Preparation of 1*H*-Pyrazole-5-carboxamides from Dilithiated C(α),*N*-Phenylhydrazones and Lithiated Ethyl Oxanilates or Lithiated Ethyl Oxamate

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Dilithiated C(α),*N*-phenylhydrazones were prepared in excess lithium diisopropylamide and condensed with either ethyl oxanilate, ethyl 4'-chlorooxanilate, or ethyl oxamate to give intermediates that were quenched and acid cyclized to substituted 1*H*-pyrazole-5-carboxamides.

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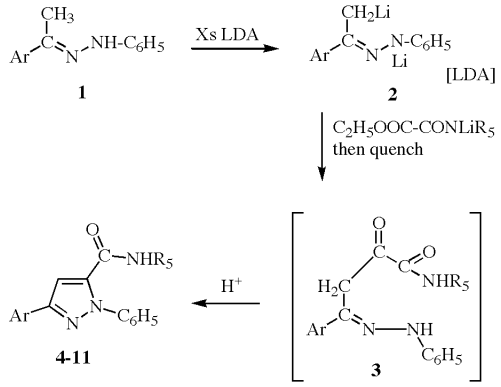
Pyrazoles, especialy 1*H*-pyrazoles, have received considerable investigative attention with regard to their syntheses, and their potential for biological applications, including agriculture, and other uses. These compounds can be prepared by several methods, such as the condensation-cyclization of: β-diketones with substituted hydrazines; α,β-unsaturated carbonyl compounds with hydrazines followed by oxidation of the resulting 4,5-dihydropyrazole; nitrilimines with substituted alkynes [1]; or dilithiated hydrazones with esters, and related electrophilic reagents [2].

The preparations and uses of substituted 1*H*-pyrazole-5-carboxamides range from simply substituted to those compounds where the other pendant groups are more complex. A favored synthetic route for 1*H*-pyrazole-5-carboxamides involves preparing a 1*H*-pyrazole-5-carboxylic acid followed by its transformation to the carboxylic acid chloride, which is then treated with an amine [3]. There are additional reports dealing with carboxylic acid amides in the 1-, 3- and 4-positions of the pyrazole ring [4-6]. The compounds have been studied for their biological potential, use in other syntheses, and a focus on spectral investigations.

The preparation of 1*H*-pyrazole-, 5-propanoic or 5-butanoic acids and *N*-carboalkoxy-1*H*-pyrazoles has been demonstrated [2b-e,7], where a variety of C(α),*N*-carboalkoxyhydrazones were dilithiated with excess lithium diisopropylamide, and these intermediates were condensed-cyclized with select carboxylic acid anhydrides, or more generally with a variety of esters. In related pyrazole preparation studies, polylithiated hydrazones have been condensed-cyclized with other anionic electrophiles, such as lithiated ethyl benzoylacetate [2c,8], lithiated methyl thiosalicylate [9], and lithiated hydroxybenzoate esters [2b].

At an earlier time, hydroxy-pyridazinones were prepared from dilithiated C(α),*N*-phenylhydrazones that were condensed-cyclized with ethyl oxalate, an electrophilic reagent related to the oxanilates or oximate used during this study. [10]. Also, there are limited reports of the condensations of ethyl oxanilates or ethyl oxamate with nucleophilic reagents, such as [11] amines or amides, which were part of a synthetic sequence. The condensation of lithiated oxamates and lithiated oxanilates, which are anionic electrophiles, with anionic nucleophiles is new.



4. Ar = C_6H_5; R_5 = 4-ClC_6H_4
5. Ar = C_6H_5; R_5 = H
6. Ar = 4-$CH_3C_6H_4$; R_5 = 4-ClC_6H_4
7. Ar = 4-$CH_3OC_6H_4$; R_5 = C_6H_5
8. Ar = 4-$CH_3OC_6H_4$; R_5 = 4-ClC_6H_4
9. Ar = 2-naphthyl; R_5 = C_6H_5
10. Ar = 2-naphthyl; R_5 = 4-ClC_6H_4
11. Ar = 4-$CH_3OC_6H_4$; R_5 = H

During the current study, several C(α),*N*-phenylhydrazones **1** were dilithiated (to **2**) with excess lithium diisopropylamide, followed by treatment with either lithiated ethyl oxanilate, lithiated ethyl 4'-chlorooxanilate, or lithiated (possible dilithiated) ethyl oxamate. When the resulting *C*-acylated intermediates were neutralized to **3** with aqueous hydrochloric acid, this was followed by heating the biphasic mixture under reflux to afford the desired heterocyclic products **4-11**. Complete cyclization did not occur in all cases; however, this initial approach utilizing a three-step, one pot procedure proved to be the prudent way to initially proceed. The best way to determine whether cyclization had occurred was to examine the infrared spectrum of the recrystallized and dried solid product. If cyclization had occurred, the one or two (sometimes with shoulders) NH or NH_2 absorptions would be less complex than that observed in a *C*-acylated product. The latter would display another NH absorption plus an enolic OH absorption. Nuclear magnetic resonance spectra, especially ^1H nmr, was only helpful and not conclusive for determining whether cyclization had occurred, since spectra of

C-acylated hydrazones displayed the enol form. The *C*-acylated phenylhydrazones **3** for pyrazoles **5, 9** and **10** were isolated and separately cyclized with benzene or toluene using a water trap and a small amount of methanesulfonic acid. The desired 1*H*-pyrazole-5-carboxamides **4-11** were prepared in 36-74 % yield.

Each pyrazole was characterized by absorption spectra with support from combustion analysis for C, H, and N. Infrared spectra displayed absorptions 3200-3400 cm^{-1} for NH and NH_2, and amide carbonyls were clearly noted between 1646-1673 cm^{-1}. The ^1H nmr spectra contained the expected aromatic absorptions and characteristic methyl in **6** (δ, 2.35 ppm), methoxy singlets in **7**, **8**, and **11** (δ, 3.78-3.80 ppm), and C_4-H were only easily identified and distinguishable from aromatic proton absorptions in **4** (δ, 7.31 ppm), and **11** (δ, 7.24 ppm). The other C_4-H absorptions in **5-10** were not readily distinguished from the other aromatic proton absorptions. By comparison, C-4 absorptions for carbons in ^{13}C nmr spectra of each product were upfield from normal aromatic carbon absorptions, and they were noted in δ, 105.5 - 107.2 ppm. The amide carbonyl carbons were displayed farther downfield from δ, 158.0 - 161.7 ppm.

The potential for condensation-cyclization of these anionic electrophilic reagents with other polylithiated anion-type nucleophilic intermediates appears good, and several of these studies are already in progress. Normally, once a general procedure is developed for a particular compound type, multi-gram quantities of pure products can usually be made, and the resulting compounds can be purified by recrystallization from common solvents. Always, the setup does not require an elaborate apparatus, and the experimental procedure is straightforward so that someone not necessarily familiar with strong base procedures can be successful.

EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected. Infrared spectra were obtained with a Nicolet Impact 410 FT-IR or a Mattson Genesis II FT-IR with Specac Golden Gate Accessory (neat). Proton and ^{13}C nuclear magnetic resonance spectra were obtained with a Varian Associates Mercury Oxford 300 MHz, nuclear magnetic resonance spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888.

General Procedure for Preparation of 1*H*-Pyrazole-5-carboxamides for **4-11**.

(Ratio of reagents - hydrazone:base:ester-amide - 1:4:1(for oxanilates); or 1:5:1 (for ethyl oxamate)): Compounds **6**, **9-11** were prepared on a 0.010 mole scale, and compounds **4, 5, 7** and **8** were prepared on a 0.015 mole scale.

A 0.010 mole scale reaction is described: In a typical reaction sequence, lithium diisopropylamide, 0.042 mole for **6**, **9**, and **10** (or 0.0525 mole for **11**), was prepared by the addition of 26-27 ml (or 33 ml for **11**) of 1.6 *M n*-butyllithium in hexanes 0.042 mole (or 0.053 mole for **11**) to a three-neck round-bottomed flask (*e.g.*, 500 ml) equipped with a nitrogen inlet tube, a pressure equalizing side arm addition funnel (*e.g.*, 125-ml), and a stir bar. The flask was cooled in an ice bath and 4.27 g (0.042 mole) or 5.34 g (0.053 mole for **11**) of diisopropylamine, dissolved in 25-30 ml of dry tetrahydrofuran (sodium/benzophenone - ketyl) (0°, nitrogen), was added from the funnel at a fast dropwise rate during 5 minutes. The solution was stirred for an additional 15-20 minutes, and then treated *via* the addition funnel with 0.010 mole of a phenylhydrazone [12] dissolved in 35-45 ml of tetrahydrofuran. After 45-60 minutes of dilithiation, 0.011 mole oxanilate or oxamate, dissolved in 50-60 ml of tetrahydrofuran, was added to the dilithiated intermediate, and the solution was stirred for 2.5 - 3 hours. Then procedure A for immediate cyclization, or procedure B, using a water trap, acid and another solvent system, was followed.

Procedure A for **4**, **6-8**, and **11**.

Then 100 ml of 3*N* hydrochloric acid was added quickly, and the two-phase mixture was well stirred and heated under reflux for approximately 60 minutes. At the end of this period, the mixture was poured into a large flask containing ice (*ca.*, 100 g), followed by the addition of 100 ml of solvent grade ether. The mixture was then neutralized with solid sodium bicarbonate, and the liquid layers or solid materials separated. If a solid appeared at this point, the biphasic mixture could be filtered using a large Buchner funnel. The aqueous layer was extracted with ether or tetrahydrofuran (2 x 75 ml), and the organic fractions were combined, filtered, evaporated, and recrystallized.

Procedure B for **5** (toluene), **9-10** (benzene).

Then 120 ml of 2*N* hydrochloric acid was added, allowed to stir for 5 minutes, which was followed by a standard work up. The mixture was poured into a large flask containing ice (*ca.*, 100 g) followed by 100 ml of solvent grade ether or tetrahydrofuran. The mixture was then neutralized with solid sodium bicarbonate, and the layers were separated. The aqueous layer was extracted with ether or tetrahydrofuran (2 x 75 ml), and the organic fractions were combined, concentrated with a rotary evaporator, and the oil or solid that resulted was dissolved in 160 ml benzene, 40 ml ethanol and 10 drops of methanesulfonic acid (70 %). The solution-mixture was fitted with a water trap and heated under reflux with good stirring for 2-3 hours, which was usually an hour after the last amount of water separated.

N-(4-Chlorophenyl)-1,3-diphenyl-1*H*-pyrazole-5-carboxamide (**4**).

This compound was prepared by the general procedure A from the condensation-cyclization of 0.015 mole of acetophenone phenylhydrazone and 0.016 mole of ethyl 4'-chlorooxanilate to yield 3.26 g (58%), mp 215-217° (ethanol). Infrared (paraffin oil): ν 3271 and 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.31 (s, 1H, C_4-H), 7.35-7.55, 7.66-7.69, 7.87-7.91 (m, 14H, ArH), and 11.01 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 106.8, 121.5, 124.3, 125.4, 125.7, 126.1, 127.9, 128.4, 128.6, 128.7, 128.8, 128.9, 132.0, 137.4, 138.4, and 150.4.

Anal. Calcd. for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.39; H, 4.58; N, 10.89.

1,3-Diphenyl-1*H*-pyrazole-5-carboxamide (**5**).

This compound was prepared by the general procedure B from the condensation-cyclization of 0.015 mol of acetophenone phenylhydrazone and 0.016 mole of ethyl oxamate to yield 1.89 g (48%), mp 202-204° (ethanol). Infrared (paraffin oil): ν 3369, 3256, 3159, and 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.35-7.53, 7.71, 7.87-7.90 and 8.18 ppm (m, C_4-H, NH_2 and ArH); ^{13}C nmr (DMSO-d_6): δ 106.2, 124.6, 125.4, 127.8, 128.3, 128.7, 128.9, 132.2, 138.8, 140.2, 150.3, and 161.0 ppm.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.04; H, 5.18; N, 15.93.

N-(4-Chlorophenyl)-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**6**).

This compound was prepared by the general procedure A from the condensation-cyclization of 0.010 mole of 4-methylacetophenone phenylhydrazone and 0.011 mole of ethyl 4'-chlorooxanilate to yield 2.45 g (63%), mp 227-228° (ethanol). Infrared (neat): ν 3276, 3245, 3185, and 1656 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.35 (s, 3H, $ArCH_3$), 7.24-7.91 (m, 14H, C_4-H and ArH) and 10.79 ppm (s, NH); ^{13}C nmr (DMSO-d_6): δ 20.8, 106.6, 121.5, 124.2, 125.3, 127.7, 127.8, 128.7, 128.8, 129.2, 129.4, 137.4, 137.8, 138.3, 139.8, 150.5, and 158.0 ppm.

Anal. Calcd. for $C_{23}H_{18}ClN_3O$: C, 71.22; H, 4.68; N, 10.83. Found: C, 71.13:, H, 4.75; N, 10.66.

1, *N*-Diphenyl-3-(4-methoxyphenyl)-1*H*-pyrazole-5-carboxamide (**7**).

This compound was prepared by the general procedure A from the condensation-cyclization of 0.015 mole of 4-methoxyacetophenone phenylhydrazone and 0.016 mole of ethyl oxanilate to yield 3.18 g (60%), mp 205-208° (ethanol-benzene). Infrared (paraffin oil): ν 3297 and 1666 cm^{-1} ; ^1H nmr (DMSO-d_6): δ 3.80 (s, 3H, $ArOCH_3$), 7.04-7.12, 7.34-7.59, 7.71-7.74, 7.88-7.91 (m, 15H, C_4-H and ArH,) and 10.73 ppm (s, NH); ^{13}C nmr (DMSO-d_6): δ 55.1, 106.3, 114.3, 119.90, 119.98, 120.5, 124.2, 124.7, 126.8, 127.7, 128.8, 138.6, 138.7, 139.9, 150.4, 158.1, and 159.5 ppm.

Anal. Calcd. for $C_{22}H_{16}N_3O_2$: C, 74.78: H, 5.18; N, 11.37. Found: C, 74.48; N, 5.19; N, 11.29.

N-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**8**).

This compound was prepared by the general procedure A from the condensation-cyclization of 0.015 mole of 4-methoxyacetophenone phenylhydrazone and 0.016 mole of ethyl 4'-chlorooxanilate to yield 3.74 g (64%), mp 216-218° (ethanol-benzene). Infrared (paraffin oil): ν 3300, 3249, and 1659 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.78 (s, 3H, $ArOCH_3$), 7.02-7.05, 7.38-7.54, 7.71-7.87 (m, 14H, C_4-H and ArH) and 10.79 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.2, 106.4, 114.3, 121.4, 121.5, 124.2, 124.6, 126.8, 127.8, 128.7, 128.9, 137.5, 138.3, 139.9, 150.4, 158.1, and 159.5 ppm.

Anal. Calcd. for $C_{22}H_{15}ClN_3O_2$: C, 68.40; H, 4.49; N, 10.41. Found: C, 68.74; H, 4.54; N, 10.28.

1, *N*-Diphenyl-3-(2-naphthyl)-1*H*-pyrazole-5-carboamide (**9**).

This compound was prepared by the general procedure B from the condensation-cyclization of 0.010 mol of 2-acetonaphthone phenylhydrazone and 0.011 mole of ethyl oxanilate to yield 2.69 g (66%), mp 171-173° (ethanol-benzene). Infrared (paraffin oil): ν *ca.* 3291, and 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.13 (t, ArH), 7.36-7.73, 7.93-8.13, 8.46-8.49 (m, ArH) and 10.75 ppm (s, NH); ^{13}C nmr (DMSO-d_6): δ 107.1, 120.0, 120.5, 123.5, 123.6, 124.1, 124.3, 125.8, 126.6, 127.7, 128.0, 128.2, 128.4, 128.7, 129.0, 129.5, 132.9, 133.2, 138.5, 138.9, 139.9, 150.4, and 158.0 ppm.

Anal. Calcd. for $C_{26}H_{19}N_3O \cdot {}^1/_2H_2O$: C, 78.67; H, 5.10; N, 10.24. Found: C, 78.37; H, 5.06; N, 10.54.

N-(4-Chlorophenyl)-3-(2-naphthyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**10**).

This compound was prepared by the general procedure B from the condensation-cyclization of 0.010 mole of 2-acetonaphthone phenylhydrazone and 0.011 mole of ethyl 4'-chlorooxanilate to yield 2.08 g (49%), mp 203-205° (ethanol-benzene). Infrared (paraffin oil): ν *ca.* 3400 broad and 1646 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.41-7.61, 7.71-7.77, 7.93-8.03, 8.10-8.13, 8.46-8.49 (m, ArH), and 10.89 ppm (s, NH); ^{13}C nmr (DMSO-d_6): δ 107.2, 121.5, 123.5, 124.1, 124.4, 125.8, 126.4, 126.6, 127.7, 127.8, 128.0, 128.2, 128.7, 128.9, 129.5, 132.9, 133.2, 137.5, 138.6, 139.9, 150.4, and 158.8 ppm.

Anal. Calcd. for $C_{26}H_{18}ClN_3O$: C, 73.67; H, 4.28; N, 9.91. Found: C, 74.08; H, 4.45; N, 9.64.

3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**11**).

This compound was prepared by the general procedure A from the condensation-cyclization of 0.010 mol of 4-methoxyacetophenone phenylhydrazone and 0.011 mol of ethyl oxamate to yield 1.08 g (36%), mp 182-183° (methanol). Infrared (neat): ν 3322, 3150, and 1673 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.78 (s, 3H, $ArOCH_3$), 6.99 (d, 2H, ArH), 7.24 (s, 1H, C_4-H), 7.35-7.47, 7.62 (m, 7H, ArH), 7.76 (d, 2H, ArH), 8.09 ppm (s, NH_2); ^{13}C nmr (DMSO-d_6) δ 55.9, 106.4, 114.0, 125.1, 125.5, 127.4, 128.2, 129.3, 139.3, 140.9, 150.8, 160.0, and 161.7 ppm.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.57; H, 5.09; N, 14.29.

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