A New Synthesis of 3-Amino-1-aryl-2-pyrazolin-5-ones

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Reaction of ethyl 3-nitropropionate with aryldiazonium chlorides in basic medium yields ethyl 3-nitro-3-(arylhydrazono)propionates. These α-nitrohydrazones are converted by catalytic hydrogenation to 3-amino-1-aryl-2-pyrazolin-5-ones, probably *via* cyclization of intermediate amidrazones produced *in situ*. This appears to be the first route to the title compounds that does not use a substituted phenyl hydrazine intermediate and offers advantages in the preparation of pyrazolinones bearing electron-rich aryl rings.

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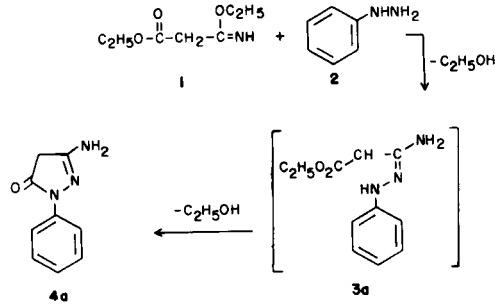
Since the preparation of 3-amino-1-phenyl-2-pyrazolin-5-one **4a** by Conrad and Zart (1) in 1906, a vast array of 1-aryl analogs has been reported. Compounds of this series have achieved practical importance in the chemistry of photographic and textile dyes (2). It appears, however, that a single type of ring synthesis has been used in preparing these substances: reaction of a phenylhydrazine **2** with a derivative of malonic acid or cyanoacetic acid, such as the imino ester **1** shown in a typical sequence (Scheme I) (2).

Scheme I

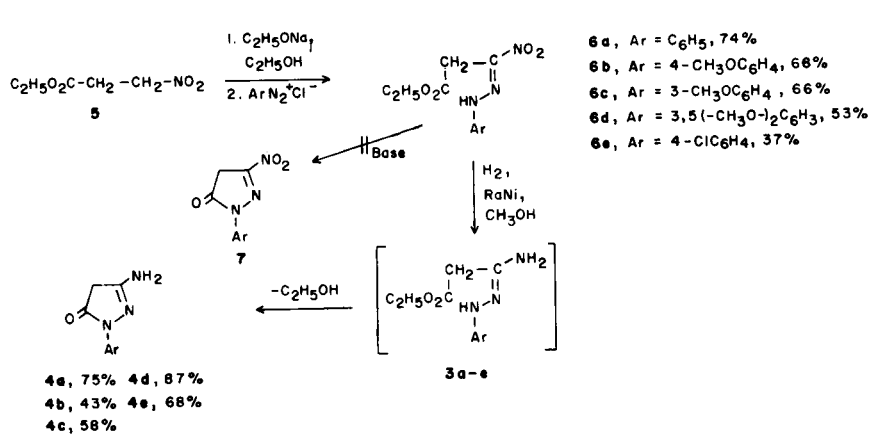


Various functional equivalents to **1** have been used (3-5), as have procedures involving isolation of intermediate amidrazones (such as **3a**) followed by acid- or base-catalyzed ring closure to the desired pyrazolinone **4a** (5-7). Nevertheless, these routes all depend upon the availability of an arylhydrazine and a suitable malonate derivative. We wish to report here a new route to these pyrazolinones; this route uses neither arylhydrazine nor malonate intermediates.

Ethyl 3-nitropropionate **5** (8,9) in ethanolic sodium ethoxide underwent azo coupling (10) with aryldiazonium chlorides to provide the yellow α-nitrohydrazones **6a-e** (Scheme II).

We expected the nitrohydrazones **6a-e** to cyclise to 1-aryl-3-nitro-2-pyrazolin-5-ones **7** when treated with base. Although deep red anions were formed from **6a** upon base treatment (11), protonation and workup always led to recovery of unchanged hydrazone. Attention was therefore turned to reduction of **6**. When subjected to 40 psi hydrogen pressure at 40° over No. 28 Raney nickel, **6a-e** afforded moderate to good yields of the desired pyrazolinones **4a-e** (Scheme II). In no case was the presumed in-

Scheme II



termediate amidrazone **3a-e** detected; the Raney nickel catalyst is probably sufficiently basic to catalyze the **3→4** cyclization.

This route offers a novel preparation of 1-aryl-3-amino-2-pyrazolin-5-ones and should prove advantageous in certain cases. Thus, while we obtained **4b** in 43% yield after purification, the classical route is reported to give only 16.5% of this substance (12).

EXPERIMENTAL (13)

α-Nitrohydrazones (**6a-e**) were prepared by the method detailed here for compound **6d**. A solution of 3.83 g (0.025 mole) of 3,5-dimethoxyaniline in 6 ml of concentrated hydrochloric acid and 14 ml of water was cooled to 0-5° and treated with a cold solution of 1.75 g (0.025 mole) of sodium nitrite in 5 ml of water. This cold diazonium solution was added to a stirred 5-10° mixture of 3.68 g (0.025 mole) of ethyl 3-nitropropionate in 50 ml of ethanol containing 3.70 g (0.054 mole) of sodium ethoxide. The reaction mixture was allowed to warm to 25°, diluted with 50 ml of water, and the yellow-orange hydrazone **6d** filtered off. Recrystallization from ethanol gave 4.09 g (53%) of analytically pure **6d**, mp 120-122° ir (Nujol mull): 3.09, 5.80, 6.30, 8.30 (br), 8.62 and 12.13 μ; nmr (deuteriochloroform) δ 10.0 (br s, 1H) 6.42 (m, 2H), 6.21 (m, 1H), 419 (q, 2H), 3.81 (s, 6H), 3.76 (s, 2H), 1.24 (t, 3H).

Anal. Calcd. for $C_{13}H_{17}N_3O_6$: C, 50.2; H, 5.50; N, 13.5. Found: C, 50.3; H, 5.26; N, 13.4.

Compound **6a** had a melting point of 107-109°; ir (mull): 3.10, 5.80, 6.29, 9.80, 13.12 and 14.33 μ; nmr (deuteriochloroform + deuterium oxide) δ 7.33 (br s, 5H), 4.20 (q, 2H), 3.78 (s, 2H), 1.22 (t, 3H).

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.6; H, 5.22; N, 16.7. Found: C, 52.4; H, 5.30; N, 16.7.

Compound **6b** had a melting point of 81-82°; ir (potassium bromide): 3.11, 5.81, 6.38, 6.79, 7.02, 7.76, 8.50 (br), 9.78, 11.93 and 13.15 μ; nmr (deuteriochloroform + deuterium oxide): δ 7.18 (q, 4H), 4.22 (q, 2H), 3.85 (s, 3H), 3.78 (s, 2H), 1.26 (t, 3H).

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.2; H, 5.38; N, 14.9. Found: C, 51.0; H, 5.32; N, 15.0.

Compound **6c** had a melting point of 65-67°; ir (mull): 3.10, 5.82, 6.23, 6.84, 8.78 and 13.44 μ; nmr: (deuteriochloroform + deuterium oxide): δ 7.38 (m, 1H), 6.96 (m, 3H), 4.18 (q, 2H), 3.92 (s, 3H), 3.83 (s, 2H), 1.31 (t, 3H).

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.2; H, 5.37; N, 14.9. Found: C, 51.6; H, 5.15; N, 14.8.

Compound **6e** had a melting point of 98-100°; ir (mull): 3.11, 5.82, 8.50 (br), 9.25, 12.18, 15.60 μ; nmr (deuteriochloroform + deuterium oxide): δ 7.20 (q, 4H), 4.25 (q, 2H), 3.81 (s, 2H), 1.30 (t, 3H).

Anal. Calcd. for $C_{11}H_{12}ClN_3O_4$: C, 46.4; H, 4.25; N, 14.8. Found: C, 46.43; H, 4.22; N, 14.50.

Pyrazolones **4a-e** were prepared by the method described here for 1-(3,5-dimethoxyphenyl)-3-amino-2-pyrazolin-5-one, **4d**.

A solution of 0.5 g of α-nitrohydrazone **6d** in 50 ml of methanol was treated with 0.3 g of No. 28 Raney nickel and hydrogenated at 40 psi hydrogen pressure at 40° for 6 hours. The mixture was then filtered to remove catalyst, evaporated to 10 ml *in vacuo*, and the crude **4d** was filtered off. Recrystallization from methanol gave 0.33 g (87%) of **4d** of mp 179-181° dec; ir (KBr): 2.96, 3.10, 5.91, 6.03, 6.21, 7.81, 8.30 and 12.07 μ; nmr (DMSO-d_6 + deuterium oxide): δ 7.12 (d, J = 2 2H), 6.18 (t, J = 2, 1H), 3.78 (s, 6H), 3.58 (s, 2H).

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.2; H, 5.56; N, 17.9. Found: C, 56.3; H, 5.67; N, 17.7.

Pyrazolinone **4a** had a melting point of 218-219° [lit (2), 219°].

Pyrazolinone **4b** had a melting point of 191-192° [lit (12), 188-190°].

Pyrazolinone **4c** had melting point of 139-142° dec; ir (mull): 2.90, 3.0, 5.91, 6.03, 6.10, 7.81, 11.61, 12.80 μ; nmr (DMSO-d_6): 7.8-6.6 (m, 4H), 5.8 (br s, 2H), 3.83 (s, 3H), 3.56 (s, 2H).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.40; N, 20.5. Found: C, 58.9; H, 5.18; N, 20.3.

Pyrazolinone **4e** had a melting point of 155-157° dec; ir (mull): 3.03, 3.10, 5.92, 6.10, 8.35, 9.24, 12.18 and 12.50 μ; nmr (DMSO-d_6): 7.92 (d, J = 6.5, 2H), 7.30 (d, J = 6.5, 2H), 6.2 (br s, 2H), 3.51 (s, 2H).

Anal. Calcd. for $C_9H_8ClN_3O$: C, 51.8; H, 3.86; N, 20.1. Found: C, 51.6; H, 3.77; N, 19.9.

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(13) Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 137 instrument; nmr spectra were obtained with Varian EM-360 and JEOLCO MH-100 spectrometers and are reported in ppm δ *vs* internal TMS.