Synthesis, Reactivity, and NMR Spectroscopy of 4,6- and 6,7-Difluoro-3-Methyl-1*H*-Indazoles

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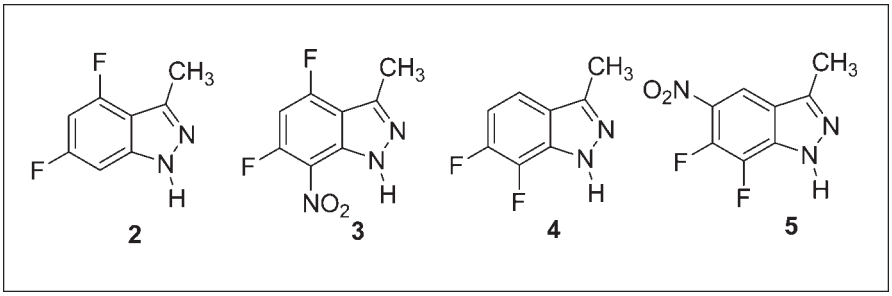
Dedicated to the memory of Professor Robert Jacquier, Université de Montpellier (France).



Four 1*H*-indazoles, two of them doubly substituted by fluorine atoms and the other two obtained by nitration of the foregoing derivatives, were prepared and fully characterized by multinuclear NMR in solution and in solid state in view of their potential nitric oxide synthase inhibition properties.

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INTRODUCTION

We have been interested in 1*H*-indazoles for many years [1–4], some of them being potent inhibitors of the nitric oxide synthase (NOS) family of isozymes [5–8]. Amongst indazoles, 3-bromo-7-nitro-1*H*-indazole **1** (NIBr) is one of those that show highest affinity for type I NOS [9]. This work is concerned with four new 1*H*-indazole derivatives bearing two fluorine substituents **2**–**5** (Scheme 1). We have already reported studies on fluorinated indazoles [10] as well as indazoles with NOS inhibitory properties [11,12].

RESULTS AND DISCUSSION

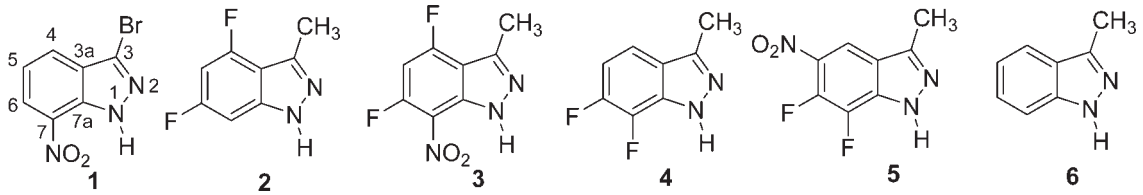
Synthesis. Compounds **2**–**5** were prepared using one of the classical methods of synthesis of this family of heterocycles [13,14]: the reaction of hydrazine with *ortho*-fluoro carbonyl derivatives (Scheme 2). Thus, starting from appropriately fluorinated acetophenones **7** and **8**, 4,6-difluoro-3-methyl-1*H*-indazole **2** and 6,7-difluoro-3-methyl-1*H*-indazole **4** were obtained with yields in pure compound of 98% and 50%, respectively. In the latter case, formation of hydrazine and azine compete, lowering the yield [15,16].

Reactivity. The nitration of 1*H*-indazole itself **9** in strongly acidic conditions affords 5-nitro-1*H*-indazole **10** as the main product together with 5,7-dinitro-1*H*-indazole **11** in minor proportion [2,17–20]. Further nitration of **10** leads to **11** [21]. Thus, formation of 6,7-difluoro-3-methyl-5-nitro-1*H*-indazole **5** from **4** is the expected reaction. However, nitration of **2** occurs at position 7 yielding 4,6-difluoro-3-methyl-7-nitro-1*H*-indazole **3**, due to the deactivating effect of both fluorine atoms at positions 4 and 6 [13,14].

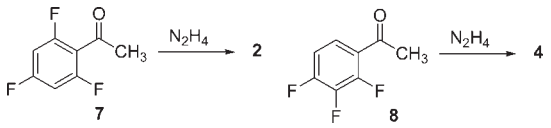
NMR results. We have gathered the solution NMR data for indazoles **2**–**5** in Tables 1 (^{1}H), 2 (^{19}F), 3 (^{13}C), and 4 (^{15}N). We have already reported the data relating to 3-methyl-1*H*-indazole **6** in $CDCl_3$ [10], but now we have recorded ^{13}C NMR and ^{15}N NMR in DMSO-d_6 for comparative purposes. Moreover, Table 5 contains the ^{13}C and ^{15}N CPMAS NMR chemical shifts for all of them. The spin-spin systems of 1,2- and 1,3-difluorobenzenes have been analyzed and the signs of the SSCC were determined [22]: we have given a negative sign to those couplings in Tables 2 and 3 that have a negative sign in difluorobenzenes.

Couplings with ^{19}F (Tables 1–3) are very sensitive to the positions of both nuclei and, consequently, they are useful for structure determination. Chemical shifts in Table 3 can be analyzed to determine the contribution of the different substituents or pairs of substituents (the F atoms are always associated two by two). The methyl group is almost insensitive (largest shift: −1.6 ppm for

Scheme 1. Indazoles.



Scheme 2. Synthesis of indazoles **2** and **4**.



the 6,7-difluoro) and C3 is only a little more sensitive (between 3.3 ppm for the 5-nitro and −1.7 ppm for the 4,6-difluoro). The substituent chemical shifts (SCS) on the six-membered ring have been averaged and are shown in Scheme 3 together with literature data on benzenes [23].

We have analyzed the ^{15}N chemical shifts in Table 4 using a presence–absence matrix (also called a Free-Wilson matrix) [24]. The effects are: on N1 −0.4 (5-NO_2), −5.4 (7-NO_2), 4.5 (4,6-diF), −3.2 (6.7-diF), and on N2 4.3 (5-NO_2), −0.4 (7-NO_2), 1.9 (4,6-diF), 4.4 (6.7-diF).

In Scheme 4, some representative coupling constants are reported, to show the analogies and differences between difluorobenzenes and difluoroindazoles.

The data in the solid state and in solution are very similar as can be seen in Figure 1. When signals (C4 and C5 of **4**) are split in the solid state, their averaged value has been used. This consistency reflects the fact that all these compounds are 1*H*-tautomers, just like most indazoles [10,18,25].

Table 1

^1H NMR chemical shifts (ppm) and coupling constants (Hz) in DMSO-d_6.

	2	3	4	5
3-CH_3	2.52	2.57	2.47	2.56
H4	–	–	7.52	8.61
			$^3J_{H5} = 8.8$	$^4J_{F6} = 6.1$
			$^4J_{F6} = 4.0$	$^5J_{F7} = 1.3$
			$^5J_{F7} = 0.7$	
H5	6.83	7.31	7.10	–
	$^3J_{F4} = {}^3J_{F6}$	$^3J_{F4} = 10.0$	$^3J_{F6} = 10.9$	
	$= 10.3$	$^3J_{F6} = 12.6$	$^3J_{H4} = 8.8$	
	$^4J_{H7} = 1.9$		$^4J_{F7} = 6.5$	
H7	7.09	–	–	–
	$^3J_{F6} = 9.0$			
	$^4J_{H5} = 1.9$			
N1H[a]	13.0	13.8	13.3	14.0

[a] Broad signal.

EXPERIMENTAL

Melting points were determined by DSC (Seiko 220C with a scanning rate of 5.0°C min^{-1}. Column chromatography: Merck silica (70–230 mesh). Microanalyses were determined at the Centro de Análisis Elemental-UCM, Madrid [Perkin Elmer 240 (CHN)].

Solution NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^1H, 100.62 MHz for ^{13}C, 376.50 MHz for ^{19}F, and 40.56 MHz for ^{15}N) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil, at 300 K. Chemical shifts (δ in ppm) are given from internal solvent, DMSO-d_6 2.49 for ^1H and 39.5 for ^{13}C, external reference $CFCl_3$ for ^{19}F and for ^{15}N NMR nitromethane (0.00) was used as external standard. Digital resolution: 1.25 Hz for ^{13}C and 0.80 Hz for ^{19}F. 2D (^1H-^{13}C) gs-HMQC, gs-HMBC and (^1H-^{15}N) gs-HMQC, gs-HMBC, were acquired and processed using standard Bruker NMR software and in nonphase-sensitive mode [26]. Variable temperature experiments were recorded on the same spectrometer. A Bruker BVT3000 temperature unit was used to control the temperature of the cooling gas stream and an exchanger to achieve low temperatures.

Solid state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra have been obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probehead. Samples were carefully packed in a 4-mm diameter cylindrical zirconia rotor with Kel-F end-caps. Operating conditions involved 3.2 μs 90° ^1H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. ^{13}C spectra were originally referenced to a

Table 2

^{19}F NMR chemical shifts (ppm) and coupling constants (Hz) in DMSO-d_6.

	2	3	4	5
F4	−117.7	−103.0	–	–
	$^3J_{H5} = 10.3$	$^3J_{H5} = 10.0$		
	$^4J_{F6} = 7.7$	$^4J_{F6} = 16.3$		
F6	−112.7	−111.3	−143.8[a]	−150.7[a]
	$^3J_{H5} = 10.3$	$^3J_{H5} = 12.6$		
	$^3J_{H7} = 9.0$	$^4J_{F4} = 16.3$		
	$^4J_{F4} = 7.7$			
F7	–	–	−160.5	−154.8
			$^4J_{H5} = 6.5$	$^3J_{F6} = 19.5$
			$^3J_{F6} = -20.5$	

[a] Complex multiplet.

Table 3

^{13}C NMR chemical shifts (ppm) and ^{13}C-^{19}F coupling constants (Hz) in DMSO-d_6.

	2	3	4	5	6
CH_3	13.2	13.1	11.4	11.1	13.0
C3	139.2	141.6	142.3	145.6	140.9
C3a	109.0	111.3	122.5	118.6	122.1
	$^2J = 21.4$	$^2J = 21.5$	[a]	[a]	
C4	155.7	159.1	116.5	116.0	119.8
	$^1J = -251.4$	$^1J = -263.7$	$^3J = 2.7$		
	$^3J = 16.2$	$^3J = 16.4$	$^4J = 7.5$		
C5	95.4	97.6	110.2	132.1	119.3
	$^2J = 30.5$	$^2J = 28.9$	$^2J = 21.4$	$^2J = 8.8$	
	$^2J = 23.5$	$^2J = 25.7$			
C6	161.1	157.6	147.4	141.6	125.8
	$^1J = -242.5$	$^1J = -265.7$	$^1J = -240.5$	$^1J = -256.2$	
	$^3J = 11.6$	$^3J = 14.4$	$^2J = 8.7$	$^2J = 12.6$	
C7	92.2	119.1	134.9	135.8	109.9
	$^2J = 26.1$	$^2J = 8.2$	$^1J = -248.8$	$^1J = -253.7$	
	$^4J = 3.9$	$^4J = 4.4$	$^2J = 16.5$		
C7a	142.7	136.5	130.6	132.1	140.8
	$^3J = 14.4$	$^3J = 12.6$	[b]	$^2J = 8.8$	
	$^3J = 12.0$	$^3J = 2.5$			

[a] No coupling constants could be measured.
[b] Complex multiplet.

Table 4

^{15}N NMR chemical shifts (ppm) and ^1H-^{15}N coupling constants (Hz).

	2	3	4	5		6
Solvent	DMSO-d_6[a]	$CDCl_3$[a]	DMSO-d_6[a]	THF-d_8[b]	DMSO-d_6[a]	
N1	−197.8	−203.2	−205.5	−205.9	−202.3	
				$^1J_{NH} = 109$	$^1J_{NH} = 105$	
N2	−69.3	−69.7	−66.8	−62.5	−71.2	
NO_2	–	[c]	–	−16.6		–

[a] At 300K.
[b] At 207 K.
[c] Not detected.

glycine sample and then the chemical shifts were recalculated to the Me_4Si [for the carbonyl atom δ (glycine) = 176.1 ppm] and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: δ ^{15}N ($MeNO_2$) = δ $^{15}N(NH_4Cl)$ − 338.1 ppm. Typical acquisition parameters for ^{13}C CPMAS were: spectral width, 40 kHz; recycle delay, 40 s; acquisition time, 30 ms; contact time, 2 ms; and spin rate, 12 kHz. To distinguish protonated and nonprotonated carbon atoms, the NQS (Non-quaternary suppression) experiment by conventional cross-polarization was recorded [26]. Typical acquisition parameters for ^{15}N CPMAS were: spectral width, 40 kHz; recycle delay, 40 s; acquisition time, 35 ms; contact time, 6 ms; and spin rate, 6 kHz.

4,6-Difluoro-3-methyl-1*H*-indazole (2). A solution of 2,4,6-trifluoroacetophenone (**7**) (0.20 g, 1.1 mmol, in 15 mL of tetrahydrofurane) was placed in a three-neck round-bottom flask equipped with a reflux condenser and 98% hydrazine monohydrate (0.09 g, 1.7 mmol) was added dropwise. Then, the

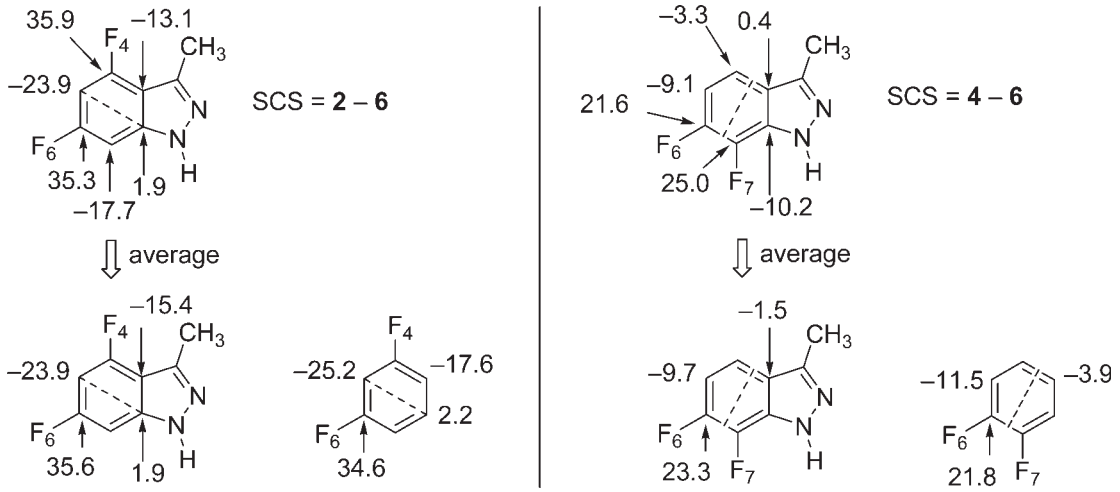
Table 5

^{13}C and ^{15}N CPMAS NMR chemical shifts (ppm).

	2	3	4	5	6 [10]**
CH_3	13.5	12.2	11.2	10.2	10.5
C3	138.7	143.9	142.2	147.2	144.5
C3a	107.9	111.5	121.1	117.6	123.6
C4	154.9	159[a]	115.2	117.6	121.2
			113.8		
C5	95.8	99.1	112.3	132.0	121.2
			109.8		
C6	160.9	159[a]	146.8	143[a]	127.9
C7	90.2	118.0	136[a]	138[a]	111.5
C7a	141.5	136.7	129.9	131.1	140.8
N1	−196.3	−196.2	−203.0	−201.5	−205.1
N2	−85.1	−73.8	−82.9	−82.1	−80.6
NO_2	–	−15.7	–	−17.0	–

[a] Broad signal.

Scheme 3. ^{13}C SCS (Substituent chemical shifts, ppm).

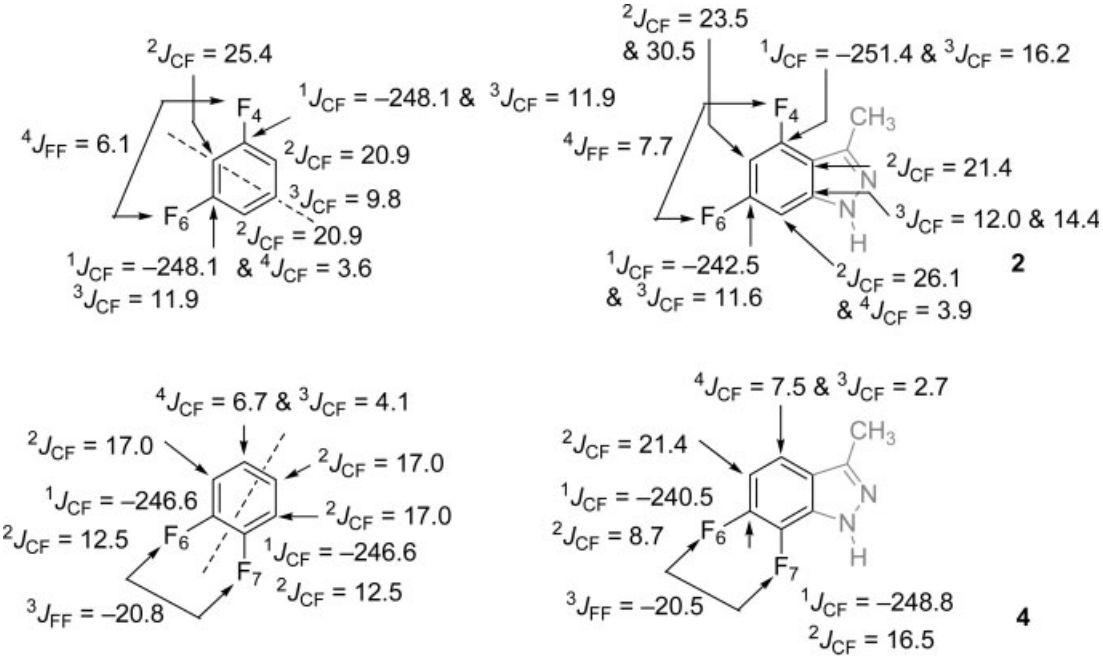


mixture was heated at 80°C during 15 h. After cooling at room temperature, the solution was decanted and the organic solvent evaporated under vacuum. The solid residue is pure **2**, mp 163.2°C (by DSC). Yield: 0.185 g, 98%. Anal. Calcd. for $C_8H_6F_2N_2$: C, 57.15; H, 3.60; N, 16.66. Found: C, 57.09; H, 3.68; N, 16.36.

4,6-Difluoro-3-methyl-7-nitro-1*H*-indazole (3). To a round-bottom flask cooled in an ice-water bath, 0.10 g of **2** (0.60 mmol) were introduced, and 0.07 g of potassium nitrate (0.7 mmol) dissolved in 1 mL of sulfuric acid 95–98% conc. (d = 1.84 g/mL) was then added dropwise. The mixture was stirred at room temperature during 24 h and poured into 5 mL of ice-water afterward, resulting in the formation of a yellowish precipitate. This mixture was maintained at 4°C for 6 h and then filtered. The solid is washed with water, filtered, and dried to obtain pure **3**, mp 213.6°C (by DSC). Yield: 0.11 g, 86%. Anal. Calcd. for $C_8H_5F_2N_3O_2$: C, 45.08; H, 2.36; N, 19.71. Found: C, 45.24; H, 2.53; N, 19.62.

6,7-Difluoro-3-methyl-1*H*-indazole (4). A solution of 2,3,4-trifluoroacetophenone (**8**) (0.20 g, 1.1 mmol, in 15 mL of tetrahydrofurane) was placed in a three-neck round-bottom flask equipped with a reflux condenser, and 98% hydrazine monohydrate (0.11 g, 2.2 mmol) was added dropwise keeping the temperature around 0°C. Then, the mixture was heated at 70°C during 24 h. After cooling at room temperature, the solution was decanted and the organic solvent evaporated under vacuum. The solid residue was chromatographed over silica using hexane/diethyl ether 7:1 as eluent, obtaining **2**, mp 182.2°C (by DSC). Yield: 0.10 g, 50%. Anal. Calcd. for $C_8H_6F_2N_2$: C, 57.15; H, 3.60; N, 16.66. Found: C, 57.15; H, 3.66; N, 16.38.

Scheme 4. ^{19}F-^{19}F and ^{13}C-^{19}F coupling constants of difluorobenzenes together with compounds **2** and **4**.



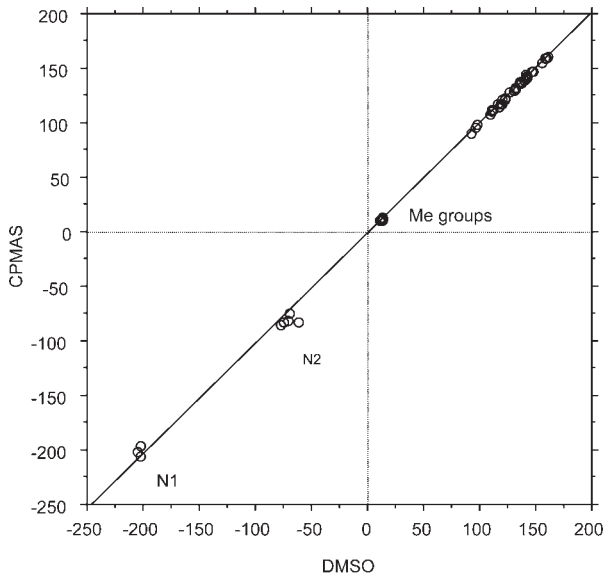


Figure 1. Comparison of ^{13}C and ^{15}N chemical shifts (ppm) in the solid-state (CPMAS) and in DMSO-d_6 solution. The straight line corresponds to CPMAS = (1.004 ± 0.005)* DMSO, $n = 48$, $R^2 = 0.999$.

6,7-Difluoro-3-methyl-5-nitro-1*H*-indazole (5). To a round-bottom flask cooled in an ice-water bath 0.11 g of **4** (0.65 mmol) were introduced, and 0.08 g of potassium nitrate (0.8 mmol) dissolved in 1 mL of sulfuric acid 95–98% conc. ($d = 1.84$ g/mL) was then added dropwise. The mixture was stirred at room temperature during 24 h and then poured into 5 mL of ice-water mixture resulting in the formation of a yellowish precipitate. The mixture was maintained at 4°C for 6 h and then filtered. The solid is washed with water, filtered, dried, and chromatographed over silica using hexane/diethyl ether 8:1 as eluent to obtain **5**, mp 167.5°C (by DSC). Yield: 0.10 g, 72%. Anal. Calcd. for $C_8H_5F_2N_3O_2$: C, 45.08; H, 2.36; N, 19.71. Found: C, 45.82; H, 2.74; N, 19.04.

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