

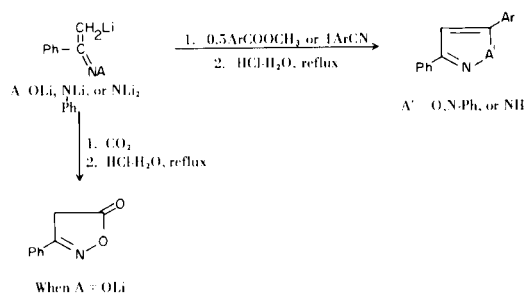
Reactions of $C(\alpha),N$ -Dilithiophenylhydrazones with Aldehydes. Acid-Cyclization to 2-Pyrazolines

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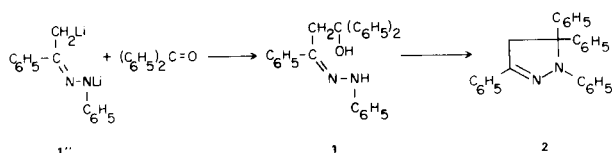
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We have recently reported new methods for the preparation of isoxazoles, 2-isoxazolin-5-ones, and pyrazoles by the condensation of $C(\alpha),N$ -dilithiophenylhydrazones, $C(\alpha),O$ -dilithiooximes, and $C(\alpha),N,N$ -trilithiohydrazones with electrophilic reagents which include esters, nitriles, and carbon dioxide (2,3,4,5,6). (Scheme 1).



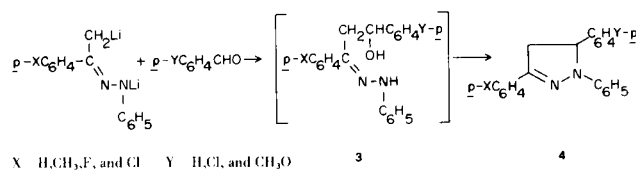
Scheme 1

The treatment of dilithiophenylhydrazones with ketones, such as benzophenone, was undertaken. For example, the phenylhydrazone of acetophenone was treated with two molar equivalents of *n*-butyllithium in tetrahydrofuran-hexane at 0°. The dianion **1''** was then treated with a molar equivalent of benzophenone. The material isolated after recrystallization from ethanol also contained a molecule of ethanol ($C_{27}H_{24}N_2O \cdot CH_3CH_2OH$), whose structure was supported by combustion analysis and absorption spectra.



The attempts to effect an acid-cyclization of **1** and related materials, by a variety of methods, met with limited success (7). The results are not readily reproducible, and a steric argument may partially account for the difficulties encountered. Further investigation may be warranted.

The condensation of these dilithiophenylhydrazones with aldehydes, such as benzaldehyde and acetaldehyde, which was followed by acid-cyclization to 2-pyrazolines, was easily reproducible. Isolation of the presumed hydroxyphenylhydrazone **3** intermediate was not necessary. The structures of the 2-pyrazolines **4** were established by comparison of melting points with those of known materials, elemental analysis when applicable, and absorption spectra. The results are summarized in the Table.



The new method for preparing 2-pyrazolines is rapid, the starting materials are readily available, and it is an unequivocal method for preparation of 3,5-disubstituted compounds. The yields recorded in the Table do not necessarily represent the maximum that can be obtained.

Acknowledgement.

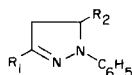
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EXPERIMENTAL

All analyses were performed by the Robertson Laboratory, Florham Park, New Jersey 07932 and M-H-W Laboratories, Garden City, Michigan 41835. Infrared spectra were obtained from a Perkin-Elmer 700 Infrared Spectrometer. Melting points were obtained in a Thomas-Hoover melting point apparatus in open tubes and are uncorrected. *n*-Butyllithium was obtained from the Lithium Corporation of America, Bessemer City, North Carolina. Tetrahydrofuran was obtained from Matheson, Coleman, and Bell and used as supplied. The phenylhydrazones were prepared by a standard method (13) and were recrystallized from ethanol, dried on a Buchner funnel, and used immediately.

TABLE
2-Pyrazolines



Compound Number	R ₁	R ₂ (from R ₂ CHO)	Name (-2-Pyrazoline)	Empirical Formula	Yield (%)	M.P. °C
I	C ₆ H ₅	C ₆ H ₅	1,3,5-Triphenyl-	C ₂₁ H ₁₈ N ₂	64	136-137 (a)
II	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅	1,5-Diphenyl-3(<i>p</i> -tolyl)-	C ₂₂ H ₂₀ N ₂	40	152-154 (b)
III	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -ClC ₆ H ₄	5(<i>p</i> -Chlorophenyl)-1-phenyl-3(<i>p</i> -tolyl)-	C ₂₂ H ₁₉ ClN ₂ (c)	36	140-142
IV	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	5(<i>p</i> -Methoxyphenyl)-1-phenyl-3(<i>p</i> -tolyl)-	C ₂₃ H ₂₂ N ₂ O	31	140-142 (d)
V	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	5(<i>p</i> -Chlorophenyl)1,3-diphenyl-	C ₂₁ H ₁₇ ClN ₂	36	129-131 (e)
VI	C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄	1,3-Diphenyl-5(<i>p</i> -methoxyphenyl)-	C ₂₂ H ₂₀ N ₂ O	34	123-124 (f)
VII	<i>p</i> -FC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	3(<i>p</i> -Fluorophenyl)-5(<i>p</i> -methoxyphenyl)-1-phenyl-	C ₂₂ H ₁₉ FN ₂ O (g)	17	132-134
VIII	<i>p</i> -FC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	5(<i>p</i> -Chlorophenyl)-3(<i>p</i> -fluorophenyl)-1-phenyl-	C ₂₁ H ₁₆ ClFN ₂ (h)	18	142-143
IX	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	3,5-Di(<i>p</i> -chlorophenyl)-1-phenyl-	C ₂₁ H ₁₆ Cl ₂ N ₂	36	149-150 (i)
X	<i>p</i> -ClC ₆ H ₄	C ₆ H ₅	3(<i>p</i> -Chlorophenyl)-1,5-diphenyl-	C ₂₁ H ₁₇ ClN ₂	21	150-151 (j)
XI	<i>p</i> -ClC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	3(<i>p</i> -Chlorophenyl)-5(<i>p</i> -methoxyphenyl)-	C ₂₂ H ₁₉ ClN ₂ O (k)	19	154-156
XII	C ₆ H ₅	CH ₃	5-Methyl-1,3-diphenyl-	C ₁₆ H ₁₆ N ₂	28	103 (l)

(a) Lit. m.p. 134°, see ref. (8). (b) Lit. m.p. 150-150.5°, see ref. (9). (c) *Anal.* Calcd. for C₂₂H₁₉ClN₂: C, 76.18; H, 5.52; N, 8.08. Found: C, 76.18; H, 5.80; N, 8.11. (d) Lit. m.p. 141°, see ref. (10). (e) Lit. m.p. 129°, see ref. (11). (f) Lit. m.p. 125-126°, see ref. (12). (g) *Anal.* Calcd. for C₂₂H₁₉FN₂O: C, 76.28; H, 5.53; N, 8.09. Found: C, 76.30; H, 5.48; N, 7.94. (h) *Anal.* Calcd. for C₂₁H₁₆ClFN₂: C, 71.90; H, 4.60; N, 7.99. Found: C, 71.75; H, 4.81; N, 7.87. (i) Lit. m.p. 151°, see ref. (10). (j) Lit. m.p. 150-150.5°, see ref. (9). (k) *Anal.* Calcd. for C₂₂H₁₉ClN₂O: C, 72.82; H, 5.28; N, 7.72. Found: C, 72.67; H, 5.31; N, 7.37. (l) Lit. m.p. 105°, see ref. (18).

Pyrazoline Synthesis.

To a stirred solution of 0.02 mole of phenylhydrazone dissolved in 100 ml. of THF, which was cooled to 0° and blanketed under nitrogen, 0.042 mole of *n*-butyllithium (in hexane) was added in 2-3 minutes. A dark-red to red-black color should be observed, which appears essential for the successful preparation of the desired materials. After 30-45 minutes, 0.022 mole of aldehyde in 25 ml. of THF was added. The mixture was stirred at 0° for 5-10 minutes, then neutralized by pouring it into 100 ml. of 3*N* hydrochloric acid (inverse neutralization). The resulting mixture was stirred and heated under reflux for 1 hour and cooled. The mixture was poured into a large flask and approximately 100 ml. of ether was added, which was followed by careful addition of sodium bicarbonate until neutralization was complete. The layers were separated, and the aqueous layer was extracted with two 50-ml. portions of ether. The organic materials were combined, dried (sodium sulfate), filtered, concentrated, and immediately taken up in ethanol. All 2-pyrazolines reported in the Table were recrystallized from ethanol.

Attempts to modify the acid-cyclization procedure (7) did not give the desired materials. Uncyclized or linearly dehydrated material was isolated instead, which contained an N-H infrared absorption in the range of 3325-3300 cm⁻¹ (chloroform solution). In addition, a good quality of *n*-butyllithium appeared to be essential. All compounds reported contained the following infrared absorption bands: 3060-3040, 3010-3000 (ArH); 2930-2910, 2875-2840 (aliphatic); 1600-1595 (always strong - usually with one or more shoulders - C=N- + aromatic). In addition, every 2-pyrazoline reported gave a very distinctive and positive Knorr's pyrazoline test (16).

Preparation of 1,3,5,5-Tetraphenyl-2-pyrazoline.

Treatment of Dilithioacetophenone Phenylhydrazone with Benzophenone.

A 5.25-g. sample (0.025 mole) sample of acetophenone phenylhydrazone was dissolved in 100 ml. of tetrahydrofuran, cooled to 0°, blanketed with dry nitrogen, and treated with 22.5 ml. of *n*-butyllithium (2.2 moles) (from Alfa Inorganics, Beverly, Mass.).

The mixture was stirred for 30 minutes, and then treated with 4.55 g. (0.025 mole) of benzophenone dissolved in 100 ml. of tetrahydrofuran. After 15 minutes of reaction time, the mixture was inversely neutralized by pouring it into a 250-ml. solution of 10-20% ammonium chloride. The layers were separated, and the aqueous layer was extracted with two 50-ml. portions of ether. The organic layers were combined, dried (magnesium sulfate), concentrated, and the oil was treated with ethanol. The crude material that crystallized was collected and recrystallized from ethanol to give 8.22 g. (75%) of material, m.p. 84-85°.

Anal. Calcd. for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.53; H, 6.77; N, 6.39; nmr (deuteriochloroform): δ 1.10 (t, 3H, CH_3), 3.57 (m, 2H, $-CH_2O-$), 3.73 (s, 2H, $-CH_2-$), and 6.67-7.42 (m, 20H, ArH and possibly NH) (Varian Associates A-60 NMR Spectrometer - TMS standard).

Cyclization of Hydroxyphenylhydrazone.

A 1.0-g. (0.0023 mole) sample of hydroxyphenylhydrazone (prepared above) was added to 10 ml. of concentrated sulfuric acid, which had been cooled to 0°. The mixture was stirred at this temperature for 1 hour and poured on to ice. After filtration and initial crystallization from ethanol, the material was recrystallized from toluene to give 0.24 g. (28%) of 1,3,5-tetraphenyl-2-pyrazoline, m.p. 222-224° [Lit. m.p. 222-223°, see ref. (17)].

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