Synthesis of 5-Amino-1,3-dimethylpyrazol-4-yl Aryl Ketones

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A convenient preparation of 5-amino-1,3-dialkylpyrazol-4-yl heterocyclic ketones is reported. They are prepared from the reaction of heterocyclic esters with the di-lithio derivative from *N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)benzamide (**1**).

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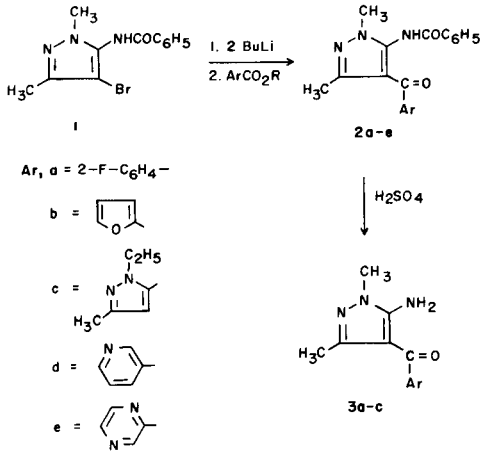
For a number of years, we have been interested in the biological properties of 5-amino-1,3-dialkylpyrazol-4-yl aryl ketones such as **3** [1]. There are many reports on the synthesis of ketones from organometallic reagents and carboxylic acid derivatives [2]. Some of these procedures have limited value for compounds of type **3a** with a 2-fluoro substituent in the aryl portion. We now report a moderately efficient and simple procedure for **3** where ketones are prepared by the reaction of aryl or heterocyclic esters with the di-lithio derivative generated from butyllithium on *N*-(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)benzamide (**1**).



In addition to methyl 2-fluorobenzoate, examples of heterocyclic esters employed were ethyl 3-pyridinecarboxylate, methyl 2-furancarboxylate, methyl 2-pyrazinecarboxylate and ethyl 4-ethyl-3-methyl-1*H*-pyrazole-5-carboxylate.

EXPERIMENTAL

Melting points were determined with a Hoover apparatus and are uncorrected. Structures were corroborated by ir and nmr spectra and elemental analysis. *N*-(4-Bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)benzamide (**1**), mp 124-126°, was prepared in 85-90% yield by bromination of *N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)benzamide [3] in glacial acetic acid.

N-[4-(2-Fluorobenzoyl)-1,3-dimethyl-1*H*-pyrazol-5-yl]benzamide (**2a**).

A solution of 10.8 g (37 mmoles) of **1** in 150 ml of tetrahydrofuran was cooled to −60° to −70° and 60 ml of *n*-butyllithium in heptane (80 mmoles) was added dropwise with stirring under nitrogen atmosphere. Stirring was continued at −60° for 1 hour, then a solution of 6 g (39 mmoles) of methyl 2-fluorobenzoate in 15 ml of tetrahydrofuran was added dropwise. After stirring at −60° for 1.5 hours, the mixture was allowed to warm to 0° and 100 ml of saturated ammonium chloride solution was added. The mixture was filtered to yield 7.4 g (59%) of **2a**, mp 220-223°; ir (potassium bromide): 1640 cm^{-1}, 1685 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.9 (s, 3H, CH_3), 3.8 (s, 3H, NCH_3), 7.0-8.0 (m, 9H, ArH), 10.1 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{16}FN_3O_2$: C, 67.64; H, 4.78; N, 12.46. Found: C, 67.52; H, 4.97; N, 12.41.

(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-fluorophenyl)methanone (**3a**).

According to a general procedure, a mixture of 7.0 (20 mmoles) of **2a** and 75 ml of 75% (v/v) sulfuric acid was stirred at 90° for 4 hours and poured into 350 ml of ice water, and filtered. The filtrate was made basic with 50% sodium hydroxide solution and extracted with dichloromethane. The extract was dried (magnesium sulfate) and the solvent evaporated *in vacuo*. The residue was crystallized from ether-petroleum ether to give 4.8 g (75%) of **3a** mp 107-109° [3]; ir (potassium bromide): 1620 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.75 (s, 3H, CH_3), 3.5 (s, 3H, NCH_3), 5.8 (s, 2H, NH_2), 7.0-7.5 (m, 4H, ArH).

N-4-(2-Furanylcarbonyl)-[1,3-dimethyl-1*H*-pyrazol-5-yl]benzamide (**2b**).

By the procedure for **2a**, the reaction of 80 ml of *n*-butyllithium with 14 g (48 mmoles) of **1**, followed by 6.5 g (50 mmoles) of methyl 2-furancarboxylate gave 6.2 g (42%) of **2b**, after recrystallization from ethyl acetate-petroleum ether, mp 177-180°; ir (potassium bromide): 1610 cm^{-1}, 1670 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.3 (s, 3H, CH_3), 3.8 (s, 3H, NCH_3), 6.5-8.0 (m, 8H, ArH), 9.7 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.00; H, 4.89; N, 13.59. Found: C, 65.62; H, 4.98; N, 13.37.

(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(2-furanyl)methanone (**3b**).

Hydrolysis of 6 g (20 mmoles) of **2b** in 55 ml of 75% sulfuric acid at 80° for 4 hours gave 2.5 g (50%) of **3b**, after recrystallization from ethyl acetate-petroleum ether, mp 117-119°; ir (potassium bromide): 1615 cm^{-1} (C=O); ^1H nmr δ 2.2 (s, 3H, CH_3), 3.5 (s, 3H, NCH_3), 5.6 (s, 2H, NH_2), 6.4 (m, 1H, olefinic H), 7 (d, 1H), and 7.4 (s, 1H) olefinic H.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.51; H, 5.44; N, 20.62.

(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-methanone (**3c**).

The treatment of 10.4 g (35 mmoles) of **1** in THF with 55 ml of *n*-butyllithium followed by 6.5 g (36 mmoles) of ethyl 1-ethyl-3-methyl-1*H*-pyrazole-5-carboxylate gave 13 g of crude product. Purification by chromatography over silica gel eluting with acetonitrile gave 7 g of waxy solid **2c**, which was still slightly impure by tlc. Hydrolysis of **2c** in 65 ml of 75% sulfuric acid at 90° for 4 hours gave **3c**, 2.8 g (60%) after recrystallization from ethyl acetate-petroleum ether, mp 149-151°; ir (potassium bromide): 1610 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 4.15 (q, 2H, CH_2), 5.5 (s, 2H, NH_2), 6.05 (s, 1H, olefinic H).

Anal. Calcd. for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.93; N, 28.32. Found:

C, 58.06; H, 6.92; N, 28.31.

N-[1,3-Dimethyl-4-(3-pyridinylcarbonyl)-1*H*-pyrazol-5-yl]benzamide (**2d**).

The reaction of 15.0 g (50 mmoles) of **1** in THF with 80 ml *n*-butyllithium followed by the addition of 7.5 g (50 mmoles) of ethyl 3-pyridinecarboxylate gave **2d** in 50% yield (8.1 g) after crystallization from ethyl acetate-petroleum ether, mp 186-188°; ir (potassium bromide): 1690 cm^{-1}, 1647 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2 (s, 3H, CH_3), 3.8 (s, 3H, NCH_3), 7.2-8.7 (m, 9H, ArH), 9.9 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.29; H, 5.17; N, 17.35.

(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methanone (**3d**) [4].

Hydrolysis of 8.0 g (0.025 mole) of **2d** in 65 ml of 75% sulfuric acid at 90° gave **3d** (56%) mp 111-114° from ethyl acetate-petroleum ether; ir (potassium bromide): 1610 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.69; N, 25.92. Found: C, 60.88; H, 5.66; N, 26.08.

N-[1,3-Dimethyl-4-(2-pyrazinylcarbonyl)-1*H*-pyrazol-5-yl]benzamide (**2e**).

Lithiation of 27.5 (94 mmoles) of **1** in THF (140 ml, 200 mmoles) *n*-butyllithium followed by reaction with 13 g (90 mmoles) of methyl 2-pyrazinecarboxylate gave 13.4 g (45% yield) of **2e**, after recrystallization from ethyl acetate-petroleum ether, mp 124-126°; ir (potassium bromide): 1700 cm^{-1}, 1635 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.3 (s, 3H, CH_3), 3.8 (s, 3H, NCH_3), 7.3, 7.8, 8.5, 8.6, 9.1 (m, 8H, ArH), 10.4 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{15}N_5O_2$: C, 63.52; H, 4.71; N, 21.80. Found: C, 63.24; H, 4.79; N, 21.60.

(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)(pyrazin-2-yl)methanone (**3e**).

This compound was obtained in 10% yield as an impure semisolid by heating 1.5 g of **2e** in 30 ml of concentrated hydrochloric acid on the steam bath for three hours; ^1H nmr (deuteriochloroform): δ 1.9 (s, 3H, CH_3), 3.5 (s, 3H, NCH_3), 5.8 (broad s, 2H, NH_2), 8.4-8.8 (m, 3H, ArH). Attempted hydrolysis of **2e** in 75% sulfuric acid or in ethylene glycol-potassium hydroxide led to extensive decomposition.

REFERENCES AND NOTES

[1a] H. A. DeWald and D. E. Butler, U. S. Patent 3,660,425 (May 1972); [b] D. E. Butler, H. A. DeWald and L. Wise, *J. Med. Chem.*, in press.

[2a] D. A. Shirley, "Organic Reactions", Vol 8, John Wiley and Sons, Inc., New York, NY, 1954, p 28; [b] M. J. Jorgensen, *ibid.*, **18**, 1 (1970).

[3] H. A. DeWald, S. Lobbenstael and D. E. Butler, *J. Med. Chem.*, **20**, 1562 (1977).

[4] This compound was prepared by Dr. D. E. Butler.