A New Route for the Preparation of Pyrazolo[3,4-c]pyridines

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Catalytic reduction of the oximes of 4-phenacyl-3(5)R-pyrazole-4-carboxylic acid esters (**4a,b**) followed by cyclisation constitutes a new appraoch to substituted pyrazolo[3,4-c]pyridines. The starting materials **4a,b** were prepared by reaction of ω-bromoacetophenone oxime and sodium salts of oxalyl derivatives **2a,b** and successive action of hydrazine on the obtained products **3a,b**. Structural assignments rested upon correct elemental analysis and spectroscopic evidences.

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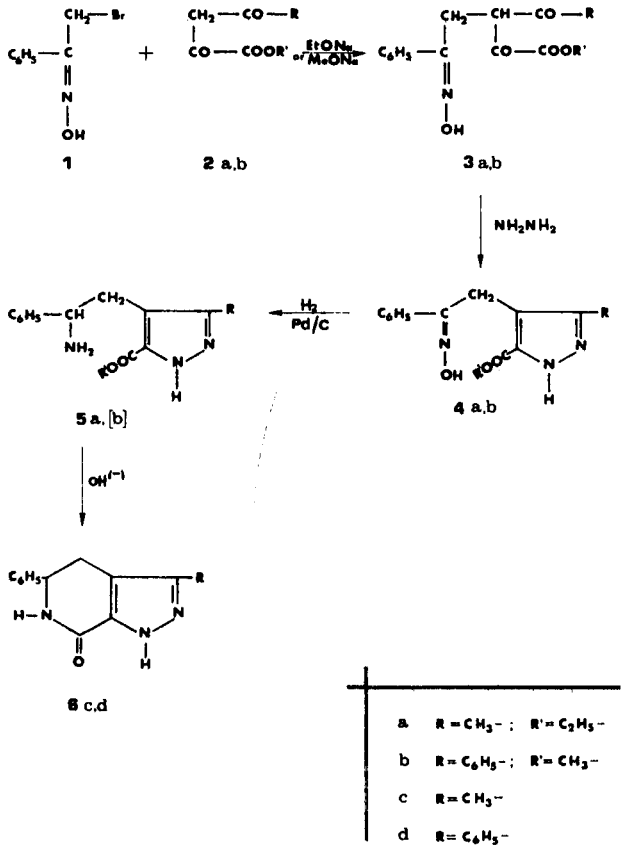
The literature contains many references to the preparation of pyrazolo[3,4-c]pyridines from pyridine derivatives (1-11). The intramolecular cyclisation of 3(2,2-diethoxyethyl)iminomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one is the only example recorded of the preparation of pyrazolo[3,4-c]pyridines starting from a pyrazole derivative (12). In view of the current interest in the biological activity of pyrazolopyridine derivatives, we wish to describe a general procedure for preparation of pyrazolo[3,4-c]pyridine derivatives, which are outlined in Scheme I.

SCHEME I



The compounds **3a,b**, obtained by action of **1** on sodium salts of **2a,b**, treated with hydrazine afforded the pyrazole derivatives **4a,b** in good yield (Scheme I). The structural assignments were based upon correct elemental data, molecular weights, determined by mass spectroscopy and spectral data (ir, nmr).

In fact, in the ir spectra of these compounds there are observed broadened absorptions for the OH and NH stretching frequencies. The nmr spectra showed, besides the expected signals of substituents a singlet at 3.50-3.80 δ attributable at CH_2 group, a broad signal at 11.40-11.50 δ (1H, OH) and at 13.10-13.70 δ (1H, pyrazolic NH) (13), which disappeared upon the addition of deuterium oxide.

Catalytic hydrogenation of **4a** with palladium on charcoal gave the amino derivative **5a**, whose nmr spectrum showed the characteristic absorption at 8.60 δ due to the amino group, exchangeable with deuterium oxide. Moreover, the ir spectrum exhibited strong absorption bands at 3520, 3350 and 3150 cm^{-1} attributable to NH_2 and pyrazole NH groups.

The product obtained by reduction of **4b** was an uncrystallizable material which was not isolated, but directly cyclized into **6d** in the same manner as for **5a**.

The spectroscopic data (ir, nmr) of the bicyclic system **6c,d** indicated that these compounds existed predominantly in the keto form. In fact, the ir spectra showed in addition to the broadened NH absorption bands in the 3μ region, a strong carbonyl band at 1680 cm^{-1}. The nmr spectra showed a very complex pattern of signals for the methylene and methynic groups and two broad resonances at the chemical shifts expected for the amidic and pyrazolic NH groups, exchangeable with deuterium oxide (see Experimental).

EXPERIMENTAL

Melting points were taken on a Buchi-Totoli apparatus and are uncorrected. Ir spectra were determined in nujol mulls with a Perkin-Elmer Infracord 137 spectrophotometer. The nmr spectra (DMSO-d_6) were obtained, using TMS as the internal standard,

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with a Jeol C-60H spectrometer. The mass spectra were measured with a Jeol JMS-01SG-2 double focusing spectrometer at 75 eV (100 μA). Exact mass measurement were performed on Ilford Q-2 photoplates; perfluorokerosene was used as a reference at resolving power better than 15000.

General Procedure for the Preparation of **3a,b** Derivatives.

To a stirred and cooled (0°) suspension of sodium salts of oxalyl derivatives **2a,b**, (obtained from 0.01 mole of sodium, 100 ml. of absolute ethanol (14) and 0.01 mole of **2a** (15) or **2b** (16)), ω-bromoacetophenone oxime (**1**) (0.01 mole) was added in small portions over a period of 15 minutes. After adding, the mixture was stirred at room temperature for 2-3 hours, then kept in the refrigerator overnight. The reaction product, precipitated directly from the reaction mixture was filtered, washed with ice-water, ether and dried (yield 80%).

Ethyl 2,4-Dioxo-3-phenacylvalerate-3-oxime (**3a**).

This compound had m.p. 140° (ethanol); ir: cm^{-1} 3300-3100 (OH, broad), 1760 and 1730 (CO).

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.80; H, 5.87; N, 4.75.

Methyl 3,4-Dibenzoyl-2-oxobutyrate-4-oxime (**3b**).

This compound had m.p. 160° (ethanol); ir: cm^{-1} 3300-3100 (OH, broad), 1770 and 1680 (CO).

Anal. Calcd. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.27; H, 5.06; N, 4.11.

General Procedure for the Preparation of **4a,b** Derivatives.

To a solution of **3a,b** (10 mmoles) in ethanol (17) (40 ml.), 15 mmoles of hydrazine hydrate were added. After refluxing for 12 hours, the solution was concentrated to small volume to give a product, which was recrystallized (yield 70-75%).

Oxime of 4-Phenacyl-3(5)methyl-5(3)carbethoxypyrazole (**4a**).

This compound had m.p. 190° (ethanol); ir: cm^{-1} 3300-3100 (NH and OH, broad); nmr: δ 1.30 (3H, t, CH_3-CH_2, J ≅ 6.0 Hz), 2.05 (3H, s, CH_3), 3.50 (2H, s, CH_2), 4.25 (2H, q, CH_3-CH_2, J ≅ 6.0 Hz), 7.20-7.70 (5H, m, C_6H_5), 11.50 (1H, s, OH, exchangeable with deuterium oxide), 13.10 (1H, broad, NH pyrazole, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.75; H, 5.96; N, 14.65.

Oxime of 4-Phenacyl-3(5)phenyl-5(3)carbomethoxypyrazole (**4b**).

This compound had m.p. 210° (ethanol); ir: cm^{-1} 3300-3050 (NH and OH, broad), 1700 (CO); nmr: δ 3.80 (3H, s, CH_3), 4.40 (2H, s, CH_2), 6.90-7.60 (10H, m, 2 x C_6H_5), 11.40 (1H, s, OH, exchangeable with deuterium oxide), 13.70 (1H, broad, NH pyrazole, exchangeable with deuterium oxide).

Exact mass measurement: Calcd. for $C_{19}H_{17}N_3O_3$: 335.125. Found: 335.125 (± 0.003).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.93; H, 5.20; N, 12.65.

Hydrogenation of **4a**. 4-(2′-Phenylethyl-2′-amino)-3(5)methyl-5(3)carbethoxypyrazole (**5a**).

To a solution of 2.5 mmoles of **4a** in ethanol (100 ml.), 150 mg. of 10% palladium on charcoal were added. The mixture was hydrogenated in a Parr apparatus at 45-50 psi, maintaining the temperature at 20°. After 24 hours the solution was filtered off and evaporated to dryness. The residue was triturated with ethanol to give a solid product, m.p. 150° (ethanol); ir: cm^{-1} 3520, 3350 and 3150 (NH_2 and NH), 1700 (CO); nmr: δ 1.30 (3H, t, CH_3-CH_2, J ≅ 7.0 Hz), 1.90 (3H, s, CH_3), 3.30 (2H, m, CH_2), 4.10-4.50 (3H, m, CH_3-CH_2 and CH), 7.20-7.50 (5H, m, C_6H_5), 8.60 (2H, broad, NH_2, exchangeable with deuterium oxide), 12.75 (1H, broad, NH pyrazole, exchangeable with deuterium oxide).

Exact mass measurement: Calcd. for $C_{15}H_{19}N_3O_2$: 273.147. Found: 273.145.

Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.87; H, 7.12; N, 15.32.

3-Methyl-5-phenyl-1*H*-4,5,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-7(6*H*)one (**6c**).

A suspension of 2.5 mmoles of **5a** in aqueous potassium hydroxide (10 mmoles in 10 ml. of water) was stirred at room temperature. The compound readily dissolved and after some minutes a precipitate was obtained, which was collected and then treated with aqueous hydrochloric acid (10%). After stirring for 30 minutes the solid precipitated was filtered off and recrystallized, m.p. 275° (ethanol); ir: cm^{-1} 3200-3050 (NH, broad), 1680 (CO); nmr: δ 2.10 (3H, s, CH_3), 2.70-3.00 (2H, m, CH_2), 4.50-5.00 (1H, m, CH), 7.10-7.50 (5H, m, C_6H_5), 7.70 (1H, broad, NH, exchangeable with deuterium oxide), 13.00 (1H, broad, NH pyrazole, exchangeable with deuterium oxide).

Exact mass measurement: Calcd. for $C_{13}H_{13}N_3O$: 227.106. Found: 227.106 (± 0.003).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.67; H, 5.90; N, 18.57.

Hydrogenation of **4b**. 3,5-Diphenyl-1*H*-4,5,6,7-tetrahydropyrazolo-[3,4-*c*]pyridin-7(6*H*)one (**6d**).

Compound **4b** (2.5 mmoles) was hydrogenated by the above method described for **4a**, maintaining the temperature at 40°. The residue was an intractable material which was directly cyclized in the same manner as **5a**, m.p. 250° (ethanol); ir: cm^{-1} 3200-3080 (broad, NH), 1680 (CO); nmr: δ 3.10-3.50 (2H, m, CH_2), 4.70-5.10 (1H, m, CH), 7.20-7.70 (10H, m, 2 x C_6H_5), 8.20 (1H, broad, NH, exchangeable with deuterium oxide), 13.60 (1H, broad, NH pyrazole, exchangeable with deuterium oxide).

Exact mass measurement: Calcd. for $C_{18}H_{15}N_3O$: 289.121. Found: 289.121 (± 0.002).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.67; H, 5.34; N, 14.61.

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