A New Efficient Route to Imidazo[4,5-*c*]pyrazol-5-ones

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Dedicated to Professor Mario Guarneri on the occasion of his 75th birthday

The synthesis of imidazo[4,5-*c*]pyrazol-5-ones (**6**) is reported. 5-Amino-4-ethoxycarbonylaminopyrazoles **3a-g** when heated at 200° for 2 hours afford **6a-g**. In a similar manner imidazo[4,5-*c*]pyrazol-5-one (**6a**) is readily obtained from 4-amino-5-ethoxycarbonylaminopyrazole (**5a**).

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Within the framework of investigation on biologically active heterocycles, we found that imidazo[4,5-*c*]pyrazoles are interesting for their biological properties as agrochemicals [1] and pharmacological agents [2]. Due to the difficulties in obtaining this heterocyclic system [3], the synthetic entries available up to now in the literature are very few and the known methods have limited applications [4]. In previous researches in this area, we proved that the intramolecular cyclodehydration of 5-alkylamino-4-nitrosopyrazoles constitutes an efficient method for the synthesis of 5-substituted imidazo[4,5-*c*]pyrazoles [5]. The cyclization of 4- or 5-isothiocyanatopyrazoles gave imidazo[4,5-*c*]pyrazole-5-thiones selectively substituted in position 4 and 6 [6,7]. Other derivatives, bearing a dimethylamino group in the 5 position were obtained through a Vilsmeier-type reaction [7].

Continuing the search for biological activity optimization, we became interested in the synthesis of imidazo-[4,5-*c*]pyrazol-5-ones. The only reported compound, 1-phenylimidazo[4,5-*c*]pyrazol-5-one, was obtained *via* the Curtius rearrangement followed by cyclization of 5-amino-4-pyrazolecarbonyl azide [4a]. Thus we decided to investigate an alternative procedure, depicted in the Scheme. The key intermediates to the target products were 5-amino-4-ethoxycarbonylaminopyrazoles **3** or 4-amino-5-ethoxycarbonylaminopyrazole (**5**).

Compounds **3** were prepared from the corresponding nitrosopyrazolylamines **1a-g**, which were reduced with hydrazine hydrate in the presence of palladized charcoal to the diamines **2a-g**. Since **2** were often unstable during the usual workup for isolation, they were directly reacted with ethyl chloroformate to give 5-amino-4-ethoxycarbonylaminopyrazoles **3a-g**. These compounds were heated at 200° for 2 hours to afford imidazo[4,5-*c*]pyrazol-5-ones **6a-g**.

In the alternative route, compound **4a**, prepared according to the literature method [8a] from 5-amino-3-methyl-4-nitroso-1-phenylpyrazole (**1a**), afforded by reduction with hydrazine hydrate in the presence of palladized charcoal the intermediate 4-amino-5-ethoxycarbonylaminopyrazole (**5a**), which was heated at 200° for 2 hours to give **6a**.

As previously found in our laboratory [9], the *N*1-*tert*-butyl group of the pyrazole moiety is cleavable in acidic medium; in the present study, 1-*tert*-butylimidazo[4,5-*c*]pyrazol-5-one (**6g**) when heated under reflux in formic acid gave the dealkylated homologue **6h**.

The structure of compounds **6** was confirmed by comparison of the ir spectrum of **6b** with the ir spectrum of the known 1-phenylimidazo[4,5-*c*]pyrazol-5-one, prepared according to the literature method [4a] *via* the Curtius rearrangement followed by cyclization of 5-amino-4-pyrazolecarbonyl azide.

The infrared spectra in potassium bromide of all compounds are characterized by absorptions at *ca* 3300, 1680, 1550 and 1260 cm^{-1}. Due to the very low solubility of compounds **6** the ^1H nmr spectra were carried out in DMSO-d_6 or trifluoroacetic acid as solvents. However, differences were observed between the spectra obtained in the two solvents. For instance compound **6a** shows a broad absorption for the methyl group at 2.2 ppm in DMSO-d_6, while three absorption at 2.34, 2.46 and 2.50 ppm are detected in trifluoroacetic acid. These patterns can be explained by the presence of tautomeric species in solution depending on the solvent.

The biological tests for the new compounds are in progress.

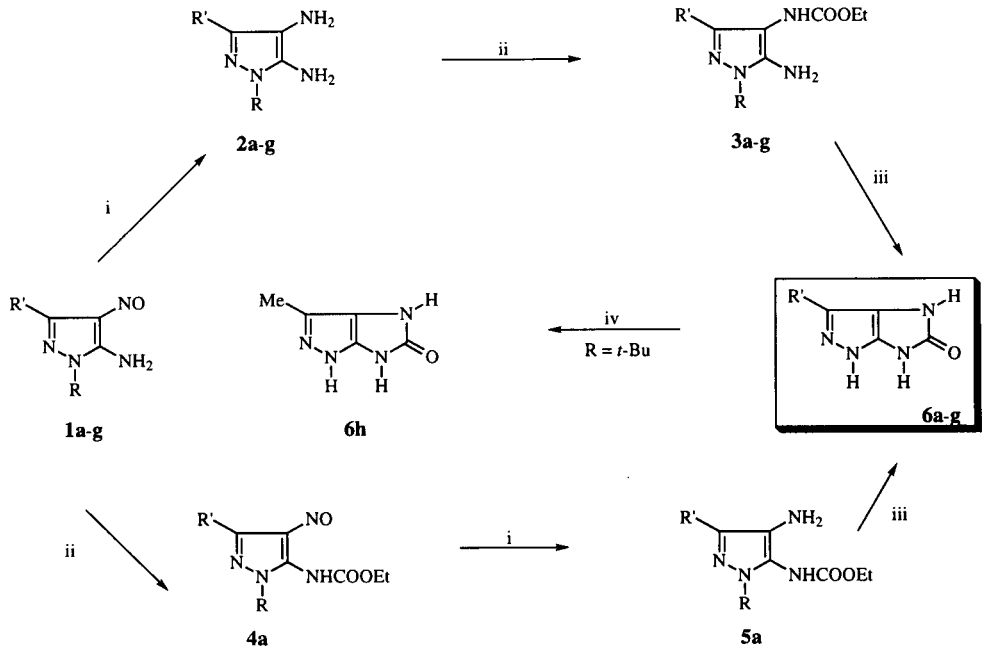
EXPERIMENTAL

Melting points were determined with a Kofler apparatus. The ir spectra were recorded on a Perkin-Elmer 299B spectrophotometer. The ^1H nmr spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Compounds **1a** [8b], **1c** [8c], **1d,e** [8d], **1f** [8e], **1g** [8f] and **4a** [8a] were prepared according to the literature methods.

5-Amino-4-nitroso-1-phenylpyrazole (**1b**).

Gaseous ethyl nitrite was bubbled through a saturated solution of 5-amino-1-phenylpyrazole [8g] (1.59 g, 10 mmoles) in

Scheme



a: R = Ph, R' = Me; **b**: R = Ph, R' = H; **c**: R = Ph, R' = Ph; **d**: R = *p*-ClPh, R' = Me; **e**: R = *m*-ClPh, R' = Me; **f**: R = Me, R' = Me; **g**: R = *t*-Bu, R' = Me

Reagents: i, 5% C/Pd, N_2H_4; ii, ClCOOEt; iii, heat at 200°, 2 hours; iv, HCOOH, reflux

ethanol for 10 minutes then a few drops of concentrated hydrochloric acid was added and the ethyl nitrite bubbling was continued for 30 minutes. The red precipitate was collected and recrystallized from ethyl acetate/petroleum ether as orange crystals, 1.51 g, yield 80%, mp 147-148° (benzene); ir (potassium bromide): 3420, 3020, 1660, 1500, 1450 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.54-7.58 (m, 5H, Ph), 8.6-10.0 (br, 3H, CH+NH_2).

Anal. Calcd. for $C_9H_8N_4O$: C, 57.44; H, 4.28; N, 29.77. Found: C, 57.6; H, 4.3; N, 29.7.

5-Amino-4-ethoxycarbonylaminopyrazoles **3a-g**.

General Procedure.

Hydrazine hydrate (99%, 0.98 ml, 20 mmoles) and 5% palladized charcoal (0.30 g) were added to a solution of the appropriate 5-amino-4-nitrosopyrazole **1** (4 mmoles) in methanol (50 ml). After heating under reflux for 5 minutes, the catalyst was removed and the filtrate was evaporated to dryness *in vacuo*. The solid was collected, washed with ethyl ether and directly reacted with ethyl chloroformate as follows. Ethyl chloroformate (0.95 ml, 10 mmoles) in ethyl acetate (10 ml) and sodium hydrogen carbonate (0.84 g, 10 mmoles) in water (20 ml) were simultaneously added to a vigorously stirred solution of the appropriate 4,5-diaminopyrazole **2** (10 mmoles) in ethyl acetate (80 ml). After 2 hours the organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated to dryness.

5-Amino-4-ethoxycarbonylamino-3-methyl-1-phenylpyrazole (**3a**).

Colorless crystals were obtained, 2.55 g, yield 98%, mp 37-38° (ligroine); ir (potassium bromide): 3350 br, 1730, 1650, 1530; ^1H nmr (deuteriochloroform): δ 1.30 (t, J = 7.1 Hz, 3H, Me), 2.16 (s, 1H, Me), 4.01 (s, 2H, NH_2), 4.20 (q, J = 7.1 Hz, 2H, CH_2), 6.10 (s, 1H, NH), 7.27-7.54 (m, 5H, Ph).

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.8; H, 6.2; N, 21.4.

5-Amino-4-ethoxycarbonylamino-1-phenylpyrazole (**3b**).

This compound was obtained as an oil, 1.98 g, yield 80%; ir (neat): 3330, 1730, 1640, 1520; ^1H nmr (deuteriochloroform): δ 1.28 (t, J = 7.0 Hz, 3H), 3.59 (br, 2H, NH_2), 4.21 (q, J = 7.0 Hz, 2H, CH_2), 6.34 (s, 1H, NH), 7.26-7.55 (m, 6H, Ph + CH).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.4; H, 5.7; N, 22.6.

5-Amino-1,3-diphenyl-4-ethoxycarbonylaminopyrazole (**3c**).

This compound was obtained as colorless crystals, 2.62 g, yield 81%, mp 120-122° (ethyl ether/petroleum ether); ir (potassium bromide): 3330 br, 1720, 1650, 1510 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7.0 Hz, Me), 4.11-4.28 (m, 4H, CH_2+NH_2), 6.26 (s, 1H, NH), 7.34-7.80 (m, 10H, 2Ph).

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 67.0; H, 5.6; N, 17.4.

5-Amino-1-(4-chlorophenyl)-4-ethoxycarbonylamino-3-methylpyrazole (**3d**).

This compound was obtained as colorless crystals, 2.36 g, yield 80%, mp 108-110° (ethyl ether/petroleum ether); ir (potas-

sium bromide): 3420, 3300 br, 1710, 1640, 1510 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7.1 Hz, 3H, Me), 2.15 (s, 3H, Me), 3.99 (br, 2H, NH_2), 4.18 (q, J = 7.1 Hz, 2H, CH_2), 6.03 (s, 1H, NH), 7.30-7.52 (m, 4H, Ph).

Anal. Calcd. for $C_{13}H_{15}ClN_4O_2$: C, 52.98; H, 5.13; Cl, 12.03; N, 19.01. Found: C, 53.0; H, 5.1; Cl, 11.9; N, 18.9.

5-Amino-1-(3-chlorophenyl)-4-ethoxycarbonylamino-3-methylpyrazole (**3e**).

This compound was obtained as an oil, 2.24 g, yield 76%; ir (neat): 3310 br, 1730, 1630, 1520 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7.0 Hz, 3H, Me), 2.17 (s, 3H, Me), 4.06 (br, 2H, NH_2), 4.19 (q, J = 7.0 Hz, 2H, CH_2), 6.00 (s, 1H, NH), 7.26-7.59 (m, 4H, Ph).

Anal. Calcd. for $C_{13}H_{15}ClN_4O_2$: C, 52.98; H, 5.13; Cl, 12.03; N, 19.01. Found: C, 52.8; H, 5.2; Cl, 12.1; N, 19.1.

5-Amino-1,3-dimethyl-4-ethoxycarbonylaminopyrazole (**3f**).

This compound was obtained as colorless crystals, 1.01 g, yield 51%, mp 105-107° (ethyl ether/petroleum ether); ir (potassium bromide): 3420, 3380, 3250, 1700, 1640, 1540 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7.1 Hz, 3H, Me), 2.07 (s, 3H, Me), 3.56 (s, 3H, NMe), 3.72 (br, 2H, NH_2), 4.18 (q, J = 7.1 Hz, 2H, CH_2), 6.04 (s, 1H, NH).

Anal. Calcd. for $C_8H_{14}N_4O_2$: C, 48.47; H, 7.12; N, 28.26. Found: C, 48.4; H, 7.1; N, 28.3.

5-Amino-1-*tert*-butyl-4-ethoxycarbonylamino-3-methylpyrazole (**3g**).

This compound was obtained as colorless crystals, 1.78 g, yield 74%, mp 78-80° (ethyl ether/hexane); ir (potassium bromide): 3410, 3360, 1740, 1710, 1650, 1510 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, J = 7.1 Hz, 3H, Me), 1.59 (s, 9H, *t*-Bu), 2.07 (s, 3H, Me), 3.66 (br, 2H, NH_2), 4.17 (q, J = 7.1 Hz, 2H, CH_2), 5.85 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{20}N_4O_2$: C, 54.98; H, 8.39; N, 23.31. Found: C, 55.1; H, 8.4; N, 23.4.

4-Amino-5-ethoxycarbonylamino-3-methyl-1-phenylpyrazole (**5a**).

Hydrazine hydrate (99%, 0.98 ml, 20 mmoles) and 5% palladized charcoal (0.30 g) were added to a solution of 5-ethoxycarbonylamino-3-methyl-4-nitroso-1-phenylpyrazole (**4a**) [8a] (1.09 g, 4 mmoles) in methanol (50 ml). After heating under reflux for 5 minutes, the catalyst was removed and the filtrate was evaporated to dryness *in vacuo,* colorless crystals, 0.48 g, yield 46%, mp 120-121° (water); ir (potassium bromide): 3410, 3340, 3200, 1710, 1630, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.24 (br, 3H, Me), 2.22 (s, 3H, Me), 2.90 (br, 2H, NH_2), 4.17 (q, J = 6.8 Hz, 2H, CH_2), 6.57 (br, 1H, NH), 7.27-7.41 (m, 5H, Ph).

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.9; H, 6.3; N, 21.4.

Imidazo[4,5-*c*]pyrazol-5-ones **6a-g**.

General Procedure.

The appropriate 5-amino-4-ethoxycarbonylaminopyrazole (**3**) or 4-amino-5-ethoxycarbonylamino-3-methyl-1-phenylpyrazole (**5a**) (1 mmole) was heated at 200° for 2 hours. The solid was collected and washed with ethyl ether.

3-Methyl-1-phenylmidazo[4,5-*c*]pyrazol-5-one (**6a**).

This compound was obtained as colorless crystals, 0.13 g, yield 62% from **3a** or 1.10 g, yield 51% from **5a**, mp >350° (methanol); ir (potassium bromide): 3300 br, 1680, 1630, 1560, 1270 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.2 (br, 3H, Me), 7.43-7.56 (m, 5H, Ph), 8.0-9.0 (br, 2H, 2NH); ^1H nmr (trifluoroacetic acid): δ three species are present in about 1:1:1 ratio 2.34 (s), 2.46 (s), 2.50 (s) (3H, Me), 7.25-7.79 (m, 5H, Ph), 8.0-9.0 (br, 2H, NH or OH).

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.5; H, 4.8; N, 26.1.

1-Phenylmidazo[4,5-*c*]pyrazol-5-one (**6b**).

The compound was obtained as colorless crystals, 0.16 g, yield 80%, mp 290° (methanol); ir (potassium bromide): 3300 br, 1670, 1630, 1580, 1510, 1260 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.40-7.70 (m, 5H, Ph), 8.0-9.0 (br, 2H, 2NH).

Anal. Calcd. for $C_{10}H_8N_4O$: C, 60.00; H, 4.03; N, 27.99. Found: C, 59.9; H, 4.1; N, 27.9.

1,3-Diphenylmidazo[4,5-*c*]pyrazol-5-one (**6c**).

This compound was obtained as colorless crystals, 0.19 g, yield 69%, mp >350° (methanol); ir (potassium bromide): 3300 br, 1670, 1630, 1510, 1270 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 7.0-7.6 (m, 10H, 2Ph), 7.0-8.5 (br, 2H, 2NH).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.4; H, 4.4; N, 20.2.

1-(4-Chlorophenyl)-3-methylmidazo[4,5-*c*]pyrazol-5-one (**6d**).

This compound was obtained as colorless crystals, 0.18 g, yield 72%, mp >350° (methanol); ir (potassium bromide): 3300 br, 1660, 1630, 1510, 1260 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ three species are present in about 1:1:1 ratio 2.28 (s), 2.35 (s), 2.47 (s) (3H, Me), 7.2-7.6 (m, 4H, Ph), 8.0-9.0 (br, 2H, NH or OH).

Anal. Calcd. for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; Cl, 14.26; N, 22.53. Found: C, 53.0; H, 3.7; Cl, 14.2; N, 22.5.

1-(3-Chlorophenyl)-3-methylimidazo[4,5-*c*]pyrazol-5-one (**6e**).

This compound was obtained as colorless crystals, 0.20 g, yield 80%, mp >350° (washed with ethyl ether); ir (potassium bromide): 3300 br, 1660, 1630, 1550, 1510, 1260 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ three species are present in about 1:1:1 ratio 2.30 (s), 2.40 (s), 2.43 (s) (3H, Me), 7.1-7.6 (4H, Ph), 8.0-9.0 (br, 2H, NH or OH).

Anal. Calcd. for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; Cl, 14.26; N, 22.53. Found: C, 53.1; H, 3.7; Cl, 14.1; N, 22.4.

1,3-Dimethylimidazo[4,5-*c*]pyrazol-5-one (**6f**).

This compound was obtained as colorless crystals, 0.10 g, yield 66%, mp >350° (methanol); ir (potassium bromide): 3300 br, 1660, 1620, 1260 cm^{-1}; ^1H nmr (DMSO-d_6): δ three species are present in about 1:1:1 ratio 1.89 (s), 1.98 (s), 2.01 (s) (3H, Me), 3.31 (s), 3.41 (s), 3.57 (s) (3H, NMe), 7.5-8.5 (br, 2H, NH or OH).

Anal. Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.3; H, 5.4; N, 36.7.

1-*tert*-Butyl-3-methylimidazo[4,5-*c*]pyrazol-5-one (**6g**).

This compound was obtained as colorless crystals, 0.05 g, yield 25%, mp >350° (washed with ethyl ether); ir (potassium

bromide): 3300 br, 1690, 1620, 1550, 1260 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 1.71 (s, 9H, *t*-Bu), 2.34 (s, 3H, Me), 7.5-8.5 (br, 2H, 2NH).

Anal. Calcd. for $C_9H_{14}N_4O$: C, 55.65; H, 7.27; N, 28.84. Found: C, 55.5; H, 7.30; N, 28.8.

Cleavage of the *tert*-Butyl Group from **6g**.

3-Methylimidazo[4,5-*c*]pyrazol-5-one (**6h**).

A suspension of **7g** (0.19 g, 1 mmole) in formic acid (5 ml) was heated under reflux for 2 hours. The solution was evaporated to give a solid which was taken up with water (10 ml), colorless crystals, 0.04 g, yield 29%, mp 277-279° (methanol); ir (potassium bromide): 3300 br, 1690, 1570, 1260 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 2.37 (s, 3H, Me), 7.5-8.5 (br, 2H, 2NH).

Anal. Calcd. for $C_5H_6N_4O$: C, 43.48; H, 4.38; N, 40.56. Found: C, 43.3; H, 4.4; N, 40.4.

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