SYNTHESIS AND REACTIONS OF LITHIATED MONOCYCLIC AZOLES CONTAINING TWO OR MORE HETERO-ATOMS. PART III: PYRAZOLES[1] †

M. Ross Grimmett[a] and Brian Iddon[b]

[a] Chemistry Department, University of Otago, P.O. Box 56, Dunedin, New Zealand, and

[b] The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, England

Abstract *- The metallation and halogen → metal exchange reactions of pyrazoles (1,2-diazoles) and the reactions of the resulting organometallic derivatives, particularly lithiated derivatives, are reviewed comprehensively.*

CONTENTS

† This series of reviews is dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

I INTRODUCTION

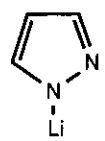
A general introduction to this series of reviews was given in Part I.[2] Parts I-III cover the literature through June 1993.

Apart from imidazoles (1,3-diazoles) pyrazoles (1,2-diazoles)[3-13] have been explored more than any of the other systems covered in this review series. Ring fragmentation of metallated pyrazoles occurs only infrequently. With some 1-substituted pyrazoles (metallation of 1-*un*substituted pyrazoles is not a practical proposition as a route to substituted pyrazoles) metallation can occur both in the substituent [α-(or lateral)metallation] as well as in position-5, if free. More work is necessary with *N*-protecting groups (e.g. the SO_2NMe_2 group) and on bromine → lithium exchange reactions, especially as a route to polysubstituted pyrazoles (e.g. from 1-protected 3,4,5-tribromopyrazoles). Few polylithiated pyrazoles are known.

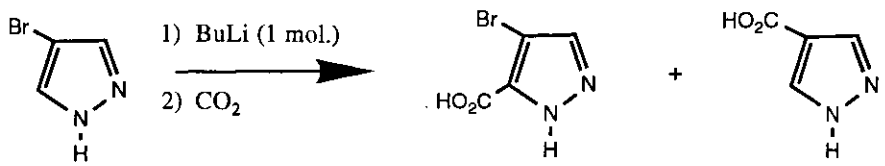
II MONOMETALLATION IN THE RING

A Pyrazole

When pyrazole is treated with one mol. equiv. of butyl- or phenyllithium the *N*-lithio-salt (**1**) is formed.[14-16] Other *N*-*un*substituted pyrazoles react similarly,[14,17] but the reaction is accompanied by a proportion of dilithiated product as is evidenced by the isolation of a mixture of carboxylic acids (**2**) (20% yield) and (**3**) (31%) after carbonation of "monolithiated" 4-bromopyrazole.[14] Similar salt formation between alkali metals and pyrazole is

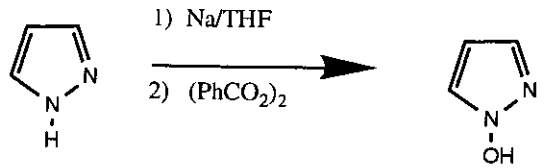


(**1**)



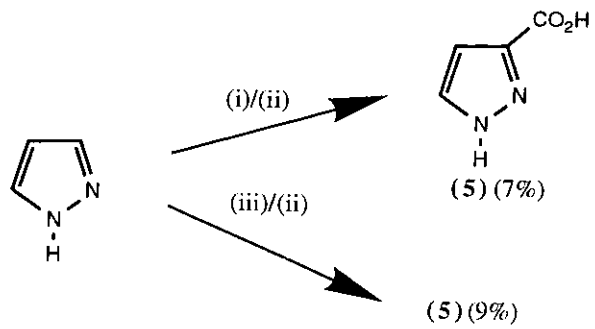
(**2**) (**3**)

utilized in the preparation of 1-hydroxypyrazoles, e.g. **4**.[18]



(**4**) (47%)

Synthetic utility is enhanced by the use of at least two mol. equiv. of the lithiating agent (see also Section III). Thus, low yields of pyrazole-3(5)-carboxylic acid (**5**) are obtained on carbonation of the products of reaction of

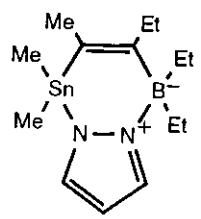


Reagents: (i) PhLi (2 mol.)/Et_2O; (ii) CO_2; (ii) BuLi (2 mol.)/Et_2O.

Scheme 1

two mol. equiv. of phenyl- or butyllithium with pyrazole (Scheme 1).[14] Such poor yields have been attributed to decreased stability of the intermediate dianion owing to repulsive interactions.[9]

Pyrazol-1-yllithium condenses with *E*-2-dimethyl(chloro)stannyl-3-diethylborylpent-2-ene [$Me_2(Cl)SnCMe{=}C(Et)BEt_2$] to give the bicyclic compound (**6**).[17]

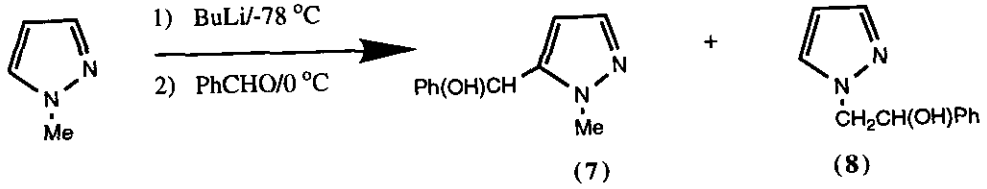


(**6**)

1-Benzyl-3,5-dimethylpyrazole yields 3,5-dimethylpyrazol-1-yllithium(or sodium) on treatment with lithium(or sodium) naphthalenide in tetrahydrofuran (THF), as shown by quenching with water, when a 78% yield of 3,5-dimethylpyrazole is obtained (see also Section IV).[19]

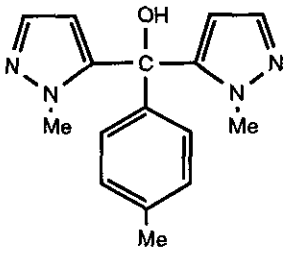
B 1-Methylpyrazoles

Depending on reaction conditions a 1-methylpyrazole can be metallated to give either or both of the 5- and α-lithiated derivatives.[9,14,20-26] Thus, Butler and Alexander reported about 30% α-metallation and 60% 5-metallation with 1,3-dimethylpyrazole (as indicated by product yields after quenching with aldehydes or ketones).[23] Katritzky and co-workers obtained a 12:1 ratio of **7** and **8** in 57% yield after consecutive treatment of 1-methylpyrazole with butyllithium at -78 °C and benzaldehyde at 0 °C (Scheme 2).[25]



(7) (8)

Scheme 2

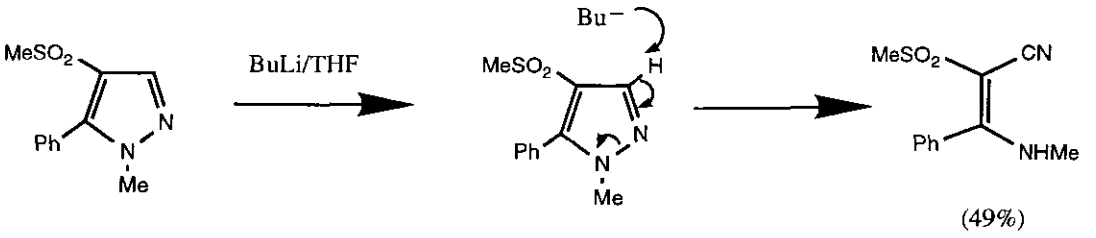


(9)

With 4-methylbenzaldehyde as the quenching electrophile only 5-substitution was observed (68%), and with methyl 4-methylbenzoate the 5,5'-*bis*-product (**9**) is formed in 21% yield. So it can be seen that *N*-substitution leads to much better yields of 5-substituted products; up to 90% of 5-lithiation can be achieved, with butyllithium superior to phenyllithium. After treatment with carbon dioxide, the respective yields of 1-methylpyrazole-5-

carboxylic acid were 66 and 39% with these reagents.[14] 1,3,5-Trimethyl- and 5-methoxy-1-methyl-3-phenylpyrazole are metallated by butyllithium exclusively in their *N*-methyl groups (Section IV).[25,27] Lateral lithiation appears to be kinetically controlled; at higher temperatures the metal rearranges to position-5.[25] The electrophile, however, also plays a role in defining the reaction products (Sections II, C, F and V).[28] Lithiation at position-5 is preferred to 3-lithiation because the "adjacent lone pair (ALP) effect" destabilizes the anion at position-3.[28-30] This "ALP effect" is observed in the relative rates of basic hydrogen-deuterium exchange for 1-methylpyrazole. Second order rate constants in MeOD-NaOMe at 139 °C demonstrate that position-5 is about 1500 times more reactive than position-3 (and about 750 times more reactive than position-4).[31] There may be instances in which the effect can be overcome because of significant covalent character in the C-Li bond.[30]

If position-5 is blocked, either ring-opening will occur preferentially (Scheme 3),[32-34] or lateral lithiation will predominate (Section IV) unless the conditions permit rearrangement. Reaction of 1,5-dimethylpyrazole with one mol. equiv. of phenyllithium in ether, followed by carbonation, gave 60% of recovered starting material, but also



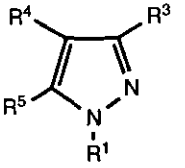
Scheme 3

34% of 1,3-dimethylpyrazole-5-carboxylic acid.[14] This demonstrates that rearrangement to the thermodynamically more stable 1,3-isomer has occurred.

Table I lists examples of pyrazoles prepared *via* the 5-lithiated derivatives. When 1-methylpyrazole is treated in turn with butyllithium and 2,6-di(*tert*-butyl)-*p*-benzoquinone, and the product catalytically dehydrogenated, the 5-aryl-1-methylpyrazole (**10**) is obtained.[26] Attack at the *N*-methyl group can be minimized by addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA).[23,35] Thus, whereas in the absence of TMEDA a mixture of silylated pyrazoles (**11**) (52% yield) and (**12**) (6%) is formed following sequential treatment of 1-methylimidazole with butyllithium (Et_2O/0 °C) and chlorotrimethylsilane, when the complexing reagent is used only compound (**11**) (72%) is obtained.[35] The use of TMEDA also allows the preparation of 1-methyl-3,5-*bis*-

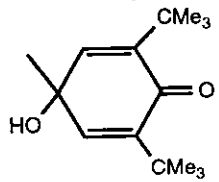
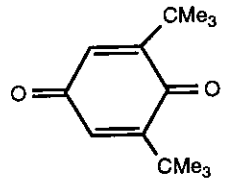
Table I

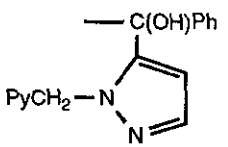
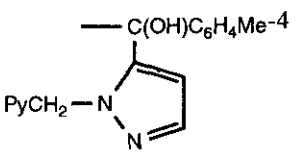
5-Substituted Pyrazoles Derived from Pyrazol-5-yllithium Derivatives[a]

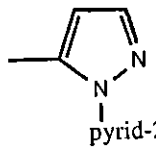
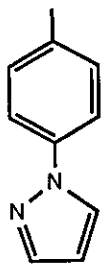
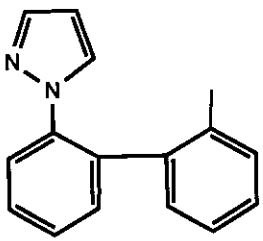


R^1	R^3	R^4	R^5	Reagent	Yield (%)	Ref.
H	CO_2H	H	H	CO_2	9, 7[b]	14
H	CO_2H	Br	H	CO_2	20	14
H[e]	CH_2Ph	H	H	$PhCH_2Br$	54[d]	16
H[e]	CH(OH)Ph	H	H	PhCHO	44[c], 53[d], 37	16
H[e]	$CH(OH)C_6H_4Me$-4	H	H	$4\text{-}MeC_6H_4CHO$	45[d]	16
H[e]	$C(OH)Ph_2$	H	H	Ph_2CO	61[d]	16
H[e]		H	H	*cyclohexanone*	51[d]	16
H[e]	SPh	H	H	Ph_2S_2	53[d]	16
H[e]	SCH_2Ph	H	H	$(PhCH_2)_2S_2$	76[d]	16
H[e]	CONHPh	H	H	PhNCO	56[d]	16

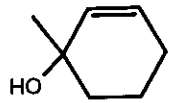
H[f]	$C(OH)(C_6H_4Cl\text{-}4)_2$	H	H	$(4\text{-}ClC_6H_4)_2CO$	36, 76	36, 37
H[g]	D	H	H	D_2O	78	38
H[g]	Me	H	H	MeI	55	38
H[g]	CH_2Ph	H	H	$PhCH_2Br$	45	38
H[g]	$C(OH)Ph_2$	H	H	Ph_2CO	48	38
H[h]	SPh	Br	H	Ph_2S_2	12[h]	39
Me	H	H	Me	Me_2SO_4	75	14
Me	H	H	CO_2H	CO_2	66, 39[b], 54	14, 20
Me	CO_2H	Br	H	CO_2	6[h]	14
Me	H	H	CH(OH)Ph	PhCHO	54, 58[i]	25, 23
Me	H	H	COPh	PhCHO (xs.)	85	23
Me	H	H	$CH(OH)C_6H_4Me\text{-}4$	$4\text{-}MeC_6H_4CHO$	68	25
Me	H	H	$CH(OH)C_6H_4NMe_2\text{-}4$	$4\text{-}Me_2NC_6H_4CHO$	29	22
Me	H	H	$CH(OH)C_6H_3ClNO_2\text{-}5,2$	$2,5\text{-}O_2NClC_6H_3CHO$	20	39a
Me	H	H	CH(OH)Py[i]	HCO_2Et	51	21
Me	H	H	$C(OH)Ph_2$	Ph_2CO	87	14
Me	H	H	$C(OH)PhC_6H_4NMe_2\text{-}4$	$4\text{-}Me_2NC_6H_4COPh$	11	22
Me	H	H	$C(OH)(C_6H_4NMe_2\text{-}4)_2$	$(4\text{-}Me_2NC_6H_4)_2CO$	—	22
Me	H	H	$C(OH)PyC_6H_4Me\text{-}4$[i]	$4\text{-}MeC_6H_4CO_2Me$	22	25
Me	H	H	C(OH)PyPh[i]	PhCOCl	—	21

Me	H	H	C(OH)Py2[i]	$(EtO)_2CO$	26	21
Me	H	H			—	26
Me	H	H	COPh	PhCN	—	24
Me	H	H	COpyrid-4-yl	pyrid-4-ylCN	5	24
Me	H	H	$SiMe_3$	Me_3SiCl	52, 72[k]	35
Me	$SiMe_3$	H	$SiMe_3$	Me_3SiCl	41[k]	35
Me	H	$SiMe_3$	$SiMe_3$	Me_3SiCl	12[k]	35
Me	Me	H	CH(OH)Ph	PhCHO	~ 35	23
Me	Me	H	$CH_2CH(OH)Ph$	2-phenyloxirane	62	23
Et	H	H	$C(OH)PyC_6H_4Me$-4[l]	$4\text{-}MeC_6H_4CO_2Me$	22[d]	25
Pr	H	H	CH(OH)Ph	PhCHO	81	23
Pr	Me	H	CH(OH)Ph	PhCHO	95[m]	23
SEM[n]	H	H	D	D_2O	60	40
SEM[n]	H	H	CO_2H	CO_2	33	40
SEM[n]	H	H	COPh	$PhCO_2Et$	32	40
SEM[n]	H	H	COPh	PhCOCl	31	40
SEM[n]	H	H	CH(OH)Ph	PhCHO	46	40
SEM[n]	H	H	SPh	Ph_2S_2	46	40

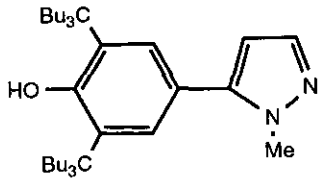
SEM[n]	H	H	$SiMe_3$	Me_3SiCl	29	40
THP[o]	C_6H_4Cl-4	H	CH_2OH	HCHO	73	9
THP[o]	C_6H_4Cl-4	H	SPh	Ph_2S_2	80	9
THP[o]	C_6H_4Cl-4	H	CONHBu-*tert*	*tert*-BuNCO	63	9
CH_2Ph	H	H	CO_2H	CO_2	57[b]	14
CH_2Py[n]	H	H	D	D_2O	90	28
CH_2Py[n]	H	H	CH(OH)Pr	PrCHO	60	28
CH_2Py[n]	H	H	$CH(OH)C_6H_4Me$-4	4-MeC_6H_4CHO	77	28
CH_2Py[n]	H	H	$C(OH)Ph_2$	Ph_2CO	20	28
CH_2Py[n]	H	H	COMe	Ac_2O	17	28
CH_2Py[n]	H	H		PhCOCl	37	28
CH_2Py[n]	H	H		4-$MeC_6H_4CO_2Et$	35	28
CHPhPy[n]	H	H	$C(OH)Ph_2$	Ph_2CO	33	28
Ph	H	H	Me	MeI	99	41
Ph	H	H	CO_2H	CO_2	39, 80, —	20, 41, 19

Ph	H	H	$C(OH)Ph_2$	Ph_2CO	43, 38	19
Ph	H	H	SMe	Me_2S_2	95	41
Ph	H	H	CH_2OMe	$MeOCH_2Cl$	80	41
Ph	H	H	$SnBu_3$	Bu_3SnCl	80	42
Ph	Me	H	CO_2H	CO_2	—	43, 19
Ph	Me	H	$C(OH)Ph_2$	Ph_2CO	45, 51	19
2,6,4-$Cl_2F_3CC_6H_2$	H	SO_2CF_3	CO_2H	CO_2	72	44
pyrid-2-yl	H	H	 pyrid-2-yl	$CuCl_2$	21	45
	H	H	q	$CuCl_2$	5, 43q	46, 47
	H	H	r	$CuI(O_2)$	11	48

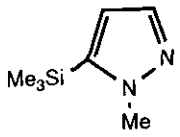
SO_2NMe_2	$C_6H_3Cl_2$-2,4	H	CN	TsCN	41	49
SO_2NMe_2	H	H	$SiMe_3$	Me_3SiCl	78	50
SO_2Ph	H	Br	Br	Br_2 (–78 → 0 °C)	32[b]	39
SO_2Ph	Br	Br	H	Br_2 (–78 → 20 °C)	31[b]	39
SO_2Ph	H	Br	D	D_2O	80[b]	39
SO_2Ph	Me[s]	Br	H	MeI	28[b]	39
SO_2Ph	CH_2Ph[s]	Br	H	$PhCH_2Br$	8[b]	39
SO_2Ph	H	Br	CO_2H	CO_2	65[b]	39
SO_2Ph	H	Br	CH(OH)Ph	PhCHO	50[b]	39
SO_2Ph	H	Br	$C(OH)Ph_2$	Ph_2CO	40[b]	39
SO_2Ph	H	Br	COPh	PhCOCl	51[b]	39
SO_2Ph	H	Br	CO_2Ph	$PhCO_2Cl$	13[b]	39
$SO_2C_6H_4Me$-4	H	H	I	I_2	92[d]	51
$SO_2C_6H_4Me$-4	H	H	Me	MeI	86[d]	51
$SO_2C_6H_4Me$-4	H	H	$CH_2CH=CH_2$	$CH_2=CHCH_2Br$	78[d,t]	51
$SO_2C_6H_4Me$-4	H	H	CH_2Ph	$PhCH_2Br$	72[d]	51
$SO_2C_6H_4Me$-4	H	H	$C(OH)Me_2$	Me_2CO	87[d]	51

$SO_2C_6H_4Me$-4	H	H		cyclohex-2-enone	79[d]	51
$SO_2C_6H_4Me$-4	H	H	CO_2Me	$ClCO_2Me$	55[d]	51
$SO_2C_6H_4Me$-4	H	H	$SiMe_3$	Me_3SiCl	100[d]	51

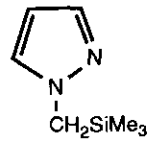
[a] With BuLi unless stated otherwise. [b] With PhLi. [c] With LDA. [d] With *tert*-BuLi. [e] After removal of hydroxymethyl protecting group. [f] After removal of dialkoxymethyl protecting group. [g] After removal of 1-pyrrolidinomethyl protecting group. [h] Protecting group (SO_2Ph) lost during work-up. [i] Ratio 66:34 with lateral metallation. [j] Py is 1-methylpyrazol-5-yl. [k] TMEDA added to minimize lateral metallation. [l] Py is 1-ethylpyrazol-1-yl. [m] A mixture of 3-(and 5)-methyl-1-propylpyrazoles was metallated. [n] SEM is [2-(trimethylsilyl)ethoxy]methyl. [o] THP is tetrahydropyran-2-yl. [p] Py is pyrazol-1-yl. [q] See **Scheme 10** for products. [r] Product is compound (**24**). [s] The initially formed 5-substituted products rearranged. [t] Converted to the higher order cuprate before addition of allyl bromide.



(10)



(11)



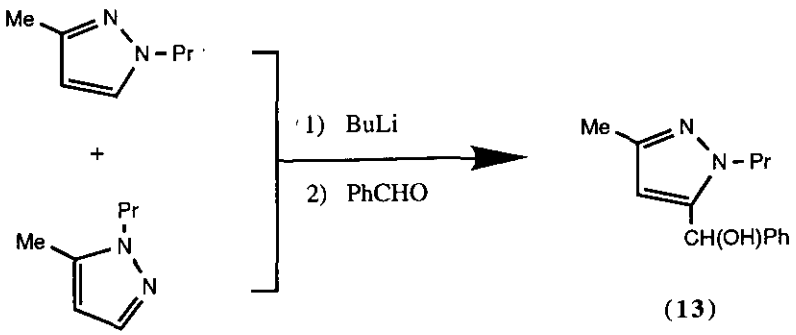
(12)

(trimethylsilyl)pyrazole from 1-methyl-3-trimethylsilylpyrazole largely uncontaminated by laterally silylated products.[35]

When it is necessary to prepare pyrazoles unsubstituted on nitrogen, *N*-methyl groups are of very limited value since only transalkylation or heating with pyridinium chloride are likely to be able to remove them.[52] A discussion of suitable *N*-protecting groups for pyrazole is included in Section II.F.

C 1-Alkylpyrazoles (other than methyl and benzyl)

Larger alkyl groups than methyl are reported to be much less subject to lateral metallation. Thus, a mixture of 3- and 5-methyl-1-propylpyrazoles treated with butyllithium and then benzaldehyde, gave 95% of the secondary alcohol (**13**) (Scheme 4). 1-Propylpyrazole and its 3-methyl derivative also give high yields of the 5-substituted



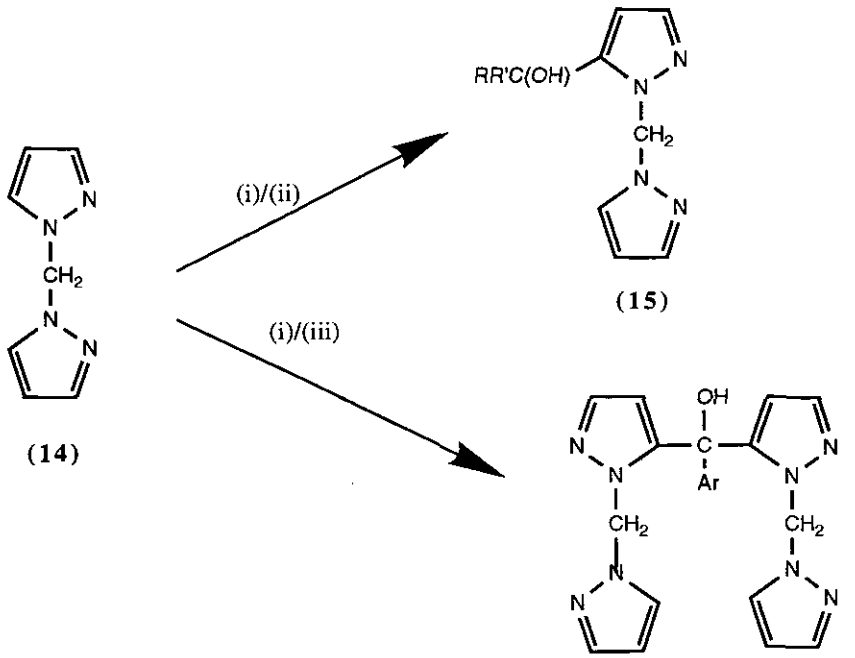
(13)

Scheme 4

alcohols under similar conditions.[23] Nevertheless, 1-ethyl-3,5-dimethylpyrazole lithiates in the α-position of the ethyl group (Section IV).[25] With position-5 available for metallation, however, 1-ethylpyrazole is converted into

the *N,N'*-diethyl analogue of compound (**9**) (21%) on successive treatment with butyllithium at -78 °C and methyl 4-methylbenzoate.[25]

Although the methylene group of *bis*(pyrazol-1-yl)methane (**14**) is doubly activated to lateral metallation by the electron-withdrawing heterorings (see Section IV), careful choice of reaction conditions and quenching reagents can favor ring-lithiation products. In particular, carbonyl electrophiles lead to 5-substituted products (**15**) (Scheme 5).[28] In two instances, reaction with benzoyl chloride and with ethyl 4-methylbenzoate, the 5-ketones were not isolated, but reacted with a second equivalent of the lithiated pyrazole to form a *bis*-alcohol (**16**)



(**14**)

(**15**)

(**16**)

Ar = Ph (30%)

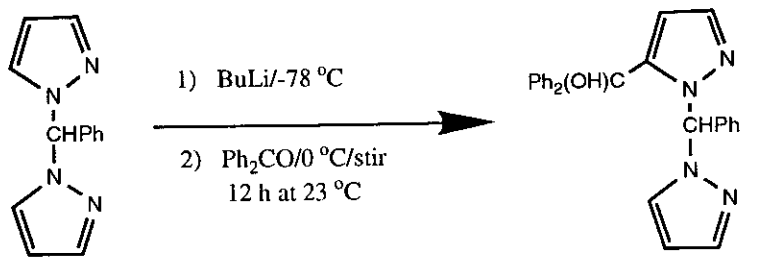
Ar = C_6H_4Me-4 (37%)

Reagents: (i)BuLi/THF/-78 °C; (ii) RCOR'/room temperature/12 h; (iii) PhCOCl/THF/ 25 °C or 4-$MeC_6H_4CO_2Et$

Scheme 5

(Scheme 5). Benzophenone converts the lithium derivative of *bis*(pyrazol-1-yl)phenylmethane (**17**) into the 5-tertiary alcohol (**18**) (Scheme 6).[28] The concept of "hard and soft acids and bases" (HSAB theory) has been

invoked recently[53] to account for the formation of up to seven out of the eight possible products that may arise through α-(or lateral)metallation of *bis*(pyrazol-1-yl)methane (**14**) in competition with its ring-metallation in



(17) **(18)** (33%)

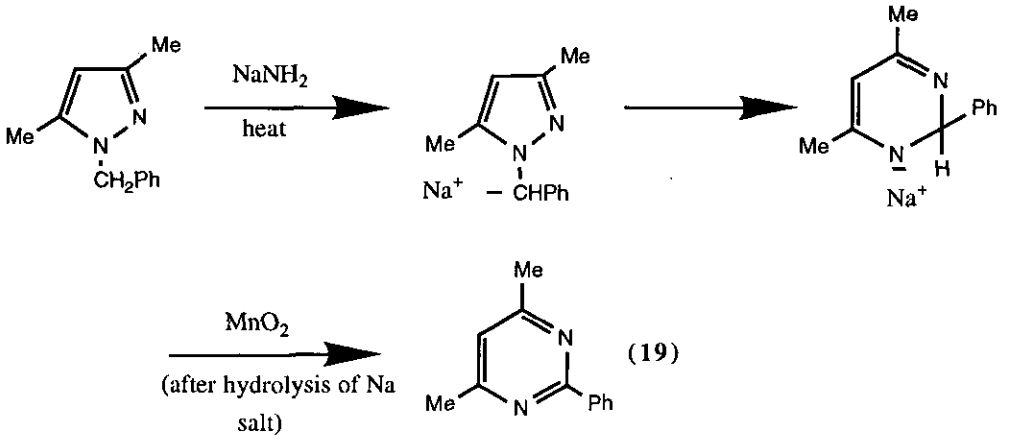
Scheme 6

position-5(or 5') [THE RESULTS OF THIS WORK ARE NOT GIVEN IN THE TABLES; complex mixtures may be produced, which are difficult to separate] (See also Section IV.A). Quenching the resulting mixture (prepared using BuLi/THF/0 °C) with a "hard" electrophile (e.g. Me_3SiCl or paraformaldehyde) favors ring substitution and either a 5-mono- or a separable mixture of a 5-mono- and a 5,5'-disubstituted product may form, depending on the amount of quenching reagent added. By contrast, "soft" electrophiles (e.g. MeI or Me_2S_2) yield mixtures of ring- and bridge-substituted products; with two or more mol. equiv. of the reagent a tetrasubstituted product may be produced. Introduction of a methylthio group into the bridge activates the remaining bridge proton and bridge disubstitution results, whereas introduction of a bridge methyl group has the opposite effect. Use of lithium diisopropylamide (LDA) favors ring substitution.[53]

D 1-Benzylpyrazole

At room temperature, α-(or laterally)metallated 1-benzylpyrazole rearranges to the thermodynamically more stable 1-benzylpyrazol-5-yllithium.[14,16,25] Thus, successive reaction of 1-benzylpyrazole with phenyllithium [ether/ 20 °C] and carbon dioxide (at -70 °C) gives 1-benzylpyrazole-5-carboxylic acid (57%).[14] Katritzky and co-workers have shown that the 5-carboxylic acid is formed if 1-benzylpyrazole is: (a) treated with phenyllithium at 23 °C in ether and then carbonated as above; (b) treated with butyllithium in THF at -78 °C, warmed to 23 °C for 1 hour, and finally carbonated at -78 °C; or (c) treated with butyllithium at -78 °C in ether, warmed to 23 °C for

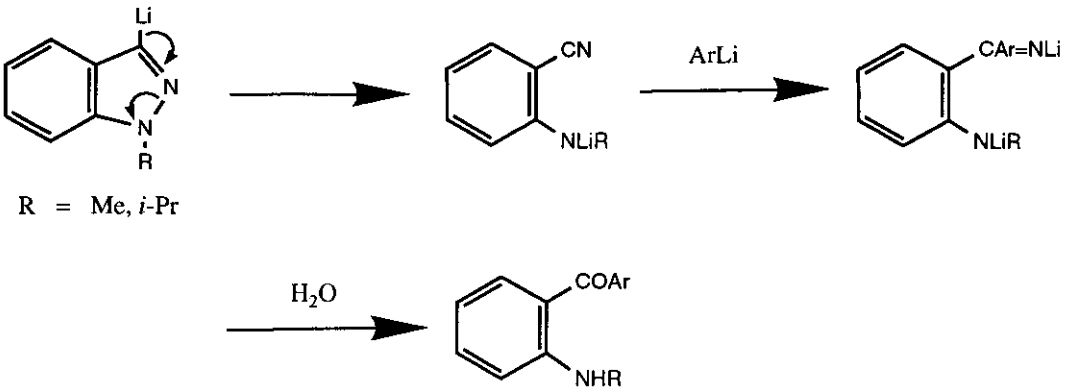
8.5 hour, then quenched with carbon dioxide at -78 °C. All of these conditions favor the formation of the thermodynamic product, with the α-lithiated isomer rearranging before reaction with the electrophile.[25] When position-5 is blocked, this rearrangement is not possible and α-lithiation in the benzyl group may predominate, although with 1-benzyl-3,5-dimethylpyrazole only ring-opened products were isolated with sodium amide (at 150-155 °C).[32] Presumably, the pyrimidines (**19**), formed when the product of sodium amide treatment is oxidized, must result from N-N bond cleavage induced by the formation of the α-anion (Scheme 7). Similar cleavage occurs when 1-methyl-, 1-methoxymethyl-, and 1-isopropylindazoles react with phenyl- or 3-



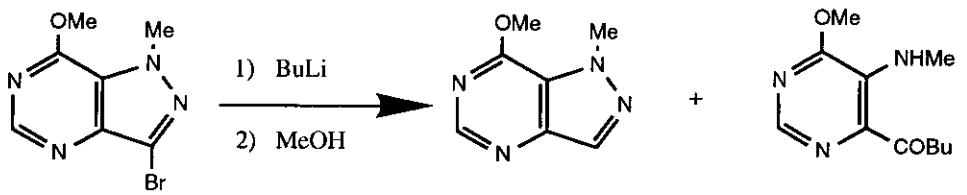
(19)

Scheme 7

methylphenyllithium to give 2-aminobenzophenones (42-63% yield) (Scheme 8).[33] The N-N bond in 1-isopropyl-3-phenylindazole is cleaved with phenyllithium, which suggests that an alternative ring-opening process is possible.[33] These reagents are less nucleophilic than butyllithium (which partially α-lithiates 1-methylindazole) and the reactions need to be conducted at elevated temperatures.[33,54] Other examples which illustrate this type of behaviour include ring-opening of the 3-sodio derivatives of 1-alkylindazoles, to give 2-cyanoanilines,[33, 55] and 1-(but not 2)substituted 7-alkoxy-3-bromopyrazolo[4,3-*d*]pyrimidines (**20**), which are opened even at low temperatures by butyllithium (Scheme 9).[56]



Scheme 8



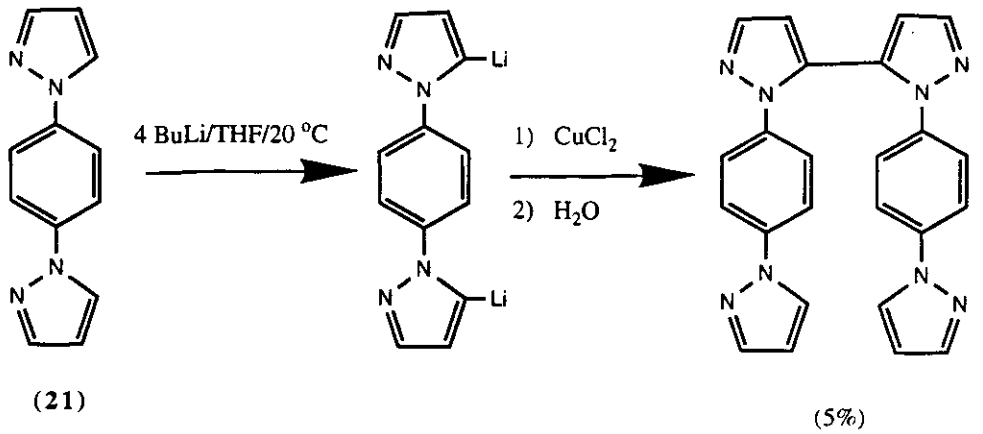
(20)

Scheme 9

O-Silylated 1-benzylpyrazole 2-oxides, generated *in situ* by treatment of the pyrazole 2-oxide with trimethylsilyl or *tert*-butyldimethylsilyl triflate in dichloromethane, undergo iterative deprotonation and *C*-silylation in the presence of lithium tetramethylpiperidide (LiTMP) first at position-3, then at position-5, to yield the corresponding 3,5-*bis*(silylated) 1-benzylpyrazole 2-oxide (31% yield when substituent is Me_3Si and 74% when it is *tert*-$BuMe_2Si$)[57] (see also ref. 58). Some 1-benzyl-3-*tert*-butyldimethylsilylpyrazole 2-oxide (13%) is formed also.

E *1-Phenyl(and other 1-aryl)pyrazoles*

Carbonation of lithiated 1-phenylpyrazole was reported to give a 39% yield of 1-phenylpyrazole-5-carboxylic acid,[20] although *ortho*-lithiation has also been reported.[14,20,27,43] Similarly, 3-methyl-1-phenylpyrazole gave the 5-carboxylic acid.[43]



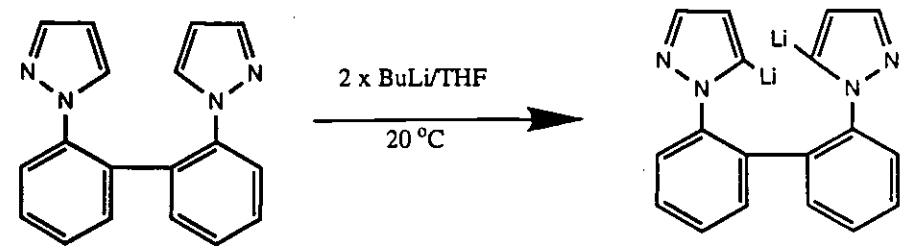
(21)

(5%)

+

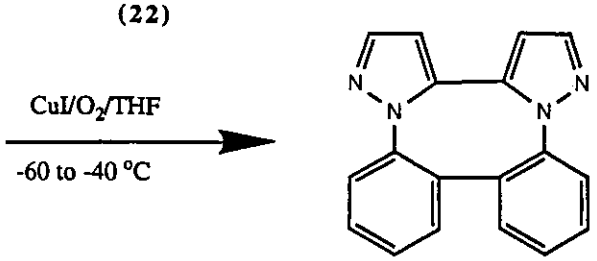
(43%)

Scheme 10



(22)

(23)



(24) (11%)

Scheme 11

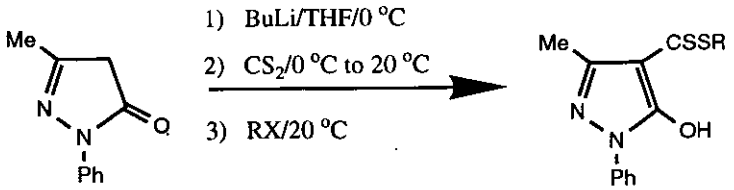
If the reaction conditions are carefully controlled exclusive 5-lithiation is possible with 1-phenylpyrazole, and pure 5-substituted derivatives can be isolated in greater than 80% yields if the lithiation is carried out with butyllithium at -65 °C in dry THF[41] or ether[42] followed by addition of the electrophile below -70 °C (Table I). When position-5 is blocked, lateral lithiation occurs instead (Section IV.D). It seems likely that 5-lithiation is kinetically controlled and *ortho*-lithiation thermodynamically controlled.

When 1,4-*bis*(pyrazol-1'-yl)benzene (**21**) is treated with four mol. equiv. of butyllithium at 20 °C (THF), lithiation occurs in both pyrazole 5-positions (thermodynamic product formed), allowing oxidative coupling in the presence of cupric chloride (Scheme 10) (see also Section IV).[46,47] Under analogous conditions (5 x BuLi/Et_2O/25 °C) 1,3,5-*tris*(pyrazol-1'-yl)benzene also lithiates to some extent at each of the 5'-positions.[59] With two mol. equiv. of butyllithium in THF the dimeric compound (**22**) yields a dilithiated species (**23**) which can be internally coupled with cuprous iodide in the presence of oxygen to give compound (**24**) (Scheme 11).[48] Likewise, 1-(pyrid-2-yl)pyrazole lithiates similarly [BuLi/Et_2O or Et_2O-THF (1:1)/20 °C] in position-5 and the resulting 5-lithiated derivative can be coupled with cuprous chloride (21% yield).[45]

1-Phenyl-3,5-*bis*(trifluoromethyl)pyrazole is metallated by one mol. equiv. of butyllithium (THF/0 °C) exclusively in position-4, as shown by quenching the mixture with chlorotrimethylsilane (95% yield).[60] With three mol. equiv. of butyllithium *ortho*-lithiation of the phenyl ring occurs also (Section IV.D). When 3-methyl-1-phenyl-5-trifluoromethylpyrazole is treated similarly (1.0 x BuLi/THF/0 °C) the 4-trimethylsilyl derivative is obtained in only 11% yield; the major products are starting material (34%) and the *ortho*-silylated product (Section IV.D).[60]

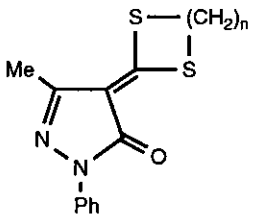
Successive reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one (**25**) with butyllithium (THF/0 °C), quenching with carbon disulfide, and alkylation gives the 4-alkyldithioate derivatives (**26**) in moderate yields (32-60%) (Scheme 12). When 1,2-dibromoethane or 1,3-dibromopropane are the alkylating agents, instead of the expected *bis*pyrazoles, cyclic ketene dithioacetals (**27**) are formed.[61]

Treatment of 4-bromo-, 4-chloro-, or 5-dimethylamino-1-phenylpyrazole with LDA in ether is reported to yield the ring-opened product, *N,N*-dimethyl-*N'*-phenylcyanoacetamidine.[62] 1,3-Diaryl-4-methylsulfonylpyrazoles undergo a ring-opening reaction analogous to that shown in Scheme 3 when treated with butyllithium (THF).[34]



(25) (26)

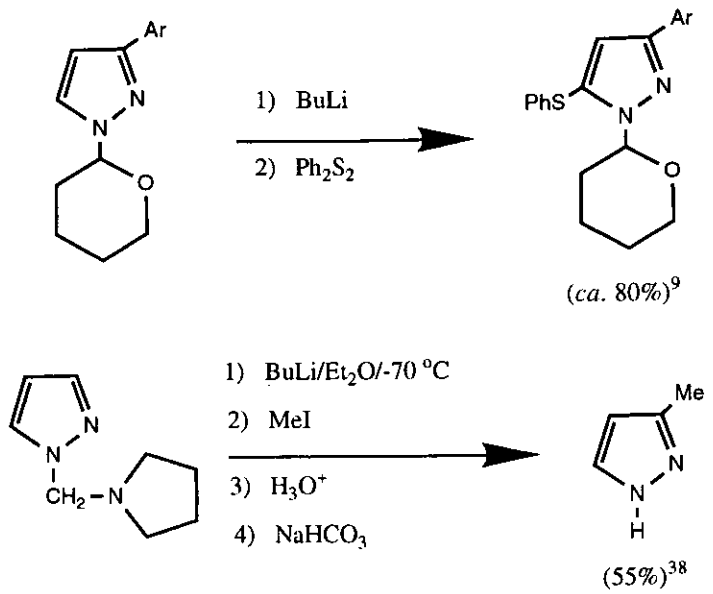
Scheme 12



(27) [n = 2 (47%), n = 3 (49%)]

F Other 1-substituted pyrazoles

Neither alkyl nor aryl groups are particularly suitable for protecting a pyrazole NH in synthetic procedures involving *C*-lithiation because lateral metallation can occur at these groups,[20,23,25,27,41,63] and they are difficult or impossible to remove later (benzyl can, of course, be removed under fairly severe oxidative or reductive conditions).[14,52] In consequence, considerable effort has been devoted to the study of readily removable protecting groups for azole ring nitrogens, leading to the use of groups such as dimethylaminosulfonyl,[49,50] phenylsulfonyl,[9,39,64,65] tosyl,[51,65] *tert*-butyldimethylsilyl,[39,66] *N,N*-dialkylaminomethyl,[38] dimethoxy(or diethoxy)methyl,[36,37] [2-(trimethylsilyl)ethoxy]methyl (SEM),[40] tetrahydropyran-2-yl,[9,67] and hydroxymethyl[16] (Scheme 13). Methylsulfonyl has also been used for *N*-protection in pyrazoles, but not as yet in lithiation processes.[68] Chadwick and co-workers[63] have discussed the use of protecting groups in imidazoles, while Katritzky and co-workers[16] and Fugina *et al.*[40] have recently summarized the analogous pyrazole chemistry.

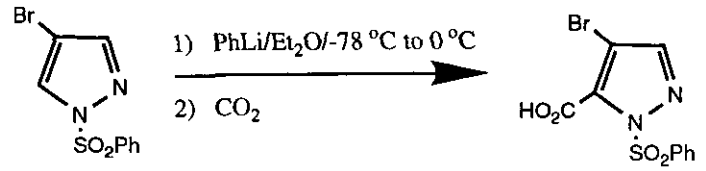


Scheme 13

In essence, all of the above substituents direct 5-lithiation or permit halogen → lithium exchange at position-4. Use of the *N,N*-dialkylamino function leads to 45-78% yields of 5-substituted pyrazoles, but suffers from the disadvantage that the *N*-protected pyrazole must be isolated and purified before metallation. Furthermore, yields are poorer than with 2-substituted imidazoles or benzimidazoles, and more hindered electrophiles (e.g. 2-iodopropane) fail to react.[38]

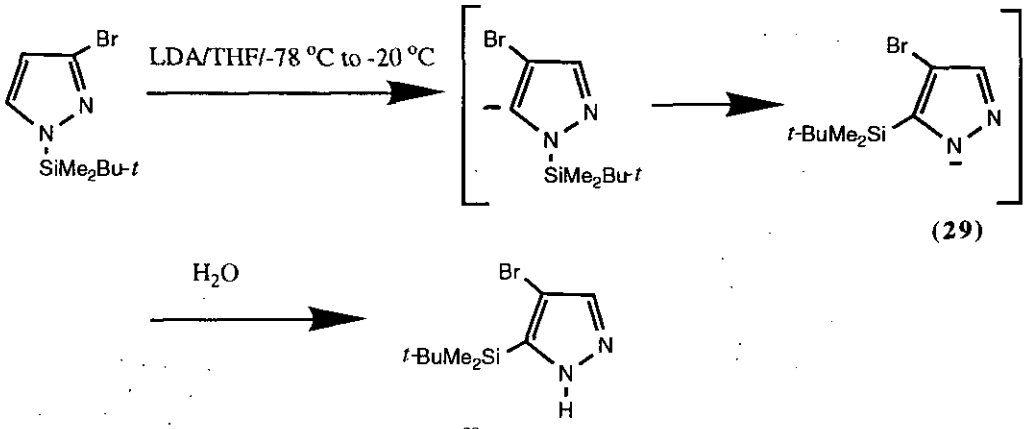
Good yields of 5-substituted pyrazoles are obtained when 1-(tetrahydropyran-2-yl)pyrazoles are metallated and quenched under mild conditions;[9] the protecting group is removed by acid hydrolysis (Scheme 13).[67]

The various *N*-sulfonyl protecting groups have enjoyed widespread application. They generally give good yields of 5-substituted products before their removal by alkaline hydrolysis. In particular, metallation of 4-bromo-1-phenylsulfonylpyrazole (**28**) (Scheme 14) with phenyllithium takes place at position-5,[39] whereas both 5- and 4-substitution are reported with 4-bromo-1-methylpyrazole[14] (butyllithium promotes bromine → lithium exchange exclusively[14,67,69,70]). Halogen → lithium exchange involves a "soft-soft" interaction.[71] Therefore, harder organolithium reagents (LDA and PhLi) should favor 5-deprotonation, an orientation also promoted by the protecting group since phenylsulfonyl is a known "*ortho*-director" which stabilizes the intermediate lithium



Scheme 14

species.[9,64] The *tert*-butyldimethylsilyl protecting group is an unsatisfactory alternative because, once the lithium derivative is formed, there is rearrangement to the thermodynamically more stable anion (**29**) (Scheme 15), a process also known to occur with 1-trimethylsilylpyrroles[72] and 1-*tert*-butyldimethylsilylindoles.[66] Subsequent addition of benzaldehyde gave no alcohol product.[39]

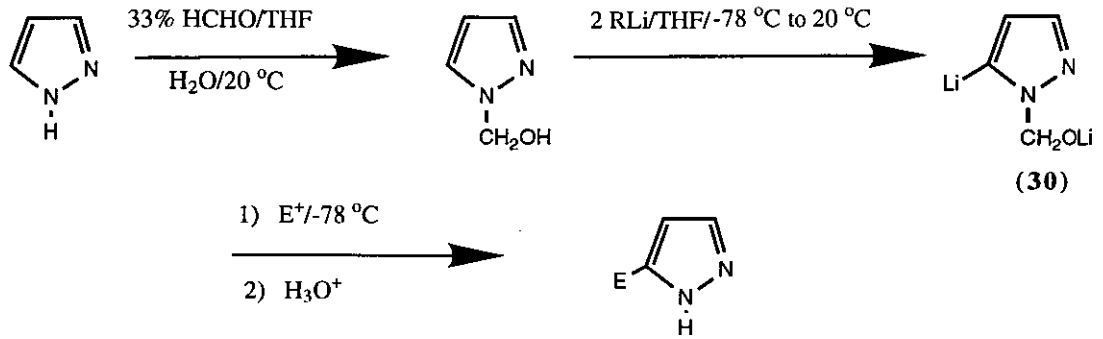


Scheme 15[39]

While most electrophiles when added to 4-bromo-1-phenylsulfonylpyrazol-5-yllithium give 5-substituted products, benzyl bromide gave a mixture which contained only minor amounts (~ 8%) of benzylated product, identified as the 3-benzylpyrazole, and iodomethane gave 28% of the 3-methyl product. Such results can be interpreted in terms of greater thermodynamic stability of 1,3-disubstituted pyrazoles under conditions which allow 1,5- $\rightleftharpoons$ 1,3-equilibration.[39] Addition of bromine to the lithium derivative gives the 4,5-dibromo product provided that the mixture is not allowed to warm up following the addition. Warming to 20 °C results in the formation of the 3,4-dibromo isomer.[39]

Noteworthy is the introduction of a nitrile group at position-5 of *N,N*-dimethyl-3-(2,4-dichlorophenyl)pyrazole-1-sulfonamide through successive metallation (BuLi/THF/-78 °C) and quenching with tosyl cyanide.[49] The dimethylaminosulfonyl group is removable using tetrabutylammonium fluoride.

Triethyl(or trimethyl) orthoformate converts pyrazoles into the 1-dialkoxyalkyl derivatives which readily metallate at position-5 (BuLi/THF). After reaction with an electrophile, the protecting group can be removed by acidifying to around pH 4.[36] Although carbon dioxide has been used successfully for *N*-protection of pyridones,[73] 1,2,3,4-tetrahydroisoquinolines,[74] phenoxazines,[75] and phenothiazines,[76] it failed for pyrazoles and other azoles.[16,38,77] A one-pot sequence uses formaldehyde both for *N*-protection and to direct lithiation into position-5 giving dilithiohemiaminals (**30**) (Scheme 16) which react readily with electrophiles. The hydroxymethyl group is labile



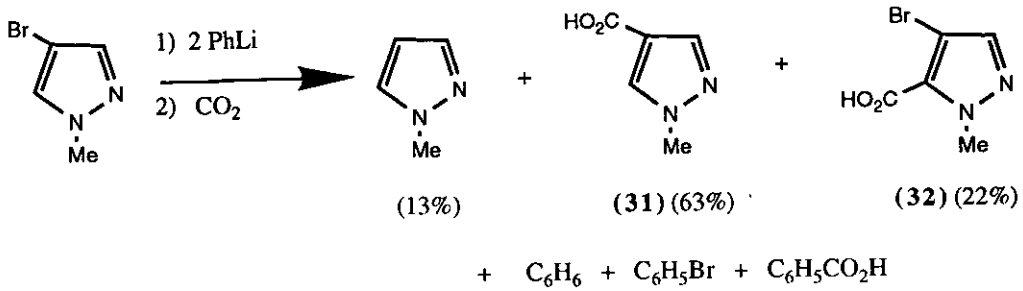
Scheme 16[16]

in dilute acid or in the presence of silica gel. Any of the reagents *n*- or *tert*-butyllithium or LDA produce compound (**30**) smoothly at -20 °C in less than 30 min.[16]

A SEM protecting group can be introduced onto a pyrazole nucleus in high yield, the resulting 1-protected pyrazoles are stable, they are readily metallated in position-5, and the resulting 5-lithiated derivatives react with a range of electrophiles [but not *N,N*-dimethylformamide (DMF)] (Table I).[40] An added advantage of the use of this protecting group is that it can be removed under mild conditions with fluoride ion.

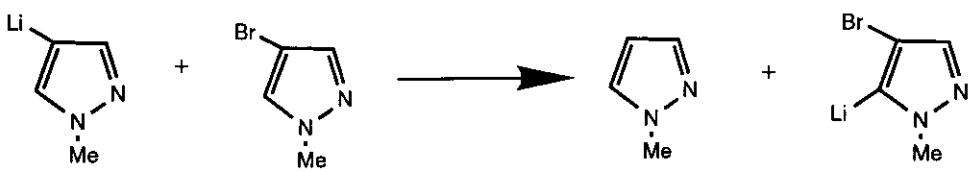
G. 4-Bromopyrazoles

4-Bromo-1-methylpyrazole can react with one mol. equiv. of phenyllithium to give products of 5-lithiation (formed *via* a transmetallation process) and of halogen → lithium exchange. Treatment of the lithiated product mixture with solid carbon dioxide gave 1-methylpyrazole (29%), 4-bromo-1-methylpyrazole (28%), bromobenzene (39%), benzene, and small quantities of 1-methylpyrazole-4-carboxylic acid and 4-bromo-1-



Scheme 17

methylpyrazole-5-carboxylic acid.[14] The difficulty of excluding water when solid carbon dioxide is used is evident, but so too is the operation of two different metallation processes. With two mol. equiv. of phenyllithium in ether, followed by carbonation, the product mixture contains a 3:1 ratio of pyrazole carboxylic acids (**31**) and (**32**) (Scheme 17). While the carboxylic acid mixture can be explained in terms of competing 5-lithiation and bromine → lithium exchange at C-4, both the 1-methylpyrazole and the 4-bromo-1-methylpyrazole-5-carboxylic acid could have been formed from the reaction between the original substrate and 1-methylpyrazol-4-yllithium (Scheme 18).[14]



Scheme 18

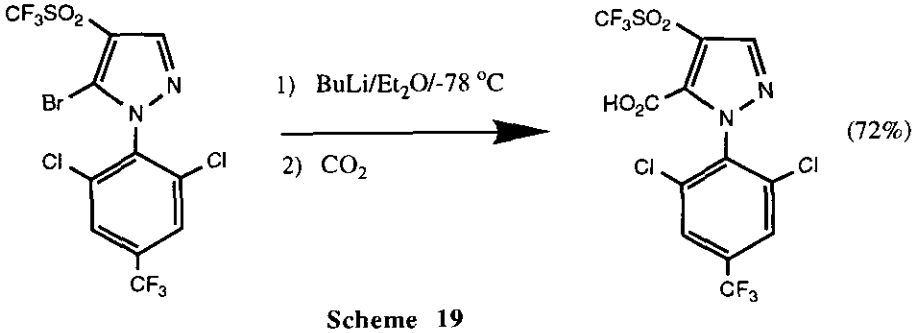
When 4-bromopyrazole was subjected in turn to reaction with phenyllithium and carbon dioxide, 4-bromopyrazole-3-carboxylic acid (35%) was obtained, along with 52% of unchanged starting material. Butyllithium, though, is much more specific for halogen → metal exchange and produces little or no 5-lithiation in these compounds (see Section III);[14] in this case the acidic products are pyrazole-4-carboxylic acid and 4-bromopyrazole-3-carboxylic acid (ratio 60:40).

III HALOGEN → LITHIUM EXCHANGE REACTIONS

Recently 1-methylpyrazol-3-yllithium has been synthesised by careful treatment of 3-bromo-1-methylpyrazole with two mol. equiv. of *tert*-butyllithium in ether at -100 °C and quenched with various electrophiles (Table II).[78] When *N*-substituted 4-bromopyrazoles are treated with an organolithium compound, halogen → lithium exchange or lithiation at position-5 (*via* transmetallation) can take place.[14] The course of the reaction is very much dependent on the nature of the metallating agent. Butyllithium leads to exclusive halogen → lithium exchange;[14, 42,67,69,70,79] phenyllithium is much less selective.[14] As halogen → lithium exchange involves a "soft-soft interaction",[71] then the softer reagents, *n*- or *sec*-butyllithium, should favor this process. Harder reagents such as phenyllithium and LDA should promote preferential 5-deprotonation.[39] When 1-SEM-4-bromopyrazole is treated with butyllithium (Et_2O or THF) bromine → lithium exchange is accompanied by α-metallation.[40]

Treatment of 4-bromo-, 4-chloro-, and 5-dimethylamino-1-phenylpyrazoles with lithium dimethylamide (in Et_2O) promotes ring opening, possibly as a consequence of base-catalysed cleavage of the N-N bond of the ring. Deprotonation at C-3 may initiate this process.[62]

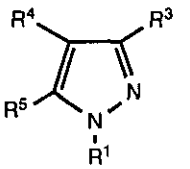
A 4- or 5-chloro group will not usually exchange with butyllithium[69,80] (see last paragraph of this Section), but a bromine at C-5 can be exchanged provided that sufficient activation is present (Scheme 19).[44]



Scheme 19

Table II

3- and 4-Substituted Pyrazoles Prepared by Halogen → Lithium Exchange



R^1	R^3	R^4	R^5	Reagent	Yield (%)	Ref.
Me	D	H	H	MeOD	26	78
Me	CO_2H	H	H	CO_2	77	78
Me	CH(OH)Me	H	H	MeCHO	62	78
Me	CH(OH)Ph	H	H	PhCHO	60	78
Me	COPh	H	H	PhCOCl	62	78
Me	NHCOPh	H	H	PhNCO	47	78
Me	SPh	H	H	Ph_2S_2	67	78
H	H	CO_2H	H	CO_2	9[a], 72[b]	14
H	H	$CH(OH)CH_2Ph$	H	$PhCH_2CHO$	43	81
H	H	CH(OH)Ph	H	PhCHO	60	81
H	H	$CH(OH)C_6H_4Cl$-4	H	4-ClC_6H_4CHO	59	81
H	H	$CH(OH)C_6H_4OMe$-4	H	4-$MeOC_6H_4CHO$	60	81

H	H	CH(OH)thien-2-yl	H	thien-2-ylCHO	36	82
H	H	CH(OH)thien-3-yl	H	thien-3-ylCHO	37	82
H	H	CH(OH)5-methylthien-2-yl	H	5-methylthien-2-ylCHO	39	82
H	H	CH(OH)4-bromothien-2-yl	H	4-bromothien-2-ylCHO	43	82
H	H	CH(OH)5-nitrothien-2-yl	H	5-nitrothien-2-ylCHO	8	82
H	H	CH(OH)pyrid-2-yl	H	pyrid-2-ylCHO	36	82
H	H	CH(OH)pyrid-3-yl	H	pyrid-3-ylCHO	37	82
H	H	CH(OH)pyrid-4-yl	H	pyrid-4-ylCHO	43	82
H	H	CH(OH)pyridazin-3-yl	H	pyridazin-3-ylCHO	39	82
H	H	CH(OH)pyridazin-4-yl	H	pyridazin-4-ylCHO	8	82
H	H	$C(OH)(C_6H_4NMe_2\text{-}4)_2$[c]	H	$(4\text{-}Me_2NC_6H_4)_2CO$	—	22
H	H	$COCH_2Ph$	H	$PhCH_2CO_2Et$	30	81
H	H	COPh	H	$PhCO_2Et$	60	81
H	H	COPh	H	PhCN	58	81
H	H	COthien-2-yl	H	thien-2-ylCO_2Et	14	82
H	H	COthien-3-yl	H	thien-3-ylCO_2Et	15	82
H	H	CO(4-bromothien-2-yl)[d]	H	4-bromothien-2-ylCHO	57	82
H	H	COpyrid-2-yl	H	pyrid-2-ylCO_2Et	24	82
H	H	COpyrid-3-yl	H	pyrid-3-ylCO_2Et	21	82
H	H	COpyrid-4-yl	H	pyrid-4-ylCO_2Et	41	82

H	H	COpyridazin-3-yl	H	pyridazin-3-ylCO_2Et	24	82
H	H	COpyridazin-4-yl	H	pyridazin-4-ylCO_2Et	10	82
H	H	COpyrimidin-4-yl	H	pyrimidin-4-ylCO_2Et	23	82
H	H	pyrazin-2-yl	H	pyrazin-2-ylCO_2Et	30	82
H	Br	CO_2H	Br	CO_2	80[b]	14
Me	H	CO_2H	H	CO_2	20[a], 52[b]	14
Me	H	$CH(OH)C_6H_4NMe_2$-4	H	4-$Me_2NC_6H_4CHO$	22	22
Me	H	CH(OH)1-methylpyrazol-4-yl	H	1-methylpyrazol-4-ylCHO	35	21
Me	H	CH(OH)1-methylpyrazol-4-yl	H	HCO_2Et	18	21
Me	H	$C(OH)Ph_2$	H	Ph_2CO	74[b]	21
Me	H	$CO(C_6H_4NMe_2$-4$)_2$	H	$(4\text{-}Me_2NC_6H_4)_2CO$	68	22
Me	H	CO_2H	Me	CO_2	77[b]	14
Me	H	COcyclopropyl	SO_2NHBu-*tert*	cyclopropylCOCl	—	79
THP	H	CH(OH)Ph	H	PhCHO	26[c]	67
Ph	H	$SnBu_3$	H	Bu_3SnCl	89	42
Me	Me	CO_2H	Cl	CO_2	85	69
Me	Me	CH(OH)Ph	Cl	PhCHO	95	69
Me	Me	$CH(OH)C_6H_3OMeCl$-3,2	Cl	2,3-$ClMeOC_6H_3CHO$	90	69
Me	Me	CH(OH)thien-3-yl	Cl	thien-3-ylCHO	95	69
Me	Me	CH(OH)5-bromothien-2-yl	Cl	5-bromothien-2-ylCHO	88	69
Me	Me	COMe	Cl	Ac_2O	75	69

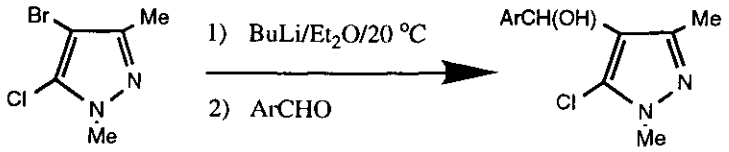
Me	Me	COC_6H_4Me-2	Cl	$(2\text{-}MeC_6H_4CO)_2O$	70	69
Me	Me	$COC_6H_4CO_2H$-2	Cl	phthalic anhydride	31	69
Me	Me	COcyclohexyl	Cl	cyclohexylCOCl	67	69
Me	Me	COC_6H_4Br-2	Cl	$2\text{-}BrC_6H_4COCl$	70	69
Me	Me	$COC_6H_4CF_3$-2	Cl	$2\text{-}F_3CC_6H_4COCl$	75	69
Me	Me	$COC_6H_4CF_3$-3	Cl	$3\text{-}F_3CC_6H_4COCl$	70	60
Me	Me	COC_6H_4OMe-2	Cl	$2\text{-}MeOC_6H_4COCl$	62	69
Me	Me	$COC_6H_3(OMe)_2$-2,3	Cl	$2,3\text{-}(MeO)_2C_6H_3COCl$	65	69
Me	Me	$COC_6H_3(OMe)_2$-2,6	Cl	$2,6\text{-}(MeO)_2C_6H_3COCl$	60	69
Me	Me	COthien-2-yl	Cl	thien-2-ylCOCl	71	69
Me	Me	COC_6H_4OMe-4	Cl	$4\text{-}MeOC_6H_4CN$	75	69
Me	Me	$COC_6H_3(OMe)_2$-3,5	Cl	$3,5\text{-}(MeO)_2C_6H_3CN$	72	69
Et	Me	COcyclohexyl	Cl	cyclohexylCOCl	72	69
Pr	Me	COC_6H_4OMe-2	Cl	$2\text{-}MeOC_6H_4COCl$	60	69
Pr	Me	$COC_6H_4CF_3$-2	Cl	$2\text{-}F_3CC_6H_4COCl$	78	69
Me	Pr	CH(OH)thien-2-yl	Cl	thien-2-ylCHO	90	69
Me	Pr-*i*	COthien-2-yl[d]	Cl	thien-2-ylCHO	79	69
Me	Bu	COthien-2-yl[d]	Cl	thien-2-ylCHO	80	69
Me	$OSiMe_2Bu$-*tert*	Me	CF_3	MeI	—	83
cyclohexyl	Me	COthien-2-yl[d]	Cl	thien-2-ylCHO	70	69

Me	Ph	$CH(OH)C_6H_4OMe$-2	Cl	2-$MeOC_6H_4CHO$	85	69
Me	Ph	CH(OH)thien-2-yl	Cl	thien-2-ylCHO	97	69
Ph	Me	CH(OH)thien-2-yl	Cl	thien-2-ylCHO	93	69
Ph	Me	COC_6H_4OMe-2	Cl	2-$MeOC_6H_4COCl$	60	69
Me	Me	CO_2H	Me	CO_2	81[b]	14
Me	Me	COC_6H_4F-2	NHCOPh	2-$FC_6H_4CO_2Me$	59	70
Me	Me	CO(2-furyl)	NHCOPh	2-furylCO_2Me	42	70
Me	Me	COpyrid-3-yl	NHCOPh	pyrid-3-ylCO_2Et	50	70
Me	Me	COpyrazin-2-yl	NHCOPh	pyrazin-2-ylCO_2Me	45	70
Me	Me	CO(1-ethyl-4-methyl-pyrazol-5-yl)	NHCOPh	1-ethyl-4-methyl-pyrazol-5-ylCO_2Et	60	70

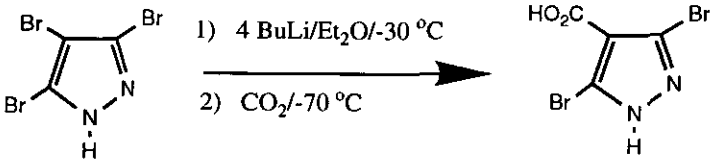
[a] With PhLi. [b] With BuLi. [c] From 4-bromo-1-triphenylmethylpyrazole; starting material and 1-triphenylmethylpyrazole isolated too. [d] After MnO_2 oxidation of the alcohol. [e] Protecting group lost.

Usually, however, 3- and 5-bromine atoms are not replaced.[5] In 7-alkoxy-3-bromopyrazolo[4,3-*d*]pyrimidines (**20**) butyllithium induces exchange at low temperatures.[56]

There are many examples of the use of bromine → lithium exchange applied to the synthesis of 4-substituted pyrazoles (Scheme 20; Table II).[14,21,22,42,67,69,70,79,83]

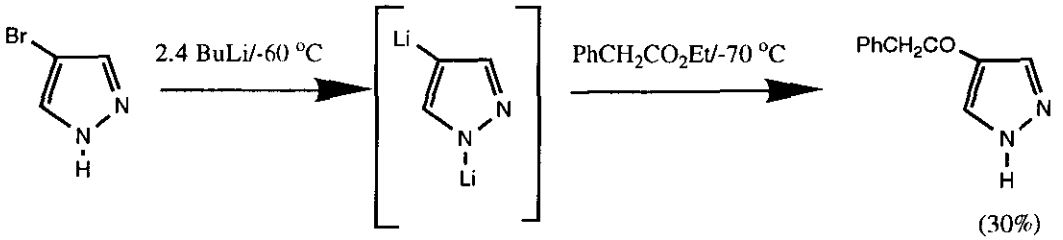


(85-97%)



(80%)

Scheme 20



(30%)

(33)

The convenient availability of 1,4-dilithiopyrazole (**33**), formed in around 75% yield when two mol. equiv. of butyllithium react with 4-bromopyrazole, provides access to a wide range of 4-substituted pyrazoles.[14,81,82] In particular, pyrazol-4-yl ketones can be obtained from reaction with esters [formation of the tertiary alcohols is avoided by addition of dilithiated species (**33**) to the electrophile] or by sequential treatment with an aldehyde and active manganese dioxide.[82]

Bromine → metal exchange reactions occur when 4-bromo-1-phenyl- and 1-benzyl-4-bromo-3,5-dimethyl-pyrazole are treated with lithium(or sodium) naphthalenide in THF but the initially generated organometallic derivatives rearrange, position-4 → position-5 in the first case and position-4 → lateral metallation in the benzyl

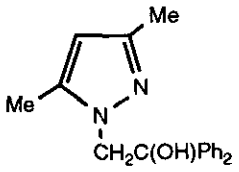
group in the second case.[19] The resulting metallated derivatives have been trapped with benzophenone or carbon dioxide. Likewise, the chlorine atom in 5-chloro-3-methyl-1-phenylpyrazole is exchanged for lithium or sodium, as shown by quenching the 5-lithiated derivative with benzophenone or carbon dioxide.[19]

IV LATERAL METALLATION

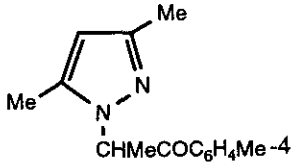
Tables III-V list products derived from lateral lithiation of pyrazole derivatives.

A 1-Methyl(and other 1-alkyl)pyrazoles

Butler and Alexander[23] found that 1-methylpyrazole was metallated by butyllithium at the *N*-methyl group (~ 30%) and in position-5 (~ 60%); 1,5-dimethyl-, 5-chloro-1,3-dimethyl-, and 5-chloro-1-methyl-3-phenyl-pyrazoles reacted predominantly at the methyl group (see also ref. 35). 1,3-Dimethylpyrazole, in contrast, was mainly lithiated at C-5, but even here some lateral metallation was observed (ratio 66:34).[23] Furthermore, it has been reported that 1,3,5-trimethyl-, 5-methoxy-1-methyl-3-phenyl-, and 1-ethyl-3,5-dimethylpyrazoles are all lithiated exclusively in the α-position[25,27] as is 1,5-dimethyl-4-(2'-phenyl)ethynylpyrazole.[84] Such α-



(34)



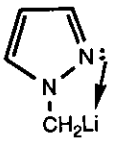
(35)

metallation appears to be a general reaction and gives good yields provided that position-5 is blocked. Thus, 1,3,5-trimethylpyrazole treated in turn with butyllithium at -78 °C and then benzophenone at 23 °C gives a high yield of the tertiary alcohol (**34**) (80% yield), and 1-ethyl-3,5-dimethylpyrazole behaves similarly to produce compound (**35**) (22%)[25] in spite of earlier assertions that higher *N*-alkyl groups do not α-metallate.[23]

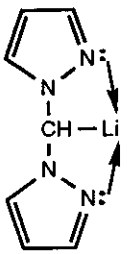
Any such lateral lithiation is kinetically controlled, and the metal will migrate to position-5 if it is free.[25] If position-5 is already substituted, ring-opening may occur instead.[32]

Similar considerations apply to 1-methylindazole which reacts with butyllithium at -15 °C to give the 1-lithiomethyl derivative; 2-methylindazole gives the 3-lithiated species in preference.[85] Coordination with the

pyridine-type nitrogen helps to stabilize the lithiomethyl species (**36**).[86] Such N···Li linkages are known to be quite ionic in character.[87,88]



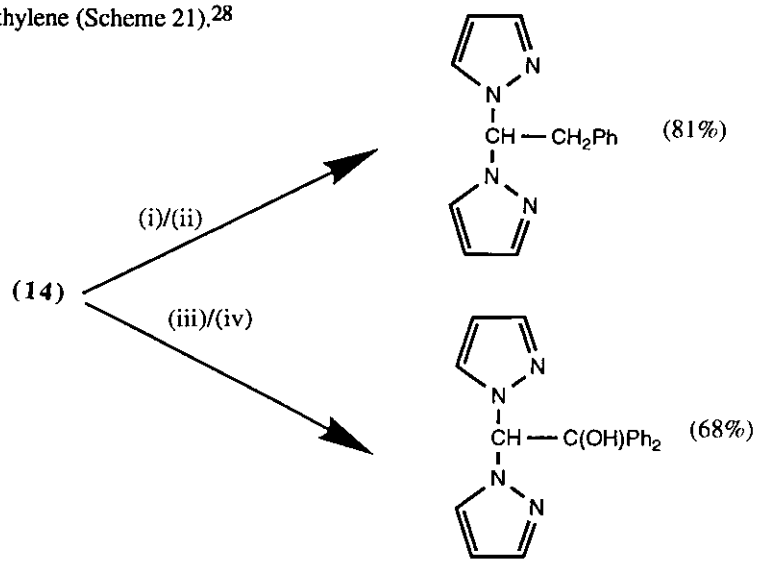
(**36**)



(**37**)

Fluoride ion (CsF or $Bu_4N^+F^-$) or potassium *tert*-butoxide induced desilylation of 1-(trimethylsilylmethyl)-pyrazole yields an anion which condenses with various carbonyl compounds.[89]

In *bis*(pyrazol-1-yl)methane (**14**), such dipole stabilization of the carbanion involves the cumulative effects of two pyrazole rings (**37**),[86] and accounts for the more facile α-lithiation of these compounds compared with 1-methylpyrazole (see also Section II.D).[28,53] Laterally-substituted products (except with "hard" electrophiles) are obtained when compound (**14**) is metallated with butyllithium (THF/0 ° or 25 °C) followed by addition of a "soft" electrophile (Scheme 21) (see also Section II.C). "Reverse addition" in which LDA in THF is added to the compound at -10 °C in the presence of the electrophile induces even carbonyl electrophiles to react exclusively at the exocyclic methylene (Scheme 21).[28]

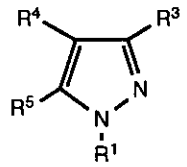


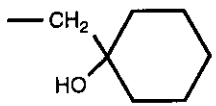
Reagents: (i) BuLi/THF/25 °C; (ii) $PhCH_2Cl$; (iii) LDA/THF; (iv) Ph_2CO/-10 °C.

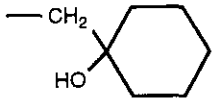
Scheme 21

Table III

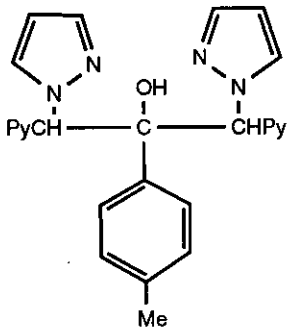
1-Substituted Pyrazoles Prepared by Lateral Metallation of 1-Alkylpyrazoles



R^1	R^3	R^4	R^5	Reagent	Yield (%)	Ref.
$CH_2CH(OH)Ph$	H	H	H	PhCHO	3, 29	25, 23
CH_2SiMe_3	H	H	H	Me_3SiCl	6	35
$CH_2CH(OH)Ph$	Me	H	H	PhCHO	< 10	23
$CH_2CH(OH)Ph$	H	H	Me	PhCHO	80	23
	H	H	Me	cyclohexanone	72	23
CH_2SiMe_3	$SiMe_3$	H	H	Me_3SiCl	6	35
$CH_2CH(OH)Ph$	Me	H	Cl	PhCHO	86	23
$CH_2C(OH)Ph_2$	Ph	H	Cl	Ph_2CO	90	23
CH_2D	Me	H	Me	D_2O	99	25

CH_2CO_2H	Me	H	Me	CO_2	82	27
Et	Me	H	Me	MeI	52	25
$CH_2CH(OH)C_6H_4Me$-3	Me	H	Me	3-MeC_6H_4CHO	84	25
	Me	H	Me	cyclohexanone	65	25
$CH_2C(OH)MePh$	Me	H	Me	MeCOPh	78	25
$CH_2C(OH)Ph_2$	Me	H	Me	Ph_2CO	80	25
CH_2COPh	Me	H	Me	PhCOCl	22	25
CH=CPhOCOPh	Me	H	Me	PhCOCl (xs.)	85	25
$CH_2COC_6H_4Me$-4	Me	H	Me	4-MeC_6H_4COCl	92	25
CH_2CO_2H	Ph	H	OMe	CO_2	93	27
CH_2CO_2H	H	C≡CPh	Me	CO_2	53	84
$CH_2CH(OH)Ph$	H	C≡CPh	Me	PhCHO	20	84
$CHMeCOC_6H_4Me$-4	Me	H	Me	4-$MeC_6H_4CO_2Me$	22	25
$CHPhCO_2H$	H	H	H	CO_2	32	25
$CHPhCH_2C_6H_4Me$-4	H	H	H	4-$MeC_6H_4CH_2Cl$	42	25
$CHPhCH(OH)C_6H_4Me$-4	H	H	H	4-MeC_6H_4CHO	54	25
$CHPhC(OH)MePh$	H	H	H	MeCOPh	62	25
$CHPhC(OH)Ph_2$	H	H	H	Ph_2CO	85	25
[a]	H	H	H	4-MeC_6H_4COCl	73	25
$CHPhCOC_6H_4Me$-4	H	H	H	4-$MeC_6H_4CO_2Me$	29	25

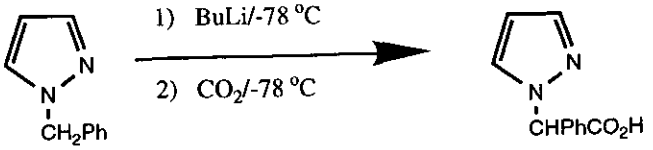
CHPhC(OH)Ph_2	Me	H	Me	Ph_2CO	66-74	19
CHMePy[b]	H	H	H	MeI	70	28
CHPyCH_2Ph[b]	H	H	H	PhCH_2Cl	81	28
CHPyCH(OH)C_6H_4Me-4[b]	H	H	H	4-MeC_6H_4CHO	61	28
CHPyC(OH)Ph_2[b]	H	H	H	Ph_2CO	68	28
CHPyCOC_6H_4Me-4[b]	H	H	H	4-Me$C_6H_4CO_2$Et	56	28
CPy=C(NH_2)Ph[b]	H	H	H	PhCN	29	28
CPyPhD[b]	H	H	H	D_2O	90	28
CPyPhMe[b]	H	H	H	MeI	50	28
CPyPhCH_2Ph	H	H	H	PhCH_2Cl	43	28
CPyPhCOPh	H	H	H	PhCOCl	67	28
CHSPhMe	Me	H	Me	MeI	66	90
CHSPhCH_2Ph	Me	H	Me	PhCH_2Br	74	90
CHSPhCH(OH)C_6H_4Me-4	Me	H	Me	4-MeC_6H_4CHO	55	90
CMe(SPh)CH_2Ph	Me	H	Me	PhCH_2Br	72	90
CH=CHPh[c]	Me	H	Me	PhCH_2Br	60	90
CH(SOPh)CH(OH)-C_6H_4Me-4	Me	H	Me	4-MeC_6H_4CHO	55	90
CHMeSiMe_2CH_2CH=CH_2[d]	H	H	H	MeI	~90	91

[a] Product is 

[b] Py is pyrazol-1-yl. [c] R^1 in starting material was CH_2SOPh. [d] See **Scheme 25** for other products.

B *1-Benzylpyrazoles* (see also ref. 92)

1-Benzylpyrazole is metallated under kinetic control at -78 °C at the methylene function, but the resultant anion rearranges rapidly at 23 °C to give the thermodynamically more stable 1-benzylpyrazol-5-yllithium.[25] If the metallation and addition of electrophile can be accomplished at low temperatures, then α-substituted products predominate (Scheme 22). Clearly 1-benzylpyrazoles will undergo ring-lithiation under thermodynamic control

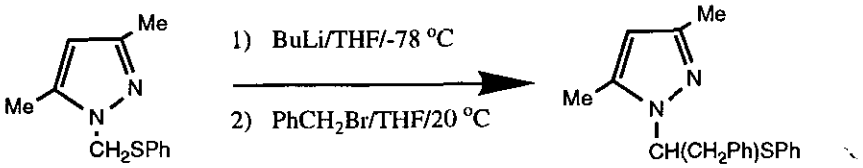


Scheme 22

provided that position-5 is free, but if this site is occupied lithiation occurs at the exocyclic site, and reactions can lead to mixtures of products.[14,25] Phenyllithium is less likely than butyllithium to give α-metallated products.[14] Exclusive lateral metallation occurs when 1-benzyl-3,5-dimethylpyrazole is treated with butyllithium in THF whereas its treatment with lithium naphthalenide results in debenzylation, to give 3,5-dimethylpyrazol-1-yl-lithium (Section I).[19]

C *1-(Substituted methyl)pyrazoles*

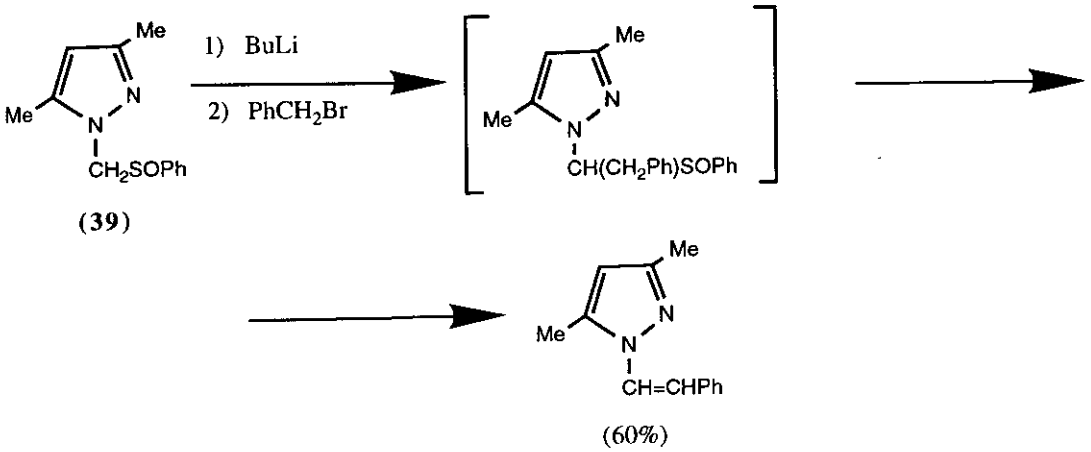
3,5-Dimethyl-1-phenylthiomethylpyrazole (**38**) (Scheme 23) is metallated at the α-position. The corresponding sulfoxide (**39**) reacts similarly, but elimination leads to the 1-styrylpyrazole (Scheme 24).[90] Desilylation of compound (**40**) occurs with cesium fluoride in diglyme at 60 °C to yield an anion which condenses with various carbonyl compounds.[93]



(38)

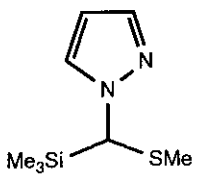
(74%)

Scheme 23



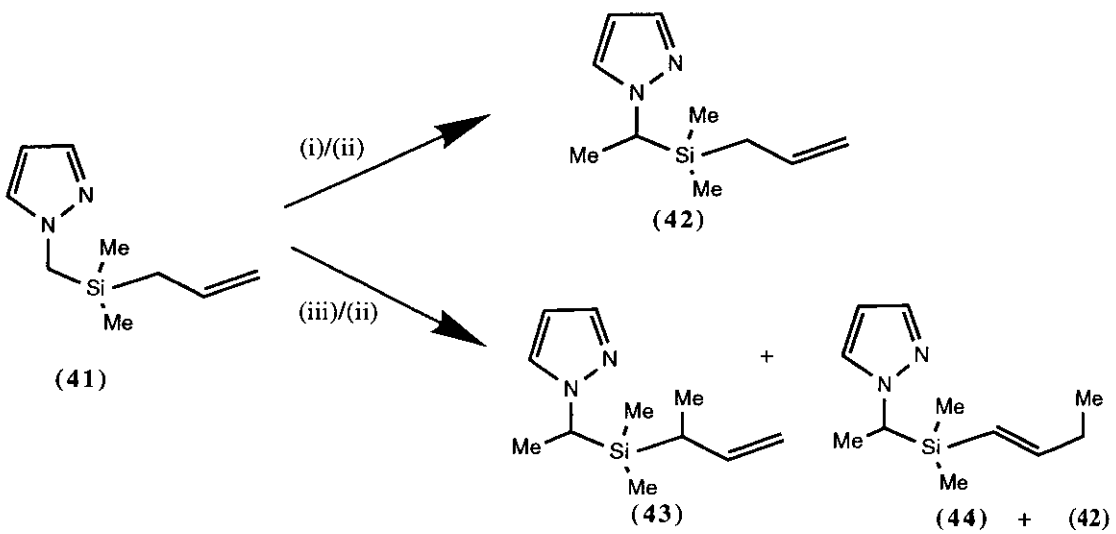
(39)

Scheme 24



(40)

In an endeavour to devise a system that would complex lithium, to form a six-membered ring, 2,2-dimethyl-1-(pyrazol-2-yl)-2-sila-4-pentene (**41**) was prepared and subjected to a lithiation-alkylation sequence. With LDA



(41) (42) (43) (44) + (42)

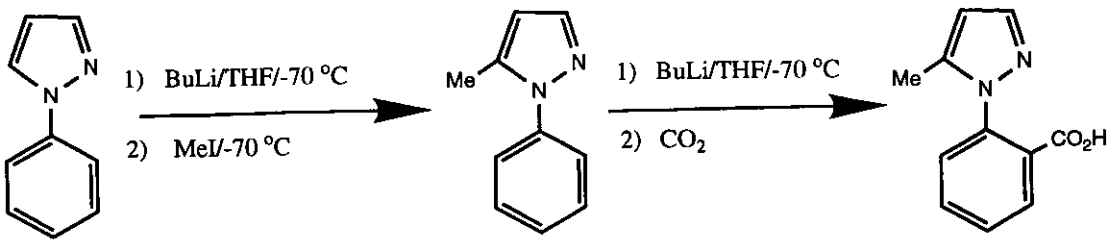
Reagents: (i) LDA/THF/-78 °C; (ii) MeI; (iii) *sec*-BuLi/THF/-78 °C.

Scheme 25

(THF/-78 °C) the exclusive product was **42**, but *sec*-butyllithium (THF/-60 °C) gave rise to dialkylated products (**43**) and (**44**) as well (Scheme 25).[91]

D 1-Arylpyrazoles

Some *ortho*-lithiation occurs in the phenyl group of 1-phenylpyrazole (Scheme 26) (see also ref. 41).[20,27,94,95]



(99%) (85%)

Scheme 26

This occurs, however, in competition with 5-metallation. An early report gave the ratio of products (as measured by yields of carboxylic acids) as 4:1 in favour of C-5 lithiation,[20] though careful control of reaction conditions can lead to exclusive metallation in that position.[14,41] In contrast, organomagnesium halides lead to predominant *ortho*-metallation (see Section VI).[94]

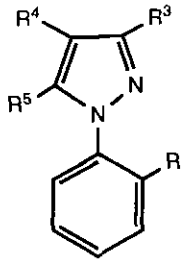
In the presence of a 5-substitutent *ortho*-lithiation occurs, although the matter is not clear-cut, since metallation of carbon substituents on the pyrazole or aryl moieties can also take place (Section IV.E).

Provided that low temperatures are used heteroring 5-lithiation predominates, but if that position is blocked *ortho*-lithiation (Table IV)[41,60] or, in some cases, lithiation at position-4[60] (Section II.E) occurs. In this respect one might suggest that, in contrast to 1-methylpyrazole, 5-lithiation of 1-phenylpyrazole is kinetically controlled and *ortho*-lithiation gives a thermodynamic product. At this time, however, compelling evidence is not available.

3,5-Dimethyl-1-phenylpyrazole is metallated with an excess of butyllithium (3.0 x BuLi/THF/0 °C) exclusively in the *ortho*-position of its phenyl ring, as shown by quenching the product with chlorotrimethylsilane (Table IV).[60] By contrast, 1-phenyl-3,5-*bis*(trifluoromethyl)pyrazole is metallated with one mol. equiv. of butyllithium exclusively in position-4 (Section II.E) but, with an excess of butyllithium (3.0 x BuLi/THF/0 °C), it gives the pyrazole *bis*(silylated) in the *ortho*-position and in position-4 (Table IV).[60]

Table IV

Products of *ortho*-Lithiation in Phenylpyrazoles



R	R^3	R^4	R^5	Reagent	Yield %	Ref.
CO_2H	H	H	H	CO_2	10[a]	20
CO_2H	H	H	Me	CO_2	85	41
SMe	H	H	Me	Me_2S_2	92	41
CO_2H	H	H	SMe	CO_2	56	41
Me	H	H	SMe	MeI	86	41
SMe	H	H	SMe	Me_2S_2	77	41
CH_2OMe	H	H	SMe	$MeOCH_2Cl$	55	41
Me	H	H	CH_2OMe	MeI	32[b]	41
CO_2H	Me	H	Me	CO_2	44	27
$SiMe_3$	Me	H	Me	Me_3SiCl	78	60
CO_2H	Me	H	OMe	CO_2	53	27
Me	Me	H	OMe	MeI	91	41
$SiMe_3$	CF_3	$SiMe_3$	CF_3	Me_3SiCl	93	60
$SiMe_3$	Me	H	CF_3	Me_3SiCl	32[c]	60
$SiMe_3$	Me	$SiMe_3$	CF_3	Me_3SiCl	76[d]	60
$SiMe_3$	CF_3	H	CH_2SiMe_3	Me_3SiCl	7[e]	60

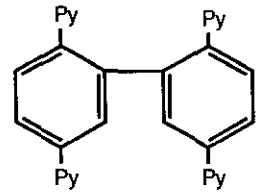
[a] 1-Phenylpyrazole-5-carboxylic acid (32% yield) obtained too. [b] An equal amount of the compound (R = R^3 = H, R^5 = CHMeOMe) formed by lateral metallation at position-5 is obtained also (BuLi/THF/-70 °C); with LDA exclusive attack at position-5 occurs. [c] Starting material (34% recovery) and the product of metallation at position-4 (Section II.E) (11% yield) produced also. [d] Lateral metallation occurs also in 3-methyl group (Section IV.E). [e] 5-Methyl-1-phenyl-3-trifluoromethylpyrazole is metallated predominantly in its 5-methyl group with an excess of butyllithium (3.0 x BuLi/THF/-70 °C) (Section IV.E).

Table V

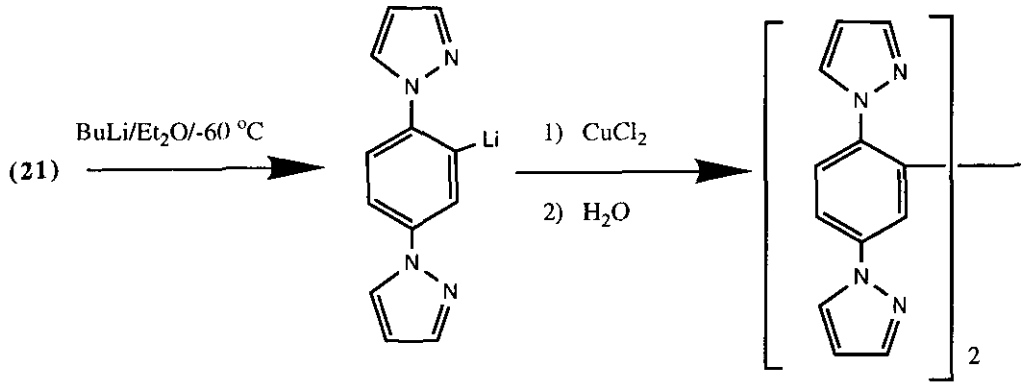
Lateral Lithiation Products of 1-Arylpyrazoles

Ar	R^3	R^4	R^5	R	Reagent	Yield %	Ref.
4-PyC_6H_4[a]	H	H	H	[b]	$CuCl_2$	28	47
2-MeC_6H_4	H	H	SMe	2-EtC_6H_4	MeI	83	41
2-MeC_6H_4	H	H	SMe	2-MeS$CH_2C_6H_4$	Me_2S_2	65	41
2-MeC_6H_4	H	H	SMe	2-$HO_2CCH_2C_6H_4$	CO_2	65	41
2-CH_2SMeC_6H_4	H	H	SMe	2-$(MeS)_2CHC_6H_4$	Me_2S_2	70	41
2-MeC_6H_4	Me	H	OMe	2-EtC_6H_4	MeI	84	41
2-MeC_6H_4	Me	H	OMe	2-$HO_2CCH_2C_6H_4$	CO_2	85	41

[a] Py = pyrazol-1-yl. [b] Coupled product =



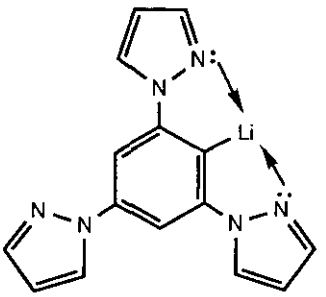
Such considerations do not seem to apply to 1,4-*bis*(pyrazol-1'-yl)benzene (**21**) which lithiates at -60 °C (Et_2O) under kinetic control in the *ortho*-position of the phenyl group, but with an excess of butyllithium at 20 °C the pyrazole 5-positions are metallated (Section II.E) (Scheme 27).[46,47] Similarly, 1,3,5-*tris*(pyrazol-1'-yl)benzene



(28%)

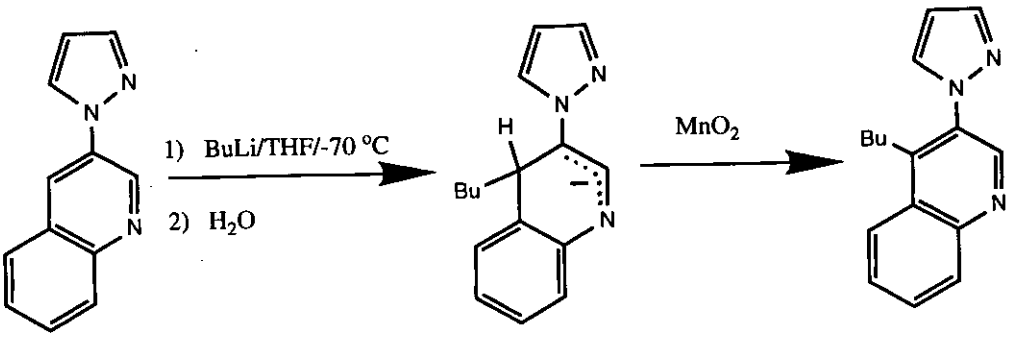
Scheme 27

is quantitatively monolithiated by one mol. equiv. of butyllithium in ether at an *ortho*-position to give compound (**45**) in which the species is stabilized by two pyrazole rings.[59]



(**45**)

When 3-(pyrazol-1'-yl)quinoline (**46**) is treated with butyllithium, a butyl group enters position-4 (Scheme 28). Nucleophilic attack rather than deprotonation has occurred, and the anion formed is able to be oxidized to a fully aromatic product. Around 2% of the 2-butyl isomer is also formed.[96,97]

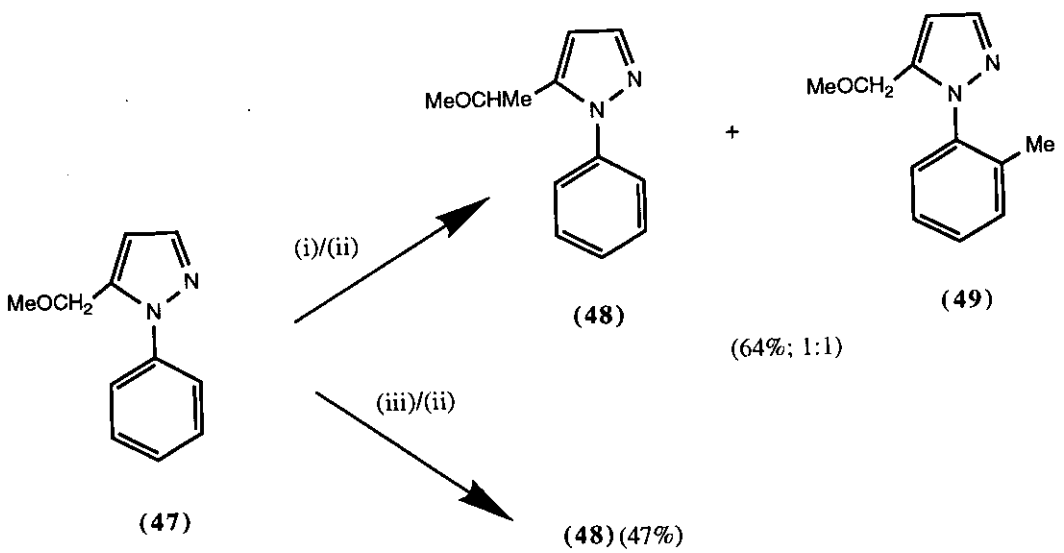


(46)

Scheme 28

E *Lateral lithiation on carbon substituents*

With an excess of butyllithium (3.0 x BuLi/THF/-70 °C; at 0 °C the resulting lithiated derivative is unstable) 5-methyl-1-phenyl-3-trifluoromethylpyrazole is metallated predominantly in its 5-methyl group, as shown by

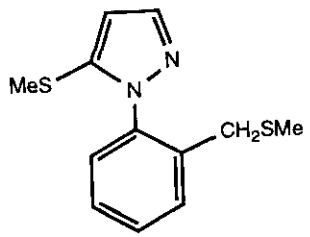


(47) **(48)** **(49)** **(48)** (47%)

Reagents: (i) BuLi; (ii) MeI; (iii) LDA.

Scheme 29

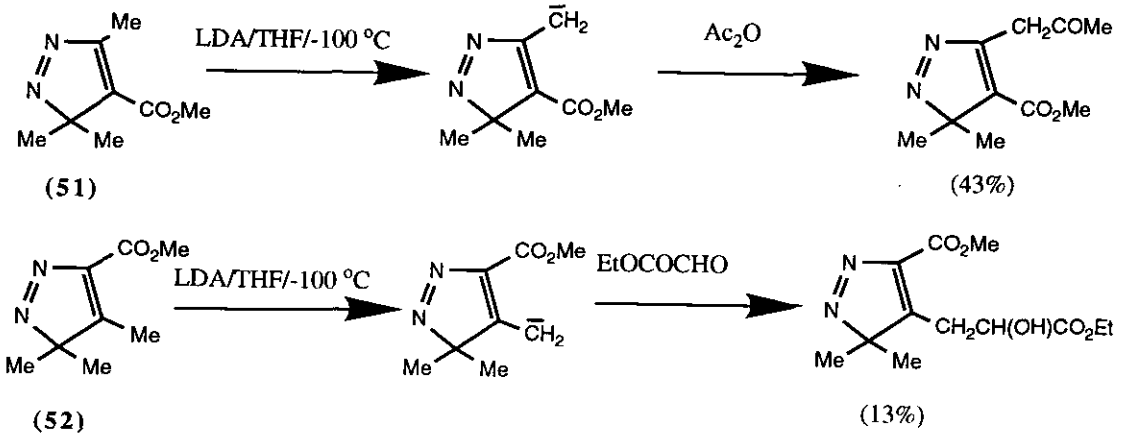
isolation of the 5-trimethylsilylmethyl derivative (37% yield) following addition of chlorotrimethylsilane; some *ortho*-metallation occurs also in the phenyl ring (Table IV).[60] By contrast the 3-methyl-5-trifluoromethyl isomer is metallated with one mol. equiv. of butyllithium (THF/0 °C) predominantly in the *ortho*-position of its phenyl ring (Section IV.D), although a small amount of the 4-metallated product is produced also (Section II.E). With an excess of butyllithium (3.0 x BuLi/THF/0 °C) this isomer is dimetallated predominantly in the *ortho*-position of the phenyl ring and in position-4, although some lateral (8%) metallation occurs in the 3-methyl group. Metallation of 5-methoxymethyl-1-phenylpyrazole (**47**) can occur at either position-5 or in the phenyl substituent, to give **48** and/or **49**. While butyllithium is non-specific, LDA leads only to **48** (Scheme 29).[41] The *ortho*-methyl group is the reactive site for butyllithium in 5-methylthio-1-(2-methylphenyl)pyrazole, while in 5-methylthio-1-(2-methylthiomethyl)phenylpyrazole (**50**) the *ortho*-methylene group is attacked.



(50)

Pyrazolenines (**51**) or (**52**) are converted into anions at -100 °C by LDA in THF. Addition of electrophiles at the same temperature gives products of lateral substitution (Scheme 30). The lower reactivity of **52** is explained in terms of delocalization of the negative charge in the carbanion equally by the annular nitrogens.[98]

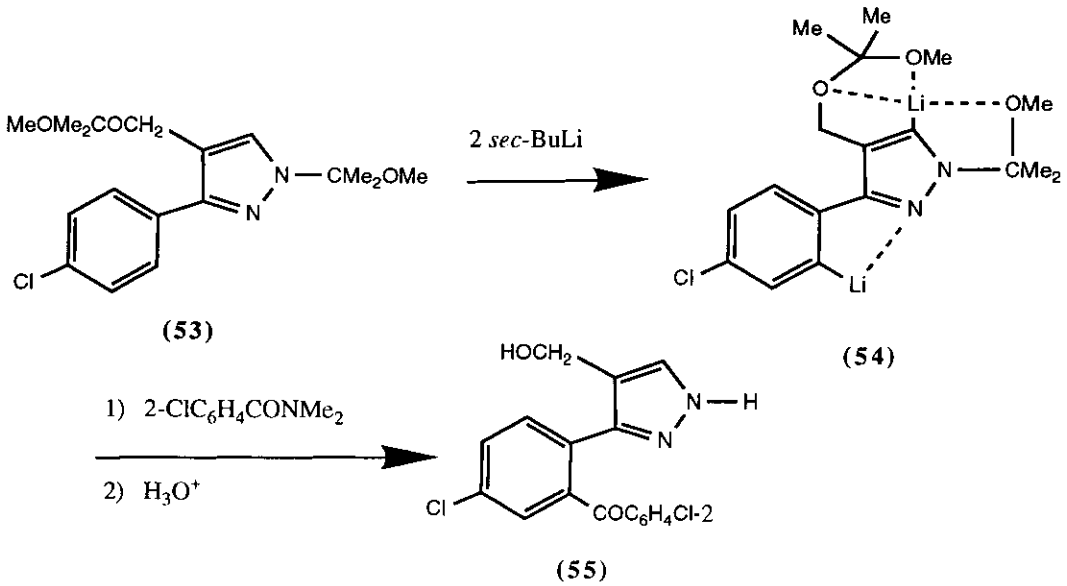
While 1-alkyl-3-arylpyrazoles can be lithiated at both position-5 and the α-position of the alkyl group,[23] both of these reactions can be suppressed by a bulky tertiary substituent (e.g. methoxyisopropyl; $MeOCMe_2$-) on the nitrogen. Lithiation then proceeds predominantly in the *ortho*-position of the 3-aryl substituent. Thus, treatment of 3-(4-chlorophenyl)-1-methoxyisopropylpyrazole in turn with *sec*-butyllithium and an aryldimethylamide gives fair yields (~ 40%) of the *ortho*-ketone products (after removal of the protecting group).[9] In 1-*tert*-butyl-3-(4-chlorophenyl)pyrazole there are two possible lithiation sites of which position-5 might be expected to be the more reactive. However, the *ortho*-position in the chlorophenyl ring is also activated by the pyrazole imine group, and careful choice of reagents can favor one or other of the sites. In THF (in which butyllithium is a solvated dimeric species[99]) most of the product is 5-substituted. In ether (in which the butyllithium is tetrameric[100])



Scheme 30

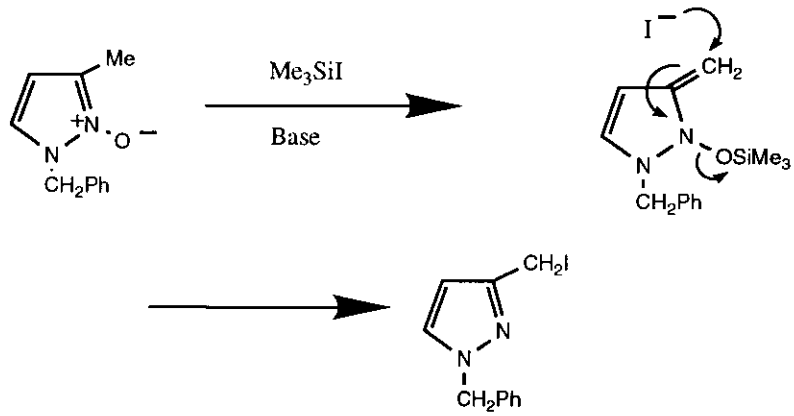
coordination of the reagent with the pyridine-type nitrogen leads to preferential abstraction of the *ortho*-proton.[9] Quite subtle differences can result in differing metallation regiochemistry especially if the electrophile is only moderately active. Illustrating this is the reactivity of the dilithiated species (**54**) derived from the doubly protected pyrazole (**53**). Since the lithiated pyrazole is less reactive than the lithiated aryl ring, then selectivity should be achieved with a tertiary amide electrophile, with the reactivity differences accentuated in this case by the three-fold chelation of the pyrazole-lithium in **54**. The *ortho*-substituted product (**55**) is therefore obtained in good yield (64%) (Scheme 31). More reactive electrophiles (e.g. dimethyl sulfoxide or deuterium oxide) are much less site-selective.[9]

1-Benzyl-3-iodomethylpyrazole is produced in 75% yield when a solution of 2-benzyl-5-methyl-1-trimethylsilyoxypyrazolium iodide (prepared *in situ* from 2-benzyl-5-methylpyrazole 1-oxide and iodotrimethylsilane) is treated with 1,2,2,6,6-pentamethylpiperidine in chloroform.[101,102] A similar result is obtained with 2-benzyl-3-methylpyrazole 1-oxide. These reactions proceed, as shown in Scheme 32, by initial deprotonation of the 5- or 3-methyl group, respectively; then iodide ion attacks the exocyclic C-atom with displacement of the trimethylsilyloxy group. 2-Benzyl-4-methylpyrazole 1-oxide, consequently, cannot react in this way.[102]



(53) (54) (55)

Scheme 31



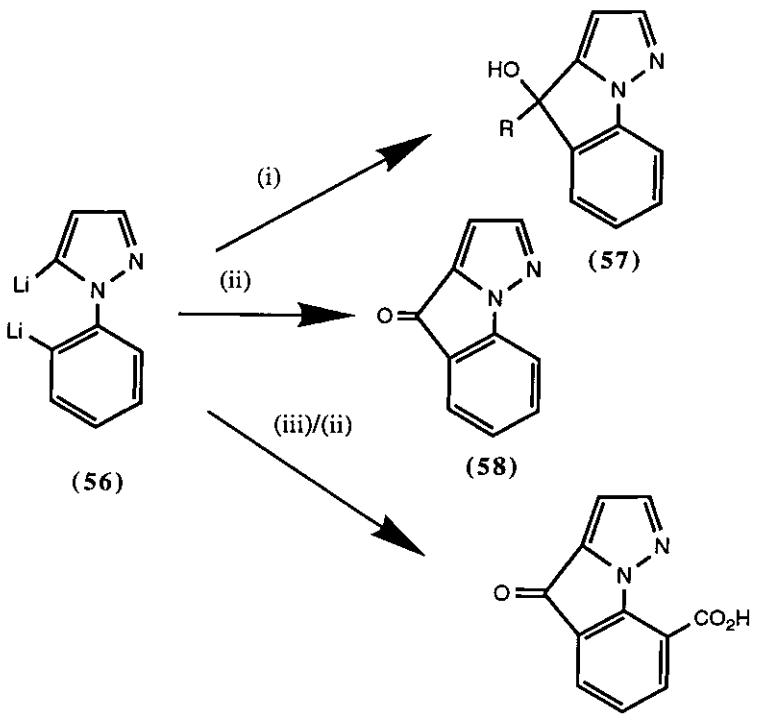
Scheme 32

V POLYLITHIATED DERIVATIVES

In contrast to imidazoles[103] there are no examples of pyrazoles in which more than one annular carbon has been metallated. Certainly there are cases where both *N*- and *C*-lithiation has occurred in the presence of two or more mol. equiv. of reagent, e.g. with 4-bromopyrazole[14,81,82] and pyrazole itself.[14] All other dimetallated species

involve anion formation both in the pyrazole ring and laterally. Some examples of this have already been considered (Section IV).

The dilithio derivative (**56**) of 1-phenylpyrazole reacts with esters to give tricyclic alcohols (**57**),[104] and 1,3,5-*tris*(pyrazol-1'-yl)benzene reacts with five mol. equiv. of butyllithium giving rise to a fivefold lithiated species metallated at each pyrazole 5-position and at two benzene sites.[59] Alley and Shirley had earlier treated **56** with carbon dioxide to give a low yield (8%) of 4-oxopyrazolo[1,5-*a*]indoline (**58**), and with a further mole of butyllithium (**56**) gave a trimetallated species which reacted with carbon dioxide to produce the product tentatively identified as **59** (26%) (Scheme 33).[20]



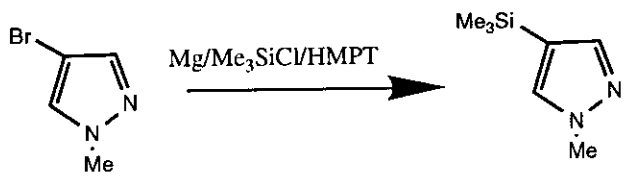
Reagents: (i) RCO_2R'; (ii) CO_2; (iii) BuLi.

Scheme 33

VI GRIGNARD DERIVATIVES

Pyrazolyl Grignard reagents have been discussed relatively recently as part of a much larger review of Grignard reagents.[11] Other reviews containing information on these compounds have appeared.[5,24,105,106]

The earliest reports suggested that a halogen in a pyrazole ring was quite inert towards magnesium,[107] and even in the presence of bromoethane only a low yield of 1-phenylpyrazole-4-carboxylic acid was isolated from reaction of 4-bromo-1-phenylpyrazole with methylmagnesium iodide followed by carbon dioxide.[108] Apparently reaction with another Grignard reagent is necessary to achieve any success, but even at the ratios of bromoethane:bromopyrazole found to be successful in the pyridines, 2:1[109] or 1:3,[110] yields were still low. It seems that the Grignard reagent forms an ether-insoluble oily complex with unreacted bromopyrazole, and this complex screens the surface of the magnesium.[111] Improved yields of the 4-carboxylic acid (42%) were achieved by "entrainment" using the magnesium-1,2-dibromoethane system,[111] and this was improved to 82% by dispersing the Grignard reagent with dry benzene before adding the carbon dioxide (a molar ratio of 4-bromo-1-phenylpyrazole:1,2-dibromoethane:magnesium of 1:3:5 was found to be the most successful).[112] Rather unexpectedly

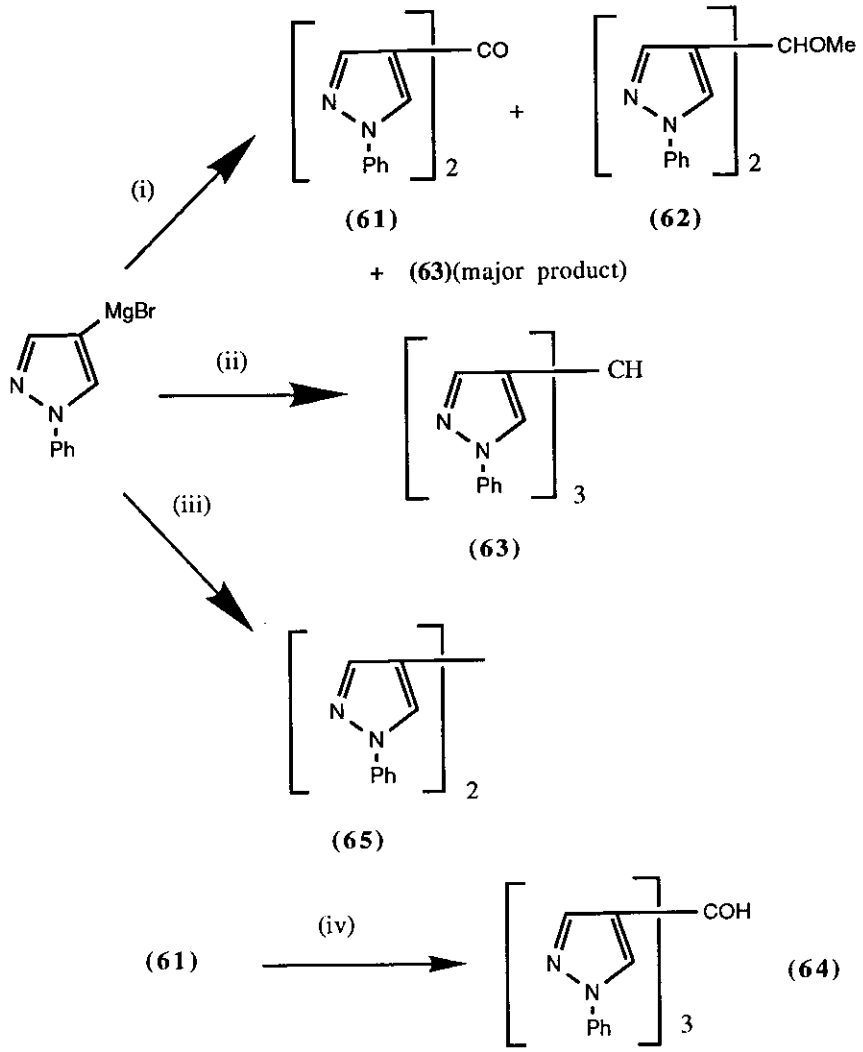


(60) (79%)

Scheme 34

this process failed for 4-bromo-1-methylpyrazole,[113] and 4-chloro-1-phenylpyrazole was also inert under these conditions.[114] Nevertheless, an *in situ* Grignard synthesis was used successfully for the synthesis of 1-methyl-4-trimethylsilylpyrazole (**60**) (Scheme 34).[35]

A wide variety of electrophiles convert 1-phenylpyrazol-4-ylmagnesium bromide or iodide into the expected products (Table VI), but oxygen, even in the presence of an excess of isopropylmagnesium bromide, failed to form 4-hydroxy-1-phenylpyrazole, and 1-phenylpyrazole-4-carbaldehyde did not yield the *bis*pyrazolyl alcohol even though its transient formation could be deduced from the isolation of the related ketone (**61**) (16% yield) and the methyl ether (**62**) (4%) (Scheme 35). The major product (**63**) is presumably derived from the tertiary alkoxide which has been reduced by a hydride transfer mechanism (Table VI).[114] It is known that one mole of



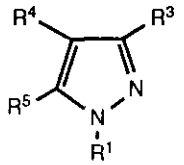
Reagents: (i) 1-Phenylpyrazole-4-carbaldehyde; (ii) 3 $(EtO)_2CO$; (iii) CoCl; (iv) 1-Phenylpyrazol-4-ylmagnesium bromide.

Scheme 35

the Grignard reagent reacts with compound (**61**) to give **64** (21% yield),[112] but three mol. equiv. of diethyl carbonate only converted the Grignard reagent into **63**. Similarly, reduced product was isolated with ethyl benzoate as the electrophile (Scheme 35).[114]

Table VI

3-, 4-, and 5-Substituted Pyrazoles *via* Grignard Derivatives[a]



R^1	R^3	R^4	R^5	Reagent	Yield (%)	Ref.
Ph	CO_2H	H	H	CO_2	18	111
Ph	C(OH)Phpyrid-4-yl	H	H	pyrid-4-ylCOPh	10	94
Me	H	$SiMe_3$	H	Me_3SiCl	79	35
Me	Me	CO_2H	Me	CO_2	31	111
CH_2Ph	Br	CO_2H	Br	CO_2	15	111
Ph	H	Br	H	Br_2	68	114
Ph	H	I	H	I_2	53	114
Ph	H	I	H	IBr	42	114
Ph	H	I	H	ICl	60	114
Ph	H	CO_2H	H	CO_2	42, 82	111, 112
Ph	H	CH(OH)Pr	H	PrCHO	45	114

Ph	H	CH(OH)Ph	H	PhCHO	48	114
Ph	H	COPh	H	2PhCHO	58	114
Ph	H	[b]	H	PyCHO[c]	—	114
Ph	H	C(OH)PyPh[c]	H	PyCOPh[c]	21	112
Ph	H	COMe	H	MeCOCl	20	112
Ph	H	COEt	H	EtCOCl	40	112
Ph	H	COPr	H	PrCOCl	47	112
Ph	H	COPr-*i*	H	*i*-PrCOCl	38	112
Ph	H	COBu-*tert*	H	*tert*-BuCOCl	35	112
Ph	H	COPh	H	PhCOCl	61	112
Ph	H	COPy[c]	H	PyCOCl[c]	67	112
Ph	H	CHPyPh[c]	H	$PhCO_2Et$	—	114
Ph	H	$CHPy_2$[c,d]	H	$(EtO)_2CO$	—	114
Ph	H	py[c]	H	CoCl	42,59	112, 114
Ph	H	H	CO_2H	CO_2	38	111
Ph	H	H	CO_2H	CO_2	31[e]	111
Ph	H	H	C(OH)Phpyrid-4-yl	pyrid-4-ylCOPh	6	111
Ph	Me	H	CO_2H	CO_2	6[e]	111

[a] Pyrazolylmagnesium bromides used unless stated otherwise. [b] Products were PyCOPy (16% yield), PyCH(OMe)Py (6%), and Py_3CH[c]. [c] Py is 1-phenylpyrazol-4-yl. [d] 3 Mol. equiv. Grignard compound used. [e] Pyrazolylmagnesium chloride.

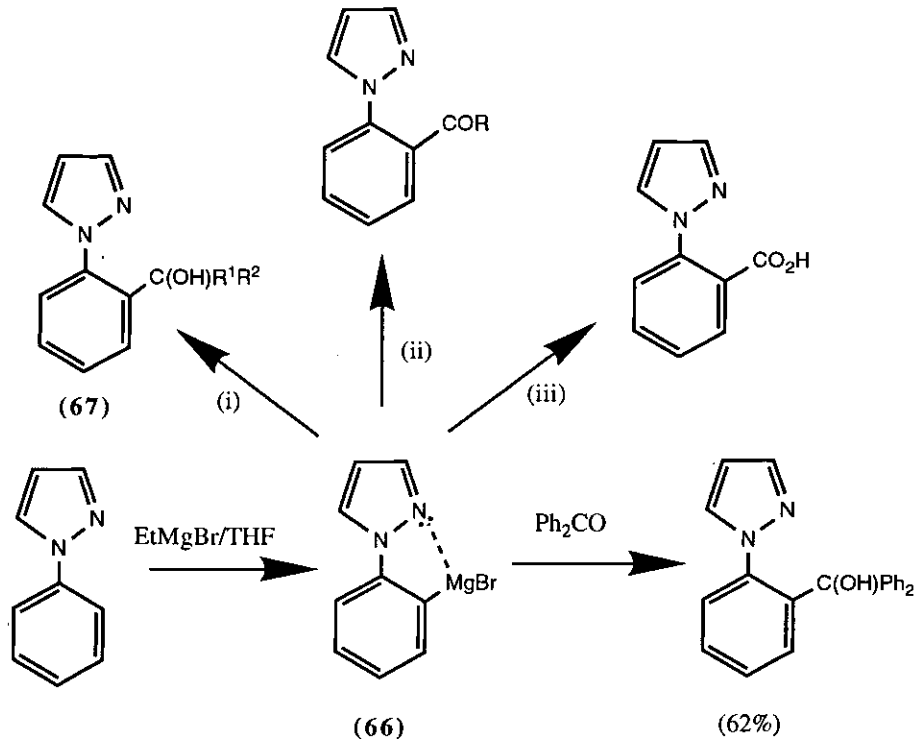
When 1-phenylpyrazol-4-ylmagnesium bromide is heated for 3 hours in refluxing benzene with anhydrous cobaltous chloride, the coupled product (**65**) is obtained in 42% yield.[112] Doubt was later cast on the efficacy of the cobaltous chloride when it was found that heating of the Grignard reagent alone gives compound (**65**) (8-28% yield, 8 hours under reflux; 55-59%, one week under reflux).[114]

Of the chloropyrazoles tested, only 5-chloro-1-phenylpyrazole gives a Grignard reagent (45%). The 3- and 4-isomers failed to react. In terms of positional reactivity position-5 is the most reactive. Yields of Grignard reagent from the isomeric monobromo-1-phenylpyrazoles were found to be: 5-bromo (92%) > 4-bromo (60%) > 3-bromo (40%). Treatment of the Grignard reagent formed from 1-benzyl-3,4,5-tribromopyrazole with carbon dioxide gave a product tentatively identified as 1-benzyl-3,4-dibromopyrazole-5-carboxylic acid.[111]

In contrast to butyllithium, ethylmagnesium bromide reacts with 1-phenylpyrazole in THF exclusively by deprotonation at the *ortho*-position of the phenyl moiety.[24,48,94] Stabilization of the magnesium species (**66**) can be achieved by complexing with the pyrazole nitrogen. Reactions with the usual carbonyl reagents give good yields of alcohol products (**67**) (Scheme 36).[94] Surprisingly, 1-(2-bromophenyl)pyrazole did not give a single product with magnesium (in THF). Rather, a mixture of three derivatives, including the *ortho*-magnesium bromide species (**66**), is formed. Subsequent reaction with 4-benzoylpyridine gave the tertiary alcohols derived from **66** [i.e. **67**], **68**, and **69** in the ratio 16:3:5 (Scheme 37).[24,94] It is surprising that ethylmagnesium bromide hardly reacts with 3,5-dimethyl-1-phenylpyrazole, while 3-phenylpyrazole is only deprotonated at nitrogen by this reagent.[24,94]

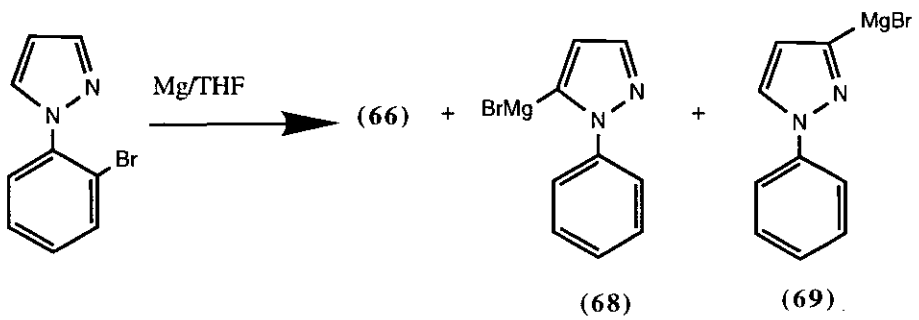
VII OTHER ORGANOMETALLIC DERIVATIVES

References to mercury derivatives of pyrazoles first appeared late last century,[115-118] and brief surveys have appeared since.[5,8,12] Reactions of 3-methyl-, 3,5-dimethyl-, and 1,3,5-trimethylpyrazoles with mercuric chloride were reported to give products such as $2C_4H_6N_2.3HgCl$ (from 3-methylpyrazole).[116] The observation that 1,3,5-trimethylpyrazole reacted showed that there is no need for a free NH for "salt formation". Some years later it was shown that mercuric acetate or mercuric chloride react with 5-chloro-3-methyl-1-phenylpyrazole to give a monomercurated product, assumed to be 4-substituted, but without any particular proof of this regiochemistry.[119] The observation[108] that mercuration of 1-phenylpyrazole gives a product capable of bromination to give 4-bromopyrazole was not unequivocal proof of 4-mercuration because a mercury group anywhere in the ring would



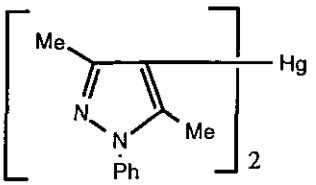
Reagents: (i) R^1COR^2; (ii) RCN; (iii) CO_2.

Scheme 36

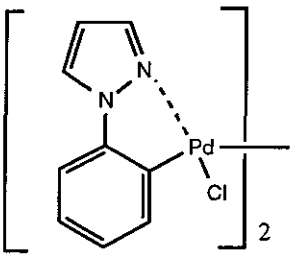


Scheme 37

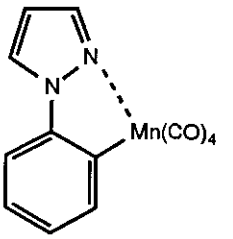
be capable of elimination under the action of liberated hydrogen bromide.[120] However, reaction of mercuric chloride with 1,3,5-trimethyl-, 5-chloro-3-methyl-1-phenylethyl-, and 1-ethyl-3,5-dimethylpyrazoles all gave products containing one HgCl group which must have been attached at C-4. 3,5-Dimethyl-1-phenylpyrazole gave, instead, a product with one mercuric chloride molecule complexed to two pyrazole residues which afforded the complex (**70**) on treatment with alkali.[120]



(**70**)



(**71**)



(**72**)

Grandberg and co-workers also studied the amount of "complex-bound" $HgCl_2$ per molecule of pyrazole, using potentiometric titration, since the degree of complexing is a function of the basic pK_a of the azole. Weakly basic pyrazoles (1-phenyl- and 5-chloro-3-methyl-1-phenylpyrazoles) had none; 3,5-dimethyl-1-phenylpyrazole had half a molecule; 1,3,5-trimethyl- and 1-ethyl-3,5-dimethylpyrazoles had one molecule. Yields of 4-mercurated products are high (47-90%). When the NH is unsubstituted, mercuration can also occur at that position, but no lateral mercuration has been observed for methyl, benzyl, or phenyl substituents.[120]

*Bis*pyrazoles have also been mercurated successfully.[121] Mercury groups on pyrazole behave in a variety of reactions just as phenylmercury chloride does.[108,120-122] Thus, nitrosylsulfuric acid converts 4-mercurated-3-phenylpyrazole into the 4-diazo product.[122]

Antipyrine is metallated by mercuric chloride in position-4.[123]

Noteworthy is the fact that the 5-lithiated derivative of 1-tosylpyrazole does not react with allyl bromide until it has been converted to the higher order cuprate derived from 2-thienyl(cyano)copper lithium.[51]

1-Phenylpyrazole metallates very readily in the *ortho*-position of the phenyl ring using palladium(II) chloride, even in dilute hydrochloric or perchloric acid,[7,124,125] to give compound (**71**) (*ca.* 80% yield). 3,5-Dimethyl-1-phenylpyrazole behaves similarly.[124] A high yield of a similar manganese complex (**72**) (71%) can be prepared

from 1-phenylpyrazole,[125] and analogous rhodium(III) and iridium(III) products can also be made.[126] These processes resemble the *ortho*-lithiation observed with 1-phenylpyrazoles (Section IV.D).

ACKNOWLEDGEMENTS

We thank Sandra Fahy for help in preparation of the manuscript.

REFERENCES

1. Part II: B. Iddon, *Heterocycles*, 1994, **37**, 1321.
2. Part I: B. Iddon, *Heterocycles*, 1994, **37**, 1263.
3. T.L. Jacobs in "Heterocyclic Compounds", ed. R.C. Elderfield, Wiley, New York, 1957, Vol. V, Ch. 2, p. 45.
4. R.H. Wiley and P. Wiley, *Chem. Heterocycl. Compds.*, 1964, **20**, 1.
5. A.N. Kost and I.I. Grandberg, *Adv. Heterocycl. Chem.*, 1966, **6**, 347.
6. R. Fusco, *Chem. Heterocycl. Compd.*, 1967, **22**, 1.
7. S. Trofimenko, *Chem. Rev.*, 1972, **72**, 497.
8. K. Schofield, M.R. Grimmett, and B.R.T. Keene, "Heteroaromatic Nitrogen Compounds: The Azoles", Cambridge University Press, 1976.
9. H.W Gschwend and H.R. Rodriguez, *Org. Reactions*, 1979, **26**, 1.
10. S.D. Sokolov, *Russ. Chem. Rev. (Engl. Transl.)*, 1979, **48**, 289.
11. Y.-H. Lai, *Synthesis*, 1981, 585.
12. J. Elguero in "Comprehensive Heterocyclic Chemistry", Vol. 5, ed. K.T. Potts, Pergamon Press, Oxford, 1984, p. 167.
13. A.R. Katritzky, L.N. Lam, S. Sengupta, and G.W. Rewcastle, *Prog. Heterocycl. Chem.*, 1989, **1**, 1.
14. R. Hüttel and M.E. Schön, *Liebigs Ann. Chem.*, 1959, **625**, 55.
15. Ref. 8, Ch. 3, p. 59.
16. A.R. Katritzky, P. Lue, and K. Akutagawa, *Tetrahedron*, 1989, **45**, 4253.
17. S. Kerschl and B. Wrackmeyer, *Z. Naturforsch.*, 1986, **41B**, 890.

18. U. Baus, W. Reuther, and R. Fikentscher, Ger. Pat. 3,820,738/1989 (*Chem. Abstr.*, 1990, **113**, 59171).

19. B.A. Tertov and A.S. Morkovnik, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1975, **11**, 343.

20. P.W. Alley and D.A. Shirley, *J. Am. Chem. Soc.*, 1958, **80**, 6271.

21. R. Hüttel, W. Schwarz, and F. Wunsch, *Chem. Ber.*, 1961, **94**, 2993.

22. R. Hüttel, W. Schwarz, J. Miller, and F. Wunsch, *Chem. Ber.*, 1962, **95**, 222.

23. D.E. Butler and S.M. Alexander, *J. Org. Chem.*, 1972, **37**, 215.

24. A. Marxer, *Lect. Heterocycl. Chem.*, 1976, **3**, S-131.

25. A.R. Katritzky, C. Jayaram, and S.N. Vassilatos, *Tetrahedron*, 1983, **39**, 2023.

26. G.I.I. Moore, U.S. Pat. 4,535,165/1985 (*Chem. Abstr.*, 1986, **104**, 34081).

27. R.G. Micetich, *Can. J. Chem.*, 1970, **48**, 2006.

28. A.R. Katritzky, A.E. Abdel-Rahman, D.E. Leahy, and O.A. Schwarz, *Tetrahedron*, 1983, **39**, 4133.

29. Y. Takeuchi, H.J.C. Yeh, K.L. Kirk, and L.A. Cohen, *J. Org. Chem.*, 1978, **43**, 3565.

30. K.L. Kirk, *J. Heterocycl. Chem.*, 1985, **22**, 57.

31. H.L. Kohn, *Diss. Abstr. Int.*, 1972, **33B**, 89.

32. B.A. Tertov and Yu.G. Bogachev, *Khim. Geterotsikl. Soedin.*, 1981, 119 (*Chem. Abstr.*, 1981, **94**, 208798).

33. B.A. Tertov, P.P. Onishchenko, Yu.V. Koshchienko, G.M. Suvorova, and E.N. Malysheva, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1982, **18**, 823.

34. M. Takahashi, T. Mamiya, H. Hasegawa, T. Nagai, and H. Wakita, *J. Heterocycl. Chem.*, 1986, **23**, 1363.

35. F. Effenberger and A. Krebs, *J. Org. Chem.*, 1984, **49**, 4687.

36. K.S. Hirsch, C.D. Jones, and H.M. Taylor, Europ. Pat. Appl. 0,165,782/1985 (*Chem. Abstr.*, 1986, **104**, 186403).

37. C.D. Jones, M.A. Winter, K.S. Hirsch, N. Stamm, H.M. Taylor, H.E. Holden, J.D. Davenport, E.V. Krumkalns, and R.G. Suhr, *J. Med. Chem.*, 1990, **33**, 416.

38. A.R. Katritzky, G.W. Rewcastle, and W.-Q. Fan, *J. Org. Chem.*, 1988, **53**, 5685.

39. G. Heinisch, W. Holzer, and S. Pock, *J. Chem.Soc., Perkin Trans. 1*, 1990, 1829.

39a. R. Kalish, E. Broger, G.F. Field, T. Anton, T.V. Steppe, and L.H. Sternbach, *J. Heterocycl. Chem.*, 1975, **12**, 49 .

40. N. Fugina, W. Holzer, and M. Wasicky, *Heterocycles*, 1992, **34**, 303.

41. R.G. Micetich, V. Baker, P. Spevak, T.W. Hall, and B.K. Bains, *Heterocycles*, 1985, **23**, 943.

42. T. Sakamoto, F. Shiga, D. Uchiyama, Y. Kondo, and H. Yamanaka, *Heterocycles*, 1992, **33**, 813.

43. H.R. Snyder, F. Verbanac, and D.B. Bright, *J. Am. Chem. Soc.*, 1952, **74**, 3243.

44. U. Jensen-Korte, R. Gehring, O. Schallner, J. Stetter, B. Becker, and B. Homeyer, Ger. Pat. 3,711,928/1988 (*Chem. Abstr.*, 1989, **110**, 135233).

45. T. Kauffmann, J. Legler, E. Ludorff, and H. Fischer, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 846.

46. T. Kaufmann and H. Lexy, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 755.

47. H. Lexy and T. Kauffmann, *Chem. Ber.*, 1980, **113**, 2749.

48. T. Kauffmann, B. Muke, R. Otter, and D. Tigler, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 714.

49. P.J. Dudfield, C.T. Ekwuru, K. Hamilton, C.E. Osbourn, and D.J. Simpson, *Synlett.*, 1990, 277.

50. F. Effenberger, M. Roos, R. Ahmad, and A. Krebs, *Chem. Ber.*, 1991, **124**, 1639.

51. K.I. Booker-Milburn, *Synlett.*, 1992, 327.

52. D.E. Butler and H.A. DeWald, *J. Org. Chem.*, 1975, **40**, 1353.

53. E. Diez-Barra, A. de la Hoz, A. Sánchez-Migallón, and J. Tejeda, *J. Chem.Soc., Perkin Trans. 1*, 1993, 1079.

54. B.A. Tertov, V.V. Bessonov, and P.P. Onishchenko, *J. Org. Chem. U.S.S.R. (Engl. Transl.)*, 1974, **10**, 2634.

55. B.A. Tertov, P.P. Onishchenko, and M.A. Kazanbieva, *J. Org. Chem. U.S.S.R. (Engl. Transl.)*, 1970, **6**, 2147.

56. T.E. Stone, E.J. Eustace, M.V. Pickering, and G.D. Daves, *J. Org. Chem.*, 1979, **44**, 505.

57. M. Begtrup and P. Vedsó, *J. Chem. Soc., Perkin Trans. 1*, 1993, 625.

58. I. Almena, M. Begtrup, and A. de la Hoz, *Acta Chem. Scand.*, 1992, **46**, 1096.

59. H. Lexy and T. Kauffmann, *Chem. Ber.*, 1980, **113**, 2755.

60. S. Iwata, C.-P. Qian, and K. Tanaka, *Chem. Lett.*, 1992, 357.

61. R. Maurelia, G. León, and A. Oliva, *Synth. Comm.*, 1990, **20**, 477.

62. R. Fusco and M. Bianchi, *Gazz. Chim. Ital.*, 1967, **97**, 410.

63. D.J. Chadwick and R.I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 1984, 481.

64. N.S. Narasimhan and R.S. Mali, *Synthesis*, 1983, 957.

65. G. Heinisch and W. Holzer, *Heterocycles*, 1988, **27**, 2443.

66. R.J. Sundberg and H.F. Russell, *J. Org. Chem.*, 1973, **38**, 3324.

67. B.-R. Tolf, R. Dahlbom, H. Theorell, and Å. Åkeson, *Acta Chem. Scand.*, 1982, **36B**, 101.

68. R.G. Christiansen, M.R. Bell, T.E. D'Ambra, J.P. Mallamo, J.L. Herrmann, J.H. Ackerman, C.J. Opalka, R.K. Kullnig, R.C. Winneker, B.W. Snyder, F.H. Batzold, and H.P. Schane, *J. Med. Chem.*, 1990, **33**, 2094.

69. D.E. Butler and H.A. DeWald, *J. Org. Chem.*, 1971, **36**, 2542.

70. H.A. DeWald, *J. Heterocycl. Chem.*, 1984, **21**, 1175.

71. T.-L. Ho, *Tetrahedron*, 1985, **41**, 3.

72. D.J. Chadwick and S.T. Hodgson, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1833.

73. A.R. Katritzky, W.-Q. Fan, A.E. Koziol, and G.J. Palenik, *Tetrahedron*, 1987, **43**, 2343.

74. A.R. Katritzky and K. Akutagawa, *Tetrahedron*, 1986, **42**, 2571.

75. A.R. Katritzky, L.M. Vazquez de Miguel, and G.W. Rewcastle, *Heterocycles*, 1987, **26**, 3135.

76. A.R. Katritzky, L.M. Vazquez de Miguel, and G.W. Rewcastle, *Synthesis*, 1988, 215.

77. A.R. Katritzky, G.W. Rewcastle, and L.M. Vazquez de Miguel, *J. Org. Chem.*, 1988, **53**, 794.

78. J.W. Pavlik and E.M. Kurzweil, *J. Heterocycl. Chem.*, 1992, **29**, 1357.

79. B.A. Wexler, Europ. Pat. 245,058/1987 (*Chem. Abstr.*, 1988, **108**, 112485).

80. T. Nakanome and I. Okada, Jpn. Kokai 02,101,064/1990 (*Chem. Abstr.*, 1990, **113**, 115299).

81. G. Heinisch, W. Holzer, and T. Huber, *Arch. Pharm.*, 1987, **320**, 1267.

82. M. Hahn, G. Heinisch, W. Holzer, and H. Schwarz, *J. Heterocycl. Chem.*, 1991, **28**, 1189.

83. K. Moedritzer and M.D. Rogers, Europ. Pat. 370,990/1990 (*Chem. Abstr.*, 1991, **114**, 6497).

84. A.N. Sinyakov and M.S. Shvartsberg, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci. (Engl. Transl.)*, 1979, **28**, 1053.

85. B.A. Tertov and P.P. Onishchenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1970, **6**, 1339.

86. A.R. Katritzky, R. Murugan, H. Luce, M. Zerner, and G.P. Ford, *J. Chem.Soc., Perkin Trans. 2*, 1987, 1695.

87. M. Alcamí, O. Mó, and M. Yáñez, *J. Phys. Chem.*, 1989, **93**, 3929.

88. M. Alcamí, O. Mó, M. Yáñez, F. Anvia, and R.W. Taft, *J. Phys. Chem.*, 1990, **94**, 4796.

89. S. Shimizu and M. Ogata, *J. Org. Chem.*, 1986, **51**, 3897.

90. A.R. Katritzky and J.N. Lam, *Can. J. Chem.*, 1989, **67**, 1144.

91. R.F. Horvath and T.H. Chan, *J. Org. Chem.*, 1989, **54**, 317.

92. A.R. Katritzky, N.E. Grzeskowiak, T. Siddiqui, C. Jayaram, and S.N. Vassilatos, *J. Chem. Res. (S)*, 1982, 26; (*M*), 0528.

93. S. Shimizu and M. Ogata, *Tetrahedron*, 1989, **45**, 637.

94. A. Marxer and M. Siegrist, *Helv. Chim. Acta*, 1974, **57**, 1988.

95. G. Rihs, H. Fuhrer, and A. Marxer, *Helv. Chim. Acta*, 1981, **64** , 769.

96. T. Kaufmann, D. Tigler, and A. Woltermann, *Tetrahedron Lett.*, 1977, 741.

97. T. Kauffmann, D. Tigler, and A. Woltermann, *Chem. Ber.*, 1982, **115**, 452.

98. M. Franck-Neumann, M. Miesch, and H. Kempf, *Tetrahedron*, 1987, **43**, 845.

99. F.A. Settle, M. Haggerty, and J.F. Eastham, *J. Am. Chem. Soc.*, 1964, **86**, 2076.

100. H.L. Lewis and T.L. Brown, *J. Am. Chem. Soc.*, 1970, **92**, 4664.

101. M. Begtrup and P. Vedsø, Abstracts of The Thirteenth International Congress of Heterocyclic Chemistry, Oregon State University, 1991, abstract no. GE8-93.

102. M. Begtrup and P. Vedsø, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2555.

103. B. Iddon, *Heterocycles*, 1985, **23**, 417.

104. R.G. Micetich, personal communication to B. Iddon (1985).

105. Ref. 8, Ch. 9, p. 222.

106. "Comprehensive Heterocyclic Chemistry", ed. A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984.

107. A. Michaelis and E. Brust, *Liebigs Ann. Chem.*, 1905, **339**, 134.

108. I.L. Finar and K.E. Godfrey, *J. Chem. Soc.*, 1954, 2293.

109. A.P. De Jonge, H.J. Den Hertog, and J.P. Wibaut, *Recl. Trav. Chim. Pays-Bas*, 1951, **70**, 989.

110. J.P. Wibaut and H.G.P. Van Der Voort, *Recl. Trav. Chim. Pays-Bas*, 1952, **71**, 798.

111. I.I. Grandberg, L.I. Gorbacheva, and A.N. Kost, *J. Gen. Chem. U.S.S.R .(Engl. Transl.)*, 1963, **33**, 503.

112. R.J. Brooklyn and I.L. Finar, *J. Chem. Soc. (C)*, 1968, 466.

113. P.B.M.W.M. Timmermans, A.P. Uijttewaal, and C.L. Habraken, *J. Heterocycl. Chem.*, 1972, **9**, 1373.

114. R.J. Brooklyn and I.L. Finar, *J. Chem. Soc. (C)*, 1969, 1515.

115. E. Buchner and M. Fritsch, *Liebigs Ann. Chem.*, 1892, **273**, 260.

116. L. Knorr and J. MacDonald, *Liebigs Ann. Chem.*, 1894, **279**, 217.

117. G.D. Rosengarten, *Liebigs Ann. Chem.*, 1894, **279**, 238.

118. B. Oettinger, *Liebigs Ann. Chem.*, 1894, **279**, 244.

119. W. Schrauth and H. Bauerschmidt, *Ber.*, 1914, **47**, 2736.

120. I.I. Grandberg, A.N. Kost, and N.N. Zheltikova, *J. Gen. Chem. U.S.S.R. (Engl. Transl.)*, 1960, **30**, 2907.

121. I.L. Finar, *J. Chem. Soc.*, 1955, 1205.

122. H.P. Patel and J.M. Tedder, *J. Chem. Soc.*, 1963, 4589.

123. M. Ragno, *Gazz. Chim. Ital.*, 1938, **48**, 741.

124. S. Trofimenko, *Inorganic Chem.*, 1973, **12**, 1215.

125. M.I. Bruce, B.L. Goodall, and I. Matsuda, *Aust. J. Chem.*, 1975, **28**, 1259.

126. M. Nonoyama, *J. Organomet. Chem.*, 1975, **86**, 263.

Received, 30th November, 1993