2-Substituted Pyrazole 1-Oxides. Preparation and Reaction with Electrophilic Reagents

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1-Substituted pyrazoles have been oxidized by peracids to 2-substituted pyrazole 1-oxides. This leads to a change in reactivity towards electrophilic attack. 2-Benzylpyrazole 1-oxide is brominated, chlorinated, and nitrated selectively at C-3. The 3-halo-substituted pyrazole 1-oxides are nitrated selectively at C-4 while their halogenation proceeds with poor mono- and regio-selectivity producing 3,4-dihalo-, 3,5-dihalo- and 3,4,5-trihalo-derivatives. Bromine at C-3 and C-5 can be used for protection since it is removed by treatment with sodium sulfite. The reactions may be followed by deoxygenation. The total sequences provide effective routes for the regioselective introduction of halogen and nitro groups into the pyrazole nucleus.

Introduction of substituents into the pyrazole nucleus by classical electrophilic or nucleophilic substitution reactions frequently gives rise to problems due to low reactivity, poor regioselectivity or poor monoselectivity. Many of these problems may be solved through activation of the nucleus by *N*-oxidation.

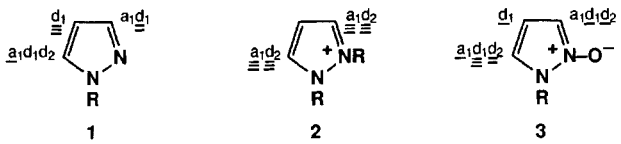
A donor–acceptor analysis[1] of 1-substituted pyrazoles (**1**) reveals that the 2-, 3-, 4-, and 5-positions may be susceptible to electrophilic attack.[2] The reactivity is anticipated to decrease in the order C-4 > C-3 > C-5 (Fig. 1). Experiments confirm most of these expectations. Thus, the pyrazole nitrogen lone-pair can be alkylated to give quaternary pyrazolium salts, oxidized to pyrazole *N*-oxides, or aminated to give *N*-aminopyrazoles.[3] Unstable *N*-bromopyrazoles have also been reported.[4]

Neutral electrophiles, like bromine, attack 1-substituted pyrazoles (**1**) primarily at the 4-position. Under forcing conditions, first the 3- and then the 5-positions are attacked.[3,4] Acidic electrophiles, such as nitric acid, protonate the pyrazole nitrogen lone pair. This deactivates the nucleus towards further electrophilic attack. Nitration therefore requires forcing conditions, and the reactivity decreases in the order C-4 > C-3 ≥ C-5.[3] Thus, selective introduction of electrophiles at the 3- and 5-positions is frequently difficult or even impossible.

Until now, activation of the pyrazole nucleus through *N*-oxidation has not been studied systematically.[5] A donor–acceptor analysis of 2-substituted pyrazole 1-oxides (**3**)†,[2] indicates that the 3- and 5-positions are activated towards both electrophiles and nucleophiles (Fig. 1). The reactivity is expected to decrease in the order C-3 > C-4,C-5 in electrophilic substitution reactions. Therefore, selective introduction of electrophiles at C-3 of the pyrazole nucleus seems possible using the activated *N*-oxides as intermediates.

The only reported substitution reactions of 2-substituted pyrazole 1-oxides are the nitration of **7** (R = Me, R′ = R″ = R‴ = H), which takes place at the 3- and then at the 5-position,[6,7] the reaction of **7** (R = Me, R′ = R″ = R‴ = H) with phosphorus oxychloride to produce 5-chloro-1-methylpyrazole (**8**; R = Me, R′ = Cl, R″ = R‴ = H),[7] and the reaction of 2-methyl-3-nitropyrazole 1-oxide (**7**; R = Me, R′ = NO_2, R″ = R‴ = H) with acetyl chloride claimed to give 1-methyl-4-nitro-5-chloropyrazole (**8**; R = Me, R′ = Cl, R″ = NO_2, R‴ = H) as the major product.[7] The lack of data on the reactivity of 2-substituted pyrazole 1-oxides may be due to the inaccessibility of such compounds devoid of *C*-substituents.

Pyrazole 1-oxides possessing alkyl or aryl groups at N-2 (**7**) have been prepared by (i) reduction of 2-hydroxypyrazole 1-oxides (**4**) followed by *N*-alkylation,[5,8] (ii) cycliza-



1 2 3

Fig. 1. Donor–acceptor analysis of pyrazoles. The designations signify reactivity in electrophilic aromatic substitution (d_1), nucleophilic addition–elimination (a_1), and reaction of carbanionic centres with electrophiles (d_2). The more bars, the higher the reactivity. The assignment of the notation is described in Ref. 2.

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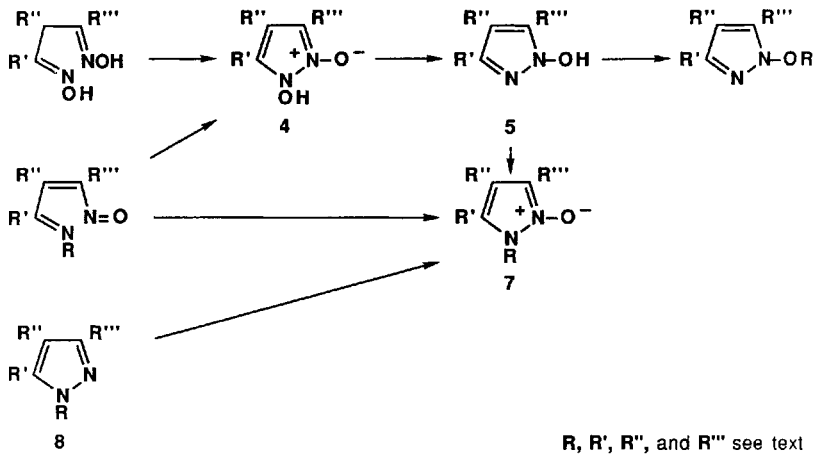
† The compounds studied have been named according to the IUPAC nomenclature. From this it follows that the numbering of ring positions starts at oxygen-substituted nitrogen atoms.



Scheme 1.

tion of 1-imino-2-nitrosoalkenes (**5**),[9] and (iii) oxidation of 1-substituted pyrazoles (**8**)[10] (Scheme 1). By the first method, only 3,5- and 3,4,5-substituted 2-hydroxypyrazole 1-oxides (**4**) have been reported. The final alkylation to give 2-substituted pyrazole 1-oxides (**7**) has only been successful for 1-hydroxyindazoles.[11] In contrast, the corresponding *N*-alkylation of 1-hydroxypyrazoles (**5**) failed.[8] The second method seems limited, giving only 3,5-disubstituted pyrazole 1-oxides. Although the third method seems an obvious preparation of 2-substituted pyrazole 1-oxides lacking *C*-substituents, only two examples of oxidation of 1-substituted pyrazoles **8** into the corresponding *N*-oxides **7** have been reported,[10,12] and difficulties have been met in attempts to prepare others.[8]

We have now improved the oxidation of pyrazoles to their *N*-oxides and determined the reactivity of these compounds in order to devise new methods for the regioselective introduction of substituents into the pyrazole nucleus.

Results and discussion

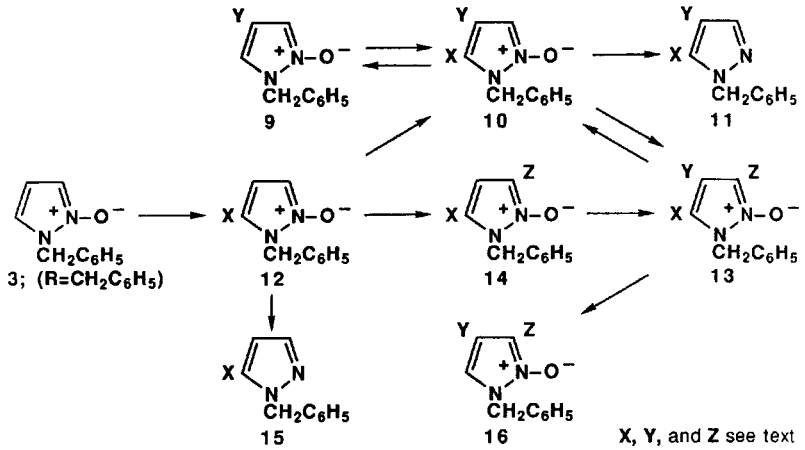
Oxidation. The reported oxidation of 1-methylpyrazole (**1**; R = Me) with hydrogen peroxide in acetic acid gave only 10 % of 2-methylpyrazole 1-oxide (**3**; R = Me). No experimental details were given, but purification of the product was difficult and required distillation.[10] However, distillation of pyrazole *N*-oxides may lead to explosion.[13] Therefore we tried to optimize the oxidation process, facilitate work-up and employ the resulting procedure in the synthesis of other pyrazole *N*-oxides.

1-Methylpyrazole was oxidized under different conditions with performic acid, peracetic acid, trifluoroperacetic acid, dichloropermaleic acid and *m*-chloroperbenzoic acid. Hydrogen peroxide was also employed. Only performic and peracetic acid were able to oxidize the pyrazole to a significant extent. However, yields never exceeded 16 %, even when the peracid was used in large excess. This was found to be due to the fact that the pyrazole *N*-oxide reacts with the peracids to give the parent pyrazole and oxygen. (Blank experiments revealed that the pyrazole *N*-oxide is stable towards hydrogen peroxide or the acids themselves). Similar oxidative deoxygenation of pyridine *N*-oxides is known.[14,15] Therefore, optimum yields of pyrazole *N*-oxide were only obtained under carefully controlled conditions. The yields of pyrazole *N*-oxides **7** tend to decrease when electron-attracting substituents are present in the pyrazole

Table 1. Preparation of 2-substituted pyrazole 1-oxides (**7**) by oxidation of 1-substituted pyrazoles (**8**).[a]

2-Substituted pyrazole 1-oxide **7**				Elution solvent[b]	R_f	Recrystallization solvent[b]	Yield (%)	M.p./°C	Yield of unchanged starting material (%)	Elemental analysis
R	R'	R''	R'''							
p-$MeOC_6H_4CH_2$[c]	H	H	H	EtOAc–MeOH (1:1)		EtOAc–hexane	13	Oil	38	$C_{11}H_{12}N_2O_2$: C, H, N.
C_6H_5	H	H	H	EtOAc–MeOH (3:1)	0.42	EtOAc–hexane	1	Oil	74	$C_9H_8N_2O$: C, H, N.
$CH_2C_6H_5$	H	Cl	H	EtOAc	0.36	EtOAc–hexane	2	Oil	71	$C_{10}H_9ClN_2O$: C, H, N.

[a]The oxidation was performed as described for the preparation of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) and the product was purified by preparative TLC, unless otherwise stated. [b]EtOAc = ethyl acetate, MeOH = methanol. [c]The compound was purified by filtration through silica gel as described for 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$).



Scheme 2.

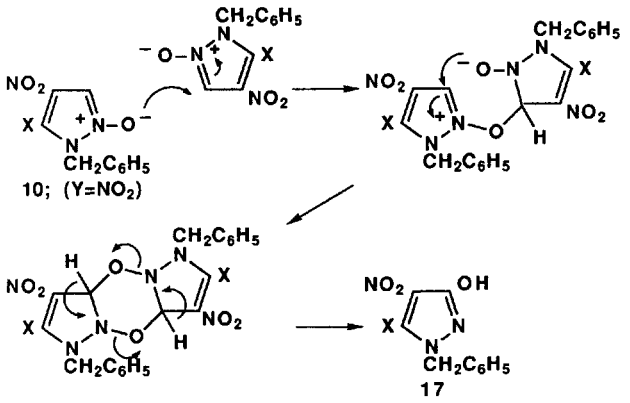
nucleus (Table 1). Although the yields of pyrazole *N*-oxides **7** are low, the procedures developed are effective in that the *N*-oxide is easily separated from unchanged starting material which can be regenerated.

Halogenation. The 3-position of 2-substituted pyrazole 1-oxides is activated towards electrophiles compared with the parent pyrazoles. These are brominated first in the 4-position.[4] In contrast, 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) first produces the 3-bromo compound (**12**; X = Br) which can be isolated in 89 % yield (Scheme 2). A substituent at C-4 does not influence the regioselectivity. Thus, bromination of 2-benzyl-4-bromopyrazole 1-oxide (**9**; Y = Br) produces the 3,4-dibromo compound (**10**; X = Y = Br) in 99 % yield.

A measure for the activation is given by the reaction of a 1:1 mixture of 1-benzylpyrazole and 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) with 0.5 equiv. of bromine in the presence of excess potassium carbonate. The result is a 1:1 mixture of 1-benzyl-4-bromopyrazole and 2-benzyl-3-bromopyrazole 1-oxide (**12**; X = Br). Chlorination also occurs under mild conditions, sulfuryl chloride producing 2-benzyl-3-chloropyrazole 1-oxide (**12**; X = Cl) in 66 % isolated yield. A substituent at C-4 does not influence the regioselectivity, 2-benzyl-4-bromopyrazole 1-oxide (**9**; Y = Br) being chlorinated first at C-3 to give **10** (X = Cl, Y = Br).

Further halogenation of 3-halo-substituted pyrazole 1-oxides proceeds with poor mono- and regio-selectivity. Treatment of 2-benzylpyrazole 1-oxide with *two* equiv. of bromine produces a 4.8:12.0:1:2.5 mixture of the 2-benzyl-3-bromopyrazole 1-oxide (**12**; X = Br), the 3,4-dibromo **10** (X = Y = Br), the 3,5-dibromo **14** (X = Z = Br) and the 2-benzyl-3,4,5-tribromopyrazole 1-oxide (**13**; X = Y = Z = Br). The last-mentioned compound became the sole product by exhaustive bromination.

Chlorination of 2-benzyl-3-chloropyrazole 1-oxide (**12**; X = Cl) is sluggish and unselective producing a mixture of 2-benzyl-3,4-dichloro- (**10**; X = Y = Cl), 2-benzyl-3,5-dichloro- (**14**; X = Z = Cl) and 2-benzyl-3,4,5-trichloropyrazole 1-oxide (**13**; X = Y = Z = Cl). These experiments indicate that the reactivity of the 4- and 5-position of 2-substituted pyrazole 1-oxides **3** must be of the same order in halogenation reactions. The structure of compounds **12** (X = Br) and **9** (Y = Br) follows from their NMR spectra as described below. The structure of the 3,4-dibromo compound **10** (X = Y = Br) was proved by the fact that it arises both by bromination of the 3-bromo compound **12** (X = Br) and of the 4-bromo compound **9** (Y = Br). The structure of the chloropyrazole *N*-oxides also follows from their NMR spectra.



Scheme 3.

Nitration. Regio- and mono-selectivity is also observed by nitration of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$). Again, the 3-position is attacked first and 2-benzyl-3-nitropyrazole 1-oxide (**12**; X = NO_2) can be prepared in quantitative yield. Further nitration takes place in the phenyl 4-position and then in the pyrazole 5-position to give 3,5-dinitro-2-(4-nitrobenzyl)pyrazole (**14**; X = Z = NO_2) as the final product. In contrast, halogen at the 3-position of the pyrazole 1-oxides **12** (X = Cl or Br) directs the first nitro group exclusively to the 4-position. The resulting 2-benzyl-

3-halo-4-nitropyrazole 1-oxides **10** (X = Cl or Br, Y = NO_2) are unstable in chloroform solution and rearrange at 20 °C to 1-benzyl-3-hydroxy-4-nitro-5-halopyrazole (**17**; X = Cl or Br). The rearrangement of **10** (X = Cl or Br, Y = NO_2) into **17** (X = Cl or Br) may follow the intermolecular course shown in Scheme 3. An intramolecular process is less likely, since the rate of the rearrangement is strongly concentration dependent. The reaction of the pyrazole 1-oxides with alkylating and acylating agents will be described in a forthcoming paper.

Debromination. Bromine at C-3 and C-5 of 2-benzyl-3,4,5-tribromopyrazole 1-oxide (**13**; X = Y = Z = Br) could be removed consecutively by treatment with aqueous methanolic sodium sulfite to give 87 % of dibrominated pyrazole 1-oxides or 93 % of 2-benzyl-4-bromopyrazole 1-oxide (**9**; Y = Br), respectively. The first step produces a 5.2:1 mixture of 2-benzyl-4,5-dibromopyrazole 1-oxide (**16**; Y = Z = Br) and 2-benzyl-3,4-dibromopyrazole 1-oxide (**10**; X = Y = Br) demonstrating that bromine at C-3 is more readily removed than bromine at C-5. The facile and regioselective removal of bromine at this position may be due to inductive stabilization of the carbanions formed upon release of the bromonium ion by the adjacent positive nitrogen atom.

Deoxygenation. The 2-substituted pyrazole 1-oxides could be deoxygenated with phosphorus trichloride to give 1-substituted pyrazoles in high yield. Therefore the reactions above when followed by deoxygenation provide efficient routes to regioselectively halo- and nitro-substituted pyrazoles. Thus, 1-benzyl-5-chloropyrazole (**15**; X = Cl), 1-benzyl-5-bromopyrazole (**15**; X = Br), and 1-benzyl-5-nitropyrazole (**15**; X = NO_2), which are otherwise difficult to prepare, become available. Better overall yields of **15** (X = Cl) and of 1-benzyl-5-bromopyrazole (**15**; X = Br) were, however, obtained by treatment of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) with phosphorus trihalide.[16]

Structure elucidation of 2-substituted pyrazole 1-oxides. The structure of the chloro compound **12** (X = Cl) was established via its deoxygenation to 1-benzyl-5-chloropyrazole (**15**; X = Cl),[17] which showed all the spectral characteristics of a 1,5-disubstituted pyrazole as follows. The signals due to the ring-protons of **15** (X = Cl) were found at 6.23 and 7.52 ppm. This is in the range where H-4 (ca. 5.9–6.3 ppm[18]) and H-3 (ca. 7.3–7.6 ppm[18]) of 1,5-disubstituted pyrazoles absorb. In contrast, H-5 of 1,3-disubstituted pyrazoles resonates at ca. 6.9–7.4 ppm. The ring carbon signal of **15** (X = Cl), split by a one-bond C–H coupling, resonates at 139.2 ppm, a shift characteristic of C-3 of 1,5-disubstituted pyrazoles (ca. 137–139 ppm[19]). In contrast, C-5 of 1-alkyl 3-substituted pyrazoles resonates at ca. 129–132 ppm. The signal at 139.2 ppm is split by a coupling to H-4 of 4.9 Hz. This is a typical C-3, H-4 coupling (ca. 5–6 Hz[19,20]), found in a 1,5-disubstituted pyrazole, the magnitude of this coupling being too small to be a C-5, H-4 coupling (ca. 9.5 Hz[19,20]) found in a 1,3-disubstituted pyrazole.

Furthermore, the two-bond C–H coupling between C-3 and H-5 in 1,3-disubstituted pyrazoles is ca. 8 Hz, while the coupling between C-5 and H-3 in 1,5-disubstituted pyrazoles is ca. 4 Hz.[19,20] Finally, C-5 couples with *N*-1-CH protons while C-3 does not.[19–21] The ring-carbon signal of **15**; X = Cl not split by one-bound coupling was the only pyrazole ring-carbon atom to be split by a three-bond coupling to the benzylic CH_2-protons. The parent 1-benzylpyrazole (**1**; R = $CH_2C_6H_5$) exhibits all these characteristic features as well (see Table 3).

The NMR-spectral features of the pyrazole 1-oxides differ from those of the parent pyrazoles. Therefore the proton and carbon signals were assigned as follows. 2-Benzyl-3-chloropyrazole 1-oxide (**12**; X = Cl) exhibits a carbon signal split not by one-bond C–H couplings but by a small coupling to the CH_2-protons. This signal must therefore be attributed to C-3. Similarly, a small coupling to the CH_2-protons identifies the C-3 signal of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$). Usually, $\delta_{C\text{-}5}$ is larger than $\delta_{C\text{-}4}$. If necessary, the C-4 and C-5 signals can be distinguished unambiguously through the greater one-bond CH-coupling of the latter. The identification of the three-carbon signals leads to assignment of H-3, H-4 and H-5 through a CH-correlated NMR spectrum.

$J_{H\text{-}3,H\text{-}4}$ and $J_{H\text{-}4,H\text{-}5}$ are similar in the parent azoles. However, in 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) $J_{H\text{-}3,H\text{-}4}$ (ca. 3.5 Hz) is larger than $J_{H\text{-}4,H\text{-}5}$ (ca. 2.5 Hz). This feature was used to assign H-3 and H-5 in 2-methylpyrazole 1-oxide (**3**; R = Me). The C-3 and C-5 signals of **3** (R = Me) could then be assigned by means of a C–H correlated spectrum. In 2-phenylpyrazole 1-oxide (**3**; R = Ph) C-3 and C-5 could only be distinguished by the longer relaxation time for C-5 also observed in **3** (R = $CH_2C_6H_5$) and **3** (R = Me).

The structure of the bromopyrazole 1-oxide **12** (X = Br) and the nitropyrazole 1-oxide **12** (X = NO_2) was established by comparison of their ^{1}H- and ^{13}C-NMR parameters with those of the chloro analogue **12** (X = Cl). The signals of 1-benzyl-5-nitropyrazole (**15**; X = NO_2) were assigned in the same way as those of the bromo analogue (**15**; X = Br).

NMR characteristics of 2-substituted pyrazole 1-oxides. To summarize, the 2-substituted pyrazole 1-oxides exhibit the following NMR spectroscopic characteristics. (i) $\delta_{H\text{-}5}$ is larger than $\delta_{H\text{-}3}$ and both are larger than $\delta_{H\text{-}4}$. (ii) $J_{H\text{-}3,H\text{-}4}$ is larger than $J_{H\text{-}4,H\text{-}5}$. (iii) $\delta_{C\text{-}3}$ and $\delta_{C\text{-}5}$ are similar but larger than $\delta_{C\text{-}4}$. (iv) All two- and three-bond C–H couplings in the ring are quite similar being in the range 5.0–7.5 Hz. (v) C-3 couples with protons at the α-position of substituents at N-2.

These characteristics were used in the identification of the substituted 2-benzylpyrazole 1-oxides **9** (X = Cl or Br), **10** (X = Y = Cl), **10** (X = Cl, Y = Br), **14** (X = Z = Cl), **14** (X = Z = Br), **14** (X = Z = NO_2) and **16** (Y = Z = Br). The structure of compound **17** (X = Cl) was ascertained through its ^{13}C NMR spectrum which showed a low-field signal

Table 2. ^{1}H NMR data of 2-substituted pyrazole 1-oxides and of pyrazoles in $CDCl_3$ with tetramethylsilane as an internal standard, when not otherwise stated.

2-Substituted pyrazole 1-oxide					$\delta_{H\text{-}3}$	$\delta_{H\text{-}4}$	$\delta_{H\text{-}5}$	δ_{Ph}	δ_{CH_2} (δ_{CH_3})	$J_{3,4}$/Hz	$J_{4,5}$/Hz	$J_{3,5}$/Hz
	R	X	Y	Z								
3	Me				6.95	6.14	7.21		(NCH$_3$: 3.77)	3.38	2.48	–
3	$CH_2C_6H_5$				6.79	6.12	7.23	7.28–7.39	5.33	3.86	2.43	1.14
3	$CH_2C_6H_4OMe$-4				6.75	6.05	7.14	7.24 7.86	5.19 (OCH$_3$: 3.78)	3.9	2.6	1.4
3	C_6H_4				7.13	6.27	7.32	7.45–7.61		3.78	2.30	
12		NO_2				7.20	7.44	7.26–7.40	5.90		3.05	
12		Cl				6.10	7.24	7.33	5.39		2.6	
12		Br				6.21	7.19	7.33	5.42		2.7	
10		Cl	NO_2				7.78	7.37–7.41	5.47			
10		Cl	Cl				7.24	7.33–7.39	5.41			
10		Cl	Br				7.23	7.37	5.43			
10		Br	NO_2				7.83	7.35–7.42	5.52			
10		Br	Br				7.29	7.36	5.44			
13		Cl	Cl	Cl				7.33–7.42	5.43			
13		Br	Br	Br				7.24–7.55	5.48			
14		Cl		Cl		6.17		7.32–7.40	5.42			
14		Br		Br		6.41		7.24–7.36	5.52			
7; R = 4-$NO_2C_6H_4$, R′ = R‴ = NO_2, R″ = H[a]						7.95		8.18 7.59	5.86			
9			Cl		6.77		7.19	7.27–7.41	5.26			1.20
9			Br		6.81		7.21	3:7.37–7.40 2:7.28–7.32	5.28			1.13
16			Br	Br	6.88			7.30–7.41	5.33			
Pyrazoles												
17		Cl						7.33–7.38	5.23			
17		Br						7.31–7.37	5.27			
15		NO_2			7.57	7.08		7.24–7.33	5.78	2.22		
15		Cl			7.52	6.23		2:7.22–7.23 3:7.30–7.34	5.34	1.99		
15		Br			7.56	6.34		3:7.29–7.38 2:7.21–7.29	5.39	1.95		

[a]With CD_3CN as the solvent.

(155.7 ppm) characteristic of oxygen-substituted C-3 carbon atoms in pyrazole nuclei.[22]

Experimental

Dichloromethane was dried over sodium hydride. Acetonitrile,[23] methanol,[24] and *N,N*-dimethylformamide[25] were dried as described in the references. All new compounds were colourless, unless otherwise stated. The purity of all compounds was confirmed by their sharp melting points. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument. The NMR data are given in Tables 2 and 3.

2-Substituted pyrazole 1-oxides. (a) 1-Methylpyrazole[26] (**1**; R = Me) (1.56 g), acetic anhydride (32.4 ml), and 60 % hydrogen peroxide (2.15 ml) were stirred at 55 °C. After 2 h and again after 4 h further hydrogen peroxide (2.15 ml) was added. After 24 h the mixture was cooled and sodium sulfite (14.3 g) in water (50 ml) was added. Stirring at 20 °C for 10 min, addition of conc. hydrochloric acid (40 ml), evaporation of the reaction mixture to dryness *in vacuo* keeping the temperature below 70 °C, addition of conc. hydrochloric acid (20 ml), evaporation to dryness, addition of methanol (30 ml) and of potassium hydroxide until pH 10, removal of the methanol, extraction with dichloromethane (20 + 2 × 10 ml), and removal of the dichloromethane gave a residue (4.51 g) which was purified by preparative TLC (two 20 cm plates, 0.1 cm thick layer of silica gel, elution with ethyl acetate–methanol [1:1]) to give 0.31 g (16 %) of 2-methylpyrazole 1-oxide (**3**; R = Me) as an oil. Anal. $C_4H_6N_2O$: C, H, N.

(b) To a solution of 1-benzylpyrazole[26] (3.0 g) in acetic anhydride (30 ml), at 55 °C, three portions of 60 % hydrogen peroxide (2.2 ml) were added at 2 h intervals. The reaction was stirred at 55 °C for further 24 h and a solution of sodium sulfite (14 g) in water (50 ml) was added with cooling in an ice bath keeping the temperature below 40 °C. The mixture was evaporated to dryness *in vacuo* at 40 °C. Water (50 ml) and 33 % aqueous sodium hydroxide (ca. 15 ml) were added to pH ca. 8. Extraction with chloroform (3 × 20 ml), drying ($MgSO_4$), and removal of the chloro-

Table 3. ^{13}C NMR data of 2-substituted pyrazole 1-oxides and of pyrazoles in $CDCl_3$ with the solvent signal (δ 76.90) as an internal standard, when not otherwise stated.

2-Substituted pyrazole 1-oxide					$\delta_{C\text{-}3}$ ($\delta_{C\text{-}1'}$)	$\delta_{C\text{-}4}$ ($\delta_{C\text{-}2'}$)	$\delta_{C\text{-}5}$ ($\delta_{C\text{-}3'}$)	δ_{CH_2} δ_{CH_3} ($\delta_{C\text{-}4'}$)	$J_{C\text{-}3}$/Hz	$J_{C\text{-}4}$/Hz	$J_{C\text{-}5}$/Hz
	R	X	Y	Z							
3	Me				119.5	101.1	119.3	CH_3: 32.4	≈195	183.4 7.5 5.3	≈195
3	$CH_2C_6H_5$				118.5 (134.2)	101.1 (127.9)	118.9 (128.9)	48.2 (128.1)	195.2 H_4 6.0 H_5 6.0 CH_2 2.8	183.3 7.2 5.5	196.6 H_4 7.3 H_3 5.1
3	C_6H_5				119.5 (134.2)	102.0 (127.9)	119.9 (128.9)	(128.1)			
12		NO_2			133.2	105.3	121.4	49.1	191.1 7.4	203.8 6.1	
12		Cl			115.1 (134.0)	100.3 (127.8)	119.1 (128.6)	46.0 (128.1)	H_4 < 0.8 H_5 9.1 CH_2 3.3	187.5 H_5 7.5	198.9 H_4 6.5
12		Br			100.4 (134.0)	104.4 (127.7)	120.3 (128.6)	47.2 (128.1)	H_4 < 1 H_5 9.1 CH_2 2.9	188.1 H_5 7.4	199.2 H_4 6.8
10		Br	NO_2		[a]	102.3	115.1	47.7		 H_5 5.1	209.0
10		Br	Br		101.7 (133.7)	92.4 (128.0)	120.4 (128.7)	48.1 (128.4)			
9			Cl		116.5[b] (133.1)	106.3 (128.6)	118.8[b] (129.2)	49.1 (128.9)			
9			Br		118.3[b] (133.1)	88.6 (129.1[c])	119.8[b] (128.7[c])	48.8 (128.5)			
14		Cl		Cl	115.5[c] (133.5)	100.4 (128.1)	119.3[c] (128.7)	47.2 (128.4)			
Pyrazoles											
17		Cl			155.7	116.5	126.0	53.6			
15		NO_2			138.1 (135.0)	107.0 (127.6)	145.3 (128.6)	56.2 (128.2)	192.1 H_4 4.2	185.8 H_3 10.5	
15		Cl			139.2 [a]	104.7 (127.0)	126.6 (128.3)	52.3 (127.5)	188.2 H_4 4.9	182.0 H_3 10.6	H_3 7.0 H_4 4.7 CH_2 3.2

[a]The signal could not be detected. [b]The signal from C-3 is distinguished from that of C-5 as being the most intense. [c]The assignments may be interchanged.

form gave 2.6 g of material which was filtered through silica gel (10 g, column diameter 2 cm) eluting with ethyl acetate–hexane (1:1, 3 × 30 ml). Removal of the solvents gave 2.1 g (70 %) of unchanged starting material. The column was then eluted with ethyl acetate–methanol (1:1, 3 × 20 ml). Removal of the solvents produced 0.61 g (18 %) of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (R_f 0.68 in ethyl acetate–methanol [1:1]), as a yellow oil. Low-temperature recrystallization from ethyl acetate (3 ml per g) gave m.p. 68–69 °C. Anal. $C_{10}H_{10}N_2O$: C, H, N.

2-(*p*-Methoxybenzyl)pyrazole 1-oxide (**3**; R = $CH_2C_6H_4OMe$-4), 2-phenylpyrazole 1-oxide (**3**; R = C_6H_5), and 4-chloro-2-benzylpyrazole 1-oxide (**9**; Y = Cl) were prepared similarly; details are given in Table 1.

Bromination. (a) A solution of bromine (0.106 ml) in dichloromethane (1.0 ml) was added at −80 °C over 2 min to a mixture of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (0.36 g), potassium carbonate (0.49 g), and dichloromethane (5.0 ml). After being stirred at −80 °C for 15 min and at 0 °C for 20 min all starting material had been consumed (TLC [ethyl acetate]). Stirring for 10 min with a solution of sodium sulfite (0.78 g) in water (7 ml), isolation of the organic solution, extraction with dichloromethane (4 × 5 ml), drying ($MgSO_4$), and removal of the dichloromethane gave 0.54 g of an oil which by preparative TLC (ethyl acetate–methanol [20:1]) produced 0.46 g (89 %) of 2-benzyl-3-bromopyrazole 1-oxide (**12**; X = Br) (R_f 0.41), m.p. 86–87 °C (ethyl acetate). Anal. $C_{10}H_9BrN_2O$: C, H, N.

The next fraction contained 0.065 g (10 %) of 2-benzyl-3,4-dibromopyrazole 1-oxide (**10**; X = Y = Br), identical with the material described below.

(b) Similar bromination of 2-benzyl-4-bromopyrazole 1-oxide (**9**; Y = Br) (0.046 g) at −80 °C for 50 min and then at −25 °C for 1.5 h gave a solution which was stirred for 10 min with a solution of sodium sulfite (0.040 g) in water (1 ml). The organic solution was isolated and the aqueous solution extracted with a further 4×2 ml of dichloromethane. Drying ($MgSO_4$) and removal of the dichloromethane gave 0.059 g (99 %) of 2-benzyl-3,4-dibromopyrazole 1-oxide (**10**; X = Y = Br), m.p. 131–132 °C (ethyl acetate–hexane). Anal. $C_{10}H_8Br_2N_2O$: C, H, N.

(c) Bromine (16 µl) was added at −78 °C with stirring to a mixture of 1-benzylpyrazole (50 mg), 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (55 mg), potassium carbonate (130 mg) and dichloromethane (2.00 ml). Stirring at −78 °C for 15 min and at 20 °C for 15 min and removal of the dichloromethane gave a 1.2:1.25:1:1 mixture (^{1}H NMR) of 1-benzylpyrazole (**3**; R = $CH_2C_6H_5$), 1-benzyl-4-bromopyrazole, and 2-benzyl-3-bromopyrazole 1-oxide (**12**; X = Br). The compounds were identified by ^{1}H NMR spectroscopy by adding the pure substances to the solution.

(d) Bromination of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (0.083 g) as described in (a) using two equiv. of bromine gave 0.150 g of a 4.8:12.0:1:2.5 mixture (^{1}H NMR) of the 3-bromo- (**12**; X = Br), the 3,4-dibromo- (**10**; X = Y = Br), the 3,5-dibromo- (**14**; X = Z = Br) and the 3,4,5-tribromo-2-benzylpyrazole 1-oxide (**13**; X = Y = Z = Br). Preparative TLC (diethyl ether–dichloromethane–hexane [1:1:1]) gave 0.019 g (10 %) of 2-benzyl-3,4,5-tribromopyrazole 1-oxide (**13**; X = Y = Z = Br) (R_f = 0.78), identical with the material below, 0.007 g (4 %) of 2-benzyl-3,5-dibromopyrazole 1-oxide (**14**; X = Z = Br) (R_f = 0.56) as an oil which was identified from its ^{1}H NMR spectrum (Table 2), 0.076 g (48 %) of 2-benzyl-3,4-dibromopyrazole 1-oxide (**10**; X = Y = Br) (R_f 0.47) identical with the material above, and 0.024 g (19 %) of 2-benzyl-3-bromopyrazole 1-oxide (**12**; X = Br) (R_f 0.09), identical with the material described above.

(e) Bromination of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (0.314 g) as described in (a) using three times the amount of bromine and potassium carbonate and increasing the reaction temperature to 20 °C gave a solution which was worked up as described in (b) to give 0.67 g (80 %) of yellow 2-benzyl-3,4,5-tribromopyrazole 1-oxide (**13**; X = Y = Z = Br) (R_f 0.80, ethyl acetate–hexane [1:1]), m.p. 114–115 °C (ethyl acetate–hexane). Anal. $C_{10}H_7Br_3N_2O$: C, H, N.

(f) Similar bromination of 2-benzyl-3-nitropyrazole 1-oxide (**12**; X = NO_2) (41 mg) at −80 °C for 5 min and then at 20 °C for 4 days gave a crude product (64 mg) which upon preparative TLC (diethyl ether–dichloromethane–hexane [1:1:1]) gave 36 mg (87 %) of unchanged starting material (**12**; X = NO_2). Harsher conditions led to complicated mixtures.

Chlorination. (a) Sulfuryl chloride (0.28 ml) was added at −80 °C over 3 min to a mixture of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (0.49 g), potassium carbonate (1.21 g), and dichloromethane (7.0 ml). After stirring at −80 °C for 15 min and at 20 °C for 3 h sodium sulfite (0.43 g) dissolved in water (10 ml) was added. Isolation of the organic solution, extraction with a further 4×5 ml of dichloromethane, drying ($MgSO_4$) and removal of the dichloromethane gave 0.57 g of a residue which was purified by preparative TLC, eluting with ethyl acetate to give 0.39 g (66 %) of 2-benzyl-3-chloropyrazole 1-oxide (**12**; X = Cl), m.p. 104 °C (ethyl acetate, low temperature). Anal. $C_{10}H_8ClN_2O$: C, H, N.

(b) Similarly, 2-benzyl-4-bromopyrazole 1-oxide (**9**; Y = Br) (0.069 g) afforded 0.078 g (100 %) of 2-benzyl-4-bromo-3-chloropyrazole 1-oxide (**10**; X = Cl, Y = Br), m.p. 144–145 °C (ethyl acetate). Anal. $C_{10}H_8BrClN_2O$: C, H, N.

(c) A 0.59 M solution of chlorine in tetrachloromethane (4.0 ml) was added over 2 min to a mixture of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (162 mg), potassium carbonate (0.65 g), iodine (10 mg) and dichloromethane (4.0 ml). After 20 min of stirring at 20 °C a further 1.0 ml of chlorine solution were added. This sequence was repeated twice. Evaporation to dryness, extraction with dichloromethane (4×4 ml), and removal of the dichloromethane gave 230 mg of an oil which was purified by preparative TLC (ethyl acetate–hexane [1:1]) to give 24 mg (12 %) of 2-benzyl-3-chloropyrazole 1-oxide (**12**; X = Cl) (R_f 0.12), identical with the material above, and 47 mg (18 %) of 2-benzyl-3,4,5-trichloropyrazole 1-oxide (**13**; X = Y = Z = Cl) (R_f 0.75), m.p. 98 °C (ethyl acetate–hexane). Anal $C_{10}H_7Cl_3N_2O$: C, H, N. The third fraction (R_f 0.45) contained a mixture of dichloro compounds which were separated by preparative TLC (dichloromethane–diethyl ether [1:1]) to afford 27 mg (12 %) of 2-benzyl-3,5-dichloropyrazole 1-oxide (**14**; X = Z = Cl) (R_f 0.74), as an oil which was reprecipitated from ethyl acetate–hexane. The second fraction contained 15 mg (7 %) of 2-benzyl-3,4-dichloropyrazole 1-oxide (**10**; X = Y = Cl) (R_f 0.62), m.p. 85–86 °C (ethyl acetate–hexane). Anal. $C_{10}H_8Cl_2N_2O$: C, H, N.

Nitration. (a) Conc. nitric acid (0.30 ml) was added with stirring at 0 °C over 2 min to a solution of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (0.31 g) in 66 % sulfuric acid (5.0 ml). Stirring at 0 °C for 1 h, dilution with water (20 ml), extraction with dichloromethane (5×5 ml), drying ($MgSO_4$), and removal of the dichloromethane afforded 0.39 g (100 %) of yellow 2-benzyl-3-nitropyrazole 1-oxide (**12**; X = NO_2), m.p. 106–107 °C (ethyl acetate). Anal. $C_{10}H_9N_3O_3$: C, H, N.

(b) Conc. nitric acid (0.36 ml) was added with stirring at 0 °C over 2 min to a solution of 2-benzylpyrazole 1-oxide (**3**; R = $CH_2C_6H_5$) (0.31 g) in 87 % sulfuric acid (9.3 ml). Stirring at 0 °C for 1.5 h and work-up as above gave 0.46 g of an oil which was separated by preparative TLC (dichloro-

methane–diethyl ether–hexane [1:1:1]) to give 0.22 g (40 %) of yellow 3,5-dinitro-2-(4-nitrobenzyl)pyrazole 1-oxide (**7**; R = 4-$NO_2C_6H_4$, R′ = R‴ = NO_2, R″ = H) (R_f 0.73), m.p. 167–168 °C (ethyl acetate). *m/z* 309 (2 %), 136 (100 %). Calc. for $C_{10}H_7N_5O_7$: 309. The next fraction contained 33 % of 3-nitro-2-(4-nitrobenzyl)pyrazole 1-oxide (R_f 0.30) as a yellow oil.

(c) As in (a), 2-benzyl-3-chloropyrazole 1-oxide (**12**; X = Cl) (0.041 g) was nitrated within 2.5 h to give 0.051 g (98 %) of yellow 2-benzyl-3-chloro-4-nitropyrazole 1-oxide (**10**; X = Cl, Y = NO_2), m.p. 114–117 °C. A 7 % solution of the compound in chloroform was completely converted at 20 °C within 3 days. Removal of the chloroform and preparative TLC (dichloromethane–diethyl ether–hexane–formic acid [20:20:20:1]) gave 64 % of 1-benzyl-3-hydroxy-4-nitro-5-chloropyrazole (**17**; X = Cl) (R_f 0.71), m.p. 116 °C (ethyl acetate–hexane). Anal. $C_{10}H_8ClN_3O_3$: C, H, N.

(d) As in (a), 2-benzyl-3-bromopyrazole 1-oxide (**12**; X = Br) (0.103 g) was nitrated within 1.5 h to give 0.126 g (99 %) of yellow 2-benzyl-3-bromo-4-nitropyrazole 1-oxide (**10**; X = Br, Y = NO_2), m.p. 78–82 °C. The compound is unstable in solution and rearranges, as does the corresponding chloro compound **10** (X = Cl, Y = NO_2), as described above into 1-benzyl-5-bromo-3-hydroxy-4-nitropyrazole (**17**; X = Br) (yield 58 %), m.p. 117 °C (ethyl acetate–hexane). Anal. $C_{10}H_8BrN_3O_3$: C, H, N.

Debromination. (a) 2-Benzyl-3,4,5-tribromopyrazole 1-oxide (**13**; X = Y = Z = Br) (0.404 g), sodium sulfite (1.26 g), methanol (11.5 ml), and water (11.5 ml) were heated to reflux with stirring for 5 h. Removal of the water, extraction with dichloromethane (4×10 ml), and removal of the dichloromethane gave 0.231 g (93 %) of 2-benzyl-4-bromopyrazole 1-oxide (**9**; Y = Br) (R_f 0.43, ethyl acetate), m.p. 88–90 °C (ethyl acetate). Anal. $C_{10}H_9BrN_2O$: C, H, N.

(b) Similar debromination of 2-benzyl-3,4,5-tribromopyrazole 1-oxide (**13**; X = Y = Z = Br) (0.244 g) at 60 °C for 20 min gave an oil which was separated by preparative TLC (diethyl ether–dichloromethane [1:1]) to give 0.042 g (73 %) of 2-benzyl-4,5-dibromopyrazole 1-oxide (**16**; Y = Z = Br) (R_f 0.75), m.p. 107 °C (ethyl acetate, low temperature). Anal. $C_{10}H_8Br_2N_2O$: C, H, N. The next fraction contained 7.8 mg (14 %) of 2-benzyl-3,4-dibromopyrazole 1-oxide (**10**; X = Y = Br) (R_f 0.58), identical with the material described above. The last fraction contained 1.6 mg (4 %) of 2-benzyl-4-bromopyrazole 1-oxide (**9**; Y = Br), identical with the material described above.

Deoxygenation. (a) 2-Benzyl-3-chloropyrazole 1-oxide (**12**; X = Cl) (0.068 g) and phosphorus trichloride (0.10 ml) were mixed and stirred with cooling in an ice bath for 0.5 h. Heating to reflux for 5 min, addition of water (1 ml), stirring at 70 °C for 1 h, addition of potassium carbonate until pH = 9, extraction with dichloromethane (3×3 ml), drying ($MgSO_4$), and removal of the dichloromethane produced 0.054 g (87 %) of 1-benzyl-5-chloropyrazole (**15**; X = Cl), identical with an authentic specimen.[17]

(b) A solution of phosphorus trichloride (0.087 ml) in chloroform (1.0 ml) was added at 0 °C to a solution of 2-benzyl-3-bromopyrazole 1-oxide (**12**; X = Br) (0.11 g) in chloroform (0.5 ml). Stirring at 0 °C for 1 h and at 50 °C for 3 h, removal of the chloroform, addition of 1.21 M methanolic sodium acetate (6.0 ml), removal of the methanol, and preparative TLC (acetone–hexane [1:4]) gave 0.10 g (98 %) of 1-benzyl-5-bromopyrazole (**15**; X = Br) as an oil. Anal. $C_{10}H_9BrN_2$: C, H, N.

(c) 2-Benzyl-3-nitropyrazole 1-oxide (**12**; X = NO_2) (0.055 g), phosphorus trichloride (0.20 ml) and chloroform (0.5 ml) were mixed at 0 °C and stirred at 60 °C for 5 h. Evaporation to dryness, addition of water, neutralization with saturated aqueous potassium carbonate, extraction with dichloromethane (3×5 ml), removal of the dichloromethane, and preparative TLC (dichloromethane–diethyl ether–hexane [1:1:1]) afforded 0.037 g (71 %) of 1-benzyl-5-nitropyrazole (**15**; X = NO_2) as a light yellow oil. Ball-tube distillation (170 °C, 1 mmHg) gave the pure compound. Anal. $C_{10}H_9N_3O_2$: C, H, N.

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