Synthesis of 1-(2,4,6-Trichlorophenyl)-3-(3-nitro- and 2-chloro-5-nitroanilino)-5-pyrazolones

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A convenient one flask synthesis of 1-aryl-3-nitroanilino-5-pyrazolones in yields of 60-65% is described. Synthesis involves initial reaction of ethyl 3-ethoxy-3-iminopropionate hydrochloride and a nitroaniline in methanol producing an imidate ester. The imidate ester is then reacted with an arylhydrazine forming an amidine. The amidine is then cyclized with base.

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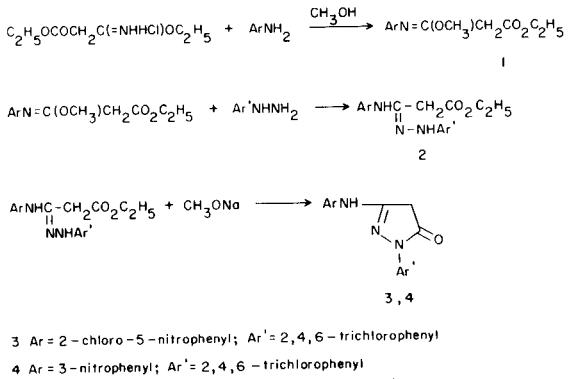
A key intermediate in the synthesis of dyes and magenta color formers (1) for photographic systems is 1-(2,4,6,-trichlorophenyl)-3-(2-chloro-5-nitroanilino)-5-pyrazolone. This intermediate and other nitrosubstituted anilino pyrazolones are very difficult to prepare by conventional means.

Anilinopyrazolones have historically been synthesized by condensation of 3-ethoxy-5-pyrazolones or 3-amino-5-pyrazolones with aniline liberating ethanol (2) or ammonia (3). These systems work poorly or not at all when electron-withdrawing groups are present on the aniline moeity.

Another method, the Smiles rearrangement, has been used to prepare 3-(*o*- and *p*-nitroanilino)-5-pyrazolones by the deacylation of the corresponding nitrophenoxyacetamido derivative (4). The *m*-nitrophenoxyacetamido derivative, however, does not rearrange. Reaction of malonic ester monoanilides with phosphorous pentachloride producing 3-chloro-3-arylaminoacrylic acid esters followed by condensation with arylhydrazines produced anilinopyrazolones (5). The latter, a multi-step sequence, is characterized by low conversions and resinous by-products.

A simple ingenious procedure for preparation of the desired nitrosubstituted anilinopyrazolones is exemplified by the following sequence of reactions.



The above sequence results in overall yields as high as 65%. While the intermediates can be isolated, high purity pyrazolones can be obtained without isolation of any intermediates in a one flask operation. The first reaction is critical involving the reaction of a substituted aniline, ethyl 3-ethoxy-3-imino-propionate hydrochloride (15 to 66 mole percent excess) and anhydrous methanol in toluene (6).

The reaction is driven to completion by distilling off methanol. Toluene insures good agitation as the methanol is distilled and allows the pot temperature to reach 110° forcing the equilibrium to the imidate ester **1**. The ammonium chloride by-product is and must be filtered at this point. The arylhydrazine is condensed with the imidate ester producing the amidine **2**. The amidine **2** was isolated and characterized by nmr, ir and elemental analysis. The ir showed amine and ester absorption, the nmr exhibited methylene abosrption as well as ethyl ester protons. The amidine is then cyclized by base to the pyrazolone **3** and **4**.

The reaction sequence must be followed exactly, addition of the hydrazine followed by the aniline derivative failed to produce a pyrazolone. Addition of acetic acid or phenol with the trichlorophenylhydrazine resulted in lower yields.

EXPERIMENTAL

Nuclear magnetic resonance spectra (nmr) were recorded on Varian A-60 spectrometer and tetramethylsilane was used as an internal standard. Infrared spectra were recorded using a Beckamn IR-10 spectrometer. Melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Reagents.

Ethyl 3-ethoxy-3-iminopropionate hydrochloride was made by the procedure of S. A. Glickman and A. C. Cope (7). Trichlorophenylhydrazine and nitrochloroaniline were purchased from Eastman Kodak and Gallard Schlessinger.

1-(2,4,6-Trichlorophenyl)-3-(2-chloro-5-nitroanilino)-5-pyrazolone (**3**).

Ethyl 3-ethoxy-3-iminopropionate hydrochloride (730 g., 3.74 moles), and 2-chloro-5-nitroaniline (386 g., 2.24 moles), anhydrous methanol (2500 ml.) and toluene (500 ml.) were allowed to react for 16 hours at room temperature. Methanol was distilled off at atmospheric pressure to a pot temperature of 110°. The reaction mixture was held 0.5 hr. at 110°. After cooling to room temperature and filtering the ammonium chloride, the filter cake is washed with cold (15 to 20°) methanol (500 ml.). Additional methanol (2000 ml.) and 2,4,6-trichlorophenylhydrazine (470.0 g., 2.24 mole) was added to the filtrate. The reaction mixture was refluxed

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16 hours. After cooling to room temperature, 25% methanolic sodium methoxide solution (484 g., 2.24 mole) was added over a 0.5 hour period. The solution was refluxed 1 hour, cooled to room temperature and neutralized to *p*H 7 with glacial acetic acid. The precipitated pyrazolone was filtered and purified by reslurrying in methanol (2500 ml.) giving 628 g. (65%) of yellow solid, m.p. 274-278° (lit. (2) m.p. 274-276°); ir (mull): 1715 cm^{-1} (C=O); nmr (deuterochloroform): δ 7.6-7.9 (m, s, aromatic H), 5.5 (s, 1, N-H), 4.0 (s, 2, C-CH_2CO).

Anal. Calcd. for $C_{15}H_8N_4O_3Cl_4$: C, 41.50; H, 1.85; N, 12.91; Cl, 32.67. Found: C, 41.33; H, 2.02; N, 13.05; Cl, 32.62.

1-(2,4,6-Trichlorophenyl)-3-(3-nitroanilino)-5-pyrazolone (**4**).

Ethyl 3-ethoxy-3-iminopropionate hydrochloride (146.0 g., 0.75 mole), 3-nitroaniline (62.0 g., 0.45 mole) and anhydrous methanol (600 ml.) were reacted for 16 hours at room temperature. Methanol was distilled off to a pot temperatue of 100°. After cooling to room temperature and filtering the ammonium chloride, the cake was washed with chilled methanol (100 ml.). Additional methanol (500 ml.) and 2,4,6-trichlorophenylhydrazine (94.5 g., 0.45 mole) was added to the filtrate. The reaction mixture was refluxed 16 hours. After cooling to room temperature, 25% methanolic sodium methoxide (96.8 g., 0.45 mole) was added over a 0.5 hour period. The solution was refluxed 1 hour, cooled to room temperature and neutralized to *p*H 7 with glacial acetic acid. The pyrazolone was isolated in 33% yield (59.0 g.), m.p. 252-256° (lit. (5) m.p. 250°; ir (mull): 3360 cm^{-1} (NH), 1710 cm^{-1} (C=O), 1350 cm^{-1} (NO_2).

Anal. Calcd. $C_{15}H_9N_4O_3Cl_3$: C, 45.08; H, 2.27; N, 14.02; Cl, 26.62. Found: C, 44.70; H, 2.48; N, 14.36; Cl, 26.25.

Ethyl 1-(2,4,6-Trichlorophenylhydrazono)-3-(2-chloro-5-nitroanilino)propionate (**2**).

Ethyl 3-ethoxy-3-iminopropionate hydrochloride (97.0 g., 0.5 mole), 2-chloro-5-nitroaniline (51.5 g., 0.3 mole) and anhydrous methanol (500 ml.) were allowed to react 16 hours at room temperature. methanol was distilled off to a pot temperature of 105°. The ammonium chloride filtered and the cake washed with methanol (100 ml.). Methanol (400 ml.) and 2,4,6-trichlorophenylhydrazine (58.6 g., 0.28 mole) added to the filtrate and the mixture refluxed 16 hours. The reaction mixture cooled to 10 to 15° and the yellow solid filtered yielding 76.6 g. (53% of theory). The material was recrystallized from acetonitrile, m.p. 121-124°; ir (mull): 1735 cm^{-1} (ester), 3370 and 3300 cm^{-1} (amine); nmr (deuterochloroform): δ 7.9-7.0 (m, 5, aromatic H), 4.2 (q, 2, J = 6 Hz, O-CH_2-CH_3), 3.8 (s, 2, O=C-CH_2-C), 1.3 (t, 3, J = 6 Hz, CH_2CH_3).

Anal. Calcd. for $C_{17}H_{14}N_4O_4Cl_4$: C, 42.52, H, 2.94; N, 11.67, Cl, 29.53. Found: C, 42.52; H, 2.94; N, 11.59; Cl, 29.40.

REFERENCES AND NOTES

(1) Gregory J. Lestina, U. S. Patent 3,519,429 (1970); see also D. J. Tracy and W. Hoffstadt, U. S. Patents 4,113,954, 4,129,739 and 4,138,571.

(2) J. R. Abbott and W. F. Coffey, U. S. Patent 3,615,506 (1971).

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(5) C. A. Maggiulli and R. E. Paine, U. S. Patent 3,254,108 (1966).

(6) D. J. Tracy, *J. Heterocyclic Chem.*, accepted for publication.

(7) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).