Pyrazole Chemistry. Part 4.[1,2] Directed Lithiation of 4-Bromo-1-phenylsulphonylpyrazole: a Convenient Approach to Vicinally Disubstituted Pyrazoles

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4-Bromo-1-phenylsulphonylpyrazole (**10**), obtained from 4-bromopyrazole (**5**) and benzenesulphonyl chloride, can be metallated regioselectively by phenyl-lithium to give the 5-lithio derivative (**15**) which upon quenching with appropriate electrophiles leads to the 4-bromo-1-phenylsulphonyl-5-substituted pyrazoles (**16**)–(**23**), (**25**), and (**26**). Compounds (**22**), (**23**), and (**25**) were found to undergo isomerisation to afford the thermodynamically more stable 4-bromo-1-phenylsulphonyl-3-substituted pyrazoles (**11**), (**24**), and (**13**) under the reaction conditions applied. The phenylsulphonyl protecting group then can be removed readily under alkaline conditions to yield the corresponding 4-bromo-3(5)-substituted 1*H*-pyrazoles (**6**), (**9**), (**28**), (**29**), and (**30**).

Vicinally disubstituted pyrazoles are valuable building blocks for polycyclic compounds containing the 1,2-diazole unit.[4] The approach so far mainly used for their synthesis is characterized by the construction of the pyrazole system from suitable open-chain compounds.[5,6] Another methodology consists of introducing a substituent into an appropriately monosubstituted pyrazole derivative.[5,6] Here we report on investigations aimed at the synthesis of various 4-bromo-3(5)-substituted pyrazoles *via* directed lithiation of a 1,4-disubstituted 1,2-diazole system.

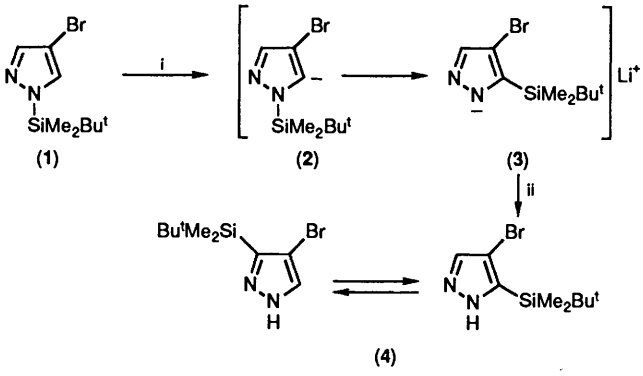
Lithiation of pyrazoles has been investigated in some detail.[7–18] The parent system is known to undergo metallation not only at N-1, but additionally at C-5(3) upon treatment with 2 equiv. of butyl-lithium.[10] The low yield (9%) of pyrazole-3(5)-carboxylic acid obtained after quenching of the dilithiated species with carbon dioxide, is explained by decreased stability of the intermediate dianion owing to repulsive interactions.[7] Better results (up to 90% lithiation in position 5 of the pyrazole ring) have been reported with pyrazoles substituted at N-1 by a methyl, benzyl, or phenyl group.[7,9,13] With respect to the synthesis of 3(5),4-disubstituted 1*H*-pyrazoles *via* the lithiation route such *N*-substituents, however, appear to be of rather limited value since their removal requires drastic conditions.[10,12] Moreover, these groups are known to be susceptible to an attack by lithiating agents.[9,13–15]

When *N*-1 substituted pyrazoles bearing a bromo substituent at C-4 are treated with organolithium compounds, proton abstraction from C-5 or halogen–metal exchange can take place.[10] The course of the reaction obviously depends on the lithiating agent employed: the use of butyl-lithium was found to lead to halogen–metal exchange exclusively,[10,16–18] whereas in the metallation of 4-bromo-1-methylpyrazole with phenyl-lithium both reaction pathways have been reported to occur simultaneously.[10]

By employing the phenylsulphonyl moiety as the *N*-protecting group and by using phenyl-lithium as the metallating species the above mentioned problems now could be overcome, and thus novel vicinally disubstituted pyrazole derivatives could be prepared readily.

Results and Discussion

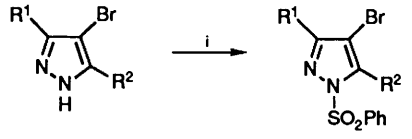
Applying the HSAB (Hard and Soft Acids and Bases) principle[19] to organometallic reactions, halogen–lithium exchange involves a soft-soft interaction.[20] Thus to direct the course of the metallation reaction of a *N*-1 protected 4-bromopyrazole towards deprotonation, the use of a harder organolithium reagent like lithium di-isopropylamide (LDA) or phenyl-lithium should be advantageous. In search of an appropriate *N*-protecting group we found the t-butyldimethylsilyl group to be insufficient. Treatment of 4-bromo-1-t-butyldimethylsilylpyrazole (**1**), which was obtained from 4-bromopyrazole (**5**) and t-butyldimethylsilyl chloride in high yield, with 1 equiv. of LDA in dry tetrahydrofuran (THF) and subsequent addition of benzaldehyde did not result in the formation of the expected phenylpyrazolylmethanol derivative. Instead, compound (**4**) was isolated, the formation of which can be explained in terms of a N to C silyl group rearrangement in (**2**) leading to the thermodynamically more stable *N*-anion (**3**) (Scheme 1). Similar observations have been reported from investigations of lithiation reactions of 1-trimethylsilylpyrroles[21] and 1-t-butyldimethylsilylindoles.[22]



Scheme 1. *Reagents and conditions:* i, LDA, −78 °C to −20 °C; ii, water.

The phenylsulphonyl group employed as *N*-substituent in the lithiation of imidazoles[23] and more successfully in the indole series,[22,24] turned out to be a suitable protecting group. This group is known to act in an *ortho*-directing manner by stabilizing the intermediate lithio species.[7,25] Additionally, it can be easily attached to the pyrazole N-1 as shown in the syntheses of compounds (**10**)–(**14**) (Scheme 2). Finally, *N*-deprotection may be expected to be readily accomplished by alkaline hydrolysis.[22]

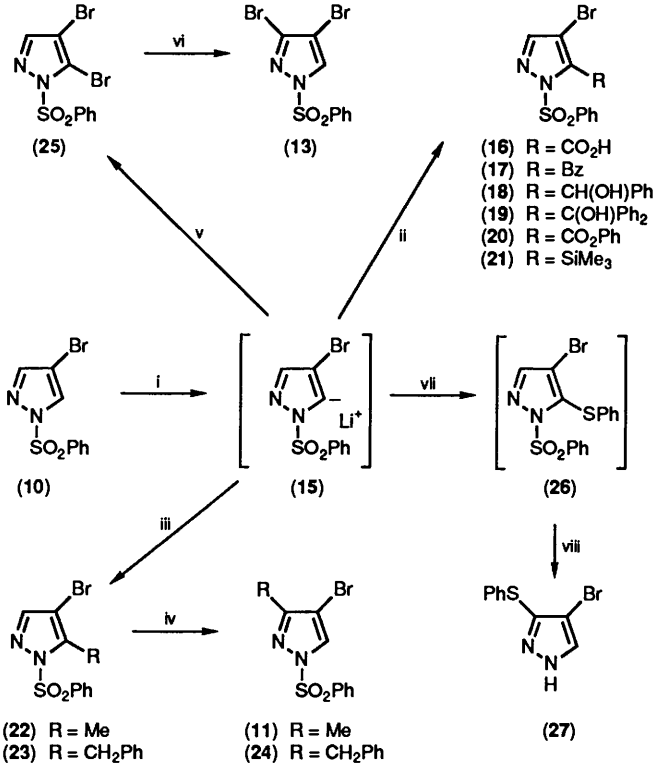
By refluxing a solution of 4-bromopyrazole (**5**) and



(5) R^1 = H, R^2 = H
(6) R^1 = Me, R^2 = H
(7) R^1 = Me, R^2 = Me
(8) R^1 = Br, R^2 = H
(9) R^1 = Bz, R^2 = H

(10) R^1 = H, R^2 = H
(11) R^1 = Me, R^2 = H
(12) R^1 = Me, R^2 = Me
(13) R^1 = Br, R^2 = H
(14) R^1 = Bz, R^2 = H

Scheme 2. *Reagents and conditions:* i, $PhSO_2Cl$–pyridine, reflux.



(16) R = CO_2H
(17) R = Bz
(18) R = CH(OH)Ph
(19) R = $C(OH)Ph_2$
(20) R = CO_2Ph
(21) R = $SiMe_3$

(22) R = Me
(23) R = CH_2Ph

(11) R = Me
(24) R = CH_2Ph

Scheme 3. *Reagents and conditions:* i, PhLi–Et_2O, −78 °C to 0 °C; ii, electrophile = CO_2, BzCl, PhCHO, Ph_2CO, $ClCO_2Ph$, Me_3SiCl, −78 °C to 20 °C; iii, electrophile = MeI, $PhCH_2Br$, −78 °C to 20 °C; iv, 14 h at 20 °C; v, Br_2, −78 °C to 0 °C; vi, 16 h at 20 °C; vii, $(PhS)_2$, −78 °C to 20 °C; viii, work-up.

benzenesulphonyl chloride in dry pyridine 4-bromo-1-phenylsulphonylpyrazole (**10**) could be prepared in 86% yield. Treatment of (**10**) with 1 equiv. of phenyl-lithium in diethyl ether followed by quenching with D_2O, resulted in a mixture containing *ca.* 80% of 4-bromo-1-phenylsulphonyl[5-^{2}H]-pyrazole as shown by means of ^{1}H NMR spectroscopy and GLC/mass spectrometry.* No halogen–metal exchange was observed under these conditions.†

Based on these results, the lithiated species (**15**) was treated with various electrophiles (Scheme 3). Employment of carbon dioxide, benzoyl chloride, benzaldehyde, benzophenone, and phenyl chloroformate resulted in the formation of the expected 5-substituted pyrazole derivatives (**16**)–(**20**) which were isolated in yields up to 65%, whereas from the reaction with diphenyl disulphide the deprotected sulphide (**27**) was obtained. Structure assignments were based on spectroscopic data together with chemical evidence as discussed below.

Although the reaction of (**15**) with an excess of iodomethane afforded *ca.* 80% of a methylated product, as indicated by the ^{1}H NMR spectrum, an analytically pure sample of this compound could be isolated in only moderate yield (28%) owing to problems encountered in chromatographic purification. In contrast, reaction of (**15**) with benzyl bromide gave a multi-component mixture containing only minor amounts of a benzylated product.

In the ^{1}H NMR spectra [$(CD_3)_2SO$ solution] of both above mentioned compounds, the signals of the pyrazole proton were observed at *ca.* 8.75 ppm. A comparison with the chemical shifts of the pyrazole protons in the starting material (**10**) [3-H: 8.03 ppm, 5-H: 8.81 ppm, in $(CD_3)_2SO$ solution] prompts us to conclude these compounds not to be the initially expected 5-alkylpyrazole derivatives (**22**) and (**23**), respectively, but to be the isomeric compounds (**11**) and (**24**). Assignment of the 3-alkyl-4-bromo-1-phenylsulphonylpyrazole structures is further supported by the ^{13}C NMR data (Table).

These findings may be interpreted in terms of enhanced thermodynamic stability of 1,3-disubstituted pyrazoles compared to the corresponding 1,5-isomers (see refs. 5, 6, 27, 28).‡ Obviously, under the conditions applied in the reactions of (**15**) with iodomethane or benzyl bromide an equilibration process resulting in the formation of the thermodynamically more favoured 3-alkyl products (**11**) and (**24**) from the initially formed 5-alkyl derivatives (**22**) and (**23**) is operating. Eventually, small amounts of the kinetic product (**22**) could be detected by ^{1}H NMR and GLC/mass spectrometry.

These considerations were further supported by the following experiment: 4-bromo-3(5)-methylpyrazole (**6**) was refluxed with benzenesulphonyl chloride in pyridine solution (= reaction under thermodynamically controlled conditions)[5] to afford a product shown to be identical with compound (**11**), which had been obtained upon treatment of (**15**) with iodomethane. In this context it should be noted that reactions of C-3(5)-substituted 1*H*-pyrazoles with acyl or sulphonyl halides usually yield the thermodynamically more stable 1,3-disubstituted compounds as the sole products.[5,6,27,28] Isomerisation of a 1,4,5-trisubstituted pyrazole system into the 1,3,4-trisubstituted congener also was observed in the course of the preparation of the trimethylsilylpyrazole derivative (**21**). Whereas in this case only traces of the C-3-trimethylsilyl isomer were formed, the product initially resulting from the reaction of (**15**) with bromine, compound (**25**), showed a high tendency to isomerize. Thus, compound (**25**) only could be

* The preferential attack of the organolithium reagent at position 5 of the pyrazole ring can be explained in terms of the adjacent lone-pair effect (ALP):[26] deprotonation in position 3 would lead to the formation of an anion destabilized by repulsive interaction with the lone-pair of N-2.

† Switching to the softer organolithium reagent s-butyl-lithium resulted in loss of selectivity: in this case also halogen-metal exchange was found to occur.

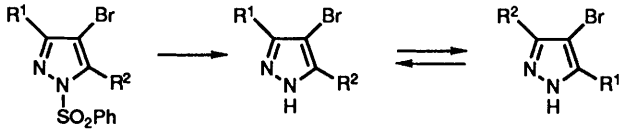
‡ Also according to the results of MO-calculations carried out with the semiempirical AM1 method[29] 1,3,4-trisubstituted pyrazole derivatives have to be considered as energetically more favoured than the 1,4,5-trisubstituted congeners [heats of formation in kcal/mol: (**14**): 192.02, (**17**): 193.47; (**13**): 195.46, (**25**): 199.11; 4-bromo-1-phenylsulphonylpyrazole-3-carboxylic acid: 107.45, (**16**): 109.69]. Only in the case of the methyl-substituted compounds (**11**) and (**22**) there is no significant difference in the heats of formation [(**11**): 182.96, (**22**): 183.08 kcal/mol). The fact that the 1,3,4-trisubstituted compound (**11**) results from the reaction of (**15**) with iodomethane as the far predominant product and as the sole product upon phenylsulphonylation of 4-bromo-3(5)-methylpyrazole (**6**), however, may be interpreted in terms of significant differences in the dipole moments [(**11**): 5.65 D, (**22**): 5.01 D, calculated with the AM1 method],[29] since favoured formation of the more polar species in polar reaction media appears to be a reasonable assumption.

Table. ^{13}C NMR chemical shifts (ppm) and ^{13}C, ^{1}H spin coupling constants (Hz) of 4-bromo-1-phenylsulphonylpyrazole derivatives.

Compd. No.	Solvent*	Chemical shifts (ppm) Pyrazole ring C-3	C-4	C-5	Benzene ring of $PhSO_2$ C-1	C-2,6	C-3,5	C-4	Other C	^{13}C, ^{1}H Coupling constants (Hz)† Pyrazole C, H 3,3	3,5	4,3	4,5	5,5	5,3	Other J
(10)[a]	A	145.98	97.38	131.82	135.68	127.69	129.89	135.31	—	197.0	7.4	8.7	5.6	203.4	3.3	—
(10)[a]	B	145.62	97.48	130.43	136.31	128.09	129.42	134.81	—	195.5	7.5	8.7	5.8	200.9	3.5	—
(11)	A	153.55	99.01	132.23	135.92	127.56	129.79	135.07	*b*	—	7.0	—	5.2	202.6	—	*c*
(12)	A	151.52	100.27	141.22	136.62	127.34	129.78	134.90	*d*			—‡				*e*
(13)[a]	A	135.75	101.20	133.88	135.75	127.93	130.08	135.07	—			—‡				—
(13)[a]	B	135.33	101.48	131.87	135.88	128.35	129.62	135.19	—	—	10.1	—	5.7	202.0	—	—
(14)	A	149.88	98.09	133.95	135.30	128.04	130.04	135.87	*f*	—	7.6	—	5.8	204.9	—	—‡
(16)	A	144.99	97.84	137.60	136.40	128.19	130.05	135.76	*g*			—‡				—‡
(17)	A	145.30	98.15	140.19	135.20	127.92	129.43	135.70	*h*	199.6	—	9.3	—	—	3.2	—‡
(18)	A	145.32	98.03	145.78	136.44	127.98	129.64	135.12	*i*	196.8	—	8.9	—	—	4.3	—‡
(20)	A	145.25	100.59	134.42	135.13	128.02	129.89	135.87	*j*			—‡				—‡
(21)	A	146.40	107.41	143.13	136.48	127.69	129.55	134.92	*k*			—‡				—‡
(24)	A	155.74	98.90	133.05	135.90	127.53	129.78	135.12	*l*	—	7.2	—	—‡	203.0	—	*m*
(25)	B	144.57	103.31	115.64	136.41	128.25	129.47	135.09	—	197.8	—	8.7	—	—	5.0	—

[a] Ref. 1. [b] CH_3: 11.72 ppm. [c] $^{1}J(CH_3)$: 129.2, ^{2}J(C-3, CH_3): 7.0, ^{3}J(C-4, CH_3): 3.8 Hz. [d] CH_3: 12.18 and 11.80 ppm. [e] $^{1}J(CH_3$ at lower field): 129.0, $^{1}J(CH_3$ at higher field): 131.5 Hz. [f] CO: 185.93, phenyl-C: 133.95 (4), 135.03 (1), 130.05 (2,6), 128.47 (3,5) ppm. [g] CO: 160.06 ppm. [h] CO: 185.90, phenyl-C: 134.91 (1), 135.14 (4), 129.91, 129.32 (2,3,5,6) ppm. [i] Phenyl-C: 140.73 (1), 127.79 (3,5), 127.20 (4), 125.98 (2,6), CHOH: (65.49) ppm. [j] CO: 157.02, phenyl-C: 149.44 (1), 129.99 (3,5), 126.90 (4), 121.01 (2,6) ppm. [k] CH_3: 1.20 ppm. [l] Phenyl-C: 135.63 (1), 128.22 (2,3,5,6), 126.31 (4), CH_2: 31.81 ppm. [m] ^{2}J(C-3, CH_2): 7.6 Hz.

* A, $(CD_3)_2SO$; B, $CDCl_3$. † Signs not determined. ‡ Not determined.



(11) R^1 = Me, R^2 = H
(12) R^1 = Me, R^2 = Me
(16) R^1 = H, R^2 = CO_2H
(17) R^1 = H, R^2 = Bz
(18) R^1 = H, R^2 = CH(OH)Ph
(19) R^1 = H, R^2 = $C(OH)Ph_2$

(6) R^1 = Me, R^2 = H
(7) R^1 = Me, R^2 = Me
(28) R^1 = H, R^2 = CO_2H
(9) R^1 = H, R^2 = Bz
(29) R^1 = H, R^2 = CH(OH)Ph
(30) R^1 = H, R^2 = $C(OH)Ph_2$

Scheme 4. *Reagents and conditions:* i, KOH–MeOH–H_2O, reflux.

isolated when the reaction mixture was worked up rapidly; prolonged reaction time (16 h at 20 °C) was found to lead to complete conversion of (**25**) into (**13**). The latter compound again was obtained by phenylsulphonylation of 3(5),4-dibromopyrazole (**8**).*

At present, we are unable to provide a satisfactory explanation for the fact that such isomerisations only occur with compounds (**22**), (**23**), and (**25**).

The phenylsulphonyl protecting group was found to be readily removed by refluxing the *N*-1 substituted pyrazole derivatives in aqueous methanolic potassium hydroxide solution. These conditions were successfully tested with compounds (**11**), (**12**), (**16**), (**17**), (**18**), and (**19**) and the hydrolysis was found to occur quantitatively as monitored by TLC.†

Thus, the corresponding 1*H*-pyrazoles (**6**), (**7**), (**28**), (**9**), (**29**), and (**30**) could be obtained in yields ranging from 60 to 93%.

All products obtained were characterized by elemental analyses as well as by their IR, ^{1}H NMR, and mass spectra; for ^{13}C NMR data of 4-bromo-1-phenylsulphonylpyrazole derivatives see Table.

The differentiation between 4-bromo-1-phenylsulphonyl-5-substituted pyrazoles and the 1,3,4-substituted isomers is based on ^{1}H NMR chemical shifts observed and on ^{13}C NMR data according to the arguments given in ref. 1. The assignments made are in good agreement with the results obtained by other authors in investigations aimed at the differentiation of isomeric pairs of alkyl 1-aryl-4-methylpyrazole-3- and -5-carboxylates.[30] In addition, reaction of 3-benzoyl-4-bromopyrazole (**9**), prepared by alkaline hydrolysis of compound (**17**), with benzenesulphonyl chloride in refluxing pyridine provided further evidence for the substitution pattern in compounds (**16**)–(**21**). According to ref. 6, under these conditions formation of 3-benzoyl-4-bromo-1-phenylsulphonylpyrazole (**14**) has to be expected. Since the isolated product turned out to be an isomer of the compound obtained upon reaction of (**15**) with benzoyl chloride, there cannot be any doubt about the 1,4,5-trisubstituted pyrazole structure of the latter.

Conclusion.—In summary, 4-bromo-3(5)-substituted 1*H*-pyrazoles were found to be readily available *via* a reaction sequence characterized by phenylsulphonylation of 4-bromopyrazole, regioselective lithiation (at C-5), reaction with an appropriate electrophile and *N*-deprotection under simple hydrolytic conditions.

Experimental

M.p.s were determined with a Reichert-Kofler hot-stage microscope and are uncorrected. IR spectra were recorded on a Jasco IRA-1 spectrophotometer. NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker AC 80 spectrometer (80 MHz for ^{1}H, 20 MHz for ^{13}C), acquisition parameters and pulse programs used were the same as those reported in ref. 1. The centre of the solvent peak was used as internal reference, which

* Interestingly, isomerisation of compound (**25**) into compound (**13**) takes place not only in solution but also when (**25**) is heated to a temperature above 100 °C as shown by TLC (silica gel, dichloromethane). Accordingly, compound (**25**) cannot be characterised by a defined melting point. For reports on thermally induced rearrangements of 1,5-disubstituted pyrazoles into 1,3-disubstituted isomers also compare refs. 5, 6, 27, and 28.

† When 4-bromo-1-phenylsulphonylpyrazoles bearing an electron-withdrawing substituent at C-5 [compounds (**16**), (**17**), and (**20**)] were dissolved in wet dimethyl sulphoxide the *N*-protecting group was removed, indicating these compounds to be particularly sensitive to hydrolytic cleavage of the N–S bond.

was related to tetramethylsilane with δ_H 7.26 ppm, δ_C 77.00 ppm for $CDCl_3$, and δ_H 2.49 ppm, δ_C 39.50 ppm for $(CD_3)_2SO$. Mass spectra were obtained on a Varian MAT 311A instrument (70 eV). GLC/mass spectrometric analyses were performed on a Hewlett Packard 5890A/5970B-MSD (70 eV) using a 12 m HP1-FS-WCOT column. MO calculations were carried out using the semiempirical AM1 method[29] as implemented in the AMPAC program package.[31] All geometries were completely optimized without making any assumptions. For TLC, Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} were used, column chromatography was carried out on Merck Kieselgel 60 (70–230 mesh), medium-pressure liquid chromatography (MPLC) was performed on Merck LiChroprep Si 60 (230–400 mesh), detection at 280 nm. All reactions employing organolithium reagents were carried out under dry argon. Diethyl ether and tetrahydrofuran were dried by passage through a column of alumina (activity I, basic); light petroleum refers to the fraction of b.p. 50–70 °C.

4-Bromo-1-t-butyldimethylsilylpyrazole (**1**).—A solution of 4-bromopyrazole (**5**)[32] (1.47 g, 10 mmol) and t-butyldimethylchlorosilane (1.51 g, 10 mmol) in dry triethylamine (20 ml) was refluxed for 16 h. The precipitated triethylamine hydrochloride was filtered off and the remaining solution was evaporated under reduced pressure. The residue was subjected to Kugelrohr-distillation affording the *title compound* as a colourless oil (2.165 g, 83%), b.p. 105–110 °C/0.1 mmHg, which solidified with time (Found: C, 41.1; H, 6.65; N, 10.55. $C_9H_{17}BrN_2Si$ requires C, 41.40; H, 6.56; N, 10.73%); $\delta_H(CDCl_3)$ 0.47 (6 H, s, Me_2Si), 0.91 (9 H, s, Bu^t), 7.58 (1 H, s, pyrazole 3-H), and 7.70 (1 H, s, pyrazole 5-H); $\delta_C(CDCl_3)$ −5.81 (Me_2Si), 17.87 (CMe_3), 25.60 (CMe_3), 94.19 (pyrazole C-4), 134.70 (pyrazole C-5), and 143.59 (pyrazole C-3); *m/z* 260 and 262 (M^+, 4%) and 75 (100).

Attempted Substitution of 4-Bromo-1-t-butyldimethylsilylpyrazole (**1**) *by Reaction with Lithium Di-isopropylamide and Subsequent Treatment with Benzaldehyde.*—1.6M Butyl-lithium in hexane (7.5 ml, 12 mmol) was added dropwise to a stirred solution of dry di-isopropylamine (1.214 g, 12 mmmol) in dry THF (10 ml) at −78 °C. The resulting mixture was stirred for 5 min at −78 °C, after which it was allowed to warm slowly to ambient temperature; stirring was then continued for additional 30 min. After this the reaction mixture was cooled to −78 °C and 4-bromo-1-t-butyldimethylsilylpyrazole (**1**) (2.61 g, 10 mmol) in dry THF (5 ml) was added. After 30 min at −78 °C the cooling bath was removed and the mixture was allowed to warm to −20 °C. After renewed cooling to −78 °C benzaldehyde (1.06 g, 10 mmol) in THF (4 ml) was added dropwise and the mixture was warmed slowly to 25 °C. Saturated aqueous ammonium chloride solution (20 ml) was added and the resulting mixture was extracted with diethyl ether (3 × 30 ml). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. From the resulting orange oil crystals separated, which were collected, washed with light petroleum, and recrystallized from this solvent to afford 4-bromo-3(5)-t-butyldimethylsilylpyrazole (**4**) as colourless crystals (289 mg, 11%), m.p. 153 °C (Found: C, 41.3; H, 6.45; N, 10.5. $C_9H_{17}BrN_2Si$ requires C, 41.40; H, 6.56; N, 10.73%); ν_{max}(KBr) 3 150 cm^{-1} (NH); $\delta_H(CDCl_3)$ 0.39 (6 H, s, Me_2Si), 0.94 (9 H, s, Bu^t), 7.59 [1 H, s, pyrazole 3(5)-H], and 10.60 (1 H, br s, exchangeable with D_2O, NH); $\delta_C(CDCl_3)$ −5.87 (Me_2Si), 17.59 (CMe_3), 26.44 (CMe_3), 102.47 (pyrazole C-4), 138.99 [pyrazole C-5(3)-Si], and 140.68 [pyrazole C-3(5)]; *m/z* 260 and 262 (M^+, 16%) and 203 and 205 (100).

Reaction of 4-Bromo-1H-pyrazoles with Benzenesulphonyl Chloride: General Procedure for the Preparation of 4-Bromo-1-phenylsulphonylpyrazole Derivatives (**10**)–(**14**).—A solution of 10 mmol of the 4-bromo-1*H*-pyrazole derivative [(**5**):[32] 1.47 g, (**6**):[33] 1.61 g, (**7**):[34] 1.75 g, (**8**):[35] 2.25 g, (**9**): 2.51 g] and benzenesulphonyl chloride (1.77 g, 10 mmol) in dry pyridine (10 ml) 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. Thus, the following compounds were obtained.

4-Bromo-1-phenylsulphonylpyrazole (**10**) [starting from (**5**)] (2.46 g, 86%) as colourless crystals, m.p. 90–91 °C (from ethanol) (Found: C, 37.65; H, 2.5; N, 9.9. $C_9H_7BrN_2O_2S$ requires C, 37.65; H, 2.46; N, 9.76%); $\delta_H[(CD_3)_2SO]$ 7.58–8.06 (5 H, m, Ph), 8.03 (1 H, s, pyrazole 3-H), and 8.81 (1 H, s, pyrazole 5-H); *m/z* 286 and 288 (M^+, 6%) and 77 (100).

4-Bromo-3-methyl-1-phenylsulphonylpyrazole (**11**) [starting from (**6**)] (2.46 g, 82%) as colourless crystals, m.p. 112–113 °C (from ethanol) (Found: C, 39.85; H, 3.0; N, 9.3. $C_{10}H_9BrN_2O_2S$ requires C, 39.88; H, 3.01; N, 9.30%); $\delta_H[(CD_3)_2SO]$ 2.15 (3 H, s, Me), 7.55–8.06 (5 H, m, Ph), and 8.72 (1 H, s, pyrazole 5-H); *m/z* 300 and 302 (M^+, 7%) and 77 (100).

4-Bromo-3,5-dimethyl-1-phenylsulphonylpyrazole (**12**) [starting from (**7**)] (2.73 g, 87%) as colourless crystals, m.p. 108–109 °C (from ethanol) (Found: C, 41.9; H, 3.45; N, 8.9. $C_{11}H_{11}BrN_2O_2S$ requires C, 41.92; H, 3.52; N, 8.89%); $\delta_H[(CD_3)_2SO]$ 2.13 (3 H, s, pyrazole 3-Me), 2.51 (3 H, s, pyrazole 5-Me), and 7.55–8.03 (5 H, m, Ph); *m/z* 314 and 316 (M^+, 7%) and 77 (100).

3,4-Dibromo-1-phenylsulphonylpyrazole (**13**) [starting from (**8**)] (2.98 g, 81%) as colourless crystals, m.p. 141–142 °C (from ethanol) (Found: C, 29.8; H, 1.75; N, 7.65. $C_9H_6Br_2N_2O_2S$ requires C, 29.53; H, 1.65; N, 7.65%); $\delta_H[(CD_3)_2SO]$ 7.55–8.08 (5 H, m, Ph), and 8.90 (1 H, s, pyrazole 5-H); *m/z* 366 (M^+, 10%) and 77 (100).

4-Bromo-1-phenylsulphonylpyrazol-3-yl phenyl ketone (**14**) [starting from (**9**)] (2.93 g, 75%) as colourless crystals, m.p. 104–106 °C (from di-isopropyl ether) (Found: C, 49.0; H, 2.8; N, 7.1. $C_{16}H_{11}BrN_2O_3S$ requires C, 49.12; H, 2.83; N, 7.16%); ν_{max} 1 660 cm^{-1} (C=O); $\delta_H[(CD_3)_2SO]$ 7.40–8.14 (10 H, m, Ph) and 9.61 (1 H, s, pyrazole 5-H); *m/z* 390 and 392 (M^+, 9%) and 77 (100).

Lithiation of 4-Bromo-1-phenylsulphonylpyrazole (**10**): *Preparation of 'Mixture A' containing the Lithio Intermediate* (**15**).—2M Phenyl-lithium in benzene–diethyl ether (3:1) (0.5 ml, 1 mmol) was added dropwise to a stirred solution of (**10**) (287 mg, 1 mmol) in dry diethyl ether (4 ml) at −78 °C. The resulting mixture (containing a white precipitate) was allowed to warm to 0 °C within 2 h, after which it was cooled again to −78 °C before treatment with electrophiles. In the following, the mixture thus obtained was designated as 'Mixture A'.

4-Bromo-1-phenylsulphonylpyrazole-5-carboxylic Acid (**16**).—Dry carbon dioxide gas was bubbled through 'Mixture A' [prepared from 1 mmol of (**10**) as described above] for 30 min at −78 °C. The reaction mixture was then allowed to warm to ambient temperature within 1.5 h, after which it was diluted with water (10 ml). The organic layer was separated and the aqueous layer was acidified to pH 1–2 with 2M hydrochloric acid (precipitation of a colourless solid); it was then exhaustively extracted with diethyl ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was washed with di-isopropyl ether to yield the *title compound* as colourless crystals (227 mg, 65%), m.p. 129–132 °C (decomp.) (Found: C, 34.7; H, 2.75; N, 8.0. $C_{10}H_7BrN_2O_4S{\cdot}H_2O$ requires C, 34.40; H, 2.60; N, 8.02%);

ν_{max}(KBr) 2 900 and 2 560 (OH) and 1 720 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 7.61–8.05 (5 H, m, Ph), 8.09 (1 H, s, pyrazole 3-H), and 13.00 (1 H, very br s, CO_2H); *m/z* 286 and 288 ($M^+ - CO_2$, 0.3%) and 77 (100).

4-Bromo-1-phenylsulphonylpyrazol-5-yl Phenyl Ketone (**17**).—To a stirred solution of benzoyl chloride (141 mg, 1 mmol) in dry diethyl ether (3 ml) 'Mixture A' [prepared from 1 mmol of (**10**) as described above] was added at −78 °C. The reaction mixture was kept at this temperature for 20 min after which it was allowed to warm to ambient temperature within 2 h. Aqueous ammonium chloride (12 ml) was added, the phases were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was digested with cold ethanol and recrystallized from tetrachloromethane to yield the *title compound* as colourless crystals (200 mg, 51%), m.p. 154–156 °C (Found: C, 48.9; H, 2.85; N, 7.0. $C_{16}H_{11}BrN_2O_3S$ requires C, 49.12; H, 2.83; N, 7.16%); ν_{max}(KBr) 1 655 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 7.50–8.00 (10 H, m, Ph) and 8.25 (1 H, s, pyrazole 3-H); *m/z* 390 and 392 (M^+, 5%) and 77 (100).

4-Bromo-1-phenylsulphonylpyrazol-5-yl(phenyl)methanol (**18**).—Benzaldehyde (106 mg, 1 mmol) in diethyl ether (2 ml) was added dropwise to 'Mixture A' [prepared from 1 mmol of (**10**) as described above] with stirring at −78 °C and the mixture was allowed to warm slowly to ambient temperature. Work-up was carried out as described for the preparation of (**17**). Digestion of the crude product with light petroleum and recrystallisation from ethanol afforded the *title compound* (196 mg, 50%) as colourless crystals, m.p. 116 °C (Found: C, 48.95; H, 3.35; N, 7.05. $C_{16}H_{13}BrN_2O_3S$ requires C, 48.87; H, 3.33; N, 7.12%); ν_{max}(KBr) 3 530 cm^{-1} (OH); δ_H[$(CD_3)_2SO$] 6.41 (1 H, br s, exchangeable with D_2O, OH), 6.60 (1 H, br s, sharp s after addition of D_2O, C*H*OH), 7.31 (5 H, m, C-Ph), 7.50–7.90 (5 H, m, S-Ph), and 7.97 (1 H, s, pyrazole 3-H); *m/z* 251 and 253 ($M^+ - SO_2Ph$, 45%) and 77 (100).

4-Bromo-1-phenylsulphonylpyrazol-5-yl(diphenyl)methanol (**19**).—Preparation of (**19**) from 'Mixture A' [prepared from 1 mmol of (**10**) as described above] and benzophenone (182 mg, 1 mmol) was carried out in a similar manner to that described for compound (**18**). Recrystallisation of the product from ethanol yielded the *title compound* (188 mg, 40%) as colourless crystals, m.p. 136–137 °C (Found: C, 56.5; H, 3.7; N, 5.9. $C_{22}H_{17}BrN_2O_3S$ requires C, 56.30; H, 3.65; N, 5.97%); ν_{max}(KBr) 3 500 cm^{-1} (OH); δ_H[$(CD_3)_2SO$] 6.68 (1 H, s, exchangeable with D_2O, OH), 7.00–7.80 (15 H, m, Ph), and 7.89 (1 H, s, pyrazole 3-H); *m/z* 468 and 470 (M^+, 5%) and 77 (100).

Phenyl 4-Bromo-1-phenylsulphonylpyrazole-5-carboxylate (**20**).—Preparation of (**20**) from 'Mixture A' [prepared from 1 mmol of (**10**) as described above] and phenyl chloroformate (157 mg, 1 mmol) was carried out in a similar manner to that described for compound (**17**). From the remaining dark orange oil colourless crystals separated, which were recrystallized from di-isopropyl ether to afford the *title compound* (59 mg, 13%) as colourless crystals, m.p. 88–91 °C (Found: C, 43.15; H, 3.15; N, 6.3. $C_{16}H_{11}BrN_2O_4S{\cdot}2H_2O$ requires C, 43.35; H, 3.41; N, 6.32%); ν_{max}(KBr) 1 735 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 7.27–8.11 (10 H, m, Ph) and 8.29 (1 H, s, pyrazole 3-H); *m/z* 406 and 408 (M^+, 2%) and 77 (100).

4-Bromo-1-phenylsulphonyl-5-trimethylsilylpyrazole (**21**).—Preparation of (**21**) from 'Mixture A' [prepared from 1 mmol of (**10**) as described above] and trimethylchlorosilane (543 mg, 5 mmol) was carried out in a similar manner to that described for compound (**18**). The remaining orange oil was subjected to column chromatography (eluant: dichloromethane–light petroleum, 9:1) to afford the *title compound* (85 mg, 24%) as a colourless oil (Found: C, 40.4; H, 4.15; N, 7.9. $C_{12}H_{15}BrN_2O_2SSi$ requires C, 40.11; H, 4.21; N, 7.80%); δ_H[$(CD_3)_2SO$] 0.53 (9 H, s, Me), 7.60–8.00 (5 H, m, Ph), and 8.01 (1 H, s, pyrazole 3-H); *m/z* 358 and 360 (M^+, 4%) and 343 and 345 ($M - CH_3$, 100).

Reaction of (**15**) (*'Mixture A'*) *with Iodomethane*.—Iodomethane (576 mg, 3 mmol) in diethyl ether (3 ml) was added to 'Mixture A' [prepared from 1 mmol of (**10**) as described above] with stirring at −78 °C. The reaction mixture was allowed to reach ambient temperature and was then stirred for additional 14 h. Work-up as described for the preparation of compound (**18**) resulted in an orange oil, which was subjected to column chromatography (eluant: dichloromethane–light petroleum, 9:1) to afford *4-bromo-3-methyl-1-phenylsulphonylpyrazole* (**11**) (83 mg, 28%), identical with an authentic sample obtained from the reaction of (**11**) with benzenesulphonyl chloride.

Reaction of (**15**) (*'Mixture A'*) *with Benzyl Bromide*.—Reaction of benzyl bromide (171 mg, 1 mmol) in diethyl ether (3 ml) with 'Mixture A' [prepared from 1 mmol of (**10**) as described above] at −78 °C was carried out in a similar manner to that of iodomethane described above. Analogous work-up led to an oily residue, which was subjected to MPLC (eluant: dichloromethane) affording *3-benzyl-4-bromo-1-phenylsulphonylpyrazole* (**24**) (29 mg, 8%) as colourless crystals, m.p. 77–79 °C (Found: C, 51.15; H, 3.55; N, 7.25. $C_{16}H_{13}BrN_2O_2S$ requires C, 50.94; H, 3.47; N, 7.43%); δ_H[$(CD_3)_2SO$] 3.91 (2 H, s, CH_2), 6.95–7.30 (5 H, m, C-Ph), 7.50–8.10 (5 H, m, SPh), and 8.75 (1 H, s, pyrazole 5-H); *m/z* 376 and 378 (M^+, 20%) and 77 (100).

Reaction of (**15**) (*'Mixture A'*) *with Bromine*.—(a) *Preparation of 4,5-dibromo-1-phenylsulphonylpyrazole* (**25**). 'Mixture A' [prepared from 1 mmol of (**10**) as described above] was treated with bromine (160 mg, 1 mmol) at −78 °C. After being stirred at this temperature for 15 min the mixture was brought to 0 °C within 1 h. Aqueous ammonium chloride (12 ml) was added and the excess of bromine was destroyed by treatment with dilute aqueous sodium thiosulphate. The layers were separated and the aqueous phase was extracted exhaustively with diethyl ether. The combined ethereal layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was digested with light petroleum–di-isopropyl ether (9:1) and recrystallized from ethanol to afford *4,5-dibromo-1-phenylsulphonylpyrazole* (**25**) (117 mg, 32%) as colourless crystals, m.p. 100–142 °C (rearrangement) (Found: C, 29.55; H, 1.8; N, 7.4. $C_9H_6Br_2N_2O_2S$ requires C, 29.53; H, 1.65; N, 7.65%); δ_H[$(CD_3)_2SO$] 7.50–8.04 (5 H, m, Ph) and 8.19 (1 H, s, pyrazole 3-H); *m/z* 366 (M^+, 2%) and 226 (100).

(b) *Preparation of 3,4-dibromo-1-phenylsulphonylpyrazole* (**13**). The reaction and the work-up procedure were carried out in a similar manner to that described for the preparation of (**25**), except that after addition of bromine the reaction mixture was allowed to reach 20 °C within 2 h and was stirred at this temperature for an additional 16 h before it was treated with aqueous ammonium chloride. Recrystallisation from ethanol afforded the *title compound* (114 mg, 31%), identical with a sample of (**13**) obtained from the reaction of (**8**) with benzenesulphonyl chloride.

Reaction of (**15**) (*'Mixture A'*) *with Diphenyl Disulphide*.—'Mixture A' [prepared from 1 mmol of (**10**) as described above]

was treated with diphenyl disulphide (240 mg, 1.1 mmol) at −78 °C. The reaction mixture was allowed to reach ambient temperature within 2 h after which it was stirred for additional 16 h. Work-up as described in the preparation of (**17**) resulted in an orange oil which was subjected to MPLC (eluant: dichloromethane) affording *4-bromo-3(5)-phenylthiopyrazole* (**27**) (30 mg, 12%) as colourless crystals, m.p. 107–108 °C (Found: C, 42.5; H, 2.7; N, 11.0. $C_9H_7BrN_2S$ requires C, 42.37; H, 2.77; N, 10.98%); ν_{max}(KBr) 3 100 cm^{-1} (NH); δ_H[$(CD_3)_2SO$] 7.00–7.50 (5 H, m, Ph), 8.07 [1 H, s, pyrazole 5(3)-H], and 13.75 (1 H, br s, exchangeable with D_2O, NH); *m/z* 254 and 256 (M^+, 96%) and 148 (100).

General Procedure for the Hydrolytic Removement of the N-Phenylsulphonyl Protecting Group.—To the 4-bromo-1-phenylsulphonylpyrazole derivative [(**11**), (**12**), (**16**), (**17**), (**18**), (**19**)] (1 mmol) in methanol (5 ml) aqueous 4M KOH (5 ml) was added and the resulting mixture was heated to reflux for 1 h. After cooling, the mixture was acidified to pH 4 with 12M HCl and methanol was removed under reduced pressure. Route A: the precipitated crystals were filtered off, washed several times with water, and dried to yield pure 1*H*-pyrazole. Route B (alternative method): the remaining aqueous phase was extracted exhaustively with diethyl ether or dichloromethane and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The remaining solid was dried to afford pure 1*H*-pyrazole. Thus were obtained: 4-bromo-3(5)-methylpyrazole (**6**) [starting from (**11**) (301 mg), *via* route B] (134 mg, 83%), m.p. 70–74 °C (lit.,[33a] m.p. 67 °C, lit.,[33b] m.p. 76–77 °C), identical in other respects with an authentic sample: 4-bromo-3,5-dimethylpyrazole (**7**) [starting from (**12**) (315 mg), *via* route B] (140 mg, 80%), m.p. 114–117 °C (lit.,[34] m.p. 118 °C), identical in other respects with an authentic sample: 4-bromopyrazole-3(5)-carboxylic acid (**28**) [starting from (**16**) (331 mg), *via* route B] (90 mg, 60%), m.p. 220–230 °C (decomp.) [lit.,[10] m.p. 237.5–239.5 °C (decomp.)], ν_{max}(KBr) 3 200 (NH), 2 500 (OH), and 1 680 cm^{-1} (C=O); *m/z* 190 and 192 (M^+, 2%) and 146 and 148 ($M - CO_2$, 100): *4-bromopyrazol-3(5)-yl phenyl ketone* (**9**) [starting from (**17**) (391 mg), *via* route A] (225 mg, 90%), as colourless crystals, m.p. 135–138 °C (Found: C, 48.0; H, 2.85; N, 11.2. $C_{10}H_7BrN_2O$ requires C, 47.84; H, 2.81; N, 11.16%); ν_{max}(KBr) 3 240 (NH) and 1 630 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 7.45–7.70 (3 H, m, Ph 3,4,5-H), 7.94–8.09 (2 H, m, Ph 2,6-H), 8.18 [1 H, s, pyrazole 5(3)-H], and 13.5 (1 H, br s, exchangeable with D_2O, NH); δ_C[$(CD_3)_2SO$] 94.70 (pyrazole C-4), 128.13 (Ph C-3,5), 129.99 (Ph C-2,6), 132.50 [br, pyrazole C-3(5), 5(3)], 132.77 (Ph C-4), 136.97 (Ph C-1), and 186.96 (CO); *m/z* 250 and 252 (M^+, 29%) and 105 (100): *4-bromopyrazol-3(5)-yl(phenyl)methanol* (**29**) [starting from (**18**) (393 mg, *via* route B] (235 mg, 93%) as a colourless powder, m.p. 145–150 °C (Found: C, 47.3; H, 3.55; N, 11.05. $C_{10}H_9BrN_2O$ requires C, 47.46; H, 3.58; N, 11.07%); ν_{max}(KBr) 3 450 (NH) and 3 200 cm^{-1} (OH); δ_H[$(CD_3)_2SO$] 5.75 (1 H, d, *J* 3.8 Hz, s after addition of D_2O, C*H*OH), 6.24 (1 H, br s, exchangeable with D_2O, OH), 7.20–7.45 (5 H, m, Ph), 7.81 [1 H, br s, pyrazole 5(3)-H], and 13.20 (1 H, br s, exchangeable with D_2O, NH); *m/z* 252 and 254 (M^+, 96%) and 155 (100): *4-bromopyrazol-3(5)-yl(diphenyl)methanol* (**30**) [starting from (**19**) (469 mg), *via* route B] (197 mg, 60%), as colourless solid foam, m.p. 61–65 °C (Found: C, 58.4; H, 3.85; N, 8.3. $C_{16}H_{13}BrN_2O$ requires C, 58.38; H, 3.98; N, 8.51%); ν_{max}(KBr) 3 200 cm^{-1} (NH, OH); δ_H[$(CD_3)_2SO$] 6.15 (1 H, br s, exchangeable with D_2O, OH), 7.26 (10 H, m, Ph), 7.90 [1 H, br s, pyrazole 5(3)-H], and 12.89 (1 H, br s, exchangeable with D_2O, NH); *m/z* 328 and 330 (M^+, 60%) and 77 (100).

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