A New Synthesis of 2-Pyrazolin-5-ones from the Condensation of C(α),N-Dilithiophenylhydrazones with Diethyl Carbonate

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C(α),N-Dilithiophenylhydrazones were prepared from phenylhydrazones in an excess of lithium diisopropylamide and condensed with diethyl carbonate followed by an acid cyclization to give 2-pyrazolin-5-ones.

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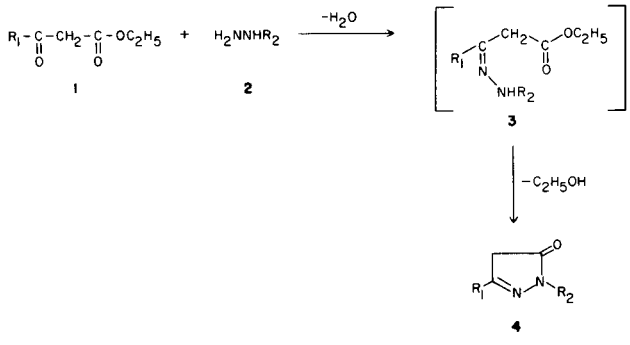
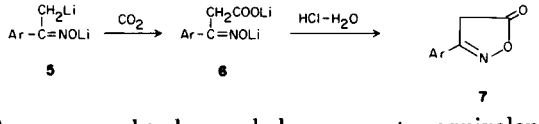
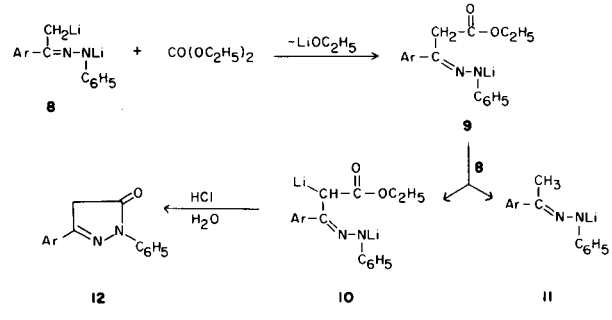
The preparation, reactions and uses of 2-pyrazolin-5-ones are well documented (2), and perhaps the most straight-forward preparative procedure involves the condensation of a β-ketoester **1** with a hydrazine **2** to give intermediate **3**, which undergoes cyclization to give 2-pyrazolin-5-one **4**.



In an earlier and somewhat related study (3), we prepared 2-isoxazolin-5-ones **7** by the carboxylation of C(α),O-dilithiooximes **5** to presumably give **6** followed by acid-catalyzed cyclodehydration. The dilithiooximes **5** were prepared by treating C(α)-oximes in tetrahydrofuran (THF) at 0° with two equivalents of *n*-butyllithium. While we were successful in the preparation and reactions of C(α),N-dilithiophenyllhydrazones **8** (4-8) with certain other electrophilic reagents, their condensation-cyclization with carbon dioxide, phosgene, methyl chloroformate, and diethyl carbonate gave trace yields, at best, of 2-pyrazolin-5-ones (9).



What appeared to be needed was an extra equivalent of base to react with **9** to give **10** instead of consuming dilithiated phenylhydrazone **8** by competitively reacting with **9** to give **10** and **11**. The mechanism proposed (4) suggests that half of **8** was consumed to give **11**, which would not react with the electrophilic reagent and eventually result in starting phenylhydrazone after neutralization. *n*-Butyllithium would not be a satisfactory base for this proposed procedure, since its nucleophilic properties would also make it competitive with **8** for electrophilic reagents (10); however, the use of lithium diisopropylamide for the preparation of **8** from the phenylhydrazone had the potential of being both a satisfactory base and a poor nucleophile.



During the current investigation, phenylhydrazones were metalated at 0° with an excess of lithium diisopropylamide (phenylhydrazone:base 1:3) to give **8a-h**, which were condensed with diethyl carbonate to give presumed precyclization intermediate **10a-h** directly by reaction with excess base. After neutralization and further treatment with hydrochloric acid, the desired pyrazolin-5-ones **12a-h** were isolated in 22-97% yield (Table). Methyl chloroformate gave lower yields of product, and its utilization in subsequent reactions was not investigated.

Pyrazolinones **12a,e,** and **g** have been prepared by other methods (11-13), and the melting points of **12a** and **12g** that we obtained corresponded well with those reported; however, **12e** had a melting point of 145° [Lit. m.p. 161° (12)] after several recrystallizations (See Table). Some 2-pyrazolin-5-ones have been reported to give inconsistent melting points (2). In addition **12a**, prepared by the condensation of phenylhydrazine with ethyl benzoylacetate had identical ir and nmr spectra when compared to the spectra of the same material prepared by this method. Interestingly, pyrazolinone **12c** exhibited carbonyl and enol ir absorptions at 1690 and 3350 cm^{-1}, respectively; however, its best nmr spectra was taken in trifluoroacetic acid, and it only displayed vinyl resonance at δ 6.60 ppm, indicative of the enol form.

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Table

2-Pyrazolin-5-ones

Compound Number	Phenylhydrazone of	Product Name (2-pyrazolin-5-one)	Empirical Formula	% Yield	M.p. C°	Spectral Data Ir/Nmr	
12a	acetophenone	1,3-diphenyl-	$C_{15}H_{12}N_2O$	97	136 (a)	1690 cm^{-1} (CO) (deuteriochloroform)	δ 3.56 (CH_2CO) (deuteriochloroform)
12b	*p*-methoxyacetophenone	3(*p*-methoxyphenyl)-1-phenyl-	$C_{16}H_{14}N_2O_2$	68	133 (b)	1690 cm^{-1} (CO) (deuteriochloroform)	δ 3.56 (CH_2CO) (deuteriochloroform)
12c	*p*-fluoroacetophenone	3(*p*-fluorophenyl)-1-phenyl-	$C_{15}H_{11}FN_2O$	69	194 (c)	1690 cm^{-1} (CO) (nujol) 3375 cm^{-1} (OH)	δ 6.60 (vinyl) (CF_3COOH) (h)
12d	*p*-methylacetophenone	3(*p*-methylphenyl)-1-phenyl-	$C_{16}H_{14}N_2O$	70	154 (d)	1695 cm^{-1} (CO) (deuteriochloroform)	δ 3.67 (CH_2CO) (deuteriochloroform)
12e	*p*-chloroacetophenone	3(*p*-chlorophenyl)-1-phenyl-	$C_{15}H_{11}ClN_2O$	57	145 (e)	1700 cm^{-1} (CO) (deuteriochloroform)	δ 3.80 (CH_2CO) (deuteriochloroform)
12f	2-phenylacetophenone	1,3,5-triphenyl	$C_{21}H_{16}N_2O$	26	192 (f)	3350 cm^{-1} (OH) (carbon disulfide)	δ 6.83-8.13 (ArH) (h) ($DMSO-d_6$)
12g	dibenzyl ketone	3-benzyl-1,4-diphenyl	$C_{22}H_{18}N_2O$	22	228-229 (g)		δ 3.47 ($-CH_2Ar$) (trifluoroacetic acid) (i)

(a) Lit. m.p. 137-138°, see reference (11). (b) Calcd: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.15; H, 5.35; N, 10.40. (c) Calcd: C, 70.86; H, 4.36; N, 11.02. Found: C, 70.60; H, 4.54; N, 10.81. (d) Calcd: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.49; H, 5.78; N, 11.01. (e) Lit. m.p. 161°, see reference (12). Some 2-pyrazolin-5-ones give inconsistent melting points; see reference (2). Calcd: N, 10.35; Found: N, 10.19. (f) Calcd: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.51; H, 5.28; N, 8.76. (g) Lit. m.p. 229-230°, see reference (13). (h) The best spectrum was obtained with this solvent. The absence of a methine proton suggests the enol form in this solvent. (i) Enol form in this solvent; the ir spectrum (nujol) was of poor quality.

Previous Claisen-type condensations for the preparation of heterocyclic materials such as isoxazoles and pyrazoles utilized the ratio of reactants: phenylhydrazone or oxime:base:ester - 1:2:0.5, and the yield was based upon the amount of ester (4). The method reported here represents a new synthetic procedure for the preparation of larger amounts of heterocyclic compound, where the yield is now based upon the amount of phenylhydrazone (phenylhydrazone:base:ester - 1:3:1). Another advantage of the method is the ready availability of $C(\alpha)$-ketones for the preparation of phenylhydrazones. In addition, the experimental procedures are readily reproducible by someone not very familiar with strong-base synthetic techniques.

EXPERIMENTAL

Combustion analyses were performed by Dr. G. I. Robertson's Microanalytical Laboratory, 73 West End Avenue, Florham Park, NJ 07932. Nmr spectra were obtained from a Varian Associates EM-300X Nuclear Magnetic Resonance Spectrometer, and chemical shifts are reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Ir spectra were obtained from a Perkin-Elmer 700 Infrared Spectrometer. Tetrahydrofuran (THF) was distilled from sodium (benzophenone) immediately before use. The *n*-butyllithium was purchased from Lithium Corporation of America, Bessemer City, North Carolina. The phenylhydrazones were prepared by a standard procedure (14). Melting points were taken in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected.

General Procedure for Preparation of 2-Pyrazolin-5-ones.

A 0.066-mole sample of *n*-butyllithium was added to a 500-ml., three-neck, round-bottomed flask which fitted with a nitrogen inlet tube, a pressure-equalized dropping funnel, and drying tube. The flask was cooled to 0° and blanketed by nitrogen. A 0.066-mole sample of diisopropylamine dissolved in 30 ml. of dry THF was added during 5 minutes and the solution was stirred for 20-30 minutes. Then 0.020 mole of phenylhydrazone dissolved in 30-40 ml. of dry THF was added, and the solution was stirred at 0° for an additional 45 minutes. The resulting dilithiohydrazone was condensed for 45-60 minutes with 0.022-mole of diethyl carbonate (5 minutes addition time) dissolved in 25-30 ml. of THF. The solution was neutralized with 100 ml. of 3*N* hydrochloric acid, and the two-phase mixture was stirred and heated under reflux for 1 hour. The mixture was then cooled, poured into a large flask with approximately 100 ml. of ether and carefully neutralized with sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with two 50-ml. portions of ether. The organic layer was combined, not dried, and concentrated (Rotovac). The resulting oil or residue was crystallized and recrystallized from ethanol and water. Methanol and water were also a satisfactory solvent combination for recrystallization.

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