The Preparation of *N*-(1*H*-Pyrazol-3-yl)arylamides and 1*H*-Pyrazol-3-amines from Polylithiated *C*(α),*N*-Thiosemicarbazones and *C*(α),*N*-Semicarbazones

Charles F. Beam*, Sharon E. Davis, Tracy L. Cordray, Kam W. Chan, Camille M. Kassis, Joanna G. Freeman Davis, G. Mark Latham, Tina S. Guion, Karen C. Hildebran, A. Cameron Church, Madlene U. Koller, and Clyde R. Metz*

Department of Chemistry and Biochemistry, College of Charleston, Charleston, South Carolina 29424

William T. Pennington

Department of Chemistry, Clemson University, Clemson, South Carolina 29634

Kevin L. Schey

Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, Charleston, South Carolina 29425

Received May 27, 1997
Revised August 26, 1997

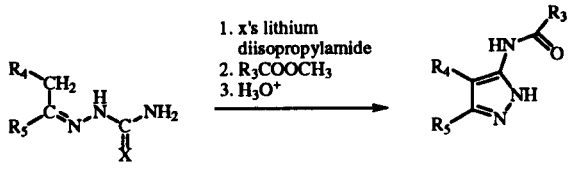
C(α),*N*-Thiosemicarbazones or *C*(α),*N*-semicarbazones were polylithiated with excess lithium diisopropylamide, and the resulting cyclized intermediates were condensed with aromatic esters to afford *N*-(1*H*-pyrazol-3-yl)arylamides. The polylithiated intermediates were also quenched with aqueous acid to give 5-substituted, 1*H*-pyrazol-3-amines.

J. Heterocyclic Chem., **34**, 1549 (1997).

We have been involved in the development of strong-base synthesis of 1*H*-pyrazoles utilizing a variety of polylithiated *C*(α),*N*-hydrazones and related regioselectively reactive intermediates (*e.g.*, dilithiated *C*(α),*N*-carboalkoxyhydrazones) [1], which were prepared by the treatment of the hydrazone-type entry compounds with either *n*-butyllithium or excess lithium diisopropylamide. This was followed by *C*-acylation with carboxylic acid esters or acid chlorides and subsequent acid cyclization of the resulting condensation intermediates to the desired heterocyclic products. Another method for 1*H*-pyrazole preparation involves the condensation/cyclization of β-diketones with hydrazines or related materials [2]. For example, utilization of the latter method has involved the dibenzoylmethane condensation/cyclization with either semicarbazide or thiosemicarbazide to give the respective 1*H*-pyrazole-1-carboxamide [3] or 1*H*-pyrazole-1-carbothioamide [4].

The potential for polylithiation of *C*(α),*N*-semicarbazones or *C*(α),*N*-thiosemicarbazones with lithium diisopropylamide followed by condensation/cyclization with esters has not been investigated by us, and earlier related reports focus on the treatment of acetophenone semicarbazone or thiosemicarbazone with Grignard reagents to afford 5-phenyl-1*H*-pyrazol-3-amine in variable yields [5]. Generally, 1*H*-pyrazol-3-amines have been prepared by treatment of phenacyl nitriles or β-chlorocinnamoyl nitriles with hydrazine [6], and their use has been quite extensive [7]. There are fewer reports concerning the preparation of *N*-aroylated, 5-phenyl-1*H*-pyrazole-3-amines [8], which have not involved strong base methods. Also, the potential usefulness of newly prepared substituted pyrazoles and related heterocyclic compounds is considerable, especially for biological screening (*e.g*, agriculture) [9].

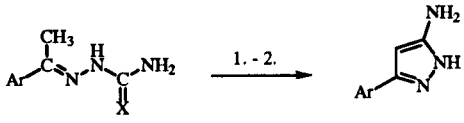
We are reporting the results of our initial study dealing with the preparation of *N*-(1*H*-pyrazol-3-yl)arylamides **1-6** and 1*H*-pyrazol-3-amines **7-9** from polylithiated *C*(α),*N*-thiosemicarbazones or *C*(α),*N*-semicarbazones. The polylithiated intermediates, prepared in an excess of lithium diisopropylamide, underwent cyclization and subsequent *N*-aroylation with several aromatic esters to give *N*-(1*H*-pyrazol-3-yl)arylamides **1-6**, or they were quenched with acid to give the 1*H*-pyrazol-3-amines **7-9**. The usual ratio of semicarbazone or thiosemicarbazone entry compound: base: ester was 1:4:1 [10] for aroylation-type condensations including salicylates [1h-j], and the ratio of reagents for preparation of 1*H*-pyrazol-3-amines **7-9** was 1:4. When smaller amounts of lithium diisopropylamide were used (*e.g.*, 1:1, 1:2 or 1:3), recovery of starting materials resulted. In earlier studies, two hours were required for the formation of *C*(α),*N*-trilithiated intermediates [1b,j] under similar conditions. At this time, it is difficult to establish that we are dealing solely with trilithiated intermediates, or a mixture of dilithiated and trilithiated intermediates. The most important *C*(α)-lithiated carbanion-type center was apparently formed along with separate *N*-anion types from each entry compound, and cyclization in basic medium probably preceded each *N*-aroylation with ester.



1. X = O or S, R_3 and R_5= C_6H_5, R_4 = H
2. X = O or S, R_3 = 2-HOC_6H_4, R_4, R_5 =-$(CH_2)_{10}$-
3. X = S, R_3 = 4-(2-phenylquinolyl), R_4 = H, R_5 = 4-FC_6H_4
4. X = S, R_3 = 3-ClC_6H_4, R_4 = H, R_5= 2-naphthyl
5. X = O, R_3 = 4-(2-phenylquinolyl), R_4, R_5 = -$(CH_2)_5$-
6. X = O, R_3 = 5-chloro-2-hydroxyphenyl, R_4 = CH_3, R_5 = C_6H_5

Illustration 1: *N*-(1*H*-Pyrazol-3-yl)arylamides.

Specifically, acetophenone thiosemicarbazone or semicarbazone was polylithiated with excess lithium diisopropylamide followed by treatment with methyl benzoate to give the same substituted pyrazole **1** in 44-97% yield. Cyclododecanone thiosemicarbazone or semicarbazone was treated with excess lithium diisopropylamide, followed by condensation with lithiated methyl salicylate to afford the same pyrazole **2**, in 49% and 48% yields, respectively. Two additional thiosemicarbazones, prepared from either 4-fluoroacetophenone or 2-acetonaphthone, were used, and after polylithiation in excess base, the former was condensed with methyl 2-phenylquinoline-4-carboxylate and the latter was condensed with methyl 3-chlorobenzoate to afford pyrazoles **3** and **4** in 27% and 34% yields, respectively. Also, cycloheptanone or propiophenone semicarbazones were polylithiated in excess base, and the former was condensed with methyl 2-phenylquinoline-4-carboxylate and the latter with methyl 5-chlorosalicylate to give pyrazoles **5** and **6** in 31% and 30% yields, respectively.



X = O or S

7-9

Ar = C_6H_5-, 4-ClC_6H_4, or 4-BrC_6H_4

Illustration 2: 1*H*-Pyrazol-3-amines.

Finally, substituted 1*H*-pyrazol-3-amines **7-9** were prepared from either the semicarbazones or thiosemicarbazones of acetophenone, 4-chloroacetophenone, or 4-bromoacetophenone, in 24-68% yields, following treatment/quench of these entry compounds with excess lithium diisopropylamide.

The structures for the compounds were established from infrared, ^1H nuclear magnetic resonance, X-ray crystallographic analysis for pyrazole **1**, and tandem mass spectra, with support from combustion analysis for C, H, and N for pyrazoles **1-6**. The infrared, *N*-carboxamide (C=O) absorptions in pyrazoles **1-6** were observed from 1646-1683 cm^{-1} [3], and NH_2/NH peaks were observed from 3200-3400 cm^{-1} in pyrazoles **1-9**. The tandem mass spectra ruled out the possibility of isomeric 1*H*-pyrazole-1-carboxamides, which were the initially anticipated products based upon earlier precedents with other substituted *C*(α),*N*-hydrazones [1, 3]. Each pyrazole **1-6** displayed $(M+H)^+$, an $(M+H-H_2O)^+$, an $(M+H\text{-aroyl})^+$, along with other expected ions, which are consistent with the *N*-aroyl structure of these products. The loss of water from the $(M+H)^+$ ion can be attributed to protonation of the carboxamide oxygen (enol form) followed by water loss leaving the iminium ion, or the less likely protonation of the N-H ring nitrogen, followed by its removal by attack of an electron pair shared by the carbon and oxygen from the carboxamide (enol form) to form the same iminium ion. None of the compounds displayed any significant fragmentation that could be attributed to an *N*-carboxamide of the isomeric 1*H*-pyrazole-1-carboxamides originally anticipated [3,11].

Table 1

Crystallographic Data for *N*-(5-Phenyl-1*H*-pyrazol-3-yl)benzamide **1**

Crystal Dimensions (mm)	0.10 x 0.22 x 0.40
Space Group	*Pbca*
a (Å)	21.129(4)
b (Å)	11.264(2)
c (Å)	10.767(2)
V(Å^3)	2562.5(8)
fw	263.30
Z	8
d_{calc} (g/cm^3)	1.365
T(°C)	-125
λ (Å)	0.71013
μ (cm^{-1})	0.8
$2\theta_{max}$ (°)	49.9
R [a]	0.042
R_w [b]	0.031

[a] $R = \Sigma[(|F_o|-|Fc|)/\Sigma|F_o|$. [b] $R_w = \{\Sigma[w(|F_o|-|F_c|)^2]/\Sigma,(w|F_o|^2)\}^{1/2}$

The X-ray data established the structure of pyrazole **1**, which implies that substituted pyrazoles **2-6** were formed in an analogous manner. Details of the data collection are reported in Table 1. The molecular structure of pyrazole **1** is shown in Figure 1 - ORTEP diagram, atomic positional parameters are listed in Table 2, and selected bond distances and angles are listed in Table 3. The molecule is nearly planar with a torsion angle of 6.19° between the least squares best planes for the heterocycle ring and the attached 5-phenyl ring and a torsion angle of 6.14° between the least squares best planes for the two phenyl rings. The carbonyl oxygen lies 0.781 Å below the least squares best plane for

the heterocyclic ring. The non-hydrogen atoms were refined anisotropically. The positions for all hydrogen atoms were obtained from difference maps; the hydrogen atoms were refined with isotropic thermal parameters. A difference map peak indicated that hydrogen atom H3 might be disordered between N2 and N3; but the presence of hydrogen bonding between N3 and O1 indicates that the current assignment is correct. The final least-squares refinement resulted in residuals R = 0.042 and R_w = 0.031. The final Fourier map had no hole deeper than -0.17 e Å^{-3} and no peak greater than 0.19 e Å^{-3} [12].

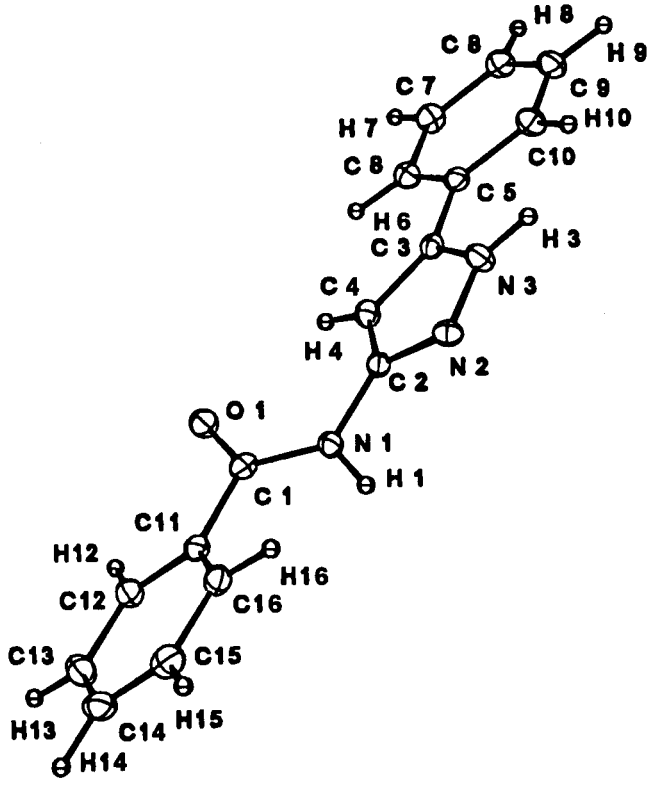


Figure 1. ORTEP diagram (30% ellipsoids for non-Hydrogen atoms) for *N*-(5-Phenyl-1*H*-pyrazol-3-yl)-benzamide **1**.

In addition to some mechanistic studies, the preparation of the polylithiated intermediates from C(α),*N*-thiosemicarbazones and C(α),*N*-semicarbazones, and their reactions with electrophilic reagents have considerable potential for development of new synthons well beyond the results described in this report. With the exception of pyrazoles **1**, and **7-9**, all future compounds targeted for preparation are new. Semicarbazones and thiosemicarbazones are much easier to prepare than β-chlorocinnamyl nitriles and other related compounds necessary for the preparation of pyrazoles such as **1-9**. We have only begun to develop the overall potential of these multiple anion type and

Table 2

Atomic Positional Parameters for the Atoms of *N*-(5-Phenyl-1*H*-pyrazol-3-yl)benzamide **1**

	x	*y*	*z*	B_{iso} (Å^2) [a]
O1	0.44633(9)	0.36301(18)	0.04896(17)	2.46(10)
N1	0.46929(11)	0.16812(24)	0.01757(22)	1.97(12)
N2	0.51266(11)	0.03903(23)	0.16438(20)	2.16(11)
N3	0.55025(12)	0.05175(24)	0.26730(22)	2.25(12)
C1	0.43938(14)	0.2706(3)	-0.01047(25)	2.02(14)
C2	0.50576(13)	0.1509(3)	0.1251(3)	1.74(13)
C3	0.56552(14)	0.1661(3)	0.29042(24)	1.74(13)
C4	0.53700(14)	0.2323(3)	0.1992(3)	2.02(15)
C5	0.60922(14)	0.2015(3)	0.3897(3)	1.86(14)
C6	0.62258(15)	0.3210(3)	0.4067(3)	2.30(14)
C7	0.66563(16)	0.3565(3)	0.4975(3)	2.52(15)
C8	0.69430(16)	0.2741(3)	0.5731(3)	2.48(15)
C9	0.68085(15)	0.1556(3)	0.5571(3)	2.66(16)
C10	0.63865(15)	0.1186(3)	0.4666(3)	2.39(15)
C11	0.39511(13)	0.2665(3)	-0.11918(25)	1.96(14)
C12	0.38156(15)	0.3708(3)	-0.1815(3)	2.41(15)
C13	0.33909(16)	0.3701(3)	-0.2804(3)	2.91(17)
C14	0.31054(16)	0.2656(4)	-0.3169(3)	2.89(17)
C15	0.32338(16)	0.1612(3)	-0.2550(3)	2.83(17)
C16	0.36579(15)	0.1619(3)	-0.1558(3)	2.28(14)
H1	0.4682(12)	0.102(3)	-0.0372(23)	2.6(7)
H3	0.5584(14)	-0.017(3)	0.319(3)	4.1(8)
H4	0.5376(11)	0.3145(22)	0.1915(20)	0.8(6)
H6	0.6009(12)	0.380(3)	0.3568(24)	3.0(7)
H7	0.6728(12)	0.442(3)	0.5082(23)	2.1(6)
H8	0.7274(13)	0.2994(24)	0.6335(23)	3.1(8)
H9	0.7014(13)	0.096(3)	0.6097(24)	3.2(7)
H10	0.6292(12)	0.0365(24)	0.4544(23)	1.8(6)
H12	0.4015(12)	0.447(3)	-0.1519(25)	2.7(7)
H13	0.3306(13)	0.449(3)	-0.3213(25)	3.3(7)
H14	0.2788(13)	0.267(3)	-0.3905(25)	3.8(7)
H15	0.3021(14)	0.085(3)	-0.2786(24)	3.3(8)
H16	0.3737(13)	0.080(3)	-0.1139(23)	3.0(7)

[a] B_{iso} is the mean of the principal axes of the thermal ellipsoid.

Table 3

Selected Bond Distances (Å) and Angles (°) for *N*-(5-Phenyl-1*H*-pyrazol-3-yl)benzamide **1**

O1-C1	1.231(4)	N3-H3	0.97(3)
N1-C1	1.350(4)	C1-C11	1.499(4)
N1-C2	1.404(4)	C2-C4	1.383(4)
N1-H1	0.95(3)	C3-C4	1.373(4)
N2-N3	1.371(3)	C3-C5	1.468(4)
N2-C2	1.337(4)	C4-H4	0 93(3)
N3-C3	1.351(4)		
C1-N1-C2	124.0(3)	C1-C11-C12	118.9(3)
C1-N1-H1	121.3(15)	C1-C11-C16	121.7(3)
C2-N1-H1	114.6(15)	N2-C2-C4	113.0(3)
N3-N2-C2	102.73(23)	N3-C3-C4	106.3(3)
N2-N3-C3	112.76(25)	N3-C3-C5	122.9 (3)
N2-N3-H3	118.6(17)	C4-C3-C5	130.6(3)
C3-N3-H3	128.2(17)	C2-C4-C3	105.2(3)
O1-C1-N1	123.4(3)	C2-C4-H4	128.1(14)
O1-C1-C11	120.4(3)	C3-C4-H4	126.7(14)
N1-C1-C11	116.1(3)	C3-C5-C6	119.1(3)
N1-C2-N2	116.8(3)	C3-C5-C10	122.1(3)
N1-C2-C4	130.2(3)		

related multiple anion type systems [1]. Future studies will consist of several parts: (1) completing the development of a higher yield synthesis of *N*-aroylated, 1*H*-pyrazole-3-amines such as pyrazoles **1-6** and the extension of the condensation to possibly include aliphatic carboxylic acid esters [13]; (2) the development of a rapid strong base synthesis of 1*H*-pyrazol-3-amines such as pyrazoles **7-9**, with the possible inclusion of *N*-substituted semicarbazones or thiosemicarbazones and other related starting materials/entry compounds; (3) the possibility of condensing *C*(α)-polylithiated intermediates with different electrophilic reagents (*e.g.*, ethyl benzoylacetate or ethyl oxamate), especially when condensation intermediates have the potential of cyclization to new heterocyclic compounds that would be very difficult or inaccessible by traditional procedures [1]; and (4) some mechanistic studies including the possibility for additional absorption spectra studies and X-ray studies for select products [14].

Even though yields of products reported here are not optimal, the current procedure readily affords multi-gram quantities of pure heterocyclic products resulting from recrystallization from routine solvents, which are in sufficient amount for spectral characterization, biological testing, and other uses. The initial experimental procedure is straightforward so that someone not necessarily familiar with strong base procedures can be successful with the reactions.

EXPERIMENTAL

Melting points were obtained with a Mel-Temp melting point apparatus in open capillary tubes and are uncorrected. Fourier Transform infrared spectra were obtained on a Nicolet Impact 410 or Mattson Polaris FT-IR. Proton magnetic resonance were obtained with a Varian Associates 360L nuclear magnetic resonance spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane standard. The molecular ion for pyrazole **8** was determined with a Hewlett Packard gas chromatograph-mass spectrometer (Hewlett Packard Series II, 5890 Gas Chromatograph and 5971A Mass Selective Detector). Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888.

Colorless crystals of pyrazole **1** were recrystallized from ethanol in order to give satisfactory crystals for X-ray determination. Single crystal data for X-ray studies were collected at -125° on a Rigaku AFC7R diffractometer at Clemson University using the ω/2θ scan mode. The unit cell dimensions were determined by a least-squares refinement based on the setting angles of 25 carefully centered reflections in the range $10.97° < 2\theta < 16.43°$. Diffraction data were collected for 2258 unique reflections with h from 0 to 25, k from 0 to 13, and l from 0 to 12. A total of 1221 reflections with $I > 2.5\sigma(I)$ were used in the structure determination.

Weights based on counting statistics were applied to the data. An empirical absorption correction, based on azimuthal scans of several moderately intense reflections, resulted in transmission factors of 0.88-1.00. All programs used in the structure determination are contained in the NRCVAX [12] system.

Liquid secondary ionization mass spectrometry (LSIMS) and tandem mass spectral determinations were conducted at the Medical University of South Carolina on a JEOL HX110/HX110 four-sector tandem mass spectrometer of EBEB configuration operating with an accelerating voltage of 10kV. Precursor ions were generated in a standard LSIMS ion source using a JEOL cesium ion gun operated at 20 kV (10-keV cesium ion beam energy). Glycerol was used as the matrix for all experiments reported here. Tandem mass spectra were recorded by focusing the ^{12}C species of the $(M + H)^+$ cluster into the collision cell (third field-free region) and attenuating the intensity to approximately 30% with helium. The collision cell was floated to 3 kV for high energy (7 keV) collisions. The mass resolution of both spectrometers was approximately 1000. The JEOL Complement data system was used to record the spectra, which are average profile data of one to four scans. Tandem mass spectra were acquired at a rate corresponding to scanning MS-II from m/z 1-6000 in 90 s with 100-Hz filtering

General Procedure for Preparation of *N*-Aroylated Pyrazoles **1-6**.

In a typical reaction sequence, lithium diisopropylamide (0.063 mole) was prepared (0.063 mole of *n*-butyllithium and 0.063 mole of diisopropylamine in 25-30 ml of dry tetrahydrofuran, 0°, nitrogen) and treated with a thiosemicarbazone (0.015 mole) dissolved in 35-45 ml of tetrahydrofuran, or a slurry of semicarbazone (0.015 mole) in a similar volume of tetrahydrofuran [10]. The more soluble thiosemicarbazones were polylithiated/condensed at 0°, and the less soluble semicarbazones were polylithiated at room temperature. After 2 hours of lithiation, the ester (0.0158 mole) dissolved in 25-35 ml of tetrahydrofuran was added to the polylithiated intermediate, and the mixture/solution was stirred from 45-120 minutes (condensation time depended upon the ester [1]). Finally, 100 ml of 3*N* hydrochloric acid was added, and the mixture was stirred, and heated under reflux for approximately one hour. The mixture was poured into ice (*ca.*, 100 g) followed by 100 ml of solvent grade ether. The mixture was then neutralized with solid sodium bicarbonate, and the layers separated. The aqueous layer was extracted with ether or tetrahydrofuran (2 x 75 ml), and the organic fractions were combined, dried, filtered, evaporated, and recrystallized.

N-(5-Phenyl-1*H*-pyrazol-3-yl)benzamide **1**.

Acetophenone thiosemicarbazone or semicarbazone was polylithiated with lithium diisopropylamide, condensed with methyl benzoate (1:4:1) to afford the same product, in 51-97% yield (from thiosemicarbazone) and 44% yield (from semicarbazone), mp 194-196° (ethanol) (lit mp 190-192° [8]); infrared (paraffin oil): cm^{-1}, several absorptions, 3200-3300 (NH), 1657 (C=O) (paraffin oil) and 1683 (methylene chloride); ^1H nmr (trifluoroacetic acid): δ ppm 7.07 (s, 1H, C_4-H) and 7.33-8.23 (m, 10H, ArH) [15]; ms: LSI 264.10 $(M+H)^+$, 246.1, 186.0, 160.0, 132.9, base peak 105.0, and 77.0; tandem ms: base peak 264.1 $(M+H)^+$, 245.95, $(M+H-H_2O)^+$, 234.02, 185.98 $(M+H-C_6H_6)^+$, 158.97 $(M+H-COC_6H_5)^{+\bullet}$, 129.96, 104.94 (benzoyl cation)$^+$, and 76.98 (phenyl cation)$^+$.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.80; H, 4.89; N, 16.06.

N-(4,5-Decamethylene-1*H*-pyrazol-3-yl)-2-hydroxybenzamide **2**.

Cyclododecanone thiosemicarbazone or semicarbazone [16] was polylithiated with excess lithium diisopropylamide, condensed with methyl salicylate (1:4:1) to give the same pyrazole **2** in 49% and 48%, respectively, mp 290-292° (xylenes/dimethyl-

formamide); infrared (paraffin oil): cm^{-1}, several absorptions, 3389 and 3313 (NH) and 1658 (C=O); ^1H nmr (trifluoroacetic acid): δ ppm 0.96-3.10 (m, 20H, $-(CH_2)_{10}-$) and 7.07-8.33 (m, 4H, ArH) [15]; ms: LSI base peak 342.2 $(M+H)^+$, 324.02 $(M+H-H_2O)^+$ and 222.2 (M + H-aroyl)$^+$; tandem ms: 342.2 $(M+H)^+$, 323.94 $(M+H-H_2O)^+$ and 222.2 (M+H-aroyl)$^+$.

Anal. Calcd. for $C_{20}H_{27}N_3O_2$: C,70.35; H, 7.96; N, 12.31. Found: C, 70.61; H, 7.87; N, 12.16. (N, 12.52 from thiosemicarbazone, separately determined).

N-(5-(4-Fluorophenyl)-1*H*-pyrazol-3-yl)-2-phenylquinoline-4-carbonylamide **3**.

4-Fluoroacetophenone thiosemicarbazone was polylithiated, condensed with methyl 2-phenylquinoline-4-carboxylate (1:4:1) [17] to pyrazole **3** in 27% yield, mp 285-287° (toluene/1-propanol); infrared (paraffin oil): cm^{-1}, several absorptions, dominant 3251 (NH) and 1650 (C=O) and; ^1H nmr (trifluoroacetic acid): δ ppm 7.17 (s, 1H C_4-H), 7.20-8.77 (m, 14H, ArH) [15]; ms: LSI 409.1 $(M+H)^+$; tandem ms: 409.1 base peak $(M+H)^+$, 391.1 $(M+H-H_2O)^+$, 378.9, 350.9, 284.9, 231.9, 204.0 (phenylquinoline cation)$^+$, 203.0, 176.9, 153.0, and 128.0.

Anal. Calcd.for $C_{25}H_{17}FN_4O$: C, 73.52; H, 4.20; N, 13.72. Found: 73.18; H, 4.31; N, 13.40.

N-(5-(3-Chlorophenyl)-1*H*-pyrazol-3-yl)-2-naphthamide **4**.

Specifically, 2-acetonaphthone thiosemicarbazone was polylithiated with lithium diisopropylamide followed by condensation/cyclization with methyl 3-chlorobenzoate (1:4:1) to pyrazole **4** in a 34% yield, mp 230-232° (toluene/1-propanol); infrared (paraffin oil): cm^{-1} several absorptions, dominant 3226 (NH) and 1646 (C=O); ^1H nmr (trifluoroacetic acid): δ ppm 7.10 (s, 1H, C_4-H), 7.37-8.50 (m, 11H, ArH) [15]; ms: LSI 348.1 $(M+H)^+$, 330 $(M+H)^+-H_2O)^+$, 301.2, 237.3 $(M+H-C_6H_4Cl)^+$ 224.9, base peak 135.5, 111 (chlorophenyl cation)‡; tandem ms: base peak 348.0, 330.0 $(M+H-H_2O)^+$, 313.0, 236.0 $(M+HC_6H_5Cl)^+$, 209.0, 138.9, and 110.9 (chlorophenyl cation)$^+$.

Anal. Calcd. for $C_{20}H_{14}ClN_3O$: C, 69.07; H, 4.06; N, 12.08. Found: C, 69.38; H, 4.15; N, 12.34.

N-(4,5-Pentamethylene-1*H*-pyrazol-3-yl)-2-phenylquinoline-4-carbonylamide **5**.

Cycloheptanone semicarbazone was polylithiated, condensed with methyl 2-phenylquinoline-4-carboxylate (1:4:1), to pyrazole **5** in 31% yield, mp 264-266° (1-propanol); infrared (paraffin oil): cm^{-1}, 3162, 3240 (NH) and 1658 (C=O); ^1H nmr (trifluoroacetic acid): δ ppm 1.43-2.12 and 2.38-3.22 (m, 10H, $-(CH_2)_5-$) and 7.65-8.72 (m, 10H, ArH) [15]; ms: LSI 383.0631 $(M+H)^+$, 365.2 $(M+H-H_2O)^+$, 232.1, 206.1, 205.1; tandem ms: base peak 383.16 $(M+H)^+$, 365.15 $(M+H-H_2O)^+$, 325.0, 232.0, 204.0 (phenylquinoline cation)$^+$.

Anal. Calcd. for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80; N, 14.65. Found: C, 75.02; H, 5.84; N, 14.41.

N-(4-Methyl-5-phenyl-1*H*-pyrazol-3-yl)-(5-chloro-2-hydroxy)-benzamide **6**.

Propiophenone semicarbazone was polylithiated, condensed with methyl 5-chlorosalicylate (1:5:1) [18] to give pyrazole **6** in 30% yield, mp 277-279° (ethanol/benzene); infrared (paraffin oil): cm^{-1}, 3167, 3237 (NH) and 1653 (C=O); ^1H nmr (trifluoroacetic acid): δ ppm 2.40 (s, 3H, C_4-CH_3) and 7.07-8.37 (m, 8H, ArH) [15]; ms: LSI base peak 328.0 $(M+H)^+$; tandem ms: base peak 328.0 $(M+H)^+$, 309.9 $(M+H-H_2O)^+$, 293.0 $(M+H-Cl)$‡, 200, 174.0, 173.0, and 154.9.

Anal. Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.24; H, 4.42; N, 12.46.

General Procedure for Preparation of 1*H*-Pyrazol-3-amines **7-9**.

When esters were not added to the polylithiated intermediates described in the previous general procedure, 100 ml of 3 *N* hydrochloric acid was added instead, and the mixture was stirred and heated under reflux for 5 minutes. The work-up at this point was the same as if the ester had been added.

5-Phenyl-1*H*-pyrazol-3-amine **7**.

Compound **7** was prepared in a 40% yield from acetophenone semicarbazone, mp 122-124° (ethanol) (lit [5a] mp 126-127°); infrared (paraffin oil): cm^{-1}, 3396, 3272, 3182; ^1H-nmr (deuteriochloroform/dimethyl sulfoxide-d_6): δ ppm 6.13 (s, broad, exchange with deuterium oxide, NH and/or NH_2) [15] and 7.35-8.17 (m, 6H, ArH and C_4-H).

5-(4-Chlorophenyl)-1*H*-pyrazol-3-amine **8**.

Compound **8** was prepared in 68% yield from 4-chloroacetophenone thiosemicarbazone, mp 166-168° (ethanol) (lit [19] mp 170-171°; 173-175°), infrared (paraffin oil): cm^{-1}, 3435, 3365, and 3317; ^1H-nmr (deuteriochloroform/dimethyl sulfoxide-d_6): δ 5.93 ppm (s, broad, exchange with deuterium oxide, NH and/or NH_2) [15] and 7.45-7.97 (m, 5H, ArH and C_4-H); GC-MS (M^+, 193, Calcd. M^+, 193).

5-(4-Bromophenyl)-1*H*-pyrazol-3-amine **9**.

Compound **9** was prepared in a 24% yield from 4-bromoacetophenone thiosemicarbazone, mp 168-170° (ethanol) (lit [20] mp 173-174°); infrared (paraffin oil): cm^{-1}, 3394, 3273, 3161 (NH and NH_2); ^1H nmr (deuteriochloroform/ dimethyl sulfoxide-d_6): δ ppm 5.95 (s, NH and/or NH_2) [15] and 7.52-7.90 (m, ArH and C_4-H).

2-Cyclododecylidene-hydrazinethiocarboxamide (Cyclododecanone Thiosemicarbazone).

The compound was prepared in a 65% yield by the condensation of cyclododecanone (0.1 mole) and thiosemicarbazide (0.105 mole) in 200 ml of ethanol with 1 ml of glacial acetic acid. The stirred mixture was heated under reflux until dissolved, 3-4 hours. Upon reduction of the volume of the solvent, crystallization occurred. After filtration, recrystallization from ethanol gave product, mp 190-192°(ethanol); infrared (paraffin oil): cm^{-1}, 3406, 3229, and 3145 (NH and NH_2); ^1H-nmr (deuteriochloroform/dimethyl sulfoxide-d_6): δ ppm 1.67-2.63 (m, $-(CH_2)_{11}-$) [15].

Anal. Calcd. for $C_{13}H_{25}N_3S$: C, 61.13; H, 9.86; N, 16.45. Found: C, 61.31; H, 9.89; N, 16.44.

Acknowledgments.

This work was supported by grants from the Research Corporation, and the Donors of the Petroleum Research Fund, Administered by the American Chemical Society. The technical assistance of Cynthia L. (Mazat) Griffith and Margaret A. Hines is also acknowledged with thanks.

REFERENCES AND NOTES

[1a] R. S. Foote, C. F, Beam, and C. R. Hauser, *J. Heterocyclic Chem.*, 7, 589 (1970); [b] C. F. Beam, R. S. Foote, and C. R. Hauser, *J.*

Chem. Soc. C, 1568 (1971); [c] C. F. Beam, R. S. Foote, and C. R. Hauser, *J. Heterocyclic Chem.*, **9**, 183 (1972); [d] C. F. Beam, D. C. Reames, C. E. Harris, L. W. Dasher, W. M. Hollinger, N. L. Shealy, R. M. Sandifer, M. Perkins, and C. R. Hauser, *J. Org Chem.*, **40**, 514 (1975); [e] C. F. Beam, R. M. Sandifer, R. S. Foote, and C. R. Hauser, *Synth. Commun.*, **6**, 5 (1976); [f] T. D. Fulmer, M. L. Livingston, L. P. Dasher, B. L. Bobb, J. D. Wilson, K. L. Sides, and C. F. Beam, *J. Heterocyclic Chem.*, **17**, 799 (1980); [g] M. J. Livingston, M. F. Chick, E. O. Shealy, D. J. Park, T. D. Fulmer, and C. F. Beam, *J. Heterocyclic Chem.*, **19**, 215 (1982); [h] C. F. Beam, H. L. Hall, A. M. Huff, R. C. Tummons, S. A. O'Grady, *J. Heterocyclic Chem.*, **21**, 1897 (1984); [i] A. M. Huff and C. F. Beam, *J. Heterocyclic Chem.*, **23**, 1343 (1986); [j] M. L. Mazat, C. F. Beam, and M. A. Hines, *Synth. Commun.*, **20**, 253 (1990); [k] D. C. Duncan, T. A. Trumbo, C. D. Almquist, T. A. Lentz, and C. F. Beam, *J. Heterocyclic Chem.*, **24**, 555 (1987); [l] A. C. Church, M. U. Koller, M. A. Hines, and C. F. Beam, *Synth. Commun.*, **26**, 3659 (1996); [m] A. C. Church, M. U. Koller, S. A. O'Grady, and C. F. Beam, *Synth. Commun.*, **26**, 2603 (1996).

[2] See R. Fusco, The Chemistry of Heterocyclic Compounds, Vol **22**, R. H. Wiley, ed, John Wiley and Sons, Inc., New York, N. Y., 2967, Chapter 3.

[3] J. Castell and R. Roser, *Anales Real Soc. Espan. Fis. Quim., (Madrid)*, **62** (Ser B), 409 (1966); *Chem. Abstr.*, **65**, 20117f (1966). In this report, the *N*-carboxamide was prepared and infrared carboxamide absorptions were reported at 1754 cm^{-1}.

[4] K. N. Zelenin, O. V. Solod, and A. B. Tomchin, *Zh. Obshch. Khim.*, **57**, 584 (1987).

[5a] D. Biquard, *Bull. Soc. Chem.*, **30**, 656 (1936); [b] S. Searles and H. M. Kash, *J. Org. Chem.*, **19**, 928 (1954).

[6a] N. S. Vul'fson, *Sbnorik Statei, Nauch-Issledovatel Inst. Org. Poluprovd. i Krasitelei*, **2**, 128 (1961); *Chem. Abstr.*, **56**, 10031c (1962); [b] D. N. Ridge, J. W. Hanifin, L. A. Harten, B. D. Johnson, J. Menschik, G. Nicolau, A. E. Sloboda, and D. E. Watts, *J. Med. Chem.*, **22**, 1385 (1979); [c] J. Cossy and J. P. Pete, *Bull. Soc. Chim. France*, **11**, 559 (1979); [d] R. S. Long, *J. Am. Chem. Soc.*, **69**, 990 (1947); [e] T. Justoni, *Gazz. Chim. Ital.*, **78**, 166 (1948); [f] E. H. Kroeker and S. M. McElvain, *J. Am. Chem. Soc.*, **56**, 1171 (1934); [g] G. Ege and P. Arnold, *Angew. Chem.*, **86**, 237 (1974); *Angew. Chem. Int. Ed. Engl.*, **13**, 206 (1974); [h] G. Ege and H. Franz, *J. Heterocyclic Chem.*, **19**, 1267 (1982); [i] P. Kurtz, H. Gold, and H. Disselknotter, *Liebig S. Vuli'fson Sbornik Statei, Nauch-Issledovatel Inst. Org. Poluprovd. i Krasiteli*, **2**, 128 (1961).

[7a] E. Ajello, S. Plescia, and G. Dattolo, *Atti Accad. Sci. Lett. Arti Palermo*, **33**, 297 (1974); [b] W. Dymek and Z. Ryznereski, *Diss. Pharm. Pharmacol.*, **22**, 419 (1970); [c] S. Checchi and G. Auzzi, *Ann. Chim. (Rome)*, **60**, 225 (1970).

[8a] S. Checchi, M. Ridi and P. Papini, *Gazz. Chim. Ital.*, 85, 1558 (1955); [b] S. Huenig and K. Huebner, *Chem. Ber.*, **95**, 937 (1962).

[9] There is considerable literature precedent for testing new pyrazoles as insecticides, fungicides, bacterocides, herbicides, and plant growth enhancers.

[10] Five percent excess base and ester; 0.015 mole entry compound 0.063 mole LDA: 0.0158 mole ester for approximate ratio of entry compound: base: ester of 1:4:1.

[11] We would expect a mass spectrum of pyrazole-*N*-carboxamides to display a molecular ion, an abundant $(M+H-NH_3)^+$ and possibly an $(M+H-NH_3-CO)^+$ ion; see also: [a] L. Orsatti, R. Seragila, P. Traldi, G. Diamantini, G. Tarzia, and A. Tontini, *J. Mass Spectrom.*, **30**, 1567 (1995); [b] K. J. Volk, R. A. Yost, and A. Brajter-Toth, *Anal. Chem.*, **61**, 1709 (1989); [c] K. Harada, K. Masuda and M. Suzuki, H. Oka, Y. Ikai, and J. Hayakawa, *Org. Mass. Spectrom.*, **28**, 1512 (1993).

[12] NRCVAX, An Interactive Program System for Structure Analysis. See: E. J. Gabe, Y. Le Page, J.-P. Charland, F. L. Lee, and P. S. White, *J. Appl. Cryst.*, **22**, 384 (1989); [b] Further data are available on request from the authors C. R. M. or W. T. P.

[13a] S. Checchi, P. Papini and M. Ridi, *Gazz. Chim. Ital.*, **85**, 1160 (1955); [b] M. H. Elnagdi, M. R. H. El-Moghayar, D. H. Fleita, E. A. A. Hafez, and S. M. Fahmy, *J. Org. Chem.*, **41**, 3781 (1976); [c] A. Costanzo, F. Bruni, A. Auzzi, S. Selleri and L. P. Vettori, *J. Heterocyclic Chem.*, **27**, 695 (1990).

[14a] Additional studies will also include ^1H and ^{13}C high field nmr studies. Instrumentation for such spectra will be available in this department in several months. [b] X-ray crystallographic analysis are necessary before reporting the condensation/cyclization of polylithiated acetophenone semicarbazone with lithiated ethyl benzoylacetate.

[15] ^1H nmr integration ratios for NH and OH intensities were variable.

[16] P. Chabrier and E. Cattelain, *Bull. Soc. Chim. France*, 48, (1950); [b] P. P. T. Sah and T. C. Daniels, *Rev. Trav. Chim.*, **69**, 1545 (1956).

[17] In an earlier investigation, methyl isonicotinate was an ester used in a condensation/cyclization with dilithiated phenylhydrazones. See also: ref [1f]

[18] The ratio initially used was different from 1:4:1, which is part of the developing general experimental procedure.

[19a] U. Simon, O. Sues and L. Homer, *Liebigs Ann. Chem.*, **697**, 17 (1966); [b] M. R. H. Elmoghayar, M. K. A. Ibrahim and F. M. Darwish, *Org. Prep. Proced. Int.* **6**, 1 (1984); [c] S. D. Larsen, C. H. Spilman, F. P. Bell, D. M. Dinh, E. Martinborough, and G. J. Wilson, *J. Med. Chem.*, **34**, 1721 (1991).

[20a] H. Hartmann and J. Liebscher, *Synthesis*, 276 (1984); [b] F. Bruni, A. Costazo, S. Selleri, G. Guerrini, R. Fontozzi, R. Pirisino, and S. Brunelleschi, *J. Pharm. Sci.*, **82**, 480 (1993).