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Formaldehyde: A Reagent for Simultaneous Protection of Heterocyclic NH and Activation of Alternative Locations to Electrophilic Attack. Part II.[1] A New Synthetic Method for the 5(3)-Substitution of N-Unsubstituted Pyrazoles

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Abstract: N-Unsubstituted pyrazole **1** is readily converted into 5-substituted [tautomeric with 3-substituted **8**] derivatives **2** in moderate to good overall yields in a one-pot sequence, using formaldehyde both for N-protection and to mediate lithiation at the 5-position. The dilithiohemiaminals **5** react with electrophiles at the pyrazole 5-position to give 5-substituted 1-lithioxymethylpyrazoles **6** which undergo smooth dehydroxymethylation under mild conditions (acid hydrolysis or silica gel) to give N-unsubstituted 5(3)-substituted pyrazoles.

The lithiation of heterocyclic compounds containing an N-H group normally leads only to the N-lithio derivative,[2] but when the nitrogen atom is substituted C-lithiation can often occur. If the N-substituent can be later removed, it serves as a protecting group for the N-H. From the synthetic point of the view, the value of a protecting group should be judged by its availability, by its ease of introduction and of removal under mild conditions which do not damage other sensitive functionalities, and by its ability to facilitate C-lithiation and subsequent reaction with electrophiles to give products in good yield.

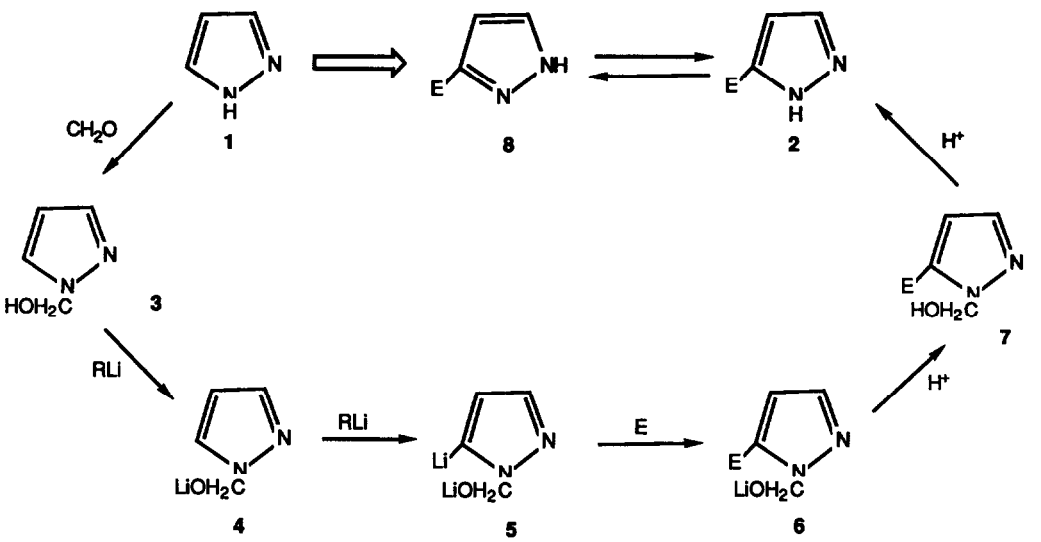
In the course of our investigations of methodologies for the protection of amines and alcohols during functionalisation, and in particular the use of carbon dioxide for protection,[3] we have been seeking alternative protecting groups which satisfy the criterion that both protection and deprotection should occur efficiently under mild conditions so as not to damage sensitive functionalities. We focused our search for such a group on the systems for which the carbon dioxide method failed, as e.g., for heterocyclic NH in rings

containing more than one heteroatom.[4] Recently, we found a satisfactory solution to this problem by using formaldehyde for simultaneous protection of heterocyclic NH and activation of alternative locations to electrophilic attack in benzimidazole.[1] We now report a successful extension of this methodology: the use of formaldehyde as a protecting group for the heterocyclic NH of pyrazole in the synthesis of 5(3)-substituted pyrazoles.

Results and Discussion.- The reaction sequence, similar to that of the previous report,[1] consists of three stages: protection, main reaction (lithiation and substitution), and work-up including deprotection; the whole carried out in a one-pot sequence. The protecting group is readily introduced by reaction of pyrazole **1** with aqueous formaldehyde (CH_2O/H_2O, 37%) in tetrahydrofuran (THF)-water at 20°C,[5,6] or with paraformaldehyde in THF at 40°C. Using paraformaldehyde, a clear homogeneous solution forms after heating at 40°C indicating the completion of the formation of **3**. Metallation is accomplished in dry THF at -78°C to -20°C by treatment with 2 equivalents of a lithiating agent. We found that n-butyllithium, t-butyllithium, or lithium diisopropylamide (LDA) all produced the di-lithiated pyrazole **5** smoothly at -20°C in less than 30 minutes. The dianion **5** was then quenched with an electrophile at -78°C; warming the solution to 20°C then gives the expected 5-substituted 1-lithioxymethylpyrazole **6**. Deprotection is accomplished readily by the acid-catalysed hydrolysis of the resulting hemiaminal **7**, or by silica gel assisted fission. The reaction mixture was quenched with aqueous ammonium chloride and diluted with diethyl ether. For acid-catalysed hydrolysis, extraction with dilute hydrochloric acid followed. For silica gel assisted fission, the residue, after evaporation of the organic solvent, was passed through a silica gel column. Under both sets of conditions, the hemiaminal **7** gave the desired products **2** [in tautomeric equilibrium with **8**] in acceptable overall yield based on pyrazole **1** (Scheme 1). Table 1 gives the results of applying this method to a variety of electrophiles.

We also investigated the dilithiation of isolated and prepurified 1-hydroxymethylpyrazole, and found that it gives the expected result (Entry 1 of Table 1).

N-Unsubstituted pyrazoles are reported to undergo metallation in the 5-position, but the yields of subsequent reactions with electrophiles are poor: e.g., with phenyllithium or n-butyllithium as lithiation agent, followed by electrophilic attack with carbon dioxide, pyrazole gave only 7% or 9% of pyrazole-3-carboxylic acid, respectively.[7] While numerous 1-N protecting groups have been developed for imidazoles,[8]



Scheme 1

much less work has been done on the protection of pyrazoles. When the 1-position of the pyrazole is blocked, metallation normally occurs at the 5-position. Thus, 1-methylpyrazole can be metallated at the 5-position to give 5-substituted 1-methylpyrazoles.[9] However, 1-phenylpyrazole undergoes lithiation competitively at the pyrazole 5-position and at the ortho position of the phenyl ring in the ratio of about 4:1.[9] Recent work[10] from our laboratory has confirmed that α-lithiation of the methyl group in methylpyrazoles occurs in 1-methylpyrazole itself as well as in analogues which have been blocked at the C-3 and C-5 positions, similar results had been reported previously.[11] Recently Micetich et al.[12] reported that with careful control of the reaction conditions exclusive lithiation at the C-5 position of 1-phenylpyrazole occurs. Clearly, neither methyl nor phenyl are suitable as protecting groups for pyrazole, not only for these reasons, but also because of the difficulty of their removal.

While the benzyl group is often used to protect the NH of heterocycles, it is unsatisfactory in lithiation reactions since competitive lithiation at the benzylic methylene group is observed.[8] A systematic study in our laboratory showed that 1-benzylpyrazole is metallated at the CH_2 group under kinetic control at low temperature and that the metallorganic intermediate could rearrange at room temperature to give the thermodynamically more stable 5-lithio-1-benzylpyrazole.[10] We have also shown that gem-bis(pyrazole-1-yl)alkanes can be lithiated both at the inter-ring carbon atom and at the 5-position of the ring.[13]

Table 1. Preparation of N-Unsubstituted-5(3)-Substituted Pyrazoles

Compds	CH_2O Source	Lithiating[b] agent	Electrophile[c]	5(3)-Substituent	Yield(%)[d]	mp	Formula	Found (calcd) C	H	N
2a	CH_2O/H_2O[a]	LDA	C_6H_5CHO	$C_6H_5CH(OH)$	47[e]	113-114[h]	$C_{10}H_{10}N_2O$	..	..	..
2a	CH_2O/H_2O	LDA	C_6H_5CHO	$C_6H_5CH(OH)$	44[e]	113-114	..	..	..	..
2a	$(CH_2O)_n$	t-BuLi	C_6H_5CHO	$C_6H_5CH(OH)$	53[e]	113-114	..	..	..	..
2a	$(CH_2O)_n$	n-BuLi	C_6H_5CHO	$C_6H_5CH(OH)$	37[e]	113-114	..	..	..	..
2b	$(CH_2O)_n$	t-BuLi	$4\text{-}CH_3C_6H_4CHO$	$4\text{-}CH_3C_6H_4CH(OH)$	45[e]	96-97	$C_{11}H_{12}N_2O$	70.23	6.43	14.99
								(70.19)	(6.43)	(14.86)
2c	$(CH_2O)_n$	t-BuLi	$(C_6H_5S)_2$	C_6H_5S	53[f]	oil[f]	$C_9H_8N_2S$[g]	61.53	4.59	15.61
								(61.34)	(4.58)	(15.90)
2d	$(CH_2O)_n$	t-BuLi	$C_6H_5CH_2Br$	$C_6H_5CH_2$	54[f]	oili	$C_{10}H_{10}N_2$	..	..	..
2e	$(CH_2O)_n$	t-BuLi	$(C_6H_5CH_2S)_2$	$C_6H_5CH_2S$	76[f]	oil[j]	$C_{10}H_{10}N_2S$	..	..	..
2f	$(CH_2O)_n$	t-BuLi	$(C_6H_5)_2CO$	$(C_6H_5)_2C(OH)$	61[f]	121-123	$C_{16}H_{14}N_2O$	76.48	5.64	11.26
								(76.78)	(5.64)	(11.19)
2g	$(CH_2O)_n$	t-BuLi	Cyclohexanone	$(CH_2)_5COH$	51[f]	122-123	$C_9H_{14}N_2O$	64.81	8.53	16.52
								(65.03)	(8.49)	(16.85)
2h	$(CH_2O)_n$	t-BuLi	C_6H_5NCO	C_6H_5NHCO	56[f]	125-127	$C_{10}H_9N_3O$	64.24	4.88	22.65
								(64.16)	(4.85)	(22.45)

[a] 1-Hydroxymethylpyrazole was used as a starting material. [b] 2.0 to 2.1 eq. of lithiating agent was added at -78°C and then at -20°C for 30-40 minutes. [c] 1.0 to 1.1 eq. of electrophile was added at -78°C. [d] Isolated overall yields of the purified 5(3)-pyrazoles calculated on the basis of N-H pyrazole used (unoptimized). [e] Deprotected by acid-catalysed dehydroxymethylation using 2 N aqueous hydrochloric acid. [f] Deprotected by passing through silica gel column using diethyl ether-hexane(2:1) as first eluate followed by ethyl acetate. [g] MS for $C_9H_8N_2S$ calculated 176.0408, found 176.0413. [h] Lit.[19] mp. 114°C. [i] Lit.[20] bp. 140-150°C(0.5 torr). [j] Lit.[21] oil.

The carbon dioxide method used as an N-H protecting group for the lithiation of indoles[14] and other nitrogen heterocycles,[15] failed for pyrazole.[16] Recently, N-(dialkylaminomethyl) protection has been successfully applied in this laboratory for the C-lithiation of imidazole, benzimidazole and pyrazole.[17] Overall yields of 45%-78% of 5-substituted pyrazoles were achieved, and the only disadvantage is the need to isolate and purify the N-dialkylaminomethylpyrazole before the main reaction. The use of tetrahydropyranyl, apparently allows metallation of pyrazole under mild conditions and gives good yields of the 5-substituted pyrazole, but unfortunately, no experimental details were given.[2]

The present one-pot hemiaminal method for 5-functionalization of pyrazole has the following advantages:

1. The protecting group is readily introduced under mild conditions using readily available reagents. No purification step is needed.

2. A variety of readily available lithiating reagents (n-butyllithium, t-butyllithium, or LDA) afford the dilithio derivative efficiently under mild conditions, and the anion is sufficiently reactive to attack a range of electrophiles, even the hindered electrophile benzophenone (Entry 9 of Table 1).

3. Deprotection is readily accomplished by shaking with aqueous hydrochloric acid or by passing through a silica gel column.

4. The whole procedure is one-pot, with moderate to good overall yields.

The ^{1}H-NMR and ^{13}C-NMR spectra data of the 5(3)-sustituted pyrazoles prepared are given in Tables 2 and 3. The CH_2 proton signal of the parent 1-hydroxylmethylpyrazole appears as a singlet at 5.5 ppm and the clearly distinguishable proton signals of pyrazole C_4-H and C_5-H together with C_3-H occur as multiplets at 6.3 ppm and at 7.6 ppm, respectively. The carbon chemical shift of CH_2 appears at 73.4 ppm and the other three pyrazole ring carbons signals show at 140.3, 106.2 and 129.9 ppm (for C-3, C-4 and C-5 respectively), in accord with the literature.[18]

After metallation, reaction with electrophile, and deprotection, the 5(3)-substituted pyrazoles obtained show the loss of the original 2H signal at 5.5 ppm (^{1}H-NMR) and the C_4-H and C_5-H (or C_3-H) of pyrazole now show clearly as doublets in the 5.80-6.87 ppm region and in the 7.01-7.46 ppm region, respectively, indicating that the substitution with electrophiles has occured at the ring. The coupling constants between the 4H and the 5H ring protons are 2-2.5 Hz, in good accord with the literature.[12] The substituted ring

Table 2. ^{1}H-NMR Chemical Shifts (δ) for 5(3)-Substituted Pyrazole (ppm)

Compd	5(3)-substituent	Pyrazole H-4	Pyrazole H-3 or H-5	Pyrazole NH[a]	Aromatic protons	Other signals
2a	$C_6H_5CH(OH)$	6.08[b]	-[c]	12.7[d]	7.25-7.50[e]	-[k]
2b	4-$MeC_6H_4CH(OH)$	6.12[b]	-[c]	12.7[d]	7.12-7.50[f]	-[l]
2c	C_6H_5S	6.38[b]	7.46[g]	12.5[d]	7.08-7.28[f]	-
2d	$C_6H_5CH_2$	5.92[b]	7.28[g]	12.5[d]	7.18[h]	-[m]
2e	$C_6H_5CH_2S$	6.18[b]	7.46[g]	12.7[d]	7.20[h]	-[n]
2f	$(C_6H_5)_2C(OH)$	5.80[b]	7.01[g]	14.8[d]	7.21[i]	-[o]
2g	$(CH_2)_5COH$	6.12[b]	7.21[g]	-[j]	-	-[p]
2h	C_6H_5NHCO	6.87[b]	7.12[g]	-[j]	7.28-8.01[e]	-[q]

[a] The chemical shift of NH depends on solvents and concentration. [b] Doublet, J = 2 Hz. [c] Pyrazole C_3 or C_5-H immersed in the other aromatic protons. [d] Broad singlet. [e] Multiplet, 6 H. [f] Multiplet, 5 H. [g] Doublet, J = 2 Hz. [h] Singlet, 5 H. [i] Singlet, 10 H. [j] NH missing. [k] 5.86 (s, 2 H, CH and OH). [l] 2.25 (s, 3 H, CH_3), 5.79 (d, 2 H, CH and OH). [m] 3.95 (s, 2 H, CH_2). [n] 4.08 (s, 2 H, CH_2). [o] 5.20 (s, 1 H, OH). [p] 1.95-1.21 (m, 10 H), 4.73 (s, 1 H, OH). [q] 10.09 (s, 1 H, NH).

Table 3. ^{13}C-NMR Chemical Shifts (δ) for 5(3)-Substituted Pyrazole (ppm)

Compd	5(3)-Substit	Pyrazole			5(3)-substituents				
		C-3	C-4	C-5					
2a	$C_6H_5CH(OH)$	144.2	101.9	135.2	68.4	110.9	126.1	126.7	127.8
2b	4-$MeC_6H_4CH(OH)$	141.6	101.9	135.7	20.6	68.8	111.0	126.1	128.4
2c	C_6H_5S	140.8	110.5	131.7	126.2	128.4	129.0	136.4	
2d	$C_6H_5CH_2$	146.9	103.7	133.3	32.9	126.1	128.3	128.5	139.9
2e	$C_6H_5CH_2S$	146.3	109.2	131.2	39.2	127.4	128.4	128.7	137.5
2f	$(C_6H_5)_2C(OH)$	146.2	105.2	132.2	78.1	127.3	127.4	127.8	153.9
2g	$(CH_2)_5COH$	133.4	100.8	111.2	21.8	25.4	38.1	68.5	
2h	C_6H_5NHCO	146.7	105.6	130.3	120.2	123.4	128.5	130.3	138.8
					160.5				

carbons of the 5(3)-sudstituted pyrazoles, except compound 2g, are shifted a little downfield at 140.8-146.7 ppm (C-3), 101.9-110.5 ppm (C-4), 130.3-135.7 ppm (C-5) as compared with the parent pyrazole, as previously reported.[13]

Compounds 2 exist in two tautomeric forms (C_3 or C_5 substituted). In the case of 2f and of 2g (each in DMSO-d6, 100 mg in 0.5 ml of solvent), two of the carbon signals (C_3 or C_5) show as broad peaks at room temperature and gradually become sharp singlets when temperature rises (ca. 50°C), indicating that the tautomerization between two forms is slow on the NMR time-scale at room temperature and reaches fast equilibrium at high temperature. A strong hydrogen bond between the NH and the OH group presumably retards the transposition of the NH proton to the adjacent nitrogen atom. The proton signals of the NH of the 5(3)-substituted pyrazoles are far more downfield at 12.5-14.1 ppm and usually depend on solvents and concentration.

In summary, 5(3)-substituted pyrazoles were synthesized in one-pot sequences in the key step of which a lithiated hemiaminal was successfully reacted with a variety of electrophiles. The particular ease of introduction and of removal which characterize our use of formaldehyde as a protecting group for pyrazole offers a significant advantage over the N-substituents previously applied for this purpose.

Experimental

General Column chromatography was carried out by using MBS silica gel (230-400 mesh). Melting points of the products were measured by a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H-NMR (200 MHz) spectra were recorded on a Varian XL200 (FT mode) spectrometer. ^{13}C-NMR (50 MHz) were recorded on a Varian XL200 (FT mode) spectrometer. Commercial pyrazole (Aldrich) was used without purification. n-Butyllithium and t-butyllithium (Aldrich) were used without further purification. LDA was freshly prepared from N,N-diisopropylamine (dried over calcium hydride and distilled) and n-butyllithium immediately before each run. Tetrahydrofuran was predried with molecular sieves 4A and freshly distilled from calcium hydride before use. Formaldehyde (37% aqueous solution, Fisher Scientific Co.) and paraformaldehyde (Fisher Scientific Co.) were used without further purification. Electrophiles were purified by standard methods before use.

Preparation of 5(3)-Substituted Pyrazoles, General Procedure.

Protection, Method A: Preparation of the hemiaminal using 37% aqueous formaldehyde.

Pyrazole (1.00 g, 14.4 mmol) was placed in a two necked flask. Tetrahydrofuran (40 ml) was added at 20°C to give a clear solution. To this, formaldehyde (1.31 g, 1.0 eq., 37% water solution) was added at 20°C and stirred for 4h to give a homogeneous solution. The solvent was removed under reduced pressure with a rotary evaporator and the residue was dried in vacuo for 24h.

Protection, Method B: Preparation of the hemiaminal using paraformaldehyde.

Pyrazole (1.00 g, 14.4 mmol) and paraformaldehyde (591 mg, 1.3 eq.) were placed in a two necked flask. The interior of the flask was evacuated and flushed with dry argon three times. Tetrahydrofuran (45 ml) was added to give a suspension. The whole was kept well-stirred at 45°C for 4h to give a homogeneous solution. TLC showed only one spot of 1-hydroxymethylpyrazole.

Preparation of 1-Hydroxymethylpyrazole: 1-Hydroxymethylpyrazole was prepared according to the literature procedure[5] by reaction of pyrazole with aqueous formaldehyde in water. The pure compound was obtained by recrystallization from chloroform-hexane; m.p. 86-87°C (Lit.[5] m.p. 88°C).

Main Reaction: Dilithiation of the hemiaminal.

The solution was cooled to -78°C to give a precipitate, and freshly prepared LDA [2.0 eq., from diisopropylamine (4.1 ml) and n-butyllithium (11.5 ml of 2.5 M hexane solution)] or t-butyllithium (17.8 ml of 1.7 M pentane solution) or n-butyllithium (11.5 ml of 2.5 M hexane solution) was added slowly at -78°C. The cooling bath was removed to allow the solution to warm to -20°C. The solution was aged at -20°C for 20-40min with well-stirring to give a white to yellow suspension. The heterogeneous solution was cooled again to -78°C and quenched with electrophile (neat if liquid, in a minimum amount of THF if solid) and the mixture was kept at -78°C for 2h and then allowed to come to ambient temperature overnight.

Work-up and Deprotection, Method A: Acid-catalysed dehydroxymethylation.

The solution was quenched with aqueous ammonium chloride at 0°C, was diluted with diethyl ether (100 ml) and was carefully extracted (with shaking) with 2N aqueous hydrochloric acid four times. The aqueous extracts were combined and basified with aqueous ammonium hydroxide with efficient stirring at 0°C. The aqueous layer was then extracted with diethyl ether or ethyl acetate and dried over sodium sulfate. The solvent was removed by rotary evaporator under reduced pressure to give the crude product which was

purified with recrystallization.

Work-up and Deprotection, Method B: Silica gel assisting dehydroxymethylation.

After quenching with aqueous ammonium chloride and dilute with diethyl ether, the organic layer was separated, washed with brine (10 ml), and dried over sodium sulfate. The solvent was removed by rotary evaporator under reduced pressure to give an oily residue. The residue was then allowed to pass a silica gel column using appropriate solvents to elute to give the product. This could be purified by distillation under vacuum if liquid or by recrystallization if solid. Physical data of the products, yields, and methods of deprotection and purification are given in Table 1.

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