N-SUBSTITUTED BROMOPYRAZOLES: SYNTHESIS AND ^{13}C NMR STUDY#

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Abstract - The synthesis of *N*-1 substituted 4-bromo-, 3,4-dibromo- and 3,4,5-tribromopyrazoles starting from the NH-pyrazoles is described. ^{13}C Nmr spectroscopic studies with the title compounds are presented, investigating the influence of substituents on ^{13}C-chemical shifts and $^{13}C,^{1}H$ spin coupling constants.

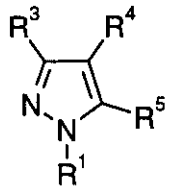
INTRODUCTION

In context with a program dedicated to the synthesis of bio-active compounds containing the pyrazole nucleus, we were interested in some *N*-substituted bromopyrazoles, which were assumed to be valuable educts for further functionalisation of this azole system.[1,2] In this study, we mainly describe three different types of bromopyrazoles, namely 4-bromo (series **b**), 3,4-dibromo (series **c**) and 3,4,5-tribromo derivatives (series **d**), containing a methyl, benzyl, phenacyl, [2-(trimethylsilyl)ethoxy]methyl (SEM), ethoxycarbonyl, acetyl, benzoyl, benzenesulfonyl and tosyl group as the *N*-1 substituent (Scheme 1). Together with their des-bromo congeners (series **a**) and four 4,5-dibromo analogues (series **e**) these compounds were systematically analyzed with regard to their ^{13}C nmr spectra in order to study how the bromo substitution on the pyrazole system as well as the the *N*-1 substituent affects ^{13}C chemical shifts and $^{13}C,^{1}H$ spin coupling constants.

 # Dedicated with best wishes to Prof. Fritz Sauter on the occasion of his 65th birthday

Scheme 1

No.	R^1		R^3	R^4	R^5
1	H	**a**	H	H	H
2	Me	**b**	H	Br	H
3	CH_2Ph	**c**	Br	Br	H
4	CH_2COPh	**d**	Br	Br	Br
5	SEM*	**e**	H	Br	Br
6	COOEt				
7	COMe				
8	COPh				
9	SO_2Ph				
10	Tos				



* SEM = $CH_2OCH_2CH_2SiMe_3$

RESULTS AND DISCUSSION

Synthesis

The synthesis of the hitherto unknown bromopyrazoles described in this study was carried out simply by reacting the appropriate NH-pyrazoles with suitable electrophiles. In most cases procedures similar to those applied in the preparation of closely related, known congeners were used.[3-9] The reaction of 3,4-dibromo-pyrazole (**1c**) with benzyl chloride and SEM chloride, respectively, led to the formation of two isomers, namely the 3,4-dibromo- and the corresponding 4,5-dibromo-*N*1-substitution product. In all other cases, the sterically less favoured 1,4,5-isomer could not be detected in the reaction mixture. This is in accordance with findings in the literature reporting the exclusive formation of the thermodynamically more stable isomer in acylation or sulfonylation reactions with asymmetrically substituted NH-pyrazoles.[1,10]

Nmr Spectroscopic Investigations

It should be pointed to the fact that recently an extensive review concerning ^{13}C nmr of pyrazoles has been published by Begtrup, Elguero and co-workers,[11] containing also some data of compounds which are included into this study. In such cases, when chemical shift values (or coupling constants) have been already published,

the corresponding reference is indicated by an entry in Table 1 or Table 2, respectively ("Compare Ref."). However, all data given in Tables 1 and 2 origin from our own recordings just in order to ensure comparable conditions regarding solvent, temperature, concentration, calibration and digital resolution.

^{13}C Chemical Shifts. In Table 1, the chemical shift data of the investigated pyrazole derivatives (**1** - **10**) are given. Assignments are mainly resting on coupling information (J-modulated spin-echo, gated decoupling), the determination of direct and long-range C-H connectivities starting from unambiguously assigned proton resonances (the latter achieved by NOE-difference experiments[12]), and on comparison with literature data[11] of closely related species.

Regarding the influence of the bromo substituent(s), from the data given in Table 1 the following trends can be extracted: replacement of pyrazole H-4 by a bromine atom (series **a** → series **b**) shifts the pyrazole C-4 resonance to lower frequencies with SCS values of -9.9 to -12.4 ppm (SCS = substituent chemical shift = chemical shift difference to the corresponding C-atom of series **a**) whereas the signals of pyrazole C-3 and pyrazole C-5 are only slightly affected (|SCS|< 1 ppm). Compounds of series **c** exhibit SCS values of -9.0 to -11.5 ppm for pyrazole C-3, -6.0 to -9.1 ppm for pyrazole C-4 and 0.7 to 2.5 ppm for pyrazole C-5. Thus, changing from series **b** to series **c** (i.e. introduction of a second bromine atom into position 3 of the pyrazole ring) leads to a noticeable downfield shift of the pyrazole C-4 resonance (3.2 - 4.3 ppm). A similar downfield shift for pyrazole C-4 (3.5 - 5.8 ppm) can be observed upon changing from 4-bromo- to 4,5-dibromo substitution pattern (**2e**, **3e**, **5e**, and **9e**). With these species SCS-ranges of 0.5 - 1.1 ppm for pyrazole C-3 and -13.6 to -15.4 ppm for pyrazole C-5 were found. Compounds of series **d** are characterized by the following SCS-ranges: -8.5 to -10.8 ppm for pyrazole C-3, -1.1 to -6.0 ppm for pyrazole C-4 and -11.8 to -14.3 ppm for pyrazole C-5. It is conspicious that the SCS-values for pyrazole C-4 are only small for compounds with electron withdrawing *N*-1 substituents (**6d** - **10d**, SCS -1.1 to -1.8 ppm) whereas derivatives (**2d** - **5d**) carrying more electron donating groups at N-1 exhibit larger SCS-values (-5.2 to -6.0 ppm). It should be mentioned that the observed SCS values are in good accordance with those found by Begtrup for various bromopyrazoles with *N*-phenyl substituent.[13]

The data in Table 1 also reflect the influence of the *N*-substituent on chemical shifts of the pyrazole nucleus. In general, an increase in the electron attracting properties of the *N*-substituent leads to a marked low field shift of δ (C-3) and δ (C-4). For pyrazole C-5 the effects are small and a smooth correlation between δ (C-5) and the

group electronegativity of the *N*-substituent is not always recognizable, here steric factors may also play an important role.

Bromo substitution on the pyrazole system also influences some ^{13}C chemical shifts of the *N*-substituent, particularly those of carbons directly attached to the pyrazole N-1. Considering derivatives with an sp^3-hybridized carbon atom at the pyrazole N-1 (compounds **2** -**5**) the following effects can be observed: attachment of a bromine atom in 4-position of the pyrazole ring shifts the N-C resonance to higher frequencies (e.g. **3a** → **3b**: 55.4 ppm → 56.3 ppm), 3,4-dibromo substitution results in a further deshielding (→ **3c**: 57.3 ppm), whereas introduction of a bromine atom in position 5 of the pyrazole nucleus leads to an upfield shift (**3c** → **3d**: 57.3 ppm → 55.9 ppm; **3b** → **3e**: 56.3 ppm → 55.3 ppm). As a possible explanation for the latter phenomenon the shielding effect of the bromo-substituent at C-5 (which is in γ-position to N-C) may serve. A contrary behaviour can be detected for compounds having an sp^2 carbon atom attached to pyrazole N-1 (compounds **6** - **8**). With these species, increasing bromo substitution at the pyrazole nucleus mostly results in a slight decrease of δ (C=O): for instance **6a**: 148.9 ppm, **6b**: 148.0 ppm, **6c**: 147.5 ppm, **6d**: 147.2 ppm; **7a**: 169.1 ppm, **7b**: 168.3 ppm, **7c**: 167.4 ppm, **7d**: 168.0 ppm.

A large number of attempts have been made to correlate ^{13}C nmr data with parameters like total charge densities or with substituent parameters originating from linear free energy relationships (e.g. Taft's constants).[14] Within this study, semiempirical AM1-calculations[15] (geometry optimisations) were carried out for structures of type **2** - **4**, **6** - **10** (series **a** - **d**). However, attempts to correlate the thus obtained total charge densities of the pyrazole carbon atoms with the corresponding ^{13}C chemical shifts in most cases met with a rather poor result. Only for pyrazole C-3 of series **a** and **b** good correlations (r = -0.98) were obtained (Figure 1).

Figure1: Correlation of ^{13}C chemical shifts and net atomic charges of pyrazole C-3 for compounds of series **a**

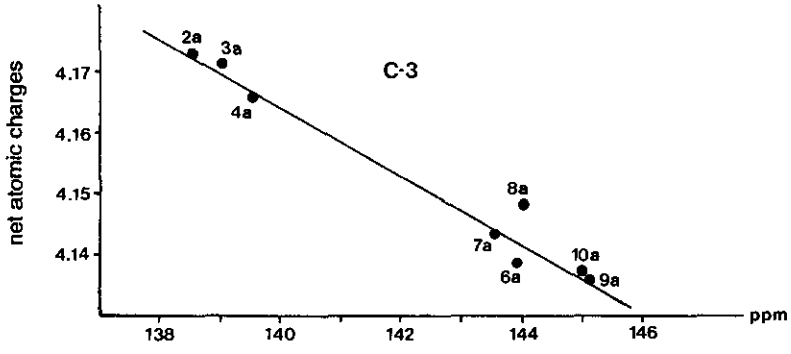


Table 1: ^{13}C Nmr chemical shifts (δ, ppm) of compounds (**1** - **10**) (in $CDCl_3$)

No.	Pyrazole-C C-3	C-4	C-5	Other Carbon Atoms	Compare Ref.
1a	133.5	104.6	133.5	--	11
1b	134.4	93.6	134.4	--	11
1c	127.8	96.9	131.5	--	--
1d	122.8	100.3	122.8	--	--
2a	138.5	104.9	129.2	38.0 (Me)	11
2b	139.4	92.6	129.8	39.2 (Me)	11
2c	127.0	95.8	131.7	40.0 (Me)	--
2d	127.5	99.3	116.6	39.3 (Me)	--
2e	139.6	96.1	115.1	38.7 (Me)	--
3a	139.0	105.5	128.8	Ph-C: 136.4 (1), 127.2 (2,6), 128.3 (3,5), 127.5 (4); 55.4 (CH_2)	11
3b	139.7	93.1	129.1	Ph-C: 135.5 (1), 127.6 (2,6), 128.6 (3,5), 128.1 (4); 56.3 (CH_2)	11
3c	127.7	96.6	131.0	Ph-C: 134.8 (1), 128.1 (2,6), 129.0 (3,5), 128.7 (4); 57.3 (CH_2)	--
3d	128.2	100.0	116.3	Ph-C: 134.7 (1), 127.6 (2,6), 128.8 (3,5), 128.3 (4); 55.9 (CH_2)	--
3e	140.5	97.0	115.1	Ph-C: 135.3 (1), 127.5 (2,6), 128.7 (3,5), 128.1 (4); 55.3 (CH_2)	--
4a	139.5	106.2	130.8	192.3 (CO); Ph-C: 133.7 (1), 127.8 (2,6), 128.6 (3,5), 134.2 (4); 57.3 (CH_2)	--
4b	140.3	93.8	131.0	191.6 (CO); Ph-C: 134.1 (1), 127.9 (2,6), 128.9 (3,5), 134.1 (4); 58.0 (CH_2)	--
4c	128.2	97.2	133.1	191.0 (CO); Ph-C: 133.9 (1), 128.0 (2,6), 129.0 (3,5), 134.4 (4); 58.4 (CH_2)	--
4d	128.8	100.2	118.0	189.9 (CO); Ph-C: 133.7 (1), 127.9 (2,6), 129.0 (3,5), 134.4 (4); 57.7 (CH_2)	--
5a	139.5	106.4	129.1	79.7 (NCH_2O), 66.3 (OCH_2C), 17.5 (CH_2Si), -1.7 ($SiMe_3$)	5
5b	140.2	94.4	129.4	80.5 (NCH_2O), 66.8 (OCH_2C), 17.6 (CH_2Si), -1.6 ($SiMe_3$)	5
5c	128.5	97.8	131.2	81.0 (NCH_2O), 67.3 (OCH_2C), 17.6 (CH_2Si), -1.6 ($SiMe_3$)	--
5d	129.1	101.2	116.8	79.7 (NCH_2O), 67.3 (OCH_2C), 17.6 (CH_2Si), -1.5 ($SiMe_3$)	--
5e	140.8	98.0	115.5	79.3 (NCH_2O), 66.9 (OCH_2C), 17.6 (CH_2Si), -1.5 ($SiMe_3$)	--
6a	143.9	108.6	130.4	148.9 (CO), 64.1 (OCH_2), 13.8 (Me)	11
6b	144.6	97.6	130.3	148.0 (CO), 64.8 (OCH_2), 13.9 (Me)	--
6c	134.9	101.9	131.9	147.5 (CO), 65.5 (OCH_2), 14.1 (Me)	--
6d	134.4	107.2	117.7	147.2 (CO), 65.7 (OCH_2), 14.0 (Me)	--
7a	143.6	109.3	127.7	169.1 (CO), 21.3 (Me)	11
7b	144.2	99.2	127.9	168.3 (CO), 20.8 (Me)	--
7c	134.3	103.3	129.3	167.4 (CO), 20.8 (Me)	--
7d	133.7	108.2	115.9	168.0 (CO), 22.8 (Me)	--
8a	144.0	109.0	130.0	165.8 (CO); Ph-C: 130.0 (1), 131.2 (2,6), 127.7 (3,5), 132.6 (4)	11
8b	144.6	99.1	130.1	164.9 (CO); Ph-C: 130.3 (1), 131.4 (2,6), 128.0 (3,5), 133.1 (4)	8
8c	134.7	103.0	131.5	163.9 (CO); Ph-C: 129.6 (1), 131.6 (2,6), 128.2 (3,5), 133.6 (4)	--
8d	133.5	107.8	117.6	164.9 (CO); Ph-C: 130.2 (1), 131.7 (2,6), 128.3 (3,5), 133.9 (4)	--
9a	145.1	108.7	131.0	Ph-C: 136.7 (1), 127.6 (2,6), 129.1 (3,5), 134.3 (4)	11
9b	145.6	97.5	130.4	Ph-C: 136.3 (1), 128.1 (2,6), 129.4 (3,5), 134.8 (4)	9
9c	135.3	101.5	131.9	Ph-C: 135.9 (1), 128.4 (2,6), 129.6 (3,5), 135.2 (4)	9
9d	134.5	106.9	116.8	Ph-C: 136.1 (1), 128.5 (2,6), 129.7 (3,5), 135.4 (4)	--
9e	144.6	103.3	115.6	Ph-C: 136.4 (1), 128.3 (2,6), 129.5 (3,5), 135.1 (4)	9
10a	145.0	108.6	131.0	Ph-C: 133.9 (1), 127.9 (2,6), 129.9 (3,5), 145.8 (4); 21.5 (Me)	11
10b	145.4	97.3	130.3	Ph-C: 133.2 (1), 128.2 (2,6), 130.0 (3,5), 146.3 (4); 21.6 (Me)	8
10c	135.0	101.2	131.7	Ph-C: 132.7 (1), 128 4 (2,6), 130.2 (3,5), 146.7 (4); 21.7 (Me)	--
10d	134.3	106.8	116.7	Ph-C: 133.1 (1), 128.6 (2,6), 130.3 (3,5), 147.1 (4); 21.8 (Me)	--

Table 2: $^{13}C,^{1}H$ Spin coupling constants (Hz) of compounds (**2** - **10**) (in $CDCl_3$)

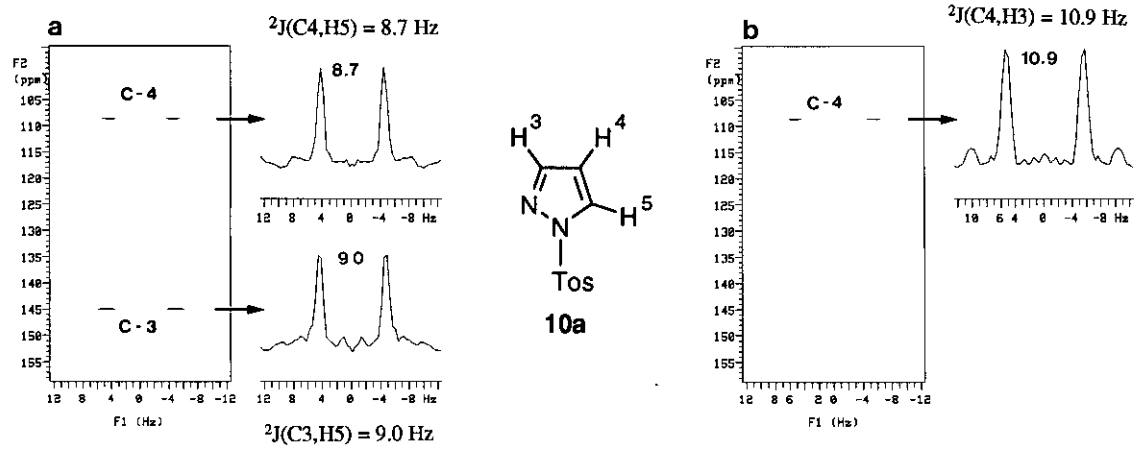
	Pyrazole System										Compare
No.	C3,H3	C3,H4	C3,H5	C4,H3	C4,H4	C4,H5	C5,H3	C5,H4	C5,H5	Other Couplings	Ref.
2a	184.7	5.7	8.3	10.5	176.5	8.7	4.7	8.7	185.7	$^{1}J(CH_3)$: 139.5; $^{3}J(C5,CH_3)$: 2.7	11
2b	191.9	--	6.9	7.9	--	6.2	3.2	--	191.8	$^{1}J(CH_3)$: 140.2, $^{3}J(C5,CH_3)$: 2.8	--
2c	--	--	9.7	--	--	5.9	--	--	193.4	$^{1}J(CH_3)$: 141.0, $^{3}J(C5,CH_3)$: 2.8	--
2d	--	--	--	--	--	--	--	--	--	$^{1}J(CH_3)$: 142.1, $^{3}J(C5,CH_3)$: 3.0	--
2e	194.5	--	--	8.1	--	--	5.4	--	--	$^{1}J(CH_3)$: 141.3, $^{3}J(C5,CH_3)$: 2.7	--
3a	184.8	5.7	8.3	10.4	176.5	8.6	4.7	8.7	185.7	$^{1}J(CH_2)$: 139.3, $^{3}J(C5,CH_2)$: 2.7	29
3b	192.0	--	7.0	8.0	--	6.0	3.5	--	193.0	$^{1}J(CH_2)$: 140.2, $^{3}J(C5,CH_2)$: 3.0	29
3c	--	--	9.6	--	--	5.8	--	--	193.7	$^{1}J(CH_2)$: 141.3, $^{3}J(C5,CH_2)$: 3.1	--
3d	--	--	--	--	--	--	--	--		$^{1}J(CH_2)$: 141.4, $^{3}J(C5,CH_2)$: 3.6	--
3e	194.8	--	--	8.4	--	--	5.5	--	--	$^{1}J(CH_2)$: 141.5, $^{3}J(C5,CH_2)$: 3.2	--
4a	185.3	5.7	8.5	10.5	176.9	8.7	4.8	9.4	186.6	$^{1}J(CH_2)$: 138.5, $^{3}J(C5,CH_2)$: 2.7	--
4b	192.5	--	7.0	7.8	--	5.8	3.4	--	193.1	$^{1}J(CH_2)$: 139.0, $^{3}J(C5,CH_2)$: 3.0	--
4c	--	--	9.6	--	--	5.8	--	--	195.2	$^{1}J(CH_2)$: 139.6, $^{3}J(C5,CH_2)$: 3.1	--
4d	--	--	--	--	--	--	--	--	--	$^{1}J(CH_2)$: 140.3, $^{3}J(C5,CH_2)$: 3.6	--
5a	185.0	5.9	8.4	10.7	176.5	8.6	4.7	9.1	186.1	$^{1}J(NCH_2)$: 157.8, $^{3}J(C5,CH_2)$: 2.9	5
5b	192.3	--	7.0	8.1	--	5.8	3.3	--	192.5	$^{1}J(NCH_2)$: 158.2, $^{3}J(C5,CH_2)$: 3.3	5
5c	--	--	9.7	--	--	5.9	--	--	194.2	$^{1}J(NCH_2)$: 159.4, $^{3}J(C5,CH_2)$: 3.2	--
5d	--	--	--	--	--	--	--	--	--	$^{1}J(NCH_2)$: 160.6, $^{3}J(C5,CH_2)$: 3.7	--
5e	194.9	--	--	8.4	--	--	5.3	--	--	$^{1}J(NCH_2)$: 159.6, $^{3}J(C5,CH_2)$: 3.1	--
6a	188.0	5.8	9.0	10.9	179.2	8.6	4.2	9.2	193.9	$^{1}J(OCH_2)$: 149.4, $^{1}J(CH_3)$: 127.6	11
6b	195.0	--	7.6	8.6	--	5.8	3.4	--	199.6	$^{1}J(OCH_2)$: 149.7, $^{1}J(CH_3)$: 127.7	--
6c	--	--	10.2	--	--	5.6	--	--	201.0	$^{1}J(OCH_2)$: 150.0, $^{1}J(CH_3)$: 127.8	--
6d	--	--	--	--	--	--	--	--	--	$^{1}J(OCH_2)$: 149.4, $^{1}J(CH_3)$: 127.8	--
7a	187.1	6.2	9.2	10.8	178.6	8.7	4.1	8.9	193.3	$^{1}J(CH_3)$: 130.6	11
7b	194.4	--	7.6	8.8	--	5.8	3.2	--	199.2	$^{1}J(CH_3)$: 131.0	--
7c	--	--	10.4	--	--	5.6	--	--	200.6	$^{1}J(CH_3)$: 131.2	--
8a	187.6	6.1	9.1	10.7	179.1	8.7	4.2	9.3	193.8		29
8b	194.6	--	7.6	8.7	--	5.8	3.2	--	199.4		29
8c	--	--	10.5	--	--	5.7	--	--	200.8		--
9a	188.8	6.1	9.0	10.9	180.1	8.6	4.4	9.7	195.5		29
9b	195.5	--	7.5	8.7	--	5.8	3.5	--	200.9		9
9c	--	--	10.1	--	--	5.7	--	--	202.0		9
9e	197.8	--	--	8.7	--	--	5.0	--	--		9
10a	188.6	6.0	9.0	10.9	179.9	8.7	4.5	9.7	195.2		29
10b	195.4	--	7.6	8.9	--	5.7	3.5	--	200.7		29
10c	--	--	10.2	--	--	5.7	--	--	201.9		--

$^{13}C,^{1}H$ Spin Coupling Constants. The coupling constants given in Table 2 (absolute values) were mainly extracted from the gated decoupled spectra (digital resolution 0.2 - 0.5 Hz/data point) which were analysed on a first-order basis; some iterative analyses using Bruker's PANIC spin-simulation program (a version of the well known LAOCOON program) revealed the necessary premises being fulfilled. Some coupling constants were unequivocally assigned on basis of 2D (δ,J) long-range INEPT experiments with selective DANTE excitation.[16] Thus, for instance, an unambiguous discrimination between ^{2}J(pyrazole C-4,pyrazole H-3) and ^{2}J(pyrazole C-4,pyrazole H-5) could be achieved for compounds of series **a** and **b**. In Figure 2, this is demonstrated for 1-tosylpyrazole (**10a**): selective excitation of the pyrazole H-5 resonance (δ 8.08 ppm) shows the signal of pyrazole C-4 as a dublet with J = 8.7 Hz (Figure 2a), whereas in a similar experiment with selective excitation of pyrazole H-3 (δ 7.68 ppm) the pyrazole C-4 resonance is split with a 10.9 Hz coupling (Figure 2b). Consecutively, ^{2}J(C4,H3) = 10.9 Hz and ^{2}J(C4,H5) = 8.7 Hz (compare ref.[17]). This technique also turned out to be valuable in discriminating different couplings the pyrazole C-5 is involved (especially with compounds **2a** - **5a**) (Figure 2c). Extracting these data unequivocally from the gated decoupled spectra in some cases can be difficult owing to complicated splitting patterns and overlapping lines (Figure 2d). It should be emphasized, that the coupling constants emerging from the 2D long-range INEPT experiments (0.78 Hz digital resolution in f1) closely resemble those extracted from the gated decoupling spectra.

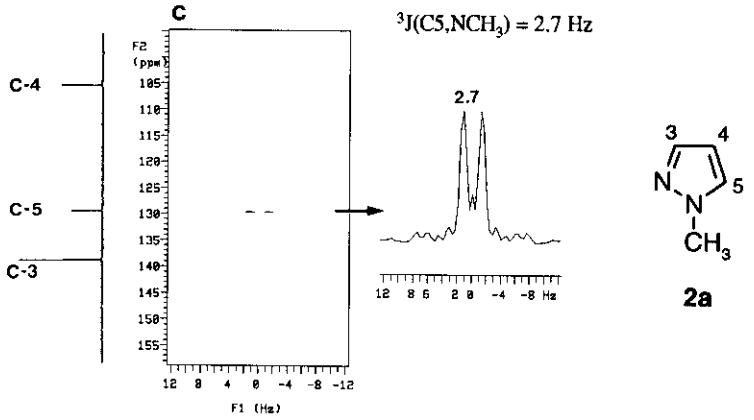
Direct coupling constants: With the investigated compounds the values for $^{1}J(^{13}C,^{1}H)$ of the pyrazole C-atoms are located in a range between 176.5 and 202.0 Hz, the relationship ^{1}J(C5,H5) > ^{1}J(C3,H3) > ^{1}J(C4,H4) being valid within one species (except **2b** with ^{1}J(C3,H3) = 191.9 Hz > ^{1}J(C5,H5) = 191.8 Hz). In accordance to a well known trend[1] all direct pyrazole C-H coupling constants increase with increasing electron-withdrawing property of the *N*-substituent, ^{1}J(C5,H5) being more sensitive in this regard. Introduction of a bromo-substituent into position 4 of the pyrazole ring leads to an enlargement of ^{1}J(C3,H3) (by 6.7 - 7.3 Hz) and ^{1}J(C5,H5) (by 5.4 - 7.3 Hz). In 3,4-dibromo compounds ^{1}J(C5,H5) is further increased by 0.7 - 2.1 Hz, for 4,5-dibromo derivatives **e** an enlargement of ^{1}J(C3,H3) of 2.3 - 2.8 Hz (always compared to the corresponding congeners of type **b**) was detected.

Considering compounds (**2** - **5**), characterized by a $-CH_2-$ or CH_3-group attached to the pyrazole N-1, within these fragments a noticeable dependence of ^{1}J from the bromo substitution on the pyrazole nucleus is evident,

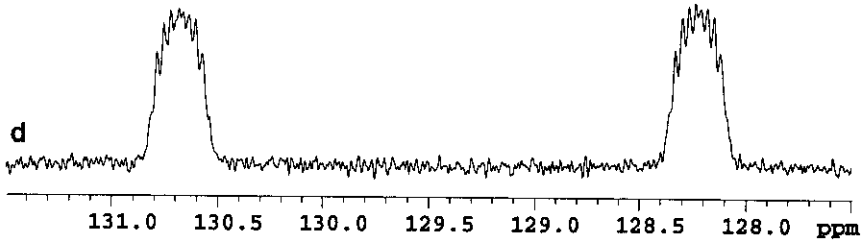
Figure 2:
a) 2D (δ,J) Long-range INEPT spectrum of **10a** resulting from selective excitation of pyrazole H-5 (optimized for J = 9 Hz); b) 2D (δ,J) Long-range INEPT spectrum of **10a** resulting from selective excitation of pyrazole H-3 (optimized for J = 10 Hz)



c) 2D (δ,J) Long-range INEPT spectrum of **2a** resulting from selective excitation of NCH_3



d) Signal of pyrazole C-5 of compound (**2a**) in the 'gated decoupling' spectrum (after Gauss multiplication)



as increasing substitution leads to increased coupling constants (for instance $^1J(CH_3)$ in *N*-methylpyrazoles **2a**: 139.5 Hz, **2b**: 140.2 Hz, **2c**: 141.0 Hz, **2e**: 141.3 Hz, **2d**: 142.1 Hz).

Geminal coupling constants: For ^2J(C3,H4) (5.7 - 6.2 Hz) and ^2J(C5,H4) (8.7 - 9.7 Hz) - both being present only in compounds of series **a** - no significant dependence from the nature of the *N*-substituent can be extracted from Table 2. The coupling constant ^2J(C4,H3) has values from 10.4 to 10.9 Hz within series **a**, switching to series **b** results in a marked decrease of the absolute values to 7.8 - 8.9 Hz. Whereas within series **a** values of ^2J(C4,H5) are nearly identical (8.6 - 8.7 Hz), in series **b** its magnitude is decreased to 5.7 - 6.2 Hz, in series **c** mostly a further slight decrease can be observed. Considering the above findings together with the well known fact that geminal $^{13}C,^1H$ coupling constants in aromatic systems decrease when an electronegative atom is attached to the coupled carbon atom[18] gives a strong hint that ^2J(C4,H5) and ^2J(C4,H3) have positive sign.

Vicinal coupling constants: Within series **a** two vicinal coupling constants are always present, namely ^3J(C3,H5) (8.3 - 9.2 Hz) and the smaller ^3J(C5,H3) (4.1 - 4.8 Hz); both coupling constants suffer a marked decrease when switching to series **b**. Expectedly, ^3J(C3,H5) in series **c** as well as ^3J(C5,H3) in series **e** are increased as here a bromo substituent is directly attached to the coupled carbon atom. Compounds (**2** - **5**) also show a vicinal coupling between pyrazole C-5 and protons of NCH_2- or NCH_3 (2.7 - 3.7 Hz) which serves as a safe criterion for the discrimination of pyrazole C-5 and C-3 resonances.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra (potassium bromide pellets or neat oils between sodium chloride discs) were recorded on a Jasco IRA-1 spectrophotometer or on a Perkin-Elmer FTIR 1605 spectrophotometer. Mass spectra were obtained on a Hewlett-Packard 5890A/5970B-MSD (glc/ms) or on a Varian MAT 311A instrument (both EI, 70 eV). Most nmr spectra were recorded on a Bruker AC 80 spectrometer (80.13 MHz for ^1H, 20.15 MHz for ^{13}C), 2D-spectra as well as some NOE-difference experiments were carried out on a Varian Unity*Plus* 300 instrument (299.95 MHz for ^1H, 75.43 MHz for ^{13}C). Except ^1H-nmr spectra of compounds (**5c**) and (**5e**) (in DMSO-d_6), all spectra were recorded from $CDCl_3$ solutions at 28°C; the solvent signal was used as an internal

standard which was related to tetramethylsilane with δ 7.26 ppm (^{1}H) and δ 77.00 ppm (^{13}C). MO-Calculations were carried out on a Sun SPARCstation 10-41 using the semiempirical AM1-method[15] implemented in the AMPAC program package.[19] Column chromatographic separations were performed on Merck Kieselgel 60 (70-230 mesh). Light petroleum refers to the fraction of bp 50-70°C. The yields given below are not optimized. The following compounds were prepared according to reported procedures: **1b**,[20] **1c**,[21] **1d**,[21] **2a**,[22] **2b**,[21] **2c**,[23] **2d**,[23] **2e**,[24] **3a**,[3] **3b**,[3] **3d**,[25] **4a**,[4] **5a**,[5] **5b**,[5] **6a**,[6] **7a**,[7] **7b**,[7] **7d**,[7] **8a**,[26] **8b**,[8] **9a**,[27] **9b**,[9] **9c**,[9] **9d**,[9] **10a**,[28] **10b**.[8] Compounds **1b** and **1d** are also commercially available.

1-Benzyl-3,4-dibromo-1*H*-pyrazole (**3c**) and 1-Benzyl-4,5-dibromo-1*H*-pyrazole (**3e**)

To a solution of sodium ethoxide prepared from 230 mg (10 mmol) of sodium and 15 ml of dry ethanol were added 2.249 g (10 mmol) of 3,4-dibromopyrazole. After 30 min of stirring, 1.266 g (10 mmol) of benzyl chloride were added and the mixture was refluxed for 12 h. After cooling, the precipitate was filtered off, the filtrate was evaporated *in vacuo* and the residue was subjected to column chromatography (eluent: dichloromethane) to afford 951 mg (30%) of **3c** (faster eluted component) and 1.844 g (58%) of **3e** (slower eluted component).

Compound (**3c**) was obtained as colorless crystals of mp 50-55°C; ^{1}H nmr ($CDCl_3$): δ 7.34 (s, 1H, pyrazole H-5), 7.29 (m, 5H, Ph-H), 5.24 (s, 2H, CH_2); ms: m/z (%) 314/316/318 (M^+, 12/24/12), 313/315/317 (11/22/13), 235/237 (10/10), 156 (11), 91 (100), 65 (19). *Anal.* Calcd for $C_{10}H_8N_2Br_2$: C, 38.01; H, 2.55; N, 8.86. Found: C, 38.22; H, 2.58; N, 8.81.

Compound (**3e**) consisted of colorless crystals of mp 64-69°C; ^{1}H nmr ($CDCl_3$): δ 7.57 (s, 1H, pyrazole H-3), 7.30 (m, 5H, Ph-H), 5.39 (s, 2H, CH_2); ms: m/z (%) 314/316/318 (M^+, 10/19/10), 313/315/317 (6/12/8), 235/237 (12/14), 156 (13), 91 (100), 65 (21). *Anal.* Calcd for $C_{10}H_8N_2Br_2$: C, 38.01; H, 2.55; N, 8.86. Found: C, 38.32; H, 2.37; N, 9.15.

2-(4-Bromo-1*H*-pyrazol-1-yl)-1-phenylethanone (**4b**)

To a solution of 1.470 g (10 mmol) of **1b** in 10 ml of dry dimethylformamide were added successively 1.166 g (11 mmol) of anhydrous sodium carbonate and 1.991 g (100 mmol) of α-bromoacetophenone and the resulting mixture was refluxed for 24 h. After cooling, the solvent was removed *in vacuo*, the oily brown residue was washed with cold water (30 ml) and purified by flash chromatography (eluent: dichloromethane - ethyl acetate,

9:1). Recrystallisation from water afforded 1.379 g (52%) of colorless needles, mp 127-128°C; ^{1}H nmr ($CDCl_3$): δ 8.04-7.92 (m, 2H, Ph H-2,6), 7.68-7.50 (m, 5H, pyrazole H-3, pyrazole H-5, Ph H-3,4,5), 5.57 (s, 2H, CH_2); ir (KBr): cm^{-1} 1699 (C=O); ms: m/z (%) 264/266 (M^+, 4/4), 105 (100), 77 (35), 51 (11). *Anal.* Calcd for $C_{11}H_9N_2OBr$: C, 49.84; H, 3.42; N, 10.57. Found: C, 49.60; H, 3.14; N, 10.45.

2-(3,4-Dibromo-1*H*-pyrazol-1-yl)-1-phenylethanone (**4c**)

Compound (**4c**) was prepared from 2.249 g (10 mmol) of **1c** and 1.991 g of α-bromoacetophenone according to the procedure given for the synthesis of **4b**. After separation of the reaction mixture by medium pressure liquid chromatography (eluent: dichloromethane - ethyl acetate, 9:1) 1.204 g (35%) of **4c** were obtained as colorless crystals with mp 129-131°C; ^{1}H nmr ($CDCl_3$): δ 8.02-7.90 (m, 2H, Ph H-2,6), 7.51 (s, 1H, pyrazole H-5), 7.68-7.50 (m, 3H, Ph H-3,4,5), 5.54 (s, 2H, CH_2); ir (KBr): cm^{-1} 1693 (C=O); ms: m/z (%) 342/344/346 (M^+, 4/8/4), 105 (100), 77 (29), 51 (10). Anal. Calcd for $C_{11}H_8N_2OBr_2$: C, 38.41; H, 2.34; N, 8.14. Found: C, 38.68; H, 2.07; N, 7.91.

2-(3,4,5-Tribromo-1*H*-pyrazol-1-yl)-1-phenylethanone (**4d**)

Compound (**4d**) was prepared from 3.048 g (10 mmol) of **1d** and 1.991 g of α-bromoacetophenone according to the procedure given for the synthesis of **4b**. Recrystallisation from ether afforded 2.326 g (55%) of pale yellow crystals, mp 114°C; ^{1}H nmr ($CDCl_3$): δ 8.03-7.91 (m, 2H, Ph H-2,6), 7.70-7.52 (m, 3H, Ph H-3,4,5), 5.64 (s, 2H, CH_2); ir (KBr): cm^{-1} 1696 (C=O); ms: m/z (%) 420/422/424/426 (M^+, 1/4/4/1), 105 (100), 77 (29), 51 (10). *Anal.* Calcd for $C_{11}H_7N_2OBr_3$: C, 31.24; H, 1.67; N, 6.62. Found: C, 31.20; H, 1.48; N, 6.60.

3,4-Dibromo-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (**5c**) and 4,5-Dibromo-1-[2-(trimethylsilyl)-ethoxy]methyl-1*H*-pyrazole (**5e**)

Under argon, 300 mg of sodium hydride (80% suspension in mineral oil, 10 mmol) were suspended in 10 ml of dry THF. Then 1.250 g (10 mmol) of **1c** in 6 ml of dry THF were added and the mixture was stirred for 30 min. After cooling to 0°C, a solution of 1.667 g (10 mmol) of [2-(trimethylsilyl)ethoxy]methyl chloride in 6 ml of THF was added slowly. Then the cooling bath was removed and the mixture was stirred at room temperature for 1.5 h. After addition of water (15 ml), the organic layer was separated, the water phase was exhaustively extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate. The

solvents were evaporated *in vacuo* and the residue was subjected to column chromatography (eluent: dichloromethane) to afford 1.365 g (38%) of **5c** (faster eluted component) and 1.318 g (37%) of **5e** (slower eluted component) as colorless oils.

Compound (**5c**): ^{1}H Nmr (DMSO-d_6): δ 8.24 (s, 1H, pyrazole H-5), 5.35 (s, 2H, NCH_2O), 3.53 (m, 2H, OCH_2C), 0.81 (m, 2H, CH_2Si), -0.06 (s, 9H, $SiCH_3$); ms: m/z (%) 311/313/315 (M^+-SiMe, 28/49/25), 281/283/285 (M^+-$SiMe_3$, 50/100/52), 238/240/242 (18/35/19), 237/239/241 (19/36/19), 201/203/205 (7/13/7), 73 (34). *Anal.* Calcd for $C_9H_{16}N_2OBr_2Si$: C, 30.35; H, 4.53; N, 7.87. Found: C, 30.45; H, 4.24; N, 7.86.

Compound (**5e**): ^{1}H Nmr (DMSO-d_6): δ 7.81 (s, 1H, pyrazole H-3), 5.45 (s, 2H, NCH_2O), 3.53 (m, 2H, OCH_2C), 0.81 (m, 2H, CH_2Si), -0.07 (s, 9H, $SiCH_3$); ms: m/z (%) 311/313/315 (M^+-SiMe, 14/25/12), 281/283/285 (M^+-$SiMe_3$, 25/57/25), 238/249/242 (19/38/19), 237/239/241 (14/28/15), 73 (100). *Anal.* Calcd for $C_9H_{16}N_2OBr_2Si$: C, 30.35; H, 4.53; N, 7.87. Found: C, 30.45; H, 4.43; N, 7.66.

3,4,5-Tribromo-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (**5d**)

Compound (**5d**) was prepared from 3.048 g (10 mmol) of **1d** and 1.667 g (10 mmol) of [2-(trimethylsilyl)-ethoxy]methyl chloride according to the procedure given for the preparation of **5c**. The raw product was purified by column chromatography (eluent: dichloromethane) to afford 1.827 g (42%) of a colorless oil; ^{1}H nmr ($CDCl_3$): δ 5.46 (s, 2H, NCH_2O), 3.63 (m, 2H, OCH_2C), 0.90 (m, 2H, CH_2Si), -0.01 (s, 9H, $SiCH_3$); ms: m/z (%) 389/391/393/395 (M^+-SiMe, 6/13/14/4), 359/361/363/365 (M^+-$SiMe_3$, 8/20/19/7), 325 (14), 329 (11), 319 (17), 318 (10), 317 (15), 139 (38), 137 (39), 73 (100). *Anal.* Calcd for $C_9H_{15}N_2OBr_3Si$: C, 24.85; H, 3.48; N, 6.44. Found: C, 25.13; H, 3.35; N, 6.26.

Ethyl 4-Bromo-1*H*-pyrazole-1-carboxylate (**6b**)

To a solution of sodium ethoxide prepared from 230 mg (10 mmol) of sodium and 15 ml of dry ethanol were added successively 1.470 g (10 mmol) of **1b** and 2.170 g (20 mmol) of ethyl chloroformate and the resulting mixture was heated to reflux for 2 h. Then the solvent and excessive ethyl chloroformate were removed *in vacuo*, the residue was treated with 50 ml of water and was then exhaustively extracted with dichloromethane. After drying over anhydrous sodium sulfate, the combined dichloromethane layers were evaporated and the residue was subjected to column chromatography (eluent: dichloromethane) to afford 942 mg (43%) of colorless needles, mp 41-42°C; ^{1}H nmr ($CDCl_3$): δ 8.17 (d, $J_{3,5}$ = 0.6 Hz, 1H, pyrazole H-5), 7.69 (d, $J_{3,5}$ = 0.6

Hz, 1H, pyrazole H-3), 4.53 (q, J = 7.1 Hz, 2H, OCH_2), 1.47 (t, J = 7.1 Hz, 3H, CH_3); ir (KBr): cm^{-1} 1754 (C=O); ms: m/z (%) 218/220 (M^+, 32/30), 159/161 (16/16), 146/148 (100/95), 119/121 (26/21). *Anal.* Calcd for $C_6H_7N_2O_2Br$: C, 32.90; H, 3.22; N, 12.79. Found: C, 33.15; H, 2.97; N, 12.80.

Ethyl 3,4-Dibromo-1*H*-pyrazole-1-carboxylate (**6c**)

Compound (**6c**) was obtained from 2.259 g (10 mmol) of **1c** and 2.170 g (20 mmol) of ethyl chloroformate following the procedure given for the preparation of **6b**. Column chromatography (eluent: dichloromethane) afforded 1.907 g (64%) of colorless crystals, mp 54-55°C; ^1H nmr ($CDCl_3$): δ 8.12 (s, 1H, pyrazole H-5), 4.54 (q, J = 7.1 Hz, 2H, OCH_2), 1.46 (t, J = 7.1 Hz, 3H, CH_3); ir (KBr): cm^{-1} 1750 (C=O); ms: m/z (%) 296/298/300 (M^+, 17/36/17), 237/239/240 (7/14/7), 224/226/228 (51/100/48), 197/199/201 (9/14/6), 118 (13). *Anal.* Calcd for $C_6H_6N_2O_2Br_2$: C, 24.19; H, 2.03; N, 9.40. Found: C, 24.45; H, 1.79; N, 9.35.

Ethyl 3,4,5-Tribromo-1*H*-pyrazole-1-carboxylate (**6d**)

Compound (**6d**) was obtained from 3.048 g (10 mmol) of **1d** and 2.170 g (20 mmol) of ethyl chloroformate following the procedure given for the preparation of **6b**. Column chromatography (eluent: dichloromethane) afforded 3.090 g (82%) of colorless crystals, mp 70-71°C; ^1H nmr ($CDCl_3$): δ 4.55 (q, J = 7.1 Hz, 2H, OCH_2), 1.48 (t, J = 7.1 Hz, 3H, CH_3); ir (KBr): cm^{-1} 1761 (C=O); ms: m/z (%) 374/376/378/380 (M^+, 7/22/21/7), 315/317/319/321 (6/17/17/6), 302/304/306/308 (34/100/97/30), 225 (12), 196 (11). *Anal.* Calcd for $C_6H_5N_2O_2Br_3$: C, 19.13; H, 1.34; N, 7.43. Found: C, 19.29; H, 1.05; N, 7.19.

1-Acetyl-3,4-dibromo-1*H*-pyrazole (**7c**)

To a solution of 451 mg (2 mmol) of **1c** and 202 mg (2 mmol) of triethylamine in 10 ml of dry benzene were added 157 mg (2 mmol) of acetyl chloride and the resulting mixture was stirred at room temperature for 24 h. Then the precipitate was filtered off, the filtrate was evaporated *in vacuo* and the remaining solid was washed with cold light petroleum to yield 484 mg (90%) of pure **7c** (according to ^1H nmr), mp 60-63°C. For elemental analysis a sample was recrystallized from light petroleum to give colorless crystals of mp 62-65°C; ^1H nmr ($CDCl_3$): δ (ppm) 8.20 (s, 1H, pyrazole H-3), 2.66 (s, 3H, $COCH_3$); ir (KBr): cm^{-1} 1730, 1746 (C=O); ms: m/z (%) 266/268/270 (M^+, 15/29/14), 224/226/228 (51/100/52). *Anal.* Calcd for $C_5H_4N_2OBr_2$: C, 22.42; H, 1.50; N, 10.46. Found: C, 22.63; H, 1.70; N, 10.70.

1-Benzoyl-3,4-dibromo-1*H*-pyrazole (**8c**)

To a solution of 2.259 g (10 mmol) of **1c** and 1.113 g (11 mmol) of triethlyamine in 15 ml of dry toluene were added dropwise 1.546 g (11 mmol) of benzoyl chloride and the resulting mixture was refluxed for 2 h. After cooling, the solution was filtered, the filtrate was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from light petroleum - ethyl acetate to yield 1.683 g (51%) of colorless crystals, mp 105-109°C; ^{1}H nmr ($CDCl_3$): δ 8.40 (s, 1H, pyrazole H-5), 8.18-8.05 (m, 2H, Ph H-2,6), 7.66-7.50 (m, 3H, Ph H-3,4,5); ir (KBr): cm^{-1} 1695 (C=O); ms: m/z (%) 328/330/332 (M^+, 5/10/5), 105 (100), 79 (42), 70 (17), 55 (15), 51 (14), 43 (22), 41 (13). *Anal.* Calcd for $C_{10}H_6N_2OBr_2$: C, 36.40; H, 1.83; N, 8.49. Found: C, 36.67; H, 1.96; N, 8.61.

1-Benzoyl-3,4,5-tribromo-1*H*-pyrazole (**8d**)

Compound (**8d**) was obtained from 3.048 g (10 mmol) of **1d** and 1.113 g (10 mmol) of benzoyl chloride following the procedure given for the preparation of **8c**. Recrystallisation from light petroleum - ethyl acetate afforded 2.249 g (55%) of colorless crystals, mp 106-107°C; ^{1}H nmr ($CDCl_3$): δ 8.01-7.90 (m, 2H, Ph H-2,6), 7.67-7.38 (m, 3H, Ph H-3,4,5); ir (KBr): cm^{-1} 1710 (C=O); ms: m/z (%) 406/408/410/412 (M^+, 16/45/44/14), 106 (73), 105 (100), 78 (28), 77 (94), 76 (21), 43 (12). *Anal.* Calcd for $C_{10}H_5N_2OBr_3$: C, 29.38; H, 1.23; N, 6.85. Found: C, 29.59; H, 1.29; N, 6.75.

1-Benzenesulfonyl-3,4,5-tribromo-1*H*-pyrazole (**9d**)

A solution of **1d** (3.048 g, 10 mmol) and benzenesulfonyl chloride (1.766 g, 10 mmol) in 12 ml of dry pyridine was heated to reflux for 2 h. After cooling, the mixture was poured into water (100 ml) and the precipitate was filtered off, washed with water and recrystallized from ethanol to yield 3.200 g (72%) of colorless crystals, mp 170-171°C; ^{1}H nmr ($CDCl_3$): δ 8.14-8.02 (m, 2H, Ph H-2,6), 7.76-7.46 (m, 3H, Ph H-3,4,5); ms: m/z (%) 442/444/446/448 (M^+, 1/3/3/1), 141 (46), 77 (100), 51 (47). *Anal.* Calcd for $C_9H_5N_2O_2Br_3S$: C, 24.30; H, 1.13; N, 6.30. Found: C, 24.30; H, 1.16; N, 6.12.

3,4-Dibromo-1-(4-toluenesulfonyl)-1*H*-pyrazole (**10c**)

Compound (**10c**) was prepared from 2.259 g (10 mmol) of **1c** and 1.907 g (10 mmol) of 4-toluenesulfonyl chloride according to the precedure given for the preparation of **9d**. Recrystallisation from ethanol yielded

1.444 g (38%) of colorless crystals, mp 125-130°C; ^{1}H nmr ($CDCl_3$): δ 8.04 (s, 1H, pyrazole H-5), 7.96-7.85 (m, 2H, benzene H-2,6), 7.41-7.31 (m, 2H, benzene H-3,5), 2.45 (s, 3H, Me); ms: m/z (%) 378/380/382 (M^+, 3/6/3), 314/316/318 (7/14/7), 224/226/228 (72/100/67), 197/199/201 (17/32/15), 155 (39), 145/147 (21/21), 120 (20), 118 (28), 91 (96), 66 (31), 65 (32). *Anal.* Calcd for $C_{10}H_8N_2O_2Br_2S$: C, 31.60; H, 2.12; N, 7.37. Found: C, 31.77; H, 2.07; N, 7.43.

1-(4-Toluenesulfonyl)-3,4,5-tribromo-1*H*-pyrazole (**10d**)

Compound (**10d**) was obtained from 3.048 g (10 mmol) of **1d** and 1.907 g (10 mmol) of 4-toluenesulfonyl chloride as described for the preparation of compound (**9d**). Recrystallisation from ethanol - dichloromethane afforded 2.432 g (53%) of colorless crystals, mp 189°C; ^{1}H nmr ($CDCl_3$): δ 8.00 -7.90 (m, 2H, benzene H-2,6), 7.42-7.32 (m, 2H, benzene H-3,5), 2.45 (s, 3H, Me); ms: m/z (%) 456/458/460/462 (M^+, 1/4/3/1), 155 (58), 92 (100), 65 (12). Anal. Calcd for $C_{10}H_7N_2O_2Br_3S$: C, 26.17; H, 1.54; N, 6.10. Found: C, 26.43; H, 1.55; N, 6.04.

ACKNOWLEDGEMENT

The authors thank Mr. E. Möllner for performing the glc/ms analyses and for recording some ir spectra. The glc/ms combination was made available by the Austrian "Fonds zur Förderung der wissenschaftlichen Forschung", Projekt P 6260C.

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Received, 11th July, 1994