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ALPHA-LITHIATION OF N-ALKYL GROUPS IN PYRAZOLES

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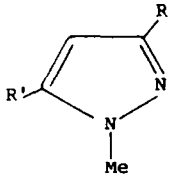
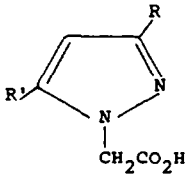
Abstract—1,3,5-Trimethylpyrazole and 1-ethyl-3,5-dimethylpyrazole undergo lithiation exclusively at the α-position of the N-alkyl group. 1-Benzylpyrazole is metallated under kinetic control at −78° at the CH_2 group, but the metallorganic intermediate rearranges rapidly at 23° to give the thermodynamically more stable 5-lithio-1-benzylpyrazole. 1-Methylpyrazole gives mixtures of α- and 5-lithiation; 1-ethylpyrazole showed only 5-lithiation. The carbanions were trapped by a variety of electrophiles.

While ring metallation of azoles in general[1] and pyrazoles in particular[2] is well known, and the phenyl group of 1-phenylpyrazole can be metallated at the *ortho*-position,[3] there have only been two reports of the α-metallation of an N-alkyl group in a simple azole. Micetich reported[4] that 1,3,5-trimethylpyrazole (**1**) and 1-methyl-3-phenyl-5-methoxypyrazole (**2**) each gave the corresponding pyrazole-1-acetic acids (**4, 5**) after treatment with n-BuLi followed by CO_2. Butler and Alexander[5] reported that the 1-Me groups in 1-methylpyrazole and 1,3-dimethylpyrazole underwent *ca* 30% of α-metallation in competition with that (*ca* 60%) at the 5-position; however, 1,5-dimethylpyrazole and 1-methyl-3-phenyl-5-chloropyrazole were metallated predominantly at the 1-Me group. The 1-pyrazolylmethyllithiums were reacted only with aldehydes and ketones (benzaldehyde, benzophenone, and cyclohexanone). Russian authors[6] have postulated α-methylation in the benzyl group of 1-benzyl-3,5-dimethylpyrazole, but only ring-opened products were isolated.





1 R = R' = Me

2 R = Ph; R' = OMe

3 R = R' = H

4 R = R' = Me

5 R = Ph; R' = OMe

Following our work on the α-metallation of alkyl groups in N-alkylazolones[7], we have now demonstrated that the α-metallation of alkyl groups in N-alkylpyrazole is a general reaction. We report here our findings on this reaction which is of potential synthetic importance as the N-(α-lithioalkyl)-pyrazoles can be reacted with a variety of electrophiles to form products often difficultly available by other routes.

We first studied 1-alkyl-3,5-dimethylpyrazoles and found that lithiation occurs exclusively at the N-alkyl group.

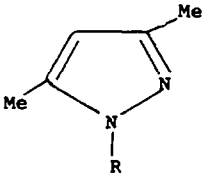
1,3,5-*Trimethylpyrazole* (**1**). The 1-lithio derivative of **1** was successfully prepared using n-BuLi at −78° and trapped with electrophiles (Table 1). The reaction with electrophiles was carried out at 23° for 5–8 hr. The lithio derivative was a pale yellow, on addition of the electrophiles the color deepened and then slowly faded.

Reactions of the 1-lithio derivative with deuterium oxide gave 1-monodeuteriomethyl-3,5-dimethyl pyrazole (**6**) with an NMR spectrum identical to starting material (Table 2) except that the N-methyl singlet was reduced in intensity. Methyl iodide afforded 1-ethyl-3,5-dimethylpyrazole (**7**) identical with an authentic sample.

m-Tolualdehyde, cyclohexanone, acetophenone and benzophenone each produced the secondary or tertiary alcohol **11**, **14**, **12** and **13**, respectively, with νOH at 3320-3300 cm^{-1}, again with the expected NMR spectra (Table 2). Acid chlorides gave ketones: **8** and **9** were obtained from *p*-toluoyl and benzoyl chloride, respectively. However, if an excess of benzoyl chloride was used, the initially produced ketone **9** reacted with a second molecule of the acyl chloride to give the unsaturated ester **10**.

1-*Ethyl*-3,5-*dimethylpyrazole* (**7**). Lithiation at −78° with t-BuLi in THF, and treatment with methyl *p*-methylbenzoate, gave ketone **15**.

1-*Benzylpyrazole* (**16**). Hüttel and Schön[9] treated **16** successively with PhLi and CO_2 and obtained the corresponding 5-carboxylic acid **17**, the structure of which was demonstrated by debenzylation to pyrazole-3-carboxylic acid.



6 CH_2D

7 Et

8 $CH_2COC_6H_4Me$-p

9 CH_2COPh

10 CH = C(Ph)OCOPh

11 $CH_2CH(OH)C_6H_4Me$-m

12 $CH_2CMe(OH)Ph$

13 $CH_2C(OH)Ph_2$

14 $CH_2C(OH)(C_5H_{10})$-cyclo

15 $CH(Me)COC_6H_4Me$-p

Table 1. Preparation of 1-substituted-3,5-dimethylpyrazoles[a]

Electrophilic Reagent	Cmpd. No.	R	Reaction time (h)	Yield (%)	M.p. (°C)	Recryst. solvent	Crystal form	Found (%) C	Found (%) H	Found (%) N	Molecular Formula	Required (%) C	Required (%) H	Required (%) N
D_2O	6	CH_2D	1	99	165-170[b]	-[d]	oil	64.5	-	25.0	$C_6H_9DN_2$	64.8	-	25.2
MeI	7	CH_2Me	5	52	170-174[b,c]	-[d]	oil	-	-	-	$C_7H_{12}N_2$	-	-	-
4-MeC_6H_4COCl	8	$CH_2COC_6H_4Me$-p	5	92	89-91	EtOAc	needles	73.5	7.1	12.2	$C_{14}H_{16}N_2O$	73.6	7.1	12.3
PhCOCl	9	CH_2COPh	8	22	87-88	EtOH	needles	72.6	6.7	13.0	$C_{13}H_{14}N_2O$	72.9	6.6	13.1
PhCOCl (excess)	10	CH=C(Ph)OCOPh	8	85	119-120	EtOAc	prisms	75.5	5.8	8.8	$C_{20}H_{18}N_2O_2$	75.4	5.7	8.8
3-MeC_6H_4CHO	11	$CH_2CH(OH)C_6H_4Me$-m	6	84	129-131	EtOAc	needles	73.0	7.9	12.2	$C_{14}H_{18}N_2O$	73.0	7.9	12.2
MeCOPh	12	$CH_2CMe(OH)Ph$	6	78	97-98	EtOAc	prisms	72.9	7.9	12.2	$C_{14}H_{18}N_2O$	73.0	7.9	12.2
PhCOPh	13	$CH_2C(OH)Ph_2$	5	80	65-66	EtOH	prisms	77.8	7.0	9.5	$C_{19}H_{20}N_2O$	78.0	6.9	9.6
$C_6H_{10}O$-cyclo	14	$CH_2C(OH)(C_5H_{10})$-cyclo	5	65			oil				$C_{12}H_{20}N_2O$	69.2	9.7	13.5

[a] Procedure B was used for the lithiation (see Experimental). [b] B.p. recorded at atmospheric pressure. [c] Lit.[8] b.p. 172-175.

[d] Purified by distillation.

Table 2. IR and NMR data for 1-substituted-3,5-dimethylpyrazoles

Cmpd. no.	R	Ir spectra[a]			^{1}H Nmr spectra[b]													
					3- and 5-Me	4-CH	α-CH				Aromatic				Others			
		νO-H	νC=O	νC=C	(6 H, 1 or 2 s)	(1 H, s)	δ	m	H	J(Hz)	δ	m	H	J(Hz)	δ	m	H	J(Hz)
6	CH_2D	-	-	-	2.3	5.8	4.1	s	2	-	-	-	-	-	-	-	-	-
7	CH_2Me	-	-	-	2.2	5.75	4.0	q	2	7	-	-	-	-	1.4	t	3	7
8	$CH_2COC_6H_4Me$-p	-	1700	-	2.2, 2.3	5.9	5.4	s	2	-	7.3-7.9	ABq	4	6.5	2.5	s	3	-
9	CH_2COPh	-	1685	-	2.15, 2.3	5.9	5.5	s	2	-	7.25-8.2	m	5	-	-	-	-	-
10	CH=C(Ph)OCOPh	-	1740	1670	1.9, 2.3	5.8	7.1	s	1	-	7.2-7.7	m	10	-	-	-	-	-
11	$CH_2CH(OH)C_6H_4$ Me-m	3300	-	-	2.0, 2.2	5.9	4.1	d	2	1	7.1-7.2	m	4	-	2.5	s	3	-
															7.3	s	1	-
12	$CH_2CMe(OH)Ph$	3300	-	-	1.9, 2.3	5.7	4.1	s	2	-	7.2-7.4	m	5	-	1.5	s	3	-
															5.9	s	1	-
13	$CH_2C(OH)Ph_2$	3320	-	-	1.9, 2.25	5.6	4.6	s	2	-	7.2-7.5	m	11	-	-	-	-	-
14	$CH_2C(OH)(C_5H_{10})$-cyclo		-	-	2.2, 2.3	5.8	4.0	s	2	-	-	-	-	-	1.3-1.6	m	10	-
															7.5	s	1	-

[a] Recorded in $CHBr_3$. [b] Recorded in $CDCl_3$; s = singlet, d = doublet, t = triplet, m = multiplet, ABq = AB quartet.

We find that the 5-carboxylic acid **17** is formed if **16** is treated with: (a) PhLi at 23° in Et_2O, followed by CO_2, or (b) n-BuLi at −78° in THF, the solution allowed to warm to 23°C for 1 h and then treated with CO_2 at −78°, or (c) n-BuLi at −78°, in Et_2O, the solution allowed to warm to 23° for $8\frac{1}{2}$ h and then treated with CO_2 at −78°. However, α-carboxylic acid **18** is formed if **16** is treated with n-BuLi at −78° and then immediately treated with CO_2 still at −78°.

Clearly, lithiation originally occurs at the α-position but then on standing the α-Li derivative isomerizes to the thermodynamically more stable 5-isomer.

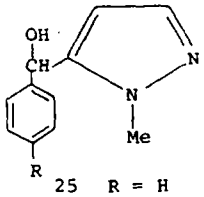
Reactions of (**16**) with n-BuLi at −78° followed by addition of *p*-tolualdehyde, acetophenone, or benzophenone in each case gave the corresponding alcohols **21**, **22**, **23**, by substitution at the benzylic center. These products each showed the characteristic NMR triplet for the 4-pyrazole ring proton, whereas the benzylic singlet had been replaced by an AB quartet (for **21**) or an 1H singlet (for **22**, **23**) (Table 3). The alcohols showed νOH at 3320 cm^{-1}, but no carbonyl absorption.

Reaction of **16** with n-BuLi and methyl *p*-toluate gave the expected ketone **19.** However, a similar reaction with *p*-toluoyl chloride afforded **24** apparently by reaction of the intermediate **19** with further lithiated pyrazole. The structure of **24** follows from νOH at 3320 cm^{-1}, elemental analysis, and the ^{1}H NMR spectrum (Experimental).

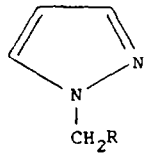
Reaction of **16** with n-BuLi at −78°, followed by addition of α-chloro-*p*-xylene gave the alkylated product **20.**

1-*Methylpyrazoles* (3). As described above the lithiation of **3** has been previously reported[5]. In our hands, successive treatment of **3** with n-BuLi (at −78°) and benzaldehyde (at 0°) gave 57% of a 12:1 mixture of the products of reaction at the 5- (**25**) and N-Me group (**27**): the products had m.ps in agreement with the lit,[5] and expected spectral properties. When *p*-tolualdehyde was used (in place of benzaldehyde), only the 5-substituted product **26** could be isolated: the structure was shown by the ^{1}H NMR spectrum, particularly the intact N-Me peak. Reaction of **3** with n-BuLi at −78°, followed by addition of methyl *p*-toluate gave alcohol **29**. Attempts to repeat the reported[10] Claisen condensation of 1-methylpyrazole and diethyl oxalate, failed.

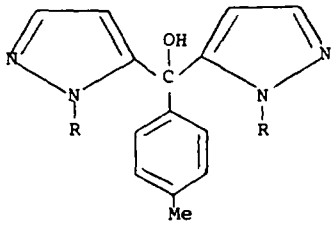
1-*Ethylpyrazole* (**28**). Reaction of **28** with *t*-BuLi at −78°, followed by addition of methyl *p*-toluate gave alcohol **30**.



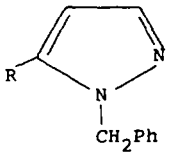
25 R = H
26 R = Me



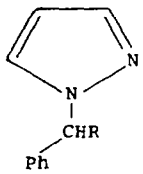
27 R = CH(OH)Ph
28 R = Me



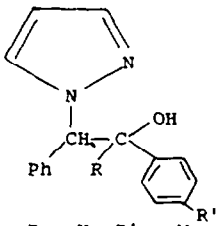
29 R = Me
30 R = Et



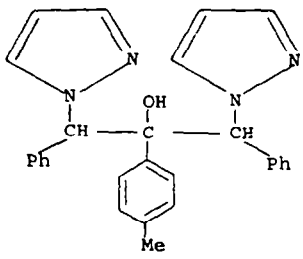
16 R = H
17 R = COOH



18 R = COOH
19 R = COC_6H_4Me-p
20 R = $CH_2C_6H_4Me$-p



21 R = H; R' = Me
22 R = Me; R' = H
23 R = Ph; R' = H



24

CONCLUSIONS

Clearly pyrazoles tend to undergo ring lithiation under thermodynamic control provided a 3- or 5-position is open. However if these positions are occupied, and under kinetic control even if they are not, lithiation can occur at the α-carbon of a N-substituent.

Previous examples are known of metallation of heterocycles in more than one position, e.g. lithiation of furan- and thiophene-2-carboxylates at the 3- and 5-positions.[11] 4-Methoxy-6-methyl-2-pyrone is metallated under kinetic conditions by Pr^i_2NLi at the 3-position, but under equilibrium conditions the 6-methyl group is lithiated.[12] ω-Lithio-n-butylbenzene rearranges to the α-lithioisomer on standing.[13]

EXPERIMENTAL

M.ps were determined with a Thomas Model 40 (Koffler Type) "Hot Stage" apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 283B spectrophotometer. ^{1}H NMR spectra were recorded on a Varian A60-A and a Jeol JNM-PMX 60 spectrometer, ^{13}C NMR on a Jeol FX 100 spectrometer, and mass spectra (MS) on a AEI MS30 mass spectrometer.

Table 3. IR and NMR data for 1-(α-substituted benzyl)pyrazoles

Cmpd. no.	α-Substituent	IR spectra[a]		^{1}H NMR spectra[b]										
		νO-H	νC=O	3-CH (1 H, d, J = 2.2 Hz)	4-CH (1 H, t, J = 2.5 Hz)	5-CH (1 H, d, J = 2.5 Hz)	α-CH (1 H) δ	m	J(Hz)	Aromatic (m) δ	H	Other δ	m	H
18	COOH[c]	3450	1725	8.2	6.75	7.75	6.6	s		7.1-7.8	5		-	
19	COC_6H_4Me-p	-	1695	7.7	6.3	7.55	7.17	s		7.0-7.5	9	2.35	s	3
20	$CH_2C_6H_4Me$-p	-	-	7.65	6.25	[e]	5.55	dd		6.9-7.5	10	3.6	dd	2
21	$CH(OH)C_6H_4Me$-p[d]	3350	-	8.05	6.25	7.5		ABq	8	6.9-7.5	9	2.2	s	3
22	MeC(OH)Ph	3320	-	[e]	5.9	[e]	6.4	s		7.0-7.7	12	1.35	s	3
												5.40	s	1
23	$Ph_2C(OH)$	3320	-	7.9[f]	6.25	[e]	6.75	s		7.0-7.8	17		-	

[a] Recorded in $CHBr_3$. [b] Recorded in $CDCl_3$; s = singlet, d = doublet, t = triplet, m = multiplet, ABq = AB quartet, dd = double doublet. [c] NMR recorded in $CDCl_3/CF_3COOH$ (1:1). [d] NMR recorded in $(CD_3)_2SO$. [e] In the aromatic region. [f] J=3Hz.

Materials used in all the reactions: tetrahydrofuran (THF) was refluxed over and distilled from sodium-benzophenone ketyl; n-BuLi (1.6 M in hexane), phenyllithium (1.1 M in benzene–ether 70:30), and t-BuLi (1.95 M in pentane were standardized by titration.[14]

The following were prepared by the literature method quoted: 1,3,5-trimethylpyrazole, b.p. 79–80°/35 mm, (lit.[4] b.p. 80°/35 mm); 1-ethyl-3,5-dimethylpyrazole, b.p. 171-174° 760 mm (lit.[8] b.p. 172–175°/760 mm); 1-benzylpyrazole, b.p. 134–137°/15 mm (lit.[15] b.p. 134–136°/15 mm); 1-ethylpyrazole, b.p. 134–136°/760 mm (lit.[16,17] b.p. 136–137°/760 mm); 1-methylpyrazole, b.p. 126–127°/760 mm (lit.[16] b.p. 126–127°/760 mm).

General procedure for metallation of substrates **1**, **3**, *and* **16**, *and subsequent alkylation by electrophiles.*

Procedure A. A soln of the substrate (1.00 g, 0.01 mol) in anhyd ether (20 ml) was treated with a soln of n-BuLi (0.01 mol) in hexane at −78° under N_2. The soln was stirred for 60 min at −78° and the electrophile (0.01 mol) was added at 0°. Stirring was continued for 5 hr at 23°. Water (20 ml) was added, the solvent was removed, CH_2Cl_2 (100 ml) was added and the organic layer was separated, washed with brine (10 ml), water (10 ml), and dried ($MgSO_4$). The product was crystallised from benzene–pet. ether (b.p. 40–60°).

Procedure B. As in procedure A, except that the substrate (5 or 10 mmol) in THF (10 ml) was reacted with n-BuLi (1.5 equiv). The soln was stirred for 30 min at −78° before the electrophile (5 or 10 mmol) was added. Stirring was continued for 5-8 hr at 23°.

1-[α-(p-*Methylbenzoyl*)*ethyl*]-3,5-*dimethylpyrazole* (**15**). 1-Ethyl-3,5-dimethylpyrazole (1.0 g, 8.06 mmol) in dry THF (15 ml) was treated with t-BuLi (6.2 ml of 1.95 M soln in pentane, 12.09 mmol) for 1 hr at −78°. Methyl *p*-toluate (1.2 g, 8.06 mmol) was then added, at −78°. After 20 hr at 23°, the solvent was removed (30°, 15 mm), extracted with CH_2Cl_2 (150 ml), washed with 5% NH_4Claq (50 ml), and dried with $MgSO_4$. Evaporation of the solvent (30°, 15 mm) gave a yellowish oil which was passed through a column [SiO_2, ether–n-hexane (1:1)] and the fraction with $R_f = 0.53$ was collected to give ketone **15**, as white solid: 0.43 g, (22%) m.p. 67–69°; ν_{max} ($CHBr_3$) 1680 cm^{-1} (C=O); ^1H NMR δ($CDCl_3$) 1.63 (3H, d), 2.1 (6H, d, J = 7.0 Hz), 2.25 (3H, s), 5.5 (1H, q), 5.63 (1H, s), 6.85–7.75 (4H, m); ^{13}C NMR δ ($CDCl_3$) 10.4 (q), 12.49 (q), 15.95 (q), 20.8 (q), 59.7 (d); MS *m/e* 241 ($M^+ - 1$, 0.1), 227 (1.1), 123 (100).

1-*Benzylpyrazole*-5-*carboxylic acid* (**17**). 1-Benzylpyrazole (2.1 g, 13.3 mmol) in dry ether (20 ml) was treated with PhLi [12.09 ml of 1.1 M soln in benzene–ether (70:30), 13.3 mmol]. The dark brown mixture was stirred at 23° for 4 hr, and then quenched with dry CO_2 gas, at −78°. After 21 hr at 23°, it was extracted with water (17 ml) and washed with ether (30 ml). On acidification (to pH = 1-2) with c.HCl, the acid **17** was obtained as creamy prisms: 0.5 g, (19%), m.p. 160–162°, (from EtOH lit.[9] m.p. 170–171°). (Found: C, 65.1; H, 5.1; N, 13.8. $C_{11}H_{10}N_2O_2$ requires: C, 65.3; H, 5.0; N, 13.9; ν_{max} ($CHBr_3$) 3450 (OH), 1725 cm^{-1} (C=O); ^1H NMR δ ($CDCl_3$–CF_3COOH, 2:1) 5.87 (2 H, s), 7.15 (1H, d, J = 2.5 Hz), 7.2–7.6 (5H, m), 7.85 (1H, d, J = 2.5 Hz).

1-*Benzylpyrazole*-5-*carboxylic acid* (**17**) was also obtained from 1-benzylpyrazole (1.0 g, 6.3 mmol) by the following methods: (a) in dry THF (15 ml) with n-BuLi (4.2 ml of 1.5 M soln in hexane, 6.3 mmol) for 1/2 h at −78° and for 1 hr at 23°, followed by excess dry CO_2 gas, at −78° and keeping 15 hr at 23°. Work up as before gave the acid **17** as prisms from EtOH (0.45 g, 35%), m.p. 160–162° (identical IR spectrum with authentic sample). (b) In ether (10 ml) for 15 min at 0° and 8½ hr at 23° then quenching with dry CO_2 gas, yield 0.4 g (32%) of the acid **17**, m.p. 160–162°.

α-(1-*Pyrazolyl*)*phenylacetic acid* (**18**). 1-Benzylpyrazole (1.0 g, 6.3 mmol) in dry THF (15 ml) was treated, at −78°, with n-BuLi (4.2 ml of 1.5 M soln in hexane, 6.3 mmol) and the dark brown mixture was kept at −78° for 2 hr. Then it was quenched with excess dry CO_2 gas at −78° and stirred for 7½ hr at 23° The solvent was then removed (30°/15 mm), the residue extracted with water (10 ml), washed with ether (20 ml) and the aq. layer was acidified with cooling to pH 1–2 with c.HCl to give the acid **18**, as brownish solid, which was recrystallized from EtOH as prisms: 0.4 g (32%); m.p. 144–148° (Found: C, 65.2; H, 5.1; N, 13.8. $C_{11}H_{10}N_2O_2$ requires; C, 65.3; H, 5.0; N, 13.9%);

1[(2′-*Hydroxy*-2′-(p-*methylphenyl*)-1′-*phenylethyl*)]*pyrazole* (**21**). 1-Benzylpyrazole (1.0 g, 6.3 mmol) in dry THF (10 ml) was treated with n-BuLi (4.2 ml of 1.5 M soln in hexane, 6.3 mmol). After 1/2 hr at −78°, *p*-tolualdehyde (0.74 ml, 6.3 mmol) was added and then the mixture was stirred for 26 hr at 23°. The solvent was removed (30°/15 mm), extracted with CH_2Cl_2 (150 ml) washed with 5% NH_4Claq (50 ml), and dried with $MgSO_4$. The solvent was removed (30°/15 mm) and a white solid was obtained (0.9 g) from EtOAc–pet. ether, 40–60° (1:1). Recrystallization from methanol gave alcohol **21** (1.0 g, 54%), as white prisms: m.p. 141–143° (Found: C, 77.4; H, 6.6; N, 10.0. $C_{18}H_{18}N_2O$ requires: C, 77.7, H, 6.5; N, 10.1).

1-[2′-*Hydroxy*-2′-*methyl*-1′,2′-*diphenylethyl*]*pyrazole* (**22**). 1-Benzylpyrazole (0.7 g, 5.0 mmol) was reacted with acetophenone (0.6 g, 5.0 mmol) for 5 hr, using procedure B, to give 1-[2′-*hydroxy*-2′-*methyl*-1′,2′-*diphenylethyl*]*pyrazole* (0.8 g, 62%), as prisms: m.p. 116–118° (from EtOAc) (Found: C, 77.4; H, 6.6; N, 10.0. $C_{18}H_{18}N_2O$ requires: C, 77.7; H, 6.5; N, 10.1%).

1-[2′*Hydroxy*-1′,2′,2′-*triphenylethyl*]*pyrazole* (**23**). 1-Benzylpyrazole (0.7 g, 5.0 mmol) was reacted with benzophenone (0.9 g, 5.0 mmol) for 5 hr, using procedure B, to give 1,2,2-*triphenyl*-1-(1′-*pyrazolyl*)*ethan*-2-*ol* (1.35 g, 85%), as prisms: m.p. 139–140° from EtOAc (Found: C, 81.1; H, 5.9; N, 8.2. $C_{23}H_{20}N_2O$ requires: C, 81.1; H, 5.9; N, 8.2%).

1-[α-(p-*Methylbenzoyl*)*benzyl*]*pyrazole* (**19**). 1-Benzylpyrazole (1.0 g, 6.3 mmol) in dry THF (15 ml) was treated with n-BuLi (4.2 ml of 15 M solution in hexane, 6.3 mmol). After 20 min at −78°, methyl *p*-toluate (0.95 g, 6.3 mmol) was added and the mixture was stirred for 12 hr at 23°. The solvent was removed (30°/15 mm), washed with 5% NH_4Claq (50 ml), extracted with CH_2Cl_2 (150 ml) and dried with $MgSO_4$. The ketone **19** was obtained as white solid from EtOAc–pet. ether (b.p. 40–60°) (1:1) (0.5 g, 29%). (Found: C, 78.3; H, 5.9; N, 10.0 $C_{18}H_{16}N_2O$ requires: C, 78.2; H, 5.8; N, 10.1).

1,3-*Diphenyl*-1,3-*di*-(1′-*pyrazolyl*)-2-(p-*methylphenyl*)*propan*-2-*ol* (**24**). 1-Benzylpyrazole (0.7 g, 5.0 mmol) was reacted with 4-toluoyl chloride (0.77 g, 5.0 mmol) for 7 hr, using procedure B, to give 1,3-*diphenyl*-1,3-*di*-(1′-*pyrazolyl*)-2-(p-*methylphenyl*)*propan*-2-*ol*, (1.45 g, 73%) as prisms: m.p. 195–197° from EtOAc (Found: C, 77.3; H, 6.0; N, 12.8. $C_{28}H_{26}N_4O$ requires: C, 77.4; H, 6.0; N, 12.9%); ν_{max} ($CHBr_3$) 3320 cm^{-1} (O–H); ^1H NMR δ ($CDCl_3$) 2.2 (3 H, s), 6.1 (1 H, t, J = 2 Hz), 6.8–7.3 (18 H, m), 7.4 (2 H, d, J = 2 Hz), 7.9 (1 H, s).

1-[α-(p-*Methylbenzyl*)*benzyl*]*pyrazole* (**20**). 1-Benzylpyrazole (1.0 g, 6.3 mmol) in dry THF (13 ml) was treated with n-BuLi (4.2 ml of 1.5 M soln in hexane, 6.3 mmol). After ½ hr at −78°, α-chloro-*p*-xylene (0.88 g, 6.3 mmol) was added at −78° and then the mixture was stirred for 24 hr. The solvent was removed (30°/15 mm), extracted with CH_2Cl_2 (150 ml), washed with water and dried ($MgSO_4$). The solvent was removed (30°/15 mm) and a yellowish oil was obtained which was passed through a column [SiO_2, ether–n-hexane, (1:1)] and the fraction with $R_f = 0.38$ was collected to give 1-[α-(p-*Methylbenzyl*)*benzyl*]*pyrazole* (**20**), as a colorless oil: 0.7 g, (42%); (Found: C, 82.2; H, 6.9; N, 10.7. $C_{18}H_{18}N_2$ requires: C, 82.4; H, 6.9; N, 10.7.

1-*Methyl*-5-(1′-*hydroxy*-1′-*phenylmethyl*)*pyrazole* (**25**) *and* 1-[(2′-*hydroxy*-2′-*phenylethyl*)]*pyrazole* (**27**). 1-Methylpyrazole (1.00 g, 0.01 mol) was reacted with benzaldehyde (1.06 g, 0.01 mol) using procedure A, to give an oil, which crystallized from benzene–pet. ether (b.p. 40–60°) to give a mixture of products **25** and **27** (1.3 g, 57%). Fractional

crystallization from ether yielded *1-methyl-5-(1'-hydroxy-1'-phenylmethyl)pyrazole* (1.2 g, 92.3%), as prisms: m.p. 108–109° (lit.[5] m.p. 106.5–110°); IR ($CHBr_3$) 3260 cm^{-1} (O–H); ^1H NMR δ ($CDCl_3$) 5.80 (1 H, s), 6.00 (1 H, d, $J = 2$ Hz), 7.25 (5 H, s), 7.30 (1 H, d, $J = 2$ Hz). The residue was sublimed to give *1-[(2'-hydroxy-2'-phenylethyl)]pyrazole* (0.1 g, 7.7%), as prisms: m.p. 123–125° from CH_2Cl_2 (lit.[5] m.p. 123–127°); IR ($CHBr_3$) 3260 cm^{-1} (O–H); ^1H NMR δ ($CDCl_3$) 4.00–4.30 (3 H, m), 5.20 (1 H, m), 6.20 (1 H, t, $J = 2$ Hz), 7.20 (1 H, d, $J = 2$ Hz), 7.30 (5 H, s), 7.50 (1 H, d, $J = 2$ Hz).

1-Methyl-5-[1'-hydroxy-1'-(p-methylphenyl)]pyrazole (**26**). *1-Methylpyrazole* (1.00 g, 0.01 mol) was reacted with 4-tolualdehyde (1.20 g, 0.01 mol) using procedure A, to give an oil which crystallised from benzene–pet. ether (b.p. 40–60°) to *1-methyl-5-[1'-hydroxy-1'-(p-methylphenyl)]-pyrazole* (1.67 g, 68%) [one spot by tlc using EtOAc-pet. ether (b.p. 40–60°), (1:1)], as needles: m.p. 123–124° from EtOAc; (Found: C, 71.3; H, 7.0; N, 13.9. $C_{12}H_{14}N_2O$ requires: C, 71.2; H, 7.0; N, 13.8%); ν_{max} ($CHBr_3$) 3250 cm^{-1}; ^1H NMR δ($CDCl_3$) 2.4 (3 H, s), 3.7 (3 H, s), 5.8 (1 H, s), 6.0 (1 H, d, $J = 2$ Hz), 7.2 (4 H, s), 7.3 (1 H, d, $J = 2$ Hz). Attempted sublimation of the remaining oil, gave a charred residue that was impossible to characterize. No sublimate was formed.

(p-Methylphenyl)-bis(1-methylpyrazol-5'-yl) carbinol (**29**). 1-Methylpyrazole (1.0 g, 0.01 mol) in dry THF (13 ml) was treated with n-BuLi (6.7 ml of 1.5 M soln in hexane, 0.01 mol). After 2 h and 10 min at −78°, methyl *p*-toluate (1.5 g, 0.01 mol) was added at −78°; the mixture was stirred for 20 hr at 23°.

The solvent was removed (30°/15 mm), the residue extracted with CH_2Cl_2 (150 ml), washed (water) and dried ($MgSO_4$). Solvent was removed (30°/15 mm) to give, on trituration with pet. ether (b.p. 40–60°), the alcohol **29**, as white prisms: 0.6 g, (21%); IR ν_{max} ($CHBr_3$) 3250 br, 1510 m, 1380 s, 1275 s, 1050 s, 930 s, 900 s; ^1H NMR δ (CF_3COOH) 2.5 (3 H, s), 4.25 (6 H, s), 6.46 (2 H, d, $J = 3.0$ Hz), 7.35 (4 H, ABq); ^{13}C NMR δ ($CDCl_3$) 72.6 (s), 38.7 (q), 21.0 (q); MS *m/e* 282 (M^+; 17), 109 (100).

(p-Methylphenyl)-bis (1-ethylpyrazol-5'-yl)carbinol (**30**). 1-Ethylpyrazole (0.5 g, 5.2 mmol) in dry THF (10 ml) was treated with t-BuLi (2.6 ml of 2 M soln in pentane, 5.2 mmol). After 45 min, methyl *p*-toluate (0.78 g, 5.2 mol) was added at −78° and the mixture stirred for 30 hr at 23°. The solvent was removed (30°/15 mm), extracted with CH_2Cl_2 (150 ml), washed (water) and dried ($MgSO_4$). The solvent was removed (30°/15 mm) to give the alcohol **22**, as white plates: m.p. 72–74°; 0.33 g, (21%) from ethyl acetate–pet. ether [(b.p. 40–60°) 1:1]; IR ($CHBr_3$) 3250 br, 1510 m, 1410 s, 1300 s, 1140 s, 1065 s, 935 s, 810 s; ^1H NMR δ ($CDCl_3$) 1.2 (6 H, t, $J = 7$ Hz), 2.35 (3 H, s), 4.1 (4 H, q, $J = 7$ Hz), 5.6 (2 H, d, $J = 2$ Hz), 6.0 (1 H, s), 7.15 (6 H, s); ^{13}C NMR ($CDCl_3$) 15.4 (q), 21.3 (q), 45.9 (t), 72.9 (s).

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