N-(Difluoroamino)azoles – a new class of *N*-substituted azoles

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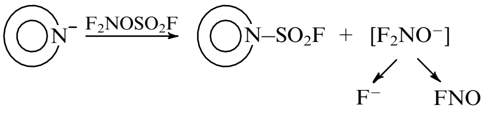
N-(Difluoroamino)azoles — a new class of N-substituted azoles — have been synthesized by reacting NH-azoles, whose NH-acidity is pK_a < 5, with O-fluorosulfonyl-N,N-difluorohydroxylamine in the presence of bases.

We have shown previously that reactions of *O*-fluorosulfonyl-*N*,*N*-difluorohydroxylamine (FH) with anions of NH-azoles occurs through replacement at the sulfur atom of the sulfonyl group in FH to give the corresponding *N*-fluorosulfonylazoles[1] (Scheme 1).



Scheme 1

On the other hand, it is known, as exemplified by the interaction of Cl^- and F^- anions with FH in acetonitrile, that FH is an ambident electrophile: the less-basic Cl^- ions react at the nitrogen atom of the NF_2 group to give $ClNF_2$ whereas the much more basic F^- ions react at the sulfur atom of the SO_2F group to give SO_2F_2.[2]

These results suggested that decreasing the basicity of azolate anions by introducing electron-withdrawing moieties may result in structures capable of substitution at the nitrogen atom of the NF_2 group, *i.e.* *N*-difluoroamination of such anions would occur.

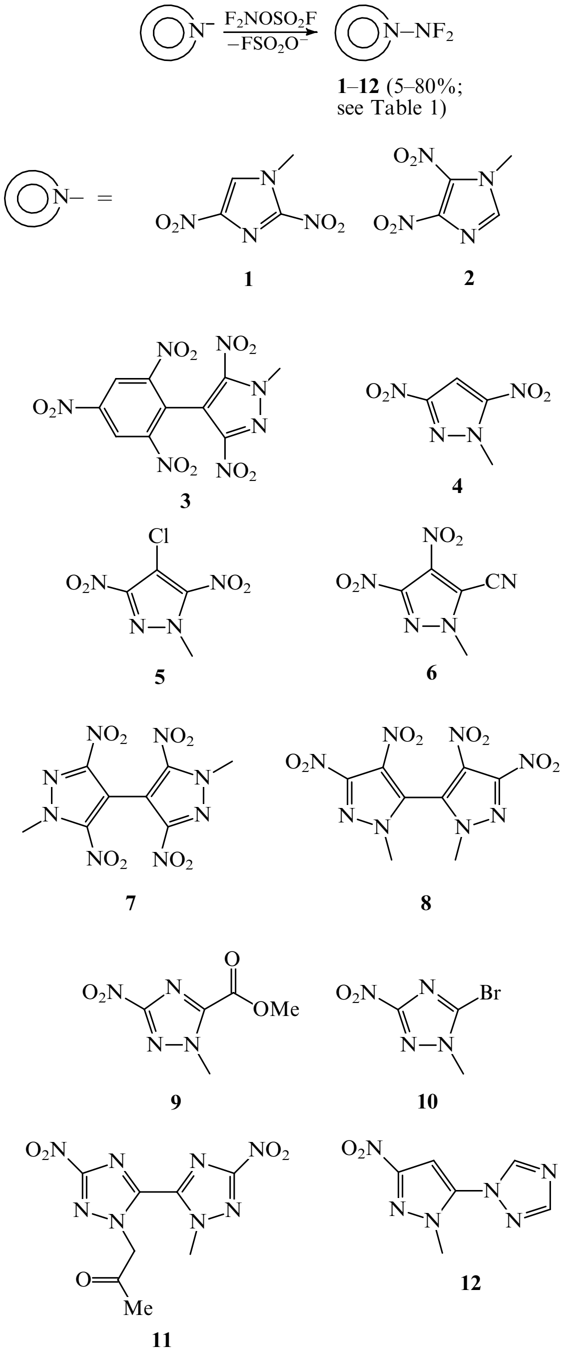
N-Unsubstituted azoles which, as we reported previously, react with FH to yield the corresponding *N*-fluorosulfonylazoles,[1] have pK_a > 6. In the case of 3,4-dinitropyrazole (pK_a 5.48)[3] and 3-nitro-1,2,4-triazole (pK_a 5.98),[3] no *N*-substituted products were detected. In the present work we have found that a further decrease in the basicity of azolate anions (the pK_a values of the corresponding NH-azoles are less than 5) results in the realization of a fundamentally different direction of the reaction: the attack of the azolate anion occurs at the nitrogen atom of the NF_2 group in FH to give *N*-substituted azoles of a hitherto unknown class — *N*-(difluoroamino)-azoles. This reaction pathway was observed over a broad range of NH-azoles, such as pyrazoles, imidazoles and 1,2,4-triazoles with pK_a < 5 (Scheme 2,[†] Table 1). This reaction is not accompanied by formation of *N*-fluorosulfonylazoles.

N-Difluoroamination of azoles was carried out under phase-transfer catalysis conditions by the procedure reported in ref. 1, but $NaHCO_3$ was used instead of NaOH. Quaternary ammonium salts or cyclic and acyclic polyethers can be used as phase-transfer catalysts. The best results were obtained using acyclic polyether PEG-400.

The compounds obtained are thermally unstable and normally decompose at temperatures below 100–120 °C.[†] **Caution!** *N*-(difluoroamino)azoles are **highly sensitive to mechanical impact**.

Despite these properties, each of the *N*-(difluoroamino)-azoles **1**–**3**, **6**–**9** and **11** were individually isolated and fully characterised (see below).

However, compounds **4**, **5**, **10** and **12** could not be isolated due to their exceedingly high lability. Their formation was confirmed and their yields were determined by ^{19}F NMR spectroscopy of the organic phase (dichloroethane). It should be noted that anions of 'superacidic' NH-azoles (pK_a < 0), such as 2,4,5-trinitroimidazole or 3,5-dinitro-1,2,4-triazole, do not react with FH.



Scheme 2

[†] Mp for: **1**, 70 °C (from CCl_4); **2**, 62 °C (from CCl_4); **3**, 127 °C (decomp., from $MeNO_2$); **6**, 78 °C (decomp., oil); **7**, 84 °C (decomp., from $CHCl_3$); **8**, 100 °C (decomp., from $CHCl_3$); **9**, 52 °C (from CCl_4); **11**, 123 °C (decomp.).

Table 1

Compound	$pK_{a(H_2O)}$ of the starting azole	Yield (%)	NMR[a] ($[^2H_6]$acetone)		
			1H (δ_{TMS})	^{19}F (δ_{CFCl_3})	^{13}C (δ_{TMS})
1[b]	2.85 (ref. 3)	38	8.79 (s, H-5)	99.51 s	137.58 (d, C-2, $^3J_{C-H} = 8.2$), 142.87 (d, C-4, $^2J_{C-H} = 2.6$), 115.11 (dt, C-5, $^1J_{C-H} = 213.2$, $^3J_{C-F} = 4.9$)
2[c]	3.39 (ref. 6)	13	8.29 (t, H-2, $^4J_{H-F} = 1.1$)	100.46 s	129.54 (dt, C-2, $^1J_{C-H} = 233.9$, $^3J_{C-F} = 5.0$), 138.37 (d, C-4, $^3J_{C-H} = 13.8$), 128.37 (s, C-5)
3	3.50[d]	80	9.39 s	101.11 s	150.34 (s, C-3), 121.0 (s, C-4), 142.4 (s, C-5), 108.47 (s, C-1′), 125.94 (dd, C-3′, $^1J_{C-H} = 181.5$, $^3J_{C-H} = 7.0$), 150.42 (s, C-4′), 152.55 (s, C-2′)
4	3.14 (ref. 3)	55	7.79 (t, $^5J_{H-F} = 5.0$)	112.10 s	153.28 (t, C-3, $^4J_{C-F} = 1.7$), 103.80 (d, C-4, $^1J_{C-H} = 199.8$), 144.24 (td, C-5, $^3J_{C-F} = 1.8$, $^2J_{C-H} = 3.3$)
5	2.92[d]	5		109.87 s	
6	4[e]	15		110.96 s	107.01 s, 123.18 s
7	1.79,[d] 3.40[d]	11		109.1 s	150.45 (s, C-3), 102.32 (t, C-4, $^4J_{C-F} = 2.1$), 141.43 (s, C-5)
8	1.80,[d] 4.70[d]	22		107.35 d (F_A), 111.46 d (F_B), ($^2J_{A-B} = 500$)	148.10 (s, C-3), 128.03 (t, C-4, $^4J_{C-F} = 1.5$), 122.20 (s, C-5)
9	3.55 (ref. 3)	22	4.31 s (Me)	110.2 s	160.10 (s, C-3), 145.65 (s, C-5), 55.0 (q, Me, $^1J_{C-H} = 150.3$), 153.86 (q, CO, $^2J_{C-H} = 4.2$)
10	3[e]	50	110.59 s		
11	2[e]	32	2.46 s (Me), 5.74 s (CH_2)	110.81 s	160.29 (s, C-3), 141.41 (t, C-5, $^3J_{C-CH_2} = 2.7$), 162.05 (s, C-3), 143.14 (s, C-5), 27.19 (q, Me, $^1J_{C-H} = 129.0$), 61.86 (t, CH_2, $^1J_{C-H} = 145.3$), 197.69 (qt, CO, $^2J_{C-Me} = 5.0$, $^2J_{C-CH_2} = 4.2$)
12	3[e]	2		111.69 s	

[a] ^1H and ^{19}F NMR shifts were recorded on a Bruker WM-250 instrument (250 MHz). ^{13}C and ^{15}N NMR shifts were recorded on a Bruker AM-300 instrument (300 MHz). [b] In $CDCl_3$, ^{15}N NMR (δ_{MeNO_2}): −36.67 (s, 2-NO_2), −25.68 (s, 4-NO_2), −127.55 (s, N-3), −62.50 (t, NF_2, $^1J_{N-F} = 168$). [c] In $CDCl_3$, ^{15}N NMR (δ_{MeNO_2}): −32.41 (s, 4-NO_2), −42.95 (s, 5-NO_2), −127.92 (d, N-3, $^2J_{N-F} = 12.6$), −69.07 (t, NF_2, $^1J_{N-F} = 166$). [d] These data were determined using a spectrometric method with an accuracy of ±0.02 pK_a units, by us in accordance with ref. 7. [e] Estimated.

The structures of *N*-(difluoroamino)azoles were confirmed by ^1H, ^{19}F, ^{13}C, ^{14}N and ^{15}N NMR (Table 1) and by IR spectroscopy as well as elemental analysis data.

In all cases, the reaction occurs regiospecifically to give only one isomer. In the case of asymmetric NH-azoles, difluoroamination involves the nitrogen atom in the ring most distant from the most electron-withdrawing group.

The signals with chemical shifts (δ_{CFCl_3}) +99 to +111 ppm in the ^{19}F NMR spectra of *N*-(difluoroamino)azoles correspond to the $N-NF_2$ group. It should be noted that the ^{19}F NMR spectrum of compound **8** contains two doublets with $^2J = 500$ Hz rather than a singlet as in the spectra of the remaining compounds, which suggests the magnetic non-equivalence of the fluorine atoms in the NF_2 group. The presence and mutual arrangement of the difluoroamine and nitro groups in *N*-(difluoroamino)azoles was confirmed by ^{13}C-$\{^1H,^{14}N\}$ triple heteronuclear resonance (Table 1). The NF_2 group manifests itself in ^{15}N NMR spectra as a triplet with chemical shifts ranging from −62 to −69 ppm and $^1J_{N-F}$ coupling constants from 166 to 168 Hz.

In addition to the absorption bands of NO_2, CH and CO (where present), the IR spectra of *N*-(difluoroamino)azoles contain a band in the region 860–890 cm^{-1}, typical of the N—F bond.

The structure of compound **8** was reliably confirmed by X-ray diffraction analysis (Figure 1).[‡]

The bis-pyrazole frame of the molecule is nonplanar. The bilateral angle between the pyrazole rings is 60.6°, which suggests the absence of conjugation between them (the C-4—C-42 bond length is 1.460 Å). The significant rotation of the rings around the C-4—C-42 bond can result from steric contacts between the substituents, namely NO_2 and NF_2. In fact, the intramolecular nonvalent distances N-13···N-132 (3.121 Å) and N-15···O-152 (2.875 Å) differ insignificantly from the corresponding sums of the van der Waals radii (3.00 and 2.90 Å, respectively). The nitro groups at adjacent carbon atoms, C-1 and C-5, are rotated 19 and 36° relative to the ring plane, the O-115···O-211 distance being 2.820 Å. In the other half of the molecule, the nitro groups at the C-12 and C-52 atoms are rotated 86 and 12°, respectively, around the N_{nitro}—C_{ring} bonds, and the N-12···O-252 distance is 2.876 Å. The bond lengths and bond angles in the molecules are close to the standard values; the C_{ring}—N_{nitro} bond lengths lie within 1.44–1.49 Å. The N—F and N_{ring}—$N_{difluoroamine}$ bond lengths in the difluoroamine groups are, on average, 1.367 and 1.410 Å, respectively, and the FNF and NNF bond angles are 101.5 and 104.2° (average values). The crystal structure was found to contain no shortened intramolecular contacts; the packing coefficient is 0.647 (van der Waals radii according to Polling[4]).

The rigid molecular construction, which is also maintained when the compound is dissolved, explains the presence of signals relating to two magnetically non-equivalent fluorine

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[‡] Syntex-P2$_1$ diffractometer, λMo, graphite monochromator, $\theta/2\theta$-scanning, $2\theta < 60°$. The crystals of **8** are rhombic, $a = 8.092(2)$, $b = 8.322(2)$, $c = 21.339(5)$ Å, $V_{cell} = 1437.0(7)$ Å^3, $d_{calc} = 1.923$ g cm^{-3}, $Z = 4$, space group $P2_12_12_1$. Structure solving, determination of the positions and anisotropic thermal parameters of the atoms and all geometric calculations were performed using the SHELX program package. The final *R*-factor was 0.074 for 1147 independent reflections of the 1496 reflections recorded overall. The atomic coordinates, bond lengths and bond angles are deposited at the Cambridge Crystallographic Data Centre (see Notice to Authors, *Mendeleev Commun.*, 1996, issue 1).

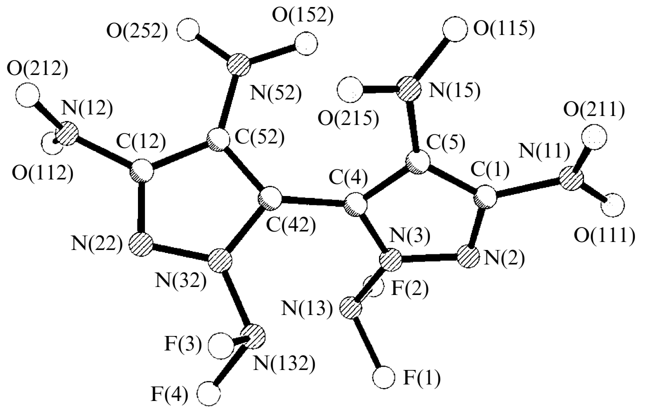

Figure 1 Structure of compound **8**.

atoms in the ^{19}F NMR spectra due to hindered rotation of the NF_2 group around the N–N bond.

Data obtained in the present work as well as those reported previously[1] confirm the ambident behaviour of FH as an electrophile, this being shown for the first time for an organic anion.

It should be noted that compounds containing an N–NF_2 moiety are very rare: apart from the *N*-(difluoroamino)azoles synthesized by us, we could find in the literature only one type of compound with this moiety, namely $R_fNFN(CF_3)NF_2$ ($R_f = CF_3$, C_2F_5) obtained by the addition of N_2F_4 to $R_fN{=}NCF_3$ under UV irradiation.[5]

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