand, the methylation of **1a** with $Me_2SO_4$ at 40º, without solvent, gave only **2b**.[9] Acetylation of **1a** yielded a single product, to which the structure **1c** must be assigned on the basis of the paramagnetic shift observed by its proton.

The starting material for the synthesis of **3a** was again 3(5)-aminopyrazole, from which we prepared 3(5)-fluoropyrazole. This compound was treated with $AcONO_2$ yielding 3-fluoro-1-nitropyrazole, which was rearranged[10] to 3(5)-fluoro-5(3)-nitropyrazole. Catalytic reduction, followed by diazotization and irradiation, as above, gave a 6% yield of 3,5-difluoropyrazole (**3a**). The methylation of a sample of **3a** with $CH_2N_2$ afforded **3b**, whereas the acetylation with $Ac_2O$ in $CH_2Cl_2$ gave **3c**.

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## REFERENCES AND NOTES

1. Fluoroazoles-IV. Precedent paper: F. Fabra, J. Vilarrasa, and J. Coll, *J. Heterocyclic Chem.*, **15**, 1447 (1978).
2. K. L. Kirk and L. A. Cohen, *J. Am. Chem. Soc.*, **93**, 3060 (1971); *ibid.*, **95**, 4619 (1973).
3. R. Naik, J. T. Witkowski, and R. K. Robins, *J. Org. Chem.*, **38**, 4353 (1973).
4. See, for instance, R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, 1973.
5. In ppm, with TFA as external reference (positive values upfield), and in $CDCl_3$ as solvent.
6. The available data, namely $J_{FF}$ = 8.5 Hz, indicate that this tautomer predominates in the **1a** $\rightleftharpoons$ **2a** equilibrium.
7. For the sake of simplicity, $\delta H$ and $J_{HF}$ are omitted here.
8. Work is in progress to synthesize other 4,5-difluoropyrazoles and, namely, 3,4,5-trifluoropyrazole, in order to check whether their $J_{F_4F_5}$ are near zero too.
9. The structure of this compound has been firmly established by comparison of its Nmr spectra with those of 3-fluoro-1-methylpyrazole and 5-fluoro-1-methylpyrazole of unambiguous structure.[1]
10. J. W. Janssen, C. L. Habraken, and R. Louw, *J. Org. Chem.*, **41**, 1758 (1976), and ref. therein.

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