PYRAZOLES 3[1] . N-1 PROTECTED 4-SUBSTITUTED PYRAZOLES - SYNTHESIS AND NMR INVESTIGATION

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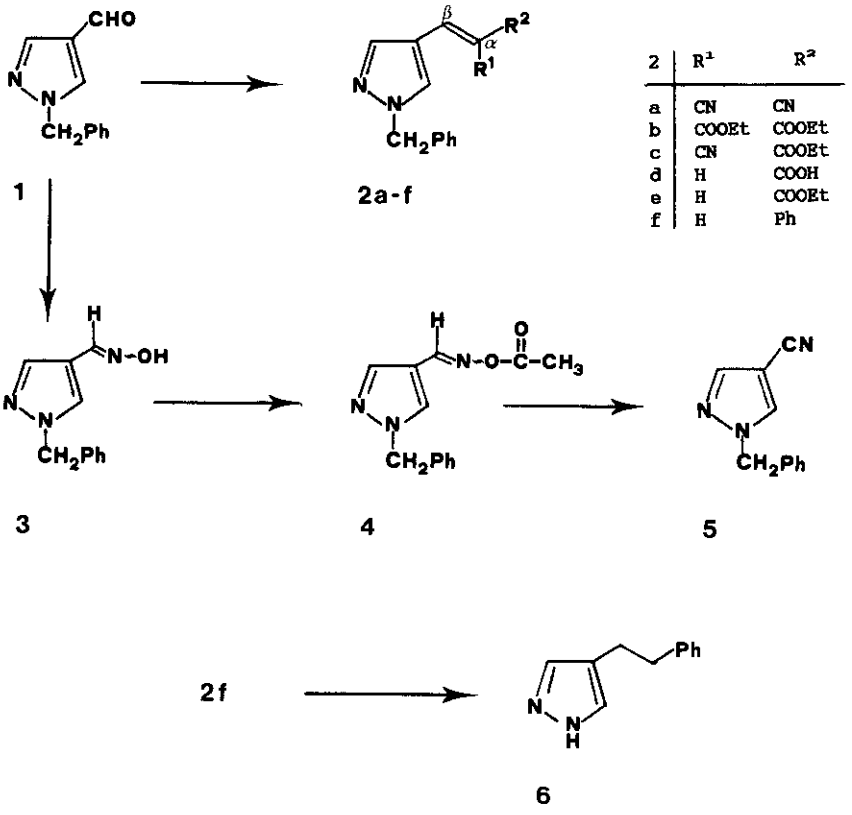
Abstract - ^{13}C-Nmr Data (chemical shifts, substituent chemical shifts (SCS), coupling constants) are reported for 26 1,4-disubstituted pyrazoles, bearing a benzyl, benzoyl or (substituted) benzenesulfonyl protecting group at N-1. The pyrazole derivatives **8a-d** were prepared from the corresponding NH-pyrazoles. In the synthesis of compounds 2-5 1-benzyl-4-pyrazolecarbaldehyde served as the starting material.

N-1 Protected pyrazoles are important synthetic intermediates in the construction of complex molecules containing the 1,2-diazole ring-system since the acidic NH-moiety strongly restricts the application of many types of standard synthetic methods. We here report on the preparation of novel 4-substituted pyrazoles bearing a benzyl or a substituted benzenesulfonyl group at N-1. Moreover, the results of a systematic ^{13}C-nmr investigation of a large variety of 1,4-disubstituted pyrazoles are reported.

Syntheses

The formyl group in 1-benzyl-4-pyrazolecarbaldehyde (**1**), which is conveniently available from 1-benzylpyrazole according to a reported procedure,[2] expectedly reacted smoothly with malonic acid and derivatives thereof thus providing access to the acrylic acid **2d** and the condensation products **2a,b,c** in reasonable yields. The styrylpyrazole derivative **2f** as well as the ethyl acrylate **2e** could be prepared from **1** by *Wittig-Horner*-type reactions. Whereas **2f** under these conditions is obtained in 72% yield[3] it turned out to be advantageous to prepare **2e** *via* esterification of **2d**. 1-Benzyl-4-pyrazolecarbonitrile (**5**) has been prepared by *Jones* from 1-benzyl-4-bromopyrazole.[4] A more convenient access to **5** is proposed in Scheme 1: refluxing of the oxime **3**, obtained quantitatively from

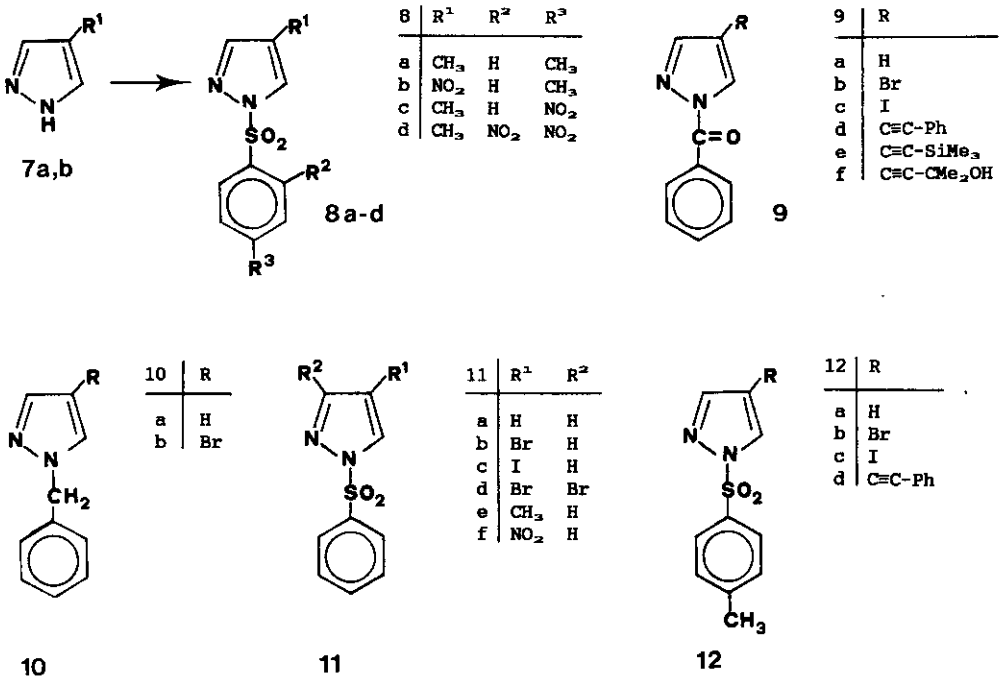
1, in acetic anhydride affords 5 in 70% yield. An attempted single step conversion of 1 into 5 (by treatment of 1 with nitroethane in acetic acid/sodium acetate according to ref.[5]) was found to give the target compound in 49% yield.



2	R^1	R^2
a	CN	CN
b	COOEt	COOEt
c	CN	COOEt
d	H	COOH
e	H	COOEt
f	H	Ph

Scheme 1

The synthesis of 1-tosylpyrazoles **12a-d** was reported previously.[1,6] In order to prepare the pyrazoles **8a-c**,[7] containing various substituted benzenesulfonyl protecting group at N-1, 4-methylpyrazole or 4-nitropyrazole[8] was allowed to react with the corresponding benzenesulfonyl chlorides in pyridine. Only for the synthesis of **8d** the employment of the silver salt of 4-methylpyrazole was required. The benzenesulfonylpyrazoles **11b-g** are accessible from the corresponding 4-substituted or 4,5-disubstituted pyrazoles by applying the method used in the synthesis of compounds **8a-c**.[9]



Scheme 2

Nmr Investigations

Nmr Spectral Measurements

All nmr spectra were recorded in 5 mm sample tubes on a Bruker AC 80 Fourier-transform spectrometer equipped with an Aspect 3000 computer. The operating frequency was 80.13 MHz for ^{1}H and 20.15 MHz for ^{13}C. The probe temperature was 25°C. ^{13}C Spectra were taken from approximately 1 M solutions, the centre of the solvent peak was used as an internal standard, which was related to TMS with δ 39.50 ppm for d_6-DMSO and δ 77.00 ppm for $CDCl_3$, respectively. ^{1}H-Coupled ^{13}C spectra were obtained using the gated decoupling technique (32 K data points). According to the spectral parameters used the digital resolution here was 0.3-0.5 Hz/point, in broad-band decoupled or J-modulated spin echo ^{13}C spectra - 0.9 Hz/point (16 K data points).

^{13}C Chemical Shifts

The chemical shifts and substituent chemical shifts (SCS) of the pyrazole-C-signals in 1,4-disubstituted pyrazoles are given in Tables 1-4.

Assignments. These were made by several methods. The signals of the quaternary pyrazole C-4 atoms in most cases could be identified easily using the J-modulated spin echo technique (switch-off delay τ= 7 ms) and NOE considerations. In the spectra of 4-nitropyrazoles[10] (**8b** and **11f**) only weak and broadened lines (quadrupol relaxation of the nitro-group ^{14}N) are observed for these carbon-atoms. The unequivocal assignment of the pyrazole C-3 and C-5 resonances, however, required comparison with chemical shift values of model substances described in the literature[11,12] and was confirmed additionally by selective heteronuclear decoupling experiments (irradiation of unambiguously assigned pyrazole-H resonances). Some additional information could be obtained from the ^{1}H-coupled spectra. For instance, with N-1-benzylpyrazoles the C-5 signals show more complicated coupling patterns than the corresponding C-3 signals due to coupling with the methylene protons. Assignments of the two CN-resonances in the spectrum of compound **2a** could be achieved simply on the basis of the $^{3}J(^{13}C,^{1}H)$ coupling constants: ($^{3}J_{trans}$ 12-14 Hz > $^{3}J_{cis}$ 6-8 Hz). Similarly, this assignment could be done for the ester carbonyl resonances in compound **2b**. In the case of compound **2c** the value of this ^{3}J-coupling constant [J(CN,alkene-H)=13.4 Hz] permits to determine the configuration.

Substituent Effects. The influence of a variation of the substituent at C-4 in 1-benzyl-, 1-benzoyl-, 1-benzenesulfonyl- and 1-tosylpyrazoles on the ^{13}C chemical shifts of pyrazole ^{13}C-resonances is shown by the SCS given in Tables 1-4. As a general trend, the C-3 resonances of all compounds listed appear at lower field than those of the corresponding C-5 atoms, whereas the C-4 atoms resonate at higher field than the C-5 atoms. The two nitro derivatives **8b** and **11f** represent the only exception to this trend, as, due to the influence of the 4-nitro groups, the C-4 signals in these compounds have larger ppm-values than the corresponding C-5 signals. Bromine as a substituent shifts the C-4 resonance signal to a higher field (about 10-14 ppm), iodine leads to a remarkably high shift (46 ppm) into the same direction, whereas attachment of a methyl group to C-4 expectedly causes a downfield shift (10 ppm). In most cases the C-5 resonance signal is more sensitive to a variation of the C-4 substituent than the C-3 signal. An

increase in the electron-withdrawing properties of the N-1 substituent ($PhCH_2$ < PhCO < $PhSO_2$ ≈ Tos < 4-nitrobenzenesulfonyl < 2,4-dinitrobenzenesulfonyl) expectedly[11] causes a shift of all ring carbon-atom signals to a lower field, as can be seen from Tables 1-4 and the data of compounds **8c,d** given in the experimental part. In 1-substituted 4-bromopyrazoles (**9b, 10b, 11b, 12b**) the C-3 signal is more sensitive to such a change of the N-1 substituent than the C-5 resonance.

Table 1: **^{13}C-Chemical Shifts of 1-Benzylpyrazoles [δ(ppm), d_6-DMSO]**

Comp.	Pyrazole-C (SCS)			Phenyl-C					Other C-Atoms
	C-3	C-4	C-5	C-1'	C-2',6'	C-3',5'	C-4'	CH_2	
1	140.04 (1.17)	124.02 (18.66)	134.62 (4.79)	136.26	127.73	128.50	127.73	55.19	184.45(C=O)
2a	141.32 (2.45)	115.90 (10.54)	135.00 (5.17)	135.98	127.93	128.61	128.01	55.27	153.13(C^{β}), 114.45(CN^1), 114.07(CN^2), 75.42(C^{α})
2b	140.41 (1.54)	114.96 (9.60)	132.68 (2.85)	136.50	127.68	128.49	127.68	54.97	166.26, 163.81(C=O), 133.06 (C^{β}),121.21(C^{α}),61.17, 60.77 (OCH_2), 13.91, 13.63(CH_3)
2c	141.55 (2.68)	115.61 (10.25)	134.63 (4.80)	136.09	127.79	128.52	127.79	55.19	162.18(C=O), 146.84(C^{β}), 116.31(CN), 97.44(C^{α}), 61.67(OCH_2), 13.88(CH_3)
2d	138.98 (0.11)	118.04 (12.68)	131.12 (1.29)	136.99	127.64	128.58	127.73	55.10	167.96(C=O), 135.22(C^{β}), 116.24 (C^{α})
2e	138.97 (0.10)	117.81 (12.45)	131.28 (1.45)	136.86	127.53	128.46	127.63	54.97	166.42(C=O), 135.50(C^{β}), 115.01(C^{α}), 59.51(OCH_2), 14.11(CH_3)
2f	137.17 (-1.70)	120.31 (14.95)	128.29 (-1.54)	137.46	127.46	128.51	127.46	54.85	137.31(1"),128.41, 126.73, 125.98,119.08 (Phenyl-C",C^{α},C^{β})
3	140.70 (1.83)	113.23 (7,87)	132.67 (2.84)	137.07	127.67	128.51	127.67	54.80	137.95(C=NOH)
5	142.49 (3.62)	90.86 (-14.50)	136.32 (6.49)	136.08	127.78	128.61	127.98	55.33	113.86(CN)
10a[a,b]	138.87 (0.00)	105.36 (0.00)	129.83 (0.00)	137.56	127.35	128.31	127.35	54.69	
10b[a]	139.18 (0.31)	91.83 (-13.53)	130.14 (0.31)	136.68	127.45	128.33	127.56	55.33	

[a] Preparation according to ref.[4]
[b] ref.[12]

Table 2: ^{13}C-Chemical Shifts of 1-Benzoylpyrazoles

Comp.	Solvent	δ (ppm) Pyrazole-C (SCS) C-3	C-4	C-5	Other C-atoms
9a[a]	$CDCl_3$	144.01 (0.00)	108.99 (0.00)	130.00 (0.00)	
	d_6-DMSO	144.62 (0.00)	109.73 (0.00)	130.52 (0.00)	
9b	$CDCl_3$	144.62 (0.61)	99.06 (-9.93)	130.11 (0.11)	ref.[1]
9c	$CDCl_3$	148.69 (4.68)	63.33 (-45.66)	134.85 (4.85)	ref.[1]
9d	$CDCl_3$	145.94 (1.93)	107.45 (-1.54)	132.31 (2.31)	ref.[1]
9e	d_6-DMSO	145.98 (1.36)	106.45 (-3.28)	133.53 (3.01)	ref.[1]
9f	d_6-DMSO	145.96 (1.34)	106.70 (-3.03)	132.49 (1.97)	ref.[1]

[a] Preparation according to ref.[13]

Table 3: ^{13}C-Chemical Shifts of 1-Benzenesulfonylpyrazoles

Comp.	Solvent	δ (ppm) Pyrazole-C (SCS) C-3	C-4	C-5	Other C-Atoms
11a[a]	d_6-DMSO	145.75 (0.00)	109.55 (0.00)	132.27 (0.00)	
11b	d_6-DMSO	145.98 (0.23)	97.38 (-12.17)	131.82 (-0.45)	ref.[9]
11c	d_6-DMSO	150.09 (4.34)	63.85 (-45.70)	135.71 (3.44)	ref.[9]
11d	d_6-DMSO	135.75 (-10.00)	101.20 (-8.35)	133.88 (1.61)	ref.[9]
11e	d_6-DMSO	147.08 (1.33)	119.92 (10.37)	129.79 (-2.48)	ref.[9]
11f	d_6-DMSO	139.85 (-5.90)	137.00 (27.45)	131.75 (-0.52)	ref.[9]

[a] Preparation according to ref.[14]

Table 4: ^{13}C-Chemical Shifts of 1-Tosylpyrazoles

Comp.	δ (ppm) in d_6-DMSO Pyrazole-C (SCS) C-3	C-4	C-5	Other C-Atoms
12a[a]	145.49 (0.00)	109.36 (0.00)	132.07 (0.00)	ref.[11,12]
12b	145.79 (0.30)	97.25 (-12.11)	131.70 (-0.37)	ref.[1]
12c	149.87 (4.38)	63.68 (-45.68)	135.55 (3.48)	ref.[1]
12d	146.86 (1.37)	106.13 (-3.23)	134.32 (2.25)	ref.[1]
8a	146.90 (1.41)	119.78 (10.42)	129.71 (-2.36)	145.69(4'), 133.66(1'), 130.09 (3',5'), 127.36(2',6'), 20.94 (tosyl-$\underline{C}H_3$), 8.15(pyrazole-$\underline{C}H_3$)
8b	139.62 (-5.87)	136.75 (27.39)	131.50 (-0.57)	147.45(4'),136.85(1'), 130.50(3', 5') 128.46(2',6'), 21.06(CH_3)

[a] Preparation according to ref.[6]

$^{13}C,^{1}H$ Spin-Spin Coupling Constants

All coupling constants were obtained from the coupled spectra (recorded with the gated decoupling technique), assuming that the spectra were essentially first order. Their values, listed in Table 5, are considered as positive, since their signs have not been determined.

$^{1}J(^{13}C,^{1}H)$: As a general trend, in all compounds investigated ^{1}J(C-5,H-5) was larger than ^{1}J(C-3,H-3). When the electron-withdrawing property of the N-1 substituent increases ($PhCH_2$ < PhCO < $PhSO_2$ ≈ Tos) also these ^{1}J coupling constants increase.[11] A similar effect is observed when permutating the substituent at C-4: switching to more electron-attracting substituents causes an increase of the above mentioned ^{1}J-coupling constants in the order of CH_3 < I < Br < NO_2.

$^{2}J(^{13}C,^{1}H)$: If there is no possibility of coupling with side chain protons, a split of the C-4 signal in the spectra of 1,4-disubstituted pyrazoles into a double doublet is observed. To assign these coupling constants correctly to ^{2}J(C-4,H-3) and ^{2}J(C-4,H-5) we investigated the coupling pattern of the C-4 resonance of a 1,3,4-trisubstituted pyrazole (**11d**). This signal is split into a doublet since only a single coupling [^{2}J(C-4,H-5)] is possible. Comparing its value (5.7 Hz) with the values observed in 1,4-disubstituted pyrazoles mentioned above (5.8-8.9 Hz and 8.1-10.6 Hz), the conclusion can be drawn as ^{2}J(C-4,H-3) > ^{2}J(C-4,H-5), and ^{2}J(C-4,H-3) as well as ^{2}J(C-4,H-5) increases when the electronegativity of the C-4 substituent decreases. The coupling constants become larger in the order of Br > I ≈ C.

$^{3}J(^{13}C,^{1}H)$: As a general rule the fact ^{3}J(C-3,H-5) > ^{3}J(C-5,H-3) can be taken from the observed values. Electron-attracting substituents in the 4-position of the pyrazole ring reduce the values of ^{3}J(C-3,H-5) as well as ^{3}J(C-5,H-3). The values become smaller in the order of I > Br > NO_2.

Table 5: $^{13}C,^{1}H$ Spin-Spin Coupling Constants of Substituted Pyrazoles (Hz)

Comp.	Solvent[a]	J(Pyrazole-C,Pyrazole-H)					
		C-3,H-3	C-3,H-5	C-4,H-3	C-4,H-5	C-5,H-5	C-5,H-3
1	a	188.7	7.1			191.3	3.0
2a[b]	a	190.5	7.0	10.3	8.4	193.4	
2b[c]	a	188.3	7.4	10.0	8.0		
2c[d]	a	189.8	7.1	10.2	8.3	192.7	
2d[e]	a	186.3	7.4				
2f	a	189.5	7.6				
3	a	188.0	7.4				
5	a	194.8	6.7	9.9	7.9		3.1
8a	a	186.7				196.4	
8b	b	200.0	6.3			203.6	2.6
9a	a	188.3	9.0	10.8	8.7	194.5	4.1
	b	187.6	9.1	10.7	8.7	193.8	4.2
9b	b	194.6	7.6	8.7	5.8	199.4	3.2
9c	b	194.3	8.1	9.9	7.0	199.3	3.5
9d	b	192.1	8.0	9.7	7.5	196.9	3.2
9e	a	193.6	7.9	9.9	7.4	198.5	3.1
9f	a	192.8	8.0	9.8	7.4	197.9	3.2
10a[f]	a	183.9	8.3	10.6	8.9	187.2	
10b	a	192.1	6.9	8.1	6.4	194.4	3.1
11a	a	189.6	8.9	10.8	8.5	197.2	4.3
11b	a	197.0	7.4	8.7	5.6	203.4	3.3
11c	a	195.7	8.0	10.3	7.1	202.6	3.8
11d	b		10.1		5.7	202.0	
11e	a	187.0	8.4			195.1	
11f	b	200.1	6.2			203.7	2.7
12a[f]	a	190.8	8.7	10.3	8.5	198.9	4.3
12b	a	196.9	7.4	8.8	5.8	203.1	3.3
12c	a	195.5	8.0	10.3	7.2	202.4	3.7
12d	a	194.4	7.7	10.1	7.3	200.8	3.5

[a] solvent: a = d_6-DMSO, b = $CDCl_3$
[b] other couplings: $^{3}J(CN^{1},H^{B})=13.8$; $^{3}J(CN^{2},H^{B})=7.9$
[c] other couplings: $^{3}J(CO^{1},H^{B})=12.2$; $^{3}J(CO^{2},H^{B})=7.5$
[d] other couplings: $^{3}J(CN,H^{B})=13.4$; $^{3}J(CO,H^{B})=6.4$
[e] other couplings: $^{3}J(CO,H^{B})=6.7$
[f] ref.[12]

^{1}H-Nmr Spectra

^{1}H-Nmr Data of all new compounds are given in the experimental part. The following trends were observed: With the acquisition parameters used (digital resolution: 0.49 Hz/point) the H-3 and H-5 resonance signals always appear as singlets; in all cases the H-5 resonates at lower field than the corresponding H-3 signal. According to the literature[15] in most cases the H-5 signal is more sensitive to a change of solvent (d_6-DMSO → $CDCl_3$, see Table 6). Additionally, for compounds **2d**, **2e** and **2f** trans-configuration has to be assigned considering the values of the $^{3}J(H,H)$ coupling constants observed.

Table 6: Influence of the Solvent on the Chemical Shift of Pyrazole-H-3 and Pyrazole-H-5 in 1,4-Disubstituted Pyrazoles [$\Delta\delta = \delta(d_6\text{-DMSO}) - \delta(CDCl_3)$]

	2a	2c	2d	2f	3	8a	8b	9b	9c	9d	11b	11c	12b	12c
$\Delta\delta$ H-3	0.07	0.18	0.32	0.30	-0.03	0.17	0.45	0.37	0.28	0.31	0.34	0.30	0.19	0.28
$\Delta\delta$ H-5	0.46	0.45	0.44	0.27	0.26	0.34	0.80	0.39	0.27	0.34	0.69	0.57	0.68	0.53

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EXPERIMENTAL

Melting points (uncorrected): Kofler hot-stage microscope; ir spectra: Jasco IRA-1 spectrophotometer; nmr spectra: Bruker AC 80 (80.13 MHz for ^1H, 20.15 MHz for ^{13}C), chemical shifts are given in ppm downfield from TMS; Mass spectra (ms): Varian MAT 311A (70 eV), carried out by Dr. Nikiforov at the "Institut für Organische Chemie" (University of Vienna). Microanalyses were performed at the "Institut für Physikalische Chemie" (University of Vienna, Dr.Zak). Preparative thin-layer chromatography (prep. TLC) was carried out on silica gel 60 F_{254} (Merck).

(1-Benzyl-4-pyrazolylmethylene)malononitrile (2a)

A solution of **1**[2] (186 mg, 1 mmol), malononitrile (66 mg, 1 mmol), glacial acetic acid (13 mg, 0.2 mmol) and one drop of piperidine in dry toluene (20 ml) was refluxed for 24 h using a water separator. The resulting reaction mixture was washed with saturated NaCl-solution, dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from diisopropyl ether - ethanol to yield 122 mg (52%) of colourless needles, mp 110-111°C. Ir(KBr): 2230 cm^{-1} (C≡N); ^1H-nmr (δ, d_6-DMSO): 8.61 (s, 1H, pyrazole-H-5), 8.36 (s, 1H, alkene-H), 8.12 (s, 1H, pyrazole-H-3), 7.32 (m, 5H, phenyl-H), 5.47 (s, 2H, CH_2); ms(m/z,%): 234 (M^+, 22), 91 (100); Anal. Calcd for $C_{14}H_{10}N_4$: C,71.78; H,4.30; N,23.92. Found: C,71.87; H,4.48; N,23.92.

Diethyl (1-Benzyl-4-pyrazolylmethylene)malonate (**2b**)

Preparation of **2b** from **1**[2] (186 mg, 1 mmol) and diethyl malonate (160 mg, 1 mmol) was carried out in a similar manner to that described for **2a**. Purification by prep. TLC (CH_2Cl_2 - ethyl acetate, 1:9). Yield: 295 mg (90%) of a colourless oil. Ir(CCl_4): 1715 cm^{-1} (C=O); ^{1}H-nmr (δ, d_6-DMSO): 8.12 (s, 1H, pyrazole-H-5), 7.69 (s, 1H, pyrazole-H-3), 7.60 (s, 1H, alkene-H), 7.30 (m, 5H, phenyl-H), 5.37 (s, 2H, CH_2), 4.41-4.05 (q, q, 4H, OCH_2), 1.30-1.13 (t, t, 6H, CH_3); ms(m/z,%): 328 (M^+, 21), 91 (100); Anal. Calcd for $C_{18}H_{20}N_2O_4$: C,65.84; H,6.14; N,8.53. Found: C,65.83; H,6.20; N,8.56.

(E)-Ethyl 3-(1-Benzyl-4-pyrazolyl)-2-cyanoacrylate (**2c**)

Preparation of **2c** from **1**[2] (186 mg, 1 mmol) and ethyl cyanoacetate (113 mg, 1 mmol) was carried out in a similar manner to that described for **2a**. Recrystallisation from diisopropyl ether - ethanol yields 197 mg (70%) of colourless needles, mp 107-110°C. Ir(KBr): 2235 (C≡N), 1710 cm^{-1} (C=O); ^{1}H-nmr (δ, d_6-DMSO): 8.65 (s, 1H, pyrazole-H-5), 8.32 (s, 1H, alkene-H), 8.21 (s, 1H, pyrazole-H-3), 7.33 (m, 5H, phenyl-H), 5.47 (s, 2H, CH_2), 4.27 (q, J=7.1Hz, 2H, OCH_2), 1.27 (t, J=7.1Hz, 3H, CH_3); ms(m/z,%): 281 (M^+, 27), 91 (100); Anal. Calcd for $C_{16}H_{15}N_3O_2$: C,68.31; H,5.37; N,14.94. Found: C,68.33; H,5.43; N,14.84.

(E)-3-(1-Benzyl-4-pyrazolyl)acrylic acid (**2d**)

A solution of **1**[2] (1.86 g, 10 mmol), malonic acid (1.56 g, 15 mmol) and 9 drops of piperidine in pyridine (13 ml) was refluxed for 5 h and poured into 2N HCl (280 ml). The mixture was extracted several times with diethyl ether, the combined organic layer was washed with water and extracted with saturated $NaHCO_3$-solution. The $NaHCO_3$-layer was acidified with conc. HCl and extracted exhaustively with diethyl ether; the combined ether layer was washed with water, dried with Na_2SO_4 and evaporated to yield 2.05 g (90%) of chromatographically pure **2d** as colourless crystals. An analytical sample was obtained by recrystallisation from diisopropyl ether - ethanol, mp 140-142°C. Ir(KBr): 1675 cm^{-1} (C=O); ^{1}H-nmr (δ, d_6-DMSO): 14.00 (s, broad, 1H, exchangeable with D_2O, COOH), 8.20 (s, 1H, pyrazole-H-5), 7.87 (s, 1H, pyrazole-H-3), 7.57, 7.37 (A-part of an AB-system, J=16Hz, 1H, alkene-H-3), 7.32 (m, 5H, phenyl-H), 6.29, 6.09 (B-part of an AB-system, J=16Hz, 1H, alkene-H-2), 5.32 (s, 2H, CH_2); ms(m/z,%): 228

(M^+, 38), 92 (100); Anal. Calcd for $C_{13}H_{12}N_2O_2$: C,68.41; H,5.30; N,12.27. Found: C,68.48; H,5.29; N,12.29.

(E)-Ethyl 3-(1-Benzyl-4-pyrazolyl)acrylate (**2e**)

a) *via* esterification of **2d**: A mixture of **2d** (228 mg, 1 mmol) and thionyl chloride (10 ml) was refluxed for 1 h, evaporated *in vacuo* and treated with absolute ethanol (3 ml). After stirring for 30 min, the reaction mixture was poured into an excess of water, and the resulting suspension was extracted with CH_2Cl_2. The organic layer was washed with water, dried with Na_2SO_4 sicc. and evaporated. Recrystallisation from light petroleum - diisopropyl ether afforded 164 mg (64%) of colourless needles, mp 66-68°C. Ir(KBr): 1700 cm^{-1} (C=O); ^{1}H-nmr (δ, d_6-DMSO): 8.23 (s, 1H, pyrazole-H-5), 7.92 (s, 1H, pyrazole-H-3), 7.65, 7.45 (A-part of an AB-system, J=16Hz, 1H, alkene-H-3), 7.29 (m, 5H, phenyl-H), 6.40, 6.20 (B-part of an AB-system, J=16Hz, 1H, alkene-H-2), 5.33 (s, 2H, CH_2), 4.13 (q, J=7.1Hz, 2H, OCH_2), 1.21 (t, J=7.1Hz, 3H, CH_3); ms(m/z,%): 256 (M^+, 13), 91 (100); Anal. Calcd for $C_{15}H_{16}N_2O_2$: C,70.29; H,6.29; N,10.93. Found: C,70.33; H 6.36; N,10.80.

b) *via Wittig-Horner*-type reaction of **1**: A mixture of **1**[2] (186 mg, 1 mmol) and triethyl phosphonoacetate (224 mg, 1 mmol) in dry DMF (3 ml) was treated with NaH (80%-suspension in paraffine oil, 39 mg, 1.3 mmol). After stirring at room temperature for 1 h, the reaction mixture was heated at 50°C for 1.5 h and poured into water; the resulting suspension was extracted with CH_2Cl_2. The extract was washed with water, dried with Na_2SO_4 and evaporated. The residue was subjected to prep. TLC (CH_2Cl_2 - ethyl acetate, 1:1) to give 77 mg (30%) of **2e**.

(E)-1-Benzyl-4-(2-phenylethenyl)pyrazole (**2f**)

A solution of **1**[2] (1.86 g, 10 mmol) and diethyl benzylphosphonate (2.28g, 10 mmol) in dry DMF (18 ml) was treated with NaH (80%-suspension in paraffine oil, 330mg, 11 mmol). After stirring at room temperature for 2 h an excess of water was added. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with water, dried with Na_2SO_4 sicc. and evaporated. Recrystallisation of the residue from light petroleum afforded 1.87 g (72%) of colourless needles, mp 103°C. ^{1}H-Nmr (δ, d_6-DMSO): 7.98 (s, 1H, pyrazole-H-5), 7.74 (s, 1H, pyrazole-H-3), 7.60-7.10 (m, 10H, phenyl-H), 6.99, 6.95, 6.74 (3 lines of an AB-system, J=16.5Hz, 2H, alkene-H), 5.31 (s, 2H, CH_2); ms(m/z,%): 260 (M^+, 45), 91 (100);

Anal. Calcd for $C_{18}H_{16}N_2$: C,83.04; H,6.19; N,10.76. Found: C,82.97; H,6.33; N,10.63.

1-Benzylpyrazole-4-carbaldoxime (3)

A mixture of 1[2] (1.86 g, 10 mmol), $H_2NOH \cdot HCl$ (1.86 g, 27 mmol), pyridine (9 ml) and ethanol (9 ml) was refluxed for 2 h and poured into water (180 ml). The resulting suspension was extracted with CH_2Cl_2, and the extract was washed with water, dried with Na_2SO_4 and evaporated to give crystals. Recrystallisation from diisopropyl ether - ethanol afforded 1.91 g (95%) of colourless needles, mp 153-155°C. Ir(KBr): 3140 (OH), 1650 cm^{-1} (C=N); ^{1}H-nmr (δ, d_6-DMSO): 11.20 (s, exchangeable with D_2O, 1H, NOH), 8.34 (s, 1H, pyrazole-H-5), 7.82 (s, 1H, pyrazole-H-3), 7.34 (s, 1H, N=CH), 7.29 (m, 5H, phenyl-H), 5.36 (s, 2H, CH_2); ms(m/z,%): 201 (M^+, 14), 92 (100); Anal. Calcd for $C_{11}H_{11}N_3O$: C,65.66; H,5.51; N,20.88. Found: C,65.77; H,5.35; N,21.08.

O-Acetyl-1-benzylpyrazole-4-carbaldoxime (4)

In acetic anhydride (0.5 ml) 201 mg (1 mmol) of 3 were dissolved under stirring at room temperature. The solution was kept in an ice-bath for 1 h and then poured onto crushed ice. The resulting mixture was extracted with CH_2Cl_2; the extract was washed with water, dried with Na_2SO_4 and evaporated *in vacuo* to afford crystals. Recrystallisation from diisopropyl ether - ethanol gave 112 mg (46%) of colourless crystals, mp 82-83.5°C. Ir(KBr): 1750 (C=O), 1630 cm^{-1} (C=N); ^{1}H-nmr (δ, d_6-DMSO)[16]: 8.47 (s, 1H, pyrazole-H-5), 7.99 (s, 1H, pyrazole-H-3), 7.92 (s, 1H, N=CH), 7.31 (m, 5H, phenyl-H), 5.43 (s, 2H, CH_2), 2.25 (s, 3H, CH_3); ms(m/z,%): 243 (M^+, 1), 91 (100); Anal. Calcd for $C_{13}H_{13}N_3O_2$: C,64.19; H,5.39; N,17.27. Found: C,64.31; H,5.54; N,17.43.

1-Benzylpyrazole-4-carbonitrile (5)

a) starting from 3: A solution of 3 (201 mg, 1 mmol) in acetic anhydride (5 ml) was refluxed for 2 h and then poured onto crushed ice. The resulting suspension was extracted with CH_2Cl_2; the extract was washed with water, dried with Na_2SO_4 and evaporated *in vacuo* to provide crystals. Recrystallisation from light petroleum - diisopropyl ether yielded 128 mg (70%) of colourless crystals, mp 62-63°C (ref.[4]: 63-64°C). Ir(KBr): 2240 cm^{-1} (C≡N); ^{1}H-nmr (δ, d_6-DMSO): 8.66 (s,

1H, pyrazole-H-5), 8.06 (s, 1H, pyrazole-H-3), 7.31 (m, 5H, phenyl-H), 5.40 (s, 2H, CH_2); ms(m/z,%): 183 (M^+, 48), 91 (100).

b) starting from **1**: A mixture of **1**[12] (186 mg, 1 mmol), nitroethane (150 mg, 2 mmol) and anhydrous sodium acetate (164 mg, 2 mmol) in glacial acetic acid (2 ml) was refluxed for 5 h. The reaction mixture was poured onto crushed ice and the resulting suspension was extracted with diethyl ether. The organic layer was washed with saturated $NaHCO_3$-solution, dried with Na_2SO_4 sicc. and evaporated *in vacuo* to give crystals. Recrystallisation from light petroleum - diisopropyl ether afforded 90 mg (49%) of **5**.

Reaction of **2f** with Na/NH_3

To a solution of **2f** (260 mg, 1 mmol) in liquid NH_3 (80 ml) at -70°C small pieces of sodium (92 mg, 4 mmol) were added with stirring. The resulting deep blue solution was kept at -70°C for 1 h, then the cooling bath was removed and ammonia was allowed to evaporate. The residue was taken up in water, the resulting solution was acidified to pH 5 with conc. HCl and extracted with CH_2Cl_2. The extract was washed with water, dried with Na_2SO_4 and evaporated to furnish crystals. Recrystallisation from light petroleum (addition of charcoal) afforded 138 mg (80%) of 4-(2-phenylethyl)pyrazole (**6**), mp 92-97°C (ref.[17]: 94-95°C).

4-Methyl-1-tosylpyrazole (**8a**)

A solution of **7a** (821 mg, 10 mmol) and p-toluenesulfonyl chloride (1.91 g, 10 mmol) in dry pyridine (5 ml) was refluxed for 1 h and then poured into water (70 ml). The resulting suspension was filtered with suction; the remaining solid was washed several times with water and recrystallized from ethanol to give 2.01 g (85%) of colourless crystals, mp 128-129°C. ^{1}H-nmr (δ, d_6-DMSO): 8.16 (s, 1H, pyrazole-H-5), 7.86-7.75 (AA'-part of an AA'BB'-system, 2H, benzene-H-2',6'), 7.70 (s, 1H, pyrazole-H-3), 7.48-7.38 (BB'-part of an AA'BB'-system, 2H, benzene-H-3',5'), 2.36 (s, 3H, tosyl-CH_3), 2.00 (s, 3H, pyrazole-CH_3); ms(m/z,%): 236 (M^+, 5), 91 (100); Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C,55.91; H,5.12; N, 11.86. Found: C,55.78; H,5.15; N,11.89.

4-Nitro-1-tosylpyrazole (**8b**)

Preparation of **8b** was carried out in a similar manner to that described for **8a**, starting from **7b**[8] (1.13 g, 10 mmol), and p-toluenesulfonyl chloride (1.91 g, 10 mmol). Yield: 1.81 g (68%) of pale yellow crystals, mp 123-124°C (EtOH, ref.[7]:116-117°C). ^{1}H-Nmr (δ, d_6-DMSO): 9.57 (s, 1H, pyrazole-H-5), 8.58 (s, 1H, pyrazole-H-3), 8.07-7.49 (AA'BB'-system, 4H, benzene-H), 2.43 (s, 3H, CH_3); ms(m/z,%): 267 (M^+, 1), 91 (100).

4-Methyl-1-(4-nitrobenzenesulfonyl)pyrazole (**8c**)

A solution of **7a** (82 mg, 1 mmol) and 4-nitrobenzenesulfonyl chloride (244 mg, 1.1 mmol) in dry pyridine (2 ml) was refluxed for 15 min. The reaction mixture was poured into water (5 ml), the resulting suspension was filtered with suction and the remaining solid was recrystallized from acetone. Yield: 227 mg (85%) of yellow crystals, mp 134-135°C. ^{1}H-Nmr (δ, d_6-DMSO): 8.48-8.12 (m, 5H, pyrazole-H-5, benzene-H), 7.80 (s, 1H, pyrazole-H-3), 2.01 (s, 3H, CH_3); ^{13}C-nmr (δ, d_6-DMSO): 150.87 (benzene-C-4'), 148.14 (pyrazole-C-3), 141.54 (benzene-C-1'), 130.29 (pyrazole-C-5), 129.11, 124.98 (benzene-C-2',3',5',6'), 120.78 (pyrazole-C-4), 8.22 (CH_3); ms(m/z,%): 267 (M^+, 23), 203 (100); Anal. Calcd for $C_{10}H_9N_3O_4S$: C,44.94; H,3.39; N,15.72. Found: C,45.15; H,3.41; N,15.62.

1-(2,4-Dinitrobenzenesulfonyl)-4-methylpyrazole (**8d**)

A solution of **7a** (82 mg, 1 mmol) in 50% EtOH-H_2O (8 ml) was treated with a solution of $AgNO_3$ (187 mg, 1.1 mmol) and conc. NH_4OH (0.75 ml) in water (5 ml). The resulting precipitate was filtered off and washed with water to give 138 mg (73%) of silver salt of **7a**, which was suspended in dry benzene (5 ml). 2,4-Dinitrobenzenesulfonyl chloride (195 mg, 0.73 mmol) was added to the suspension and the mixture was refluxed for 12 h. After cooling, the suspension was filtered to remove AgCl precipitated, the filtrate was evaporated *in vacuo* and the residue recrystallized from acetone. Yield: 175 mg (56%) of yellow crystals, mp 161-162°C. ^{1}H-Nmr (δ, d_6-DMSO): 8.98-8.17 (m, 3H, benzene-H-3',5',6'), 8.24 (s, 1H, pyrazole-H-5), 7.91 (s, 1H, pyrazole-H-3), 2.08 (s, 3H, CH_3); ^{13}C-nmr (δ, d_6-DMSO): 151.16 (benzene-C-4'), 148.66 (pyrazole-C-3), 147.25 (benzene-C-2'), 133.04 (benzene-C-1'), 130.75 (pyrazole-C-5), 132.88, 127.73, 120.74 (benzene-C 3',5',6'), 120.72 (pyrazole-C-4), 8.25 (CH_3); ms(m/z,%): 312 (M^+, 37), 231 (100);

Anal. Calcd for $C_{10}H_8N_4O_6S$: C,38.46; H,2.58; N,17.94. Found: C,38.64; H,2.53; N,17.79.

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