Synthesis of 3-Substituted-1-methylpyrazoles

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Received January 21, 1992

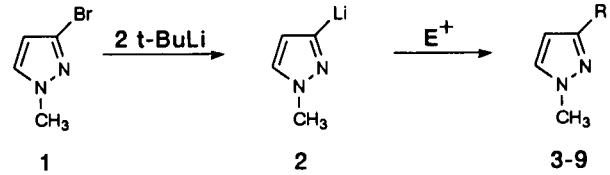
Reaction of 3-bromo-1-methylpyrazole **1** with *t*-butyllithium at −100° followed by quenching of the lithiopyrazole intermediate allows regiospecific introduction of substituents into the 3-position of the 1-methylpyrazole ring.

J. Heterocyclic Chem., **29**, 1357 (1992).

The regiospecific introduction of a functional group onto the pyrazole ring constitutes a significant challenge in heterocyclic chemistry. Synthetic methods for the preparation of 3-substituted 1-methylpyrazoles can be categorized by three general approaches. The most basic approach involves the cyclization of a 1,3-dicarbonyl compound with methylhydrazine [1,2], as in the case of the condensation of 4,4-dimethoxy-2-butanone with methylhydrazine to provide 1,3-dimethylpyrazole [3]. Alternately, the appropriately substituted pyrazole, usually prepared by a cyclization reaction, can be *N*-methylated to provide the 1-methylpyrazole with the functional group at the 3 position [4,5,6]. Finally, a 1-methylpyrazole substituted at the 3 position can be subjected to functional group interconversion to provide a different 3-substituted derivative as typified by the conversion of 3-amino-1-methylpyrazole to 3-fluoro-1-methylpyrazole by the photo-Schiemann reaction [7], or the dehydration of 1-methylpyrazole-3-carboxamide to give 3-cyano-*N*-methylpyrazole [8].

We have investigated the utilization of metalated 1-methylpyrazole as a key intermediate in the regiospecific introduction of substituents. Work in other laboratories has shown that deprotonation-lithiation of 1-methylpyrazole with organo lithium reagents occurs exclusively at C-5 [9]. The reaction of 4-bromo-1-methylpyrazole with *n*-butyllithium, however, was reported to yield products *via* metalation at C-5 and lithium-halogen exchange at C-4 [10]. A recent report of the lithium-halogen exchange in 4-bromopyrazole using *n*-butyllithium to provide 1,4-dilithiopyrazole [11], which can be regiospecifically substituted at the 4 position, has prompted us to report our results.

We have observed that under strictly controlled experimental conditions, metalation of 3-bromo-1-methylpyrazole (**1**) with *t*-butyllithium can be restricted to the C-3 position. To confirm this several 3-substituted 1-methylpyrazoles were prepared *via* the lithio derivative **2** formed upon lithium-halogen exchange of 3-bromo-1-methylpyrazole (**1**).



1 **2** **3-9**

Preliminary investigations of the lithium-halogen exchange using 3-bromo-1-methylpyrazole (**1**) and *t*-butyllithium indicated that the best yields of 3-substituted 1-methylpyrazole products were obtained when the reaction was carried out at low temperature using freshly dried solvent. Thus, metalation was accomplished in dry ether at −100° (ethanol/liquid nitrogen bath) by the slow addition of two equivalents of *t*-butyllithium (1.7 *M* in *n*-pentane) at a rate of 0.5 ml per minute. The low temperature was maintained for 1 hour and during the time when the reaction was quenched by addition of an electrophile. Warming the resulting solution led to the formation of the expected 3-substituted 1-methylpyrazoles. Neither the rate of electrophile addition nor the rate of warming the reaction mixture appreciably affects the yield of product.

Bromo-lithium exchange was confirmed by quenching the lithiated intermediate with methanol-d. The mass spectrum of the isolated product **3** exhibited a parent ion at m/z 83 consistent with substitution of bromine by deuterium. The location of the deuterium at position 3 of the pyrazole ring was confirmed by comparison of the downfield portion of the ^{1}H nmr spectrum of the deuterated product **3** with the ^{1}H nmr spectrum of the undeuterated 1-methylpyrazole. Thus, the signal at 7.45 ppm due to the C-3 proton in 1-methylpyrazole [12] was absent in the spectrum of the deuterated product. In addition, the resonance due to the C-4 proton, which appears as a triplet in the ^{1}H nmr spectrum of 1-methylpyrazole, was observed as a doublet (J_{H_4,H_5} = 2.2 Hz) in the ^{1}H nmr spectrum of **3**, as required for a 3-substituted 1-methylpyrazole. These spectral data confirm that the C-3 bromine in **1** has been replaced by deuterium in **3**.

Table 1
Reaction of 3-Lithio-N-Methylpyrazole With Electrophiles

Compound No.	Electrophile	R =	Yield (%)
3	MeOD	D	26
4	CO_2	COOH	77
5	CH_3CHO	$CH_3CH(OH)$	62
6	C_6H_5CHO	$C_6H_5CH(OH)$	60
7	C_6H_5COCl	C_6H_5CO	62
8	C_6H_5NCO	C_6H_5NHCO	47
9	$(C_6H_5)_2S_2$	C_6H_5S	67

1-Methylpyrazoles **4-8** were prepared by quenching lithioderivative **2** with the electrophiles shown in Table 1. Derivatives **4**, **5**, and **8** are known compounds and their identities were confirmed by comparing their measured physical and spectroscopic properties with those reported in the literature. In addition, treatment of 1-methylpyrazole-3-carboxylic acid (**4**) with thionyl chloride followed by slow addition of aniline led to the formation of anilide **8**, with physical and spectroscopic properties identical to the product obtained by reaction of **2** with phenylisocyanate.

Compounds **6** and **7** have not been previously reported. Their structures were confirmed by elemental analysis and by their spectroscopic properties. Thus, the mass spectra of **6** and **7** exhibited parent ions at m/z 188 and 186, respectively, consistent with replacement of the bromine in 1 by the appropriate electrophile. Furthermore, whereas a signal in their ^{1}H nmr spectra attributable to the C-3 proton of the pyrazole ring was absent, each compound exhibited the characteristic one-proton doublets (JH_4,H_5 = 2.2 Hz) for the H_4 and H_5 pyrazole ring protons. In addition to signals due to the phenyl protons in **6** and **7**, the ^{1}H nmr spectrum of **6** in anhydrous dimethyl sulfoxide-d_6 exhibited two one-proton doublets (J = 4.7 Hz) at 5.62 and 5.72 ppm due to the protons attached to the carbinol carbon and the oxygen respectively. As demanded by these assignments, addition of deuterium oxide was accompanied by disappearance of the signal at 5.72 ppm due to the hydroxy proton while the absorption due to the proton attached to the carbinol carbon collapsed to a singlet.

EXPERIMENTAL

Melting points were determined on a MeL Temp capillary melting point apparatus and are uncorrected. The ^{1}H (200 MHz) and ^{13}C (50.3 MHz) nmr spectra were recorded in the solvent indicated on a Bruker AC-200 spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1620 FT-IR or Perkin-Elmer 1720 FT-IR spectrometer. Mass spectra were recorded using an HP 5970B mass selective detector interfaced to an HP 5880 capillary gas chromatograph. Elemental Analysis were determined by Desert Analytics, Tucson, AZ.

3-Amino-1-methylpyrazole was prepared by the condensation of 2-chloroacrylonitrile with methylhydrazine [1]. 3-Bromo-1-methylpyrazole (**1**) was prepared by the Sandmeyer reaction using 3-amino-1-methylpyrazole [13]. *t*-Butyllithium (1.7 *M* in *n*-pentane) was obtained from Aldrich and used without further purification.

General Procedure for the Lithiation of 3-Bromo-1-methylpyrazole (1) and Quenching of the Reaction Mixture with an Electrophile to Provide 3-Substituted 1-Methylpyrazoles 4-8.

To a stirred solution of 0.96 g (6.0 mmoles) of **1** dissolved in 30 ml of anhydrous ether at −100° (ethanol/liquid nitrogen bath) under argon was added dropwise 8.0 ml (13 mmoles) of **t**-butyllithium over 15 minutes. After the addition was complete the solution was stirred at −100° for 1 hour. The solution was quenched by addition of an electrophile (30 mmoles, neat if liquid, in a minimum of anhydrous ether if solid) and the mixture was allowed to warm to room temperature overnight.

1-Methylpyrazole-3-carboxylic Acid (4).

The main reaction was quenched with a slurry of 5.0 g of carbon dioxide in anhydrous ether. The resulting solution was extracted with water (2 x 50 ml). The aqueous extract was cooled to 0-5°, acidified to *p*H 2, warmed to room temperature, and continuously extracted for 48 hours with dichloromethane. The extract was dried, concentrated, and the resulting solid was crystallized from chloroform to yield a white solid, 0.58 g (77%) of **3**, mp 145.5-146.0° [17]; ^{1}H nmr (deuteriochloroform with 2 drops of deuteriomethanol): δ 3.97 (s, 3H), 5.20 (s, 1H), 6.82 (d, 1H, J = 2.2 Hz), 7.42 (d, 1H, J = 2.2 Hz); ^{13}C nmr (deuteriochloroform with 2 drops deuteriomethanol): 184.2 (C, COOH), 143.2 (C-3), 131.6 (C-5), 109.1 (C-4); ir (potassium bromide): 3113 (COOH), 1698 (C=O), 1504 (C=C); 1309 (C=C), 1176 (C=N) cm^{-1}.

1-(1-Methyl-3-pyrazolyl)ethanol (5).

The main reaction was quenched with freshly distilled acetaldehyde and the resulting solution was extracted with saturated ammonium chloride (3 x 15 ml). The aqueous extracts were combined, extracted with methylene chloride (3 x 15 ml), dried over sodium sulfate, concentrated by simple distillation, and the residue was vacuum distilled to provide 0.46 g (62%) of **4**, bp 103°, 1.2 torr (lit [14] 110-112°, 2.5 torr); ^{1}H nmr (deuteriochloroform): δ 1.50 (t, 3H, J = 6.7 Hz), 3.60 (s, 1H), 3.80 (s, 3H), 4.92 (q, 1H, J = 6.7 Hz) 6.13 (d, 1H, J = 2.2 Hz), 7.26 (d, 1H, J = 2.2 Hz); ^{13}C nmr (deuteriochloroform): δ 156.5 (C-3), 130.9 (C-5), 130.9 (C-5), 102.1 (C-4), 62.2 (C, C-OH), 39.2 (N-CH_3), 21.5 (CH_3, C-OH); ir (film): 3370 (OH), 2974 (C=CH), 1521 (C=C), 1371 (C=C) cm^{-1}.

1-(1-Methyl-3-pyrazoloy)phenylmethanol (6).

The main reaction was quenched with freshly distilled benzaldehyde and the resulting solution was extracted with 3*N* hydrochloric acid (3 x 15 ml). The aqueous extracts were combined, neutralized with saturated sodium bicarbonate, extracted with dichloromethane (3 x 15 ml), and dried over sodium sulfate. The solvent was evaporated and the residue was distilled (Kugelrohr) to yield 0.65 g (60%) of **4**, oven temperature 90° (0.10 torr); ^{1}H nmr (deuteriochloroform): δ 3.65 (s, 3H), 4.20 (s, 1H), 5.82 (s, 1H), 5.99 (d, 1H, J = 2.2 Hz), 7.1-7.5 (m, 6H); ^{13}C nmr (deuteriochloroform): δ 155.3 (pyrazole C-3), 143.0 (Ph C-1), 130.9 (pyrazole C-5), 128.1 (Ph C-2), 127.2 (Ph C-4), 126.2 (Ph C-3), 103.2 (pyrazole C-4), 70.3 (C-OH), 38.3 (CH_3); ir (film): 3292 (OH), 1515 (C=C), 1402 (C=C), 1191 (C=N) cm^{-1}; ms: m/z (%) 188 (24), 110 (100), 105 (36), 83 (71), 77 (80), 51 (48).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.42; N, 14.88. Found: C, 69.83; H, 6.05; N, 15.08.

3-Benzoyl-1-methylpyrazole (7).

The main reaction was quenched with benzoyl chloride, then washed with saturated sodium carbonate (3 x 10 ml), dried and concentrated. The residue was separated by column chromatography (silica gel, hexane:ethyl acetate, 8/1), providing 0.66 g (62%) of **5** which was further purified by crystallization from benzene/hexane, mp 39.5-40.0°; ^{1}H nmr (deuteriochloroform): δ 3.99 (s, 3H), 6.93 (d, 1H, J = 2.2 Hz), 7.4-7.5 (m, 4H), 8.2-8.3 (m, 2H); ^{13}C nmr (deuteriochloroform): 184.0 (C=O), 150.6 (pyrazole C-3), 139.3 (Ph C-1), 132.4 (Ph C-2), 131.1 (pyrazole C-5), 130.3 (Ph

C-4), 128.0 (Ph C-5), 109.4 (pyrazole C-4), 39.5 (CH_3); ir (potassium bromide): 1650 (CO), 1594 (C=C), 1490 (C=C), 1246 (C=N) cm^{-1}; ms: m/z (%) 186 (72), 109 (100), 105 (36), 77 (78), 51 (57).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.10; H, 5.41; N, 14.83.

1-Methylpyrazole-3-(*N*-phenyl)carboxamide (**8**).

The main reaction was quenched with freshly distilled phenylisocyanate, then washed with (3 x 15 ml) of saturated ammonium chloride, dried and concentrated. The oily residue was distilled (Kugelrohr) to give 0.50 g (45%) of **8**, oven temperature 150° (0.04 torr). Crystallization of the white solid from benzene/hexane provided **8**, mp 80.5-81.5° (lit [18] 87-89°); ^1H nmr (deuteriochloroform): δ 3.91 (s, 3H), 6.88 (d, 1H, J = 2.2 Hz), 6.1-7.9 (m, 6H), 8.70 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 159.7 (C=O) 146.5 (pyrazole, C-3), 137.9 (Ph C-4), 119.5 (Ph C-3), 107.1 (pyrazole C-4), 123.8 (Ph C-4), 119.5 (Ph C-3), 107.1 (pyrazole C-4), 39.3 ($N-CH_3$); ir (potassium bromide) 3377 (NH), 1685 (CO) cm^{-1}; ms: m/z (%) 201 (20), 109 (100), 77 (4), 54 (13).

Acknowledgement.

We are pleased to acknowledge the Camille and Henry Dreyfus Foundation for partial support for the purchase of the nmr spectrometer and to the Perkin-Elmer Corporation for support in the form of equipment grants.

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