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N-Dealkylation of Pyrazoles Using Pyridine Hydrochloride

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We wish to report that N-alkylpyrazoles can be conveniently N-dealkylated by heating in anhydrous pyridine hydrochloride at reflux temperature. We fortuitously observed this N-dealkylation when 5-chloro-1,3-dimethylpyrazol-4-yl-o-methoxyphenyl ketone¹ was heated for 16 hr at 215° with this reagent and the product was shown to be 3-methyl[1]benzopyrano[2,3-c]pyrazol-4(1H)-one (1) (Scheme I).



There are only a few reports on the removal of N substituents from pyrazoles²⁻⁶ and most of these N substituents are of such low stability as to preclude their use for protective purposes. Thus base and heat have been shown to remove the N-hydroxymethyl,² N-substituted aminomethyl,² and N-2,4-dinitrophenyl³ groups. Also oxidative reagents remove particularly sensitive N-substituents.^{4,5} The most synthetically useful N-protecting group in pyrazole chemistry is the N-benzyl group⁶ (readily removed by sodium and liquid ammonia reduction, but suffering the usual disadvantages associated with this method of removal). Therefore, we decided to test the generality of this N-dealkylation (Scheme II). N-Alkylcarboxylic acid amides, anilides,⁷ and N-methyl- and N-ethylphenothiazine⁸ have been dealkylated by this reagent. The generality of this reaction has

Scheme II



been questioned, since N-alkylcarbazoles are unaffected by this reagent.9

Results

Both simple and complex N-methylpyrazoles as well as N-ethylpyrazoles (see compounds 5 and 8, Table I) and one example of an N-methylindazole (see compound 3) were successfully N-dealkylated. The reaction was successful with a wide variety of substituents on the carbon atoms of the pyrazole ring, including both electron-attracting and -releasing substituents. Wide differences in the rate of Ndealkylations were observed [see time of heating, Table I, and comparison of synthesis of 6 from 1.3-dimethylpyrazol-5-yl phenyl ketone¹⁰ or the isomeric 1,5-dimethylpyrazol-3-yl phenyl ketone (9) in Experimental Section]. This is a rapid, simple method and gives reasonably good yields of N-unsubstituted pyrazoles. The examples include a number of compounds that would be difficult or impossible to prepare by other methods. While the examples have included only N-methyl and N-ethyl substituents, in analogy with the known N,N'-dealkylations of N,N'-pyrazolium and N, N'-indazolium quaternary salts^{11,12} other alkyl groups should be removed with equal facility.

Mechanistic Considerations. The reaction most likely proceeds by protonation of the pyrazole ring and the formation of the alkyl halide by the attack of chloride ion and expulsion of the neutral N-dealkylated pyrazole. The high temperature drives out the low-boiling alkyl halide, helping to drive the reaction to completion. This is consistent with the mechanism in the N,N'-dealkylations of N,N'-dialkylpyrazolium halides.¹¹ Examination of the crude product in the synthesis of 6 demonstrated the presence of an Nmethyl shift as reported in N,N'-dealkylations of Nmethyl-N'-alkylpyrazolium salts.¹¹

Experimental Section¹³

Reagents and Starting Materials. The pyridine was purchased from J. T. Baker Chemical Co. The following compounds were synthesized as described in the references given: 5-chloro-1,3-dialkylpyrazol-4-yl aryl ketones;¹ 1,3-dimethylpyrazol-5-yl phenyl ketone;¹⁰ 1-ethyl-3-methyl-4-nitropyrazol-5-yl phenyl ketone;¹⁴ 1,3,5-trimethylpyrazole;¹⁵ 5-amino-1,3-dimethylpyrazole;¹⁶ 1,5-dimethyl-3-pyrazolecarboxamide;¹⁷ 1.3-dimethyl-1H-indazole.18

General Procedure. Anhydrous pyridine hydrochloride was freshly prepared by the method of Curphey et al.¹⁹ (dried by distillation up to 210° and cooled under a stream of N_2). The pyrazole was added to a three- to tenfold molar excess of the reagent and the mixture was stirred at 180-218° for 1-40 hr. Products less basic than pyridine could be isolated by dilution of the cooled reaction mixture with water followed by filtration or extraction with diethyl ether or chloroform. The extracts were dried $(MgSO_4)$ and concentrated and the products were recrystallized. If the product was a stronger base than pyridine, it was isolated by addition of an excess of 29% ammonia and extraction. Many of the keto pyrazoles were best separated from unreacted starting material by extraction into 1 N sodium hydroxide solution followed by neutralization with an equivalent amount of hydrochloric acid.

3-Methylpyrazol-5-yl Phenyl Ketone (6). 1,3-Dimethylpyrazol-5-yl phenyl ketone¹⁰ was treated with the reagent for 1 hr at 218°. A VPC on the crude reaction mixture showed a three-component mixture: starting material (5%), 6 (80%), and an unknown, 9 (15%). Two recrystallizations from toluene yielded 6 (52%) (see Table I for physical data). The unknown 9 was shown to be the

Table I N-Delakylated Products^a



Compd	R ₄	R ₅	Temp, ℃	Heating period, hr ^b	Yield, %c	Мр, ⁰С	Recrystn solvent ^d	Empirical formula	Ir, cm- ¹ (N H; C===C)
1			215	16	61	298-300	A	$C_{11}H_8N_2O_2$	3205; 1650
2	Н	CH3	180	16	70	106–107 ^e			
3	$\langle \rangle$		210	40	72	112–113 ^f			
4	Н	HNC(=O)Ph	2 18	0.75	60^{g} $(40)^{h}$	210-212	В	$\mathbf{C}_{11}\mathbf{H}_{11}\mathbf{N}_{3}\mathbf{O}$	3300; 1648
5	NO_2	O==CPh	210	3	56^{i}	138-140	C	$C_{11}H_9N_3O_3$	3260; 1658
6	н О	O=CPh	21 8	1	52 ^j	110–112	D	$C_{11}H_{10}N_2O$	3225, 3160; 1630
7	С́Рһ О	Cl	200	3	63	169-171	E	$C_{11}H_9ClN_2O$	3235; 1630
8	$\overset{\ }{\mathrm{C}}$ -o-ClPh	Cl	200	3	$62 (69)^k$	135-137	F	$\mathbf{C}_{11}\mathbf{H}_{8}\mathbf{Cl}_{2}\mathbf{N}_{2}\mathbf{O}$	3195; 1660

^a Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed. Mass spectra were also taken and indicated the correct molecular weights, as well as the absence of the higher molecular weight and more volatile N-alkyl starting materials. Dealkylations of starting materials with N-ethyls are indicated in footnotes i and k. ^b Too extensive a heating time appeared to be important only when the products were susceptible to further reactions, i.e., compounds 7 and 8. ^c The yields are those isolated and purified. Yields were not maximized and changes in the temperature, heating time, and isolation procedures would improve them. ^d A. Soxhleted from insolubles using THF; B, CH₃OH-Et₂O; C, Et₂O; D, toluene; E, toluene-petroleum ether; F, toluene-cyclohexane. ^e Lit. mp 106-107°; L. Knorr and G. D. Rosengarten, Justus Liebigs Ann. Chem., 279, 237 (1894).⁷ Lit. mp 113°; E. Fischer and J. Tafel, ibid., 227, 303 (1885).^g From starting material 12 with only one N-methyl to be removed.^h From starting material 11 with two N-methyls to be removed.ⁱ An example of N-ethyl removal. J Crude yield by VPC 80% + 15% N-methyl shift. * First yield from N-methyl removal, second yield from N-ethyl removal.

Chemical Shifts for Compounds in Table I ^a									
Compd	N-H	3-CH ₃	R ₄	R ₅					
1	10-11 (very broad)	2.63	7.2–8.3 (4 H)						
4	12.1 (broad singlet)	2.24	6.42 (1 H)	7.2-8.2 (5 H) 10.66 (1 H)					
5	11–12 (very broad)	2.48	·	7.2-8.2 (5 H)					
6	13-14 (very broad)	2.21	6.63 (1 H)	8.0-8.4 (2 H) 7.3-7.8 (3 H)					
7	13-14 (very broad)	2.22	7.2-7.9 (5 H)						
8	13-14 (very broad)	2.28	7.4–7.7 (4 H)						
a \$	(TMS) (Ma Si) in	DMSO	d.						

 $a \delta$ (TMS) (Me₄Si) in DMSO- d_{6} .

product of N-methyl transfer, i.e., 1,5-dimethylpyrazol-3-yl phenyl ketone (9). This was proven by comparison of VPC retention time, NMR spectrum location of the N-methyl and 4-H, and mixture melting point (after isolation by column chromatography) with a sample synthesized in the following manner. 1,5-Dimethyl-3-pyrazolecarboxamide¹⁷ was dehydrated using phosphorus oxychloride to yield 1,5-dimethyl-3-pyrazolecarbonitrile (10, 80%), mp 68-69° (from EtOH). Anal. Calcd for C₆H₇N₃: C, 59.50; H, 5.82; N, 34.70. Found: C, 59.11; H, 5.98; N, 34.16. 10 was treated with an excess of phenyl Grignard reagent and after acid hydrolysis yielded 9 (73%), mp 55–57°. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.96; H, 6.07; N, 13.99. Found: C, 72.30; H, 6.11; N, 13.99.

Rate of the Dealkylation Reaction of 1,5-Dimethylpyrazol-3-yl Phenyl Ketone (9). When 9 was treated with the reagent for 3 hr at 218° [three times the time period used to produce 95% dealkylation of 1,3-dimethylpyrazol-5-yl phenyl ketone¹⁰], VPC analysis showed only a 50% conversion to 6 along with 50% 9. The rate difference may be due to a slower rate of protonation due to differences in the basicities of the 1,5 vs. the 1,3 ketone in the reagent or a lower susceptibility of attack on the N-alkyl bond due to the different relationship with the electron-withdrawing carbonyl group.

N-(1,3-Dimethylpyrazol-5-yl)-N-methylbenzamide (11). 5-Amino-1,3-dimethylpyrazole¹⁶ was treated in chloroform with 1 equiv of benzoyl chloride in the presence of an excess of calcium hydroxide to yield N-(1,3-dimethylpyrazol-5-yl)benzamide (12, 89%), mp 133-135° from toluene. Anal. Calcd for C₁₂H₁₃N₃O: C, 66.96; H, 6.19; N, 19.52. Found: C, 66.85; H, 6.13; N, 19.37. 12 was treated with iodomethane and sodium methoxide in THF to yield 11 (82%), mp 98–100° from ethyl acetate–petroleum ether. Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.32. Found: C, 68.02; H, 6.71; N, 18.45.

Registry No.-1, 54384-65-5; 2, 67-51-6; 3, 3176-62-3; 4, 52566-42-4; 5, 54384-66-6; 6, 54384-67-7; 7, 54384-68-8; 8, 54384-69-9; 9, 54384-70-2; 10, 54384-71-3; 11, 54384-72-4; 12, 54384-73-5; pyridine hydrochloride, 628-13-7; 5-chloro-1,3-dimethylpyrazol-4-ylo-methoxyphenyl ketone, 29938-78-1; 1,3,5-trimethylpyrazole, 1072-91-9; 1,3-dimethyl-1*H*-indazole, 34879-84-0; 1-ethyl-3methyl-4-nitropyrazol-5-yl phenyl ketone 26308-47-4; 1,3-dimethylpyrazol-5-yl phenyl ketone, 32500-76-8; 1,3-dimethyl-5-chloro-pyrazol-4-yl phenyl ketone, 29938-70-3; 5-chloro-1,3-dimethylpyrazol-4-yl o-chlorophenyl ketone, 29938-74-7; 5-chloro-1-ethyl-3methylpyrazol-4-yl o-chlorophenyl ketone, 29938-93-0; 1,5-di-methyl-3-pyrazolecarboxamide, 54384-74-6; 5-amino-1,3-dimethylpyrazole, 3524-32-1.

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Addition of Benzyne to cis- and trans-1,3-Pentadiene

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The addition of benzyne to alkyl-substituted dienes can conceivably give [2 + 2], [2 + 4], and "ene" reaction products.¹ When the diene can achieve the s-cis conformation, [2 + 4] addition predominates over [2 + 2] addition.² When an ene reaction is possible, it predominates over the [2 + 2]reaction path in most olefins.^{3,4} We wish to report the addition of benzyne to cis- and trans-1,3-pentadiene, which surprisingly shows no ene product.

Benzyne, generated from benzenediazonium 2-carboxylate,⁷ adds to trans-1,3-pentadiene giving two isomeric adducts, 1 (46%) and 2 (16%). Compound 1 had an NMR spectrum consistent with 1-methyl-1,4-dihydronaphthalene. In addition, oxidation of 1 with dichlorodicyanoquinone resulted in 1-methylnaphthalene, which was identical with an authentic sample. The NMR data for 2 are in Table I.



When cis-1,3-pentadiene was used as the benzyne trap, 2-cis-propenylbenzocyclobutene (3) was formed in 24% yield. The NMR spectrum of 3 is very similar to that of 2(see Table I). Oxidation of 3 with KMnO₄-NaIO₄ resulted in acetic acid and benzocyclobutene-2-carboxylic acid, which was identical with authentically prepared material.⁸ No 3 was observed by NMR when the trans diene was used and no 2 was found when the cis diene was used. If benzyne

Table I Nmr Spectra of cis- and trans-2-Propenylbenzocyclobutene зH CH. H⁵ H^2 H Н_б H₃ Aromatic H₁ H₂ H_4 and H_5 7.134 3.45 2.84 4.05 5.68 1.68 3.52 2.86 4.38 1.76 7.15.6 $J_{1.3}$ $J_{2.3}$ $J_{5.6}$ $J_{1.2}$

^a In CCl₄/Me₄Si. Chemical shifts reported in parts per million (δ) . Coupling constants reported in hertz.

5.2

5.3

4.5

5.2

2.6

2.7

2

3

2

3

13.8

14.0

was produced by the reaction of o-bromofluorobenzene with magnesium,^{2a} cis-trans isomerization of the diene occurred (GLC analysis). Thus, 1 was observed when cis-1,3pentadiene was used as the benzvne trap. When benzenediazonium 2-carboxylate was used as the benzyne precursor, no cis-trans diene isomerization was observed.

The [2 + 4]/[2 + 2] ratio observed when benzyne adds to trans-1,3-pentadiene (3.9:1) is essentially the same as the ratio found when it adds to 1,3-butadiene (4.1^{2e}). It is not surprising that the methyl group little affects the addition of benzyne to this diene. This report also shows that benzyne is unable to give a [2 + 4] addition product with *cis*-1,3-pentadiene owing to this diene's inability to achieve the required s-cis conformation.⁹ In fact, maleic anhydride is the only dienophile reported to give a [2 + 4] product with the cis diene.^{10,11} Since benzyne has an alternate reaction pathway ([2 + 2] addition), it is not required to partake in an inherently undesirable [2 + 4] addition to the cis diene.12

In dienes which have no conformational peculiarities, ene addition predominates over [2 + 2] addition. It is therefore noteworthy that no ene product is observed when benzyne adds to 1,3-pentadiene. Owing to rotation of the methyl group, a suitable conformation must be available for what is apparently a concerted ene reaction.^{1b} The answer here might lie in an especially facile [2 + 2] addition of benzyne to 1,3-pentadiene. The determining factor could be a sterically less restricted approach to the terminal double bond in the pentadienes which is not possible in the other dienes that have been studied. Indeed, there could be a great inherent tendency for benzyne to undergo a [2 + 2]addition than an ene reaction with any diene.14 This tendency may be masked by steric effects in most dienes.^{15,16}

Experimental Section

General. The NMR spectra were obtained on a Varian Associates A-60 spectrometer. A Beckman IR-10 was used for the ir spectra. Mass spectra were determined on a Hitachi Model RMU-6E spectrometer at an ionizing voltage of 70 eV. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Gasliquid phase chromatography was conducted on a Varian A-90P instrument. Tetrahydrofuran was distilled from lithium aluminum hydride before use. cis- and trans-1,3-pentadiene (PCR, Inc., greater than 99% geometric purity) were distilled before use.

Generation of Benzyne in the Presence of cis-1.3-Pentadiene. To 0.025 mol of benzenediazonium 2-carboxylate⁷ was added 30 ml of chloroform and 2.04 g of cis-1,3-pentadiene (0.030 mol). The mixture was heated at 40-45° for 4.5 hr. After cooling, GLC analysis showed no trans-1,3-pentadiene. The solvent was removed under vacuum. The product, 3, was isolated using column chromatography (alumina, n-pentane) and weighed 0.724 g (24%