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Reference Data

^{13}C Chemical Shifts and ^{1}H–^{13}C Coupling Constants of *N*-Phenyl-, *N*-*p*-Fluorophenyl- and *N*-*o*-Nitrophenylpyrazoles

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The ^{13}C chemical shifts and some ^{1}H–^{13}C coupling constants of twelve *N*-arylpyrazoles are reported. The assignments were made by using the effects of a fluorine substituent and two-dimensional techniques.

KEY WORDS ^{13}C NMR chemical shifts ^{1}H–^{13}C coupling constants *N*-Arylpyrazoles

INTRODUCTION

In the course of the preparation of a review on the ^{13}C NMR of pyrazoles (1168 different pyrazoles, often in several solvents),[1] we discovered that some simple cases have not been studied or were only studied when the resolution of spectrometers was low and the two-dimensional techniques were unavailable. We therefore decided to study the twelve *N*-arylpyrazoles whose structures are shown in Scheme 1.

The ^{13}C chemical shifts of 1-phenyl-3-methylpyrazole (**1**) and 1-phenyl-5-methylpyrazole (**2**) have been reported,[2–5] but not the corresponding coupling constants. Compounds **3**–**5** were chosen in order to clarify the problem of assigning *N*- and *C*-phenyl carbons, and the *p*-fluoro derivatives **8** and **9** in order to use the fluorine substituent effects[6] to assign the carbons of the *N*-phenyl group. Finally, very few *o*-nitrophenylpyrazoles are found in the literature; the only reported examples, to our knowledge, are 3-amino derivatives where the carbons of the *o*-nitro substituent were not assigned.[7]

RESULTS AND DISCUSSION

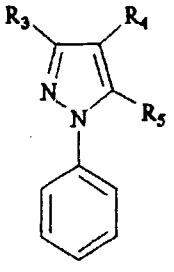
The data for compounds **1**–**12** are reported in Table 1. The spectra were recorded in DMSO-d_6 and, in some cases, in $CDCl_3$. The ^{13}C NMR spectrum of 1-phenylpyrazole (**13**) has been described: the chemical shifts in deuteriochloroform[2,8] and in DMSO-d_6[9] and the coupling constants in Ref. 10.

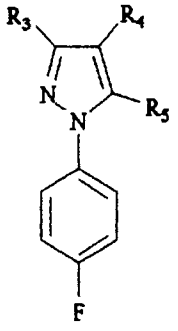
The assignment of the *N*-phenyl carbons of **5** and **6** was made from those of the corresponding *p*-fluorophenyl derivatives **8** and **9**. For **10** we first assigned the protons of the *o*-nitrophenyl substituent, using the fact that the proton α to the nitro group (H-3′) absorbs at lowerfield.[11] A NOESY experiment (solvent, DMSO-d_6) shows that H-4′ resonates at 7.62 ppm. The remaining two protons were assigned by their multiplicity. A HETCOR experiment related the protons and carbons of this compound. The same approach was used for **11**.

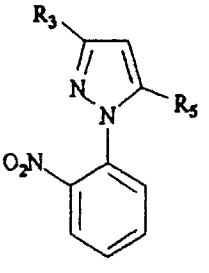
In the 1,3,5-triarylpyrazoles **5**, **6**, **8** and **9** all the aromatic protons absorb as a unique complex multiplet, except for the *ortho* protons of the coplanar 3-phenyl substituent (see Experimental). These protons are deshielded owing to the proximity of the lone pair on N-2 when neither the pyrazole nor the phenyl rings are twisted.[11,12] A 2D ^{13}C, ^{1}H shift correlation experiment for **8** shows that the deshielded *ortho* protons absorbing at 7.91 ppm are linked to *ortho* carbons which absorb at 125.43 ppm, i.e. to the *ortho* carbons of the 3-phenyl group.

The Bu^t ^{13}C signals are very close to each other, whereas the ^{1}H NMR signals are different. The ^{1}H NMR assignment was carried out using a NOESY experiment: the Bu^t group close to the phenyl is that absorbing at 1.15 ppm (**7** in $CDCl_3$). On the other hand, a HETCOR experiment showed that the corresponding ^{13}C NMR signal is that at 30.85 ppm, thus allowing its assignment to the 5-*tert*-butyl group.

The *ortho* carbons of the *N*-phenyl group are very sensitive to steric effects (in some cases the difference between the chemical shifts of the *ortho* and *meta* carbons has been used.[2,13,14] In the *N*-phenyl series the *ortho* carbons absorb, in DMSO-d_6, at 118.4







1, $R_3 = CH_3$, $R_4 = R_5 = H$
2, $R_3 = R_4 = H$, $R_5 = CH_3$
3, $R_3 = C_6H_5$, $R_4 = R_5 = H$
4, $R_3 = R_4 = H$, $R_5 = C_6H_5$
5, $R_3 = R_5 = C_6H_5$, $R_4 = H$
6, $R_3 = R_5 = C_6H_5$, $R_4 = CH_3$
7, $R_3 = R_5 = t\text{-}C_4H_9$, $R_4 = H$

8, $R_3 = R_5 = C_6H_5$, $R_4 = H$
9, $R_3 = R_5 = C_6H_5$, $R_4 = CH_3$

10, $R_3 = R_5 = H$
11, $R_3 = R_5 = CH_3$
12, $R_3 = R_5 = t\text{-}C_4H_9$

Scheme 1

Table 1. ^{13}C chemical shifts (ppm) and ^{1}H–^{13}C coupling constants (Hz) of *N*-arylpyrazoles

Compound	Solvent	C-3	C-4	C-5	*N*-substituent 1′	2′	3′	4′	5′	6′	R_3	R_4	R_5
1	$CDCl_3$	150.22 ^2J=5.1, ^3J=8.5, ^2J(Me)=6.7	107.25 ^1J=175.3, ^2J=8.0, ^3J(Me)=3.3	127.05 ^1J=185.8, ^2J=9.4	139.95	118.49	129.07	125.61	129.07	118.49	CH_3: 13.48 ^1J=127.3	—	—
	DMSO-d_6	149.64 ^2J=5.2, ^3J=8.5, ^2J(Me)=6.6	107.70 ^1J=175.4, ^2J=8.0, ^3J(Me)=3.3	128.08 ^1J=188.3, ^2J=9.7	139.88	117.92	129.43	125.57	129.43	117.92	CH_3: 13.52 ^1J=127.1	—	—
2	$CDCl_3$	139.21 ^1J=184.2, ^2J=5.7, ^4J(Me)=0.6	106.36 ^1J=174.8, ^2J=10.3, ^3J(Me)=3.6	138.02 ^2J=8.6, ^3J=4.7, ^2J(Me)=6.6	139.30	124.18	128.43	126.94	128.43	124.18	—	—	CH_3: 11.75 ^1J=128.8 ^3J(H-4): 1.2
	DMSO-d_6	139.57 ^1J=183.0, ^2J=5.8, ^4J(Me)=0.6	107.11 ^1J=175.0, ^2J=10.3, ^3J(Me)=3.6	138.45 ^2J=8.6, ^3J=4.9, ^2J(Me)=6.6	139.77	124.39	129.08	127.31	129.08	124.39	—	—	CH_3: 12.05 ^1J=129.0 ^3J(H-4): 1′2
3	$CDCl_3$	152.77 ^2J=4.5, ^3J=8.2	104.89 ^1J=176.0, ^2J=8.2	127.90 ^1J=186.9, ^2J=8.9	140.06	118.92	129.30	126.20	129.30	118.92	C_6H_5: C-1′: 132.95 C-2′,6′: 125.71 C-3′5′: 128.50 C-4′: 127.90	—	—
	DMSO-d_6	151.97 ^2J=4.5, ^3J=8.3	105.47 ^1J=177.1, ^2J=8.3	129.43 ^1J=190.1, ^2J=9.3	139.72	118.33	129.62	126.27	129.62	118.33	C_6H_5: C-1′: 132.79 C-2′,6′: 125.55 C-3′,5′: 128.83 C-4′: 128.15	—	—
4	$CDCl_3$	139.94 ^1J=185.7, ^2J=5.5	107.49 ^1J=176.3, ^2J=10.5	142.61 ^2J=8.2, ^3J=4.1	139.77	124.83	128.51	127.82	128.51	124.83	—	—	C_6H_5: C – 1′: 130.24 C-2′,6′: 128.39 C-3′,5′: 128.09 C-4′: 127.04
	DMSO-d_6	140.21 ^1J=185.8, ^2J=5.5	108.06 ^1J=176.8, ^2J=10.6	142.15 ^2J=8.3, ^3J=4.0, ^4J(H-2′,6′)=4.0	139.90	125.14	128.25	127.54	128.25	125.14	—	—	C_6H_5: C-1′: 130.17 C-2′,6′: 128.54 C-3′,5′: 128.98 C-4′: 128.25
5	DMSO-d_6	151.15	105.43 ^1J=176.6	144.27	139.87	125.52	129.20	127.89	129.20	125.52	C_6H_5: C-1′: 132.76 C-2′,6′: 125.35 C-3′,5′: 128.73 C-4′: 128.19	—	C_6H_5: C-1′: 130.06 C-2′,6′: 128.57 C – 3′,5′: 128.90 C-4′: 129.00

6	DMSO-d_6	150.06	113.64	141.25	139.72	124.55	128.81	127.04	128.81	124.55	C_6H_5: C-1′: 133.42 C-2′,6′: 127.39 C-3′,5′: 128.52 C-4′: 128.39	CH_3: 9.88 ^1J = 127.3	C_6H_5: C-1′: 129.97 C-2′,6′: 128.61 C-3′,5′: 129.86 C-4′: 127.62
7	$CDCl_3$	160.34 ^2J = 4.4, ^3J(Me) = 4.4	100.16 ^1J = 171.2	153.00 ^2J = 8.8, ^3J(Me) = 4.4	142.60	128.99	128.47	128.66	128.47	128.99	t-C_4H_9: C: 31.87 CH_3: 30.64 ^1J = 125.6	—	t-C_4H_9: C: 31.91 CH_3: 30.85 ^1J = 125.6
	DMSO-d_6	159.08	99.97	152.56	142.30	128.79	128.53	128.79	128.53	128.79	t-C_4H_9: C: 31.48 CH_3: 30.46	—	t-C_4H_9: C: 31.66 CH_3: 30.59
8	DMSO-d_6	151.12	105.29 ^1J = 176.6	144.35	136.26 $^4J(^{19}F)$ = 2.7	127.50 $^3J(^{19}F)$ = 8.7	116.00 $^2J(^{19}F)$ = 23.0	161.10 $^1J(^{19}F)$ = 245.3	116.00 $^2J(^{19}F)$ = 23.0	127.50 $^3J(^{19}F)$ = 8.7	C_6H_5: C-1′: 132.64 C-2′,6′: 125.43 C-3′,5′: 128.70 C-4′: 128.13	— —	C_6H_5: C-1′: 129.81 C-2′,6′: 128.58 C-3′,5′: 128.80 C-4′: 128.58
9	DMSO-d_6	150.10 ^3J(H-2′,6′) = 4.0	113.58 ^2J(Me) = 6.3	141.38 ^3J(H-2′,6′) = 3.7	136.18 $^4J(^{19}F)$ = 2.9	126.66 $^3J(^{19}F)$ = 8.7	115.64 $^2J(^{19}F)$ = 23.0	160.59 $^1J(^{19}F)$ = 244.6	115.64 $^2J(^{19}F)$ = 23.0	126.66 $^3J(^{19}F)$ = 8.7	C_6H_5: C-1′: 133.36 C-2′,6′: 127.38 C-3′,5′: 128.51 C-4′: 128.44	CH_3: 9.85 ^1J = 127.5	C_6H_5: C-1′: 129.74 C-2′,6′: 128.64 C-3′,5′: 129.86 C-4′: 127.63
10	$CDCl_3$	142.12 ^1J = 187.1, ^2J = 5.6, ^3J = 8.5	108.04 ^1J = 178.7, ^2J(H-5) = 8.3, ^2J(H-3) = 10.4	129.62 ^1J = 189.2, ^2J = 9.2, ^2J = 4.6	133.23	144.46	124.86 ^1J = 169.3	128.28 ^1J = 167.3	132.92 ^1J = 165.6	126.03 ^1J = 166.3	—	—	—
	DMSO-d_6	142.07 ^1J = 186.9, ^2J = 5.9, ^3J = 8.5	108.71 ^1J = 178.6, ^2J(H-5) = 8.6, ^2J(H-3) = 10.4	130.54 ^1J = 191.3, ^2J = 9.5, ^3J = 4.3	132.18	143.95	124.92 ^1J = 169.6	128.49 ^1J = 166.0	133.36 ^1J = 166.6	125.42 ^1J = 167.2	—	—	—
11	$CDCl_3$	150.08	106.56 ^1J = 173.7, ^3J(Me) = 6.8, ^3J(Me) = 3.4	140.69	132.82	146.12	124.76 ^1J = 171.0	129.00 ^1J = 167.2	132.97 ^1J = 165.6	129.15 ^1J = 166.7	CH_3: 13.20 ^1J = 127.4	—	CH_3: 11.04 ^1J = 128.8
	DMSO-d_6	149.21 ^2J = 6.2, ^2J(Me) = 6.2	107.09 ^1J = 175.0, ^3J(Me) = 6.7, ^3J(Me) = 3.4	141.22 ^2J = 8.4, ^2J(Me) = 6.6	131.71	146.16	125.30 ^1J = 171.3	129.14 ^1J = 167.8	133.93 ^1J = 166.5	130.01 ^1J = 166.4	CH_3: 13.22 ^1J = 127.4	—	CH_3: 11.28 ^1J = 129.0
12	$CDCl_3$	162.49	101.47 ^1J = 172.3	154.07	136.25	146.94	125.29 ^1J = 169.0	129.76 ^1J = 164.1	132.78 ^1J = 165.3	131.13 ^1J = 166.2	t-C_4H_9: C: 31.88 CH_3: 30.36 ^1J = 125.9, ^4J = 4.8	—	t-C_4H_9: C: 32.02 CH_3: 30.51 ^1J = 126.1, ^4J = 4.8
	DMSO-d_6	161.22 ^2J = 4.1, ^3J(Me) = 4.1	101.07 ^1J = 172.6	153.78 ^2J = 8.1, ^3J(Me) = 4.1	135.15	146.74	125.01 ^1J = 170.9	130.38 ^1J = 166.3	133.30 ^1J = 166.6	130.65 ^1J = 167.8	t-C_4H_9: C: 31.56 CH_3: 30.17 ^1J = 126.4, ^4J = 4.1	—	t-C_4H_9: C: 31.74 CH_3: 30.35 ^1J = 126.4, ^4J = 4.1

Reference Data

Table 2. ^{1}H chemical shifts (ppm) and some ^{1}H–^{1}H coupling constants (Hz) of *N*-arylpyrazoles

Compound	Solvent	Position 3	Position 4	Position 5	*N*-Aryl
3	$CDCl_3$	7.93 (2H, H-*o*)	6.79 (d), $J(45) = 2.5$	7.97 (d)	7.78 (2H, H-*o*), 7.28–7.52 (6H, H-*m* and H-*p*, 3-Ph and 1-Ph)
4	$CDCl_3$	7.73 (d), $J(34) = 1.8$	6.51 (d)		7.20–7.33 (10H, m)
7	$CDCl_3$	1.32	6.00	1.15	7.39 (5H, s)
	DMSO-d_6	1.23	6.09	1.10	7.32–7.49 (5H, m)
8	DMSO-d_6	7.91 (2H, H-*o*)	7.15		7.21–7.48 (12H, m)
9	DMSO-d_6	7.76 (2H, H-*o*)	2.15		7.12–7.51 (12H, m)
10	$CDCl_3$	7.74 (d), $J(34) = 1.8$	6.50 (q)	7.72 (d), $J(45) = 2.5$	7.87 (H-3, $J^o = 8.0$, $J^m = 1.4$), 7.54 (H-4'), 7.69 (H-5'), 7.59 (H-6')
	DMSO-d_6	7.75 (d), $J(34) = 1.7$	6.55 (q)	8.30 (d), $J(45) = 2.5$	7.99 (H-3', $J^o = 7.8$, $J^m = 1.2$), 7.62 (H-4'), 7.80 (H-5'), 7.74 (H-6')
11	$CDCl_3$	2.18	5.96 (q)	2.12 (d), $J(45) = 0.4$	7.90 (H-3', $J^o = 8.0$, $J^m = 1.5$), 7.50 (H-4'), 7.63 (H-5'), 7.42 (H-6')
	DMSO-d_6	2.09	6.08 (q)	2.17 (d), $J(45) = 0.4$	8.05 (H-3', $J^o = 8.0$, $J^m = 1.3$), 7.65–7.87 (H-4', H-5', H-6')
12	$CDCl_3$	1.28	6.07	1.19	8.02 (H-3', $J^o = 7.6$, $J^m = 1.3$), 7.65 (H-4', H-5', H-6')
	DMSO-d_6	1.17[a]	6.15	1.16[a]	8.09 (H-3', $J^o = 7.5$, $J^m = 1.1$), 7.75–7.85 (H-4', H-5', H-6')

[a] These could be interchanged.

(pyrazole),[9] 123.9 (3,5-dimethylpyrazole)[3] and 128.8 ppm (**7**). In the *N*-*o*-nitrophenyl series the corresponding chemical shifts for C-6' are 125.4 (**10**), 130.0 (**11**) and 130.6 (**12**) ppm. The presence of the nitro group induced a similar rotation of the aryl residue in the two last cases.

EXPERIMENTAL

Synthesis

Compounds **1–6**, **10** and **11** are known (see above discussion and Ref. 15). Although **3** and **4** have already been described, their synthesis in pure form is dificult and deserves to be reported. Ethyl benzoylpyruvate sodium salt (16.25 g)[16] was dissolved at 0 °C in ethanol (20 ml), water (10 ml) and concentrated sulphuric acid (5.2 ml). After the addition of phenylhydrazine (7.3 g) at 0 °C, the mixture was refluxed for 1 h and neutralized with 33% sodium hydroxide solution. The ethanol was removed, dichloromethane added and the precipitate filtered and extracted with dichloromethane. After washing with water and extraction of the water phase with dichloromethane, the organic solvent was dried and evaporated, yielding 18.5 g (94%) of a 14:1 mixture (^{1}H NMR) of 1,5-diphenyl-3-ethoxycarbonylpyrazole and 1,3-diphenyl-5-ethoxycarbonylpyrazole, which were separated by flash chromatography [ethyl acetate–hexane (1:8)]. These esters were saponified (33% sodium hydroxide solution) and decarboxylated (1 h at 250 °C) into the corresponding pyrazoles **4** and **3**. Compound **3** was purified by flash chromatography [dichloromethane–diethyl ether–hexane (1:1:13)].

The *N*-arylpyrazoles **7** and **12** were prepared by refluxing the corresponding *N*-arylhydrazines and β-dicarbonyl derivatives in ethanol with a small amount of hydrochloric acid.[15] The yields were high (about 80% after purification). For the preparation of **8** and **9**, the *p*-fluorophenylhydrazine hydrochloride was first treated with 1 equiv. of $NaHCO_3$ in ethanol and then reflexed with the β-dicarbonyl derivative for 12 h. After addition of HCl and refluxing for another 12 h, the products were separated in 70% yield. The new compounds have the following melting points (ethanol): **7**, 111–112 °C; **8**, 106–107 °C; **9**, 120–121 °C; and **12**, 79–80 °C. The ^{1}H NMR data for pyrazoles **3**, **4**, **7**, **8**, **9**, **10**, **11** and **12** are given in Table 2.

Spectroscopy

The study of **1–4** was carried out in Copenhagen on a Bruker AM-200 spectrometer and that of **5–12** in Madrid (UNED) on a Bruker AC-200 spectrometer. The conditions employed for both spectrometers were similar;[17,18] for instance, the spectra were recorded using the gated decoupling technique for *ca.* 20% concentration, except for those of **1**, **2** and **4**, which were recorded for *ca.* 10% concentration. Proton decoupled ^{13}C NMR spectra were obtained using the CP ^{1}H decoupling mode, a pulse angle of 30° and a delay time of 0–5 s. TMS was used as the internal standard.

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