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A NEW GENERAL AND EFFICIENT SYNTHESIS OF IMIDAZO[4,5-*c*]PYRAZOLE DERIVATIVES

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Abstract: A new general and efficient synthesis of imidazo[4,5-c]pyrazoles (5) is reported. The key step of this synthetic procedure is the intramolecular cyclodehydration of 5-alkylamino-4-nitrosopyrazoles (4), which affords the title compounds (5) in good yields.

In recent years we have been studying heterocyclic systems containing the pyrazole ring,[1] mainly because of their biological properties.[2] In the course of our research we have been interested in the synthesis and in the biological activity of imidazo[4,5-*c*]pyrazole derivatives (**5**).[3]

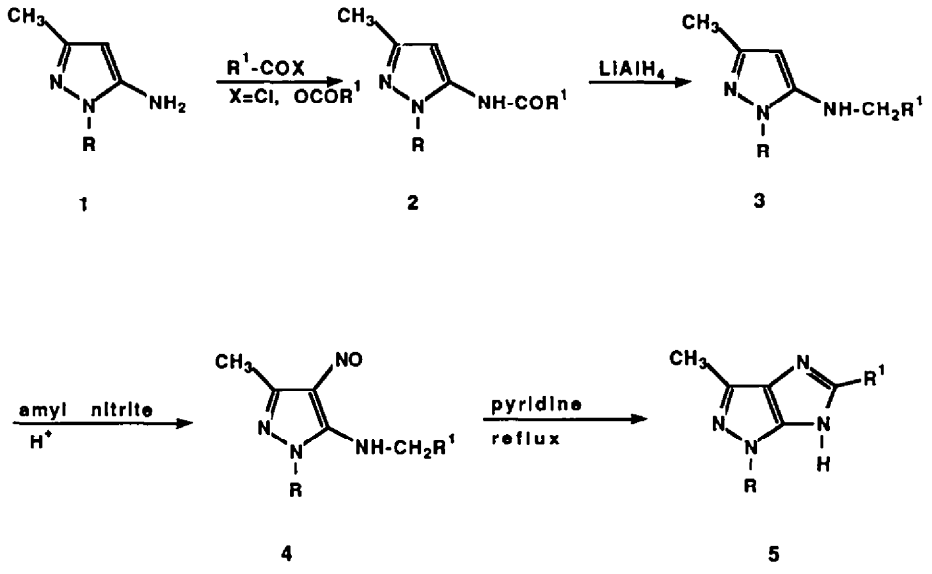
A few examples of synthesis of these compounds have been described but up to now no biological study has been reported. A survey of literature revealed that the synthetic approaches to this class of compounds are restricted to the following: a) the Curtius rearrangement followed by cyclisation of 4-carbonylazido-5-aminopyrazoles,[4] b) the cyclisation of 4-nitro-5-benzylaminopyrazoles,[5] c) the reaction of 4,5-diamino-pyrazoles with carbon disulphide[6] and d) the cycloaddition of diazomethane onto 5-nitroimidazoles.[7]

As none of these synthetic approaches is of general application, we decided to investigate a new general route to the synthesis of the target compounds (**5**).

In the first exploratory attempts, we followed the classical methods used for the purine and benzimidazole synthesis based on the condensation of aromatic *ortho*-diamines with carbonyl compounds. However, our efforts to obtain the ring (**5**) through the reactions of 4,5-diaminopyrazole with formic acid[8] or with dimethylformamide in the presence of $POCl_3$[9] did not afford the desired products. These results agree with the observations by Elguero on the difficulties of obtaining the ring system (**5**) from *ortho*-diaminopyrazoles.[10] Attempts to obtain (**5**) through the reaction of 4-nitroso-5-aminopyrazoles with benzyltrimethylammonium iodide in dimethylformamide, a method used in purine synthesis,[11] did not give the expected heterocycles. Similarly, the reactions of 4-nitroso-5-aminopyrazoles with acylating agents, followed by reduction of the nitroso group and intramolecular cyclisation, also failed to give the system (**5**).

On the other hand, it has been described that the imidazole ring can be obtained from α-alkylimino oximes[12] or α-alkylamino nitroso derivatives[13] through the incorporation into the imidazole ring of the methylene group

linked to nitrogen.Therefore, we decided to investigate the new synthetic route to imidazo[4,5-*c*]pyrazoles (**5**) as outlined in Scheme 1.



For compounds (**2**)-(**5**):

a: R= CH_3, R^1= CH_3; **b**: R= CH_3, R^1= C_6H_5; **c**: R= C_6H_5, R^1= CH_3; **d**: R= C_6H_5, R^1= C_6H_5; **e**: R= 4-ClC_6H_4, R^1= CH_3; **f**: R= 4-ClC_6H_4, R^1= C_6H_5; **g**: R= 3-ClC_6H_4, R^1= CH_3; **h**: R= 3-ClC_6H_4, R^1= C_6H_5; **i**: R= 2-ClC_6H_4, R^1= CH_3; **j**: R= 2-ClC_6H_4, R^1= C_6H_5; **k**: R= 4-FC_6H_4, R^1= CH_3; **l**: R= 4-FC_6H_4, R^1= C_6H_5; **m**: R= 3-FC_6H_4, R^1 = CH_3; **n**: R= 3-FC_6H_4, R^1 = C_6H_5; **o**: R= 2-FC_6H_4, R^1 = CH_3; **p**: R= 2-FC_6H_4, R^1 = C_6H_5.

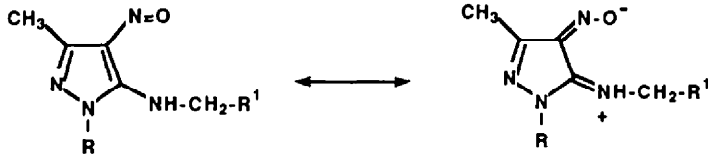
SCHEME 1

Acylation of the 5-aminopyrazoles (**1**) with benzoyl chloride or with acetic anhydride gave the 5-acylaminopyrazoles (**2**). Reduction of compounds (**2**) with $LiAlH_4$ afforded the corresponding 5-alkylaminopyrazoles (**3**). Nitrosation of compounds (**3**) with amyl nitrite in the presence of hydrochloric acid yielded the 5-alkylamino-4-nitrosopyrazoles (**4**). Cyclisation of compounds (**4**) to imidazo[4,5-*c*]pyrazoles (**5**) was achieved by heating (**4**) in boiling pyridine for 15-90 min.

All these reactions gave the desired compounds in good yield. The spectral data of the compounds (**2**)-(**5**) agree with the reported structures. The ^1H NMR spectra showed the disappearance of the methylene group linked to nitrogen after the cyclisation of 5-alkylamino-4-nitrosopyrazoles (**4**) to imidazo[4,5-*c*]pyrazoles (**5**).

This cyclisation can be related to the condensation of nitroso derivatives with acidic methylene groups and in particular to the conversion of 4-alkylamino-5-nitrosouracils into xanthines[13] and of *ortho*-nitroso *t*-anilines into benzoimidazoles[14].

The easy cyclisation observed in the present reaction may be explained by an increased acidity of methylene hydrogens due to the presence of positive nitrogen in mesomer (**4'**). The contribution of (**4'**) to the real structure is likely to be significant, as has been demonstrated for analogous α-nitroso alkylamino derivatives[15].



4 **4'**

Biological tests on the compounds (**5**) are in progress and will be reported in due course.

EXPERIMENTAL SECTION

Melting points were determined on open capillary tubes on a Büchi apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 157G spectrometer. ^{1}H NMR were recorded on a Perkin-Elmer R32 (90 MHz) with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ), and coupling constants (J) are in Hertz. Column chromatography was performed on silica gel Kieselgel 60 Merck (70-230 mesh ASTM).

Procedures for the Preparation of 5-Acylamino-1-alkyl/aryl-3-methylpyrazoles (2a-p).

5-Acetamido-3-methyl-1-phenylpyrazole (2c).

Compound (**2c**) was obtained according to literature[16] by heating at 100°C a mixture of (**1**, R=C_6H_5) (8.66 g, 50 mmol) and acetic anhydride (13 mL): colourless crystals, 8.30 g (77%); mp 108-109°C; IR (KBr) 3250, 1665, 1595, 1570, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H), 2.25 (s, 3H), 6.3 (s, 1H), 7.4 (m, 5H), 7.9 (br, 1H). Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.8; H, 6.1; N, 19.4.

The same procedure was applied for the synthesis of the following compounds:

5-Acetamido-1,3-dimethylpyrazole (2a).

(**2a**) was obtained in 78% yield from (**1**, R=CH_3); mp 46-50°C; IR (KBr) 3230, 1670, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 2.15 (s, 3H), 3.55 (s, 3H), 5.95 (s, 1H), 9.25 (br, 1H). Anal. Calcd. for $C_7H_{11}N_3O$: C, 54.89; H, 7.24; N, 27.43. Found: C, 54.9; H, 7.2; N, 27.4.

5-Acetamido-1-(4-chlorophenyl)-3-methylpyrazole (2e).

(**2e**) was obtained in 83% yield from (**1**, R=4-ClC_6H_4); mp 168-169°C; IR (KBr) 3200, 1665, 1560, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.3 (s, 3H), 6.35 (s, 1H), 7.4-7.5 (A_2B_2, J=9Hz, 4H), 7.7 (br, 1H). Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.6; H,4.7; N, 16.8.

5-Acetamido-1-(3-chlorophenyl)-3-methylpyrazole (2g).

(**2g**) was obtained in 80% yield from (**1**, R=3-ClC_6H_4); mp 103-104°C; IR (KBr) 3200, 1675, 1600, 1545, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (s, 3H), 2.25 (s, 3H), 6.3 (s, 1H) 7.3-7.5 (m, 4H), 7.8 (br, 1H). Anal. Calcd for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.7; H, 4.6; N, 16.8.

5-Acetamido-1-(2-chlorophenyl)-3-methylpyrazole (2i).

(**2i**) was obtained in 83% yield from (**1**, R=2-ClC_6H_4); mp 147-148°C; IR (KBr) 3180, 1655, 1550, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (s, 3H), 2.25 (s, 3H), 6.35 (s, 1H), 7.3-7.7 (m, 5H). Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.8; H, 4.9; N, 16.9.

5-Acetamido-1-(4-fluorophenyl)-3-methylpyrazole (2k).

(**2k**) was obtained in 75% yield from (**1**, R=4-FC_6H_4); mp 165-167°C; IR (KBr) 3260, 1675, 1575, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (s, 3H), 2.24 (s, 3H), 6.29 (s, 1H), 7.05-7.35 (m, 4H), 7.80 (br, 1H). Anal. Calcd. for $C_{12}H_{12}FN_3O$: C, 61.79; H, 5.19; N, 18.02. Found: C, 61.7; H, 5.0; N, 18.2.

5-Acetamido-1-(3-fluorophenyl)-3-methylpyrazole (2m).

(**2m**) was obtained in 79% yield from (**1**, R=3-FC_6H_4); mp 94-95°C; IR (KBr) 3240, 1700, 1615, 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 2.54 (s, 3H), 6.31 (s, 1H), 7.02-7.40 (m, 4H), 7.85 (br, 1H). Anal. Calcd. for $C_{12}H_{12}FN_3O$: C, 61.79; H, 5.19; N, 18.02. Found: C, 61.7; H, 5.1; N, 18.0.

5-Acetamido-1-(2-fluorophenyl)-3-methylpyrazole (2o).

(**2o**) was obtained in 82% yield from (**1**, R=2-FC_6H_4); mp 85-86°C; IR (KBr) 3200, 1680, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (s, 3H), 2.3 (s, 3H), 6.35 (s, 1H), 7.2-7.7 (m, 5H). Anal. Calcd. for $C_{12}H_{12}FN_3O$: C, 61.79; H, 5.19; N, 18.02.Found: C, 61.8; H, 5.2; N, 17.8.

5-Benzamido-3-methyl-1-phenylpyrazole (2d).

A solution of benzoyl chloride (2.3 mL, 20 mmol) in ethyl acetate (50 mL) was added dropwise to a vigorously stirred mixture of (**1**, R=C_6H_5) (3.46 g, 20 mmol) in ethyl acetate (90 mL) and of 0.5N sodium hydrogen carbonate (44 mL). The reaction mixture was heated at 60°C for 4 h. The mixture was cooled and the organic phase was washed with 5% sodium carbonate, water, 1N hydrochloric acid and water. The organic phase was dried over sodium sulphate and evaporated to dryness to give a solid, which was purified by recrystallisation from ethyl acetate-light petroleum: white crystals of (**2d**), 3.78 g, 68% yield, mp 119-121°C (Lit.[17] mp 113°C from benzene and light petroleum), IR (KBr) 3250, 1660, 1600, 1570, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3 (s, 3H), 6.55 (s, 1H), 7.5 (m, 5H), 7.5-7.9 (m, 5H), 8.25 (br, 1H). Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.4; H, 5.5; N, 15.3.

The same procedure was applied for the synthesis of the following compounds:

5-Benzamido-1-(4-chlorophenyl)-3-methylpyrazole (2f).

(**2f**) was obtained in 70% yield from (**1**, R=4-ClC_6H_4); mp 195-196°C; IR (KBr) 3210, 1680, 1655, 1570, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 6.4 (s, 1H), 7.4-7.5 (A_2B_2, J=9Hz, 4H), 7.5-8.0 (m, 5H) 9.3 (br, 1H). Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.5; H, 4.6; N, 13.5.

5-Benzamido-1-(3-chlorophenyl)-3-methylpyrazole (2h).

(**2h**) was obtained in 58% yield from (**1**, R=3-ClC_6H_4); mp 143-145°C; IR (KBr) 3150, 1650, 1600, 1540, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H), 6.45 (s, 1H), 7.3-7.8 (m, 9H), 8.3 (br, 1H). Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.2; H, 4.3; N, 13.4.

5-Benzamido-1-(2-chlorophenyl)-3-methylpyrazole (2j).

(**2j**) was obtained in 56% yield from (**1**, R=2-ClC_6H_4); mp 124-125°C; IR (KBr) 3180, 1685, 1600, 1570, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H), 6.55 (s, 1H), 7.3-7.8 (m, 9H), 7.9 (br, 1H). Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.5; H, 4.7; N, 13.2.

5-Benzamido-1-(4-fluorophenyl)-3-methylpyrazole (2l).

(**2l**) was obtained in 79% yield from (**1**, R=4-FC_6H_4); mp 151-152°C; IR (KBr) 3200, 1655, 1575, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 6.48 (s, 1H), 7.10-7.70 (m, 9H), 8.13 (s, 1H). Anal. Calcd. for $C_{17}H_{14}FN_3O$: C, 69.14; H, 4.78; N, 14.23. Found: C, 68.9; H, 4.7; N, 14.4.

5-Benzamido-1-(3-fluorophenyl)-3-methylpyrazole (2n).

(**2n**) was obtained in 58% yield from (**1**, R=3-FC_6H_4); mp 138-139°C; IR (KBr) 3250, 1655, 1600, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 6.48 (s, 1H), 7.25-7.74 (m, 9H), 8.3 (s, 1H). Anal. Calcd. for $C_{17}H_{14}FN_3O$: C, 69.14; H, 4.78; N, 14.23. Found: 69.0; H, 4.9; N, 14.5.

5-Benzamido-1-(2-fluorophenyl)-3-methylpyrazole (2p).

(**2p**) was obtained in 68% yield from (**1**, R=2-FC_6H_4); mp 146-147°C; IR (KBr) 3450, 3200, 1680, 1655, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 6.57 (s, 1H), 7.25-7.70 (m, 9H), 7.95 (br, 1H). Anal. Calcd. for $C_{17}H_{14}FN_3O$: C, 69.14; H, 4.78; N, 14.23. Found: C, 69.3; H, 4.8; N, 14.5.

5-Benzamido-1,3-dimethylpyrazole (2b).

A suspension of (**1**, R=CH_3) (4.44 g, 40 mmol) and benzoyl chloride (2,3 mL, 20 mmol) in anhydrous benzene (120 mL) was heated under reflux for 1 h and then filtered; the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate-light petroleum to give (**2b**) (3.28 g, 76% yield) as white crystals: mp 135-136°C (Lit.[18] mp 133-135°C from toluene); IR (KBr) 3230, 1660, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.57 (s, 3H), 6.0 (s, 1H), 7.5-8.0 (m, 5H), 8.5 (br, 1H). Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.8; H, 6.2; N, 19.5.

General Procedure for the Preparation of 1-Alkyl/aryl-5-alkylamino-3-methylpyrazoles (3a-p).

5-Ethylamino-3-methyl-1-phenylpyrazole (3c).

A solution of (**2c**) (5.59 g, 26 mmol) in anhydrous tetrahydrofuran (33 mL) was added dropwise to a suspension of $LiAlH_4$ (1.97 g, 52 mmol) in anhydrous tetrahydrofuran (20 mL), heated under reflux and kept in a nitrogen atmosphere. After additional 4 h reflux, the suspension was cooled, made alkaline with sodium hydroxide and filtered over celite. The filtrate was evaporated to a solid residue that was dissolved in ethyl acetate and washed with water. After being dried over sodium sulphate the solution was evaporated to dryness to give (**3c**) as an oil (4.47 g, 85% yield); IR (neat) 3280, 1600, 1560, 1525, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t, J=8Hz, 3H), 2.25 (s, 3H), 3.1(q, J=8Hz, 2H), 3.8 (br, 1H, D_2O exchangeable), 5.35 (s, 1H), 7.3-7.6 (m, 5H). Anal. Calcd. for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.4; H, 7.3; N, 20.8.

The same procedure was applied to the synthesis for the following compounds:

1,3-Dimethyl-5-ethylaminopyrazole (3a).

(**3a**) was obtained in 56% yield from (**2a**); oil; IR (neat) 3260, 1570, 1540, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J=7.5Hz, 3H), 2.15 (s, 3H), 3.1 (q, J=7.5Hz, 2H), 3.3 (br, 1H, D_2O exchangeable), 3.52 (s, 3H), 5.25 (s, 1H). Anal. Calcd. for $C_7H_{13}N_3$: C, 60.4; H, 9.41; N, 30.19. Found: C, 60.4; H, 9.3; N, 29.9.

5-Benzylamino-1,3-dimethylpyrazole (3b).

(**3b**) was obtained in 71% yield from (**2b**); mp 94-95°C; IR (KBr) 3250, 1575, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.55 (s, 3H), 3.6 (br, 1H, D_2O exchangeable), 4.25 (d, J=6Hz, 2H), 5.3 (s, 1H), 7.35 (s, 5H). Anal. Calcd. for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.4, H, 7.3, N, 20.9.

5-Benzylamino-3-methyl-1-phenylpyrazole (3d).

(**3d**) was obtained in 89% yield from (**2d**); oil; IR (neat) 3250, 1600, 1590, 1570, 1525, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3H), 4.2 (br, 2H), 4.3 (br, 1H, D_2O exchangeable), 5.35 (s, 1H), 7.3-7.6 (m, 5H). Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.3; H, 6.6; N, 15.9.

1-(4-Chlorophenyl)-5-ethylamino-3-methylpyrazole (3e).

(**3e**) was obtained in 67% yield from (**2e**); oil; IR (neat) 3250, 1600, 1585,1560, 1520, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t, J=8Hz, 3H), 2.2 (s, 3H), 3.1 (m, 2H), 3.65 (br, 1H, D_2O exchangeable), 5.35 (s, 1H), 7.35, 7.45 (A_2B_2, J=9Hz, 4H). Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.15; H, 5.99; N, 17.83. Found: C, 61.3; H, 5.8; N, 17.7.

5-Benzylamino-1-(4-chlorophenyl)-3-methylpyrazole (3f).

(**3f**) was obtained in 67% yield from (**2f**); mp 75-77°C; IR (KBr) 3470, 3280, 1600, 1585, 1560,1525, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3H), 4.0 (br, 1H, D_2O exchangeable), 4.25 (d, J=7Hz, 2H), 5.4 (s, 1H), 7.35 (s, 5H), 7.40, 7.45 (A_2B_2, J=9Hz, 4H). Anal. Calcd. for $C_{17}H_{16}ClN_3$: C, 68.57; H, 5.42; N, 14.11. Found: C, 68.4; H, 5.2; N, 14.2.

1-(3-Chlorophenyl)-5-ethylamino-3-methylpyrazole (3g).

(**3g**) was obtained in 68% yield from (**2g**); oil; IR (neat) 3200, 1595, 1565, 1520, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t, J=7Hz, 3H), 2.20 (s, 3H), 3.1 (m, 2H), 3.7 (br, 1H), 5.4 (s, 1H), 7.2-7.7 (m, 4H). Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.15; H, 5.99; N, 17.83. Found: C, 60.8; H, 5.9; N, 17.8.

5-Benzylamino-1-(3-chlorophenyl)-3-methylpyrazole (3h).

(**3h**) was obtained in 70% yield from (**2h**); oil; IR (neat) 3200, 1600, 1570, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 4.2 (br, 2H+1H), 5.3 (s, 1H), 7.2-7.6 (m, 9H). Anal. Calcd. for $C_{17}H_{16}ClN_3$: C, 68.57; H, 5.42; N, 14.11. Found: 68.4; H, 5.6; N, 14.0.

1-(2-Chlorophenyl)-5-ethylamino-3-methylpyrazole (3i).

(**3i**) was obtained in 67% yield from (**2i**); oil; IR (neat) 3250, 1570, 1530, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t, J=7Hz, 3H), 2.25 (s, 3H), 3.2 (m, 2H+1H), 5.25 (s, 1H), 7.4-7.5 (m, 4H). Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.15; H, 5.99; N, 17.83. Found: C, 61.3; H, 5.6; N, 17.5.

5-Benzylamino-1-(2-chlorophenyl)-3-methylpyrazole (3j).

(**3j**) was obtained in 67% yield from (**2j**); oil; IR (neat) 3250, 1575, 1535, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 3.65 (br, 1H), 4.3 (d, J=7Hz, 2H), 5.35 (s, 1H), 7.3-7.6 (m, 9H). Anal. Calcd. for $C_{17}H_{16}ClN_3$: C, 68.57; H, 5.42; N, 14.11. Found: C, 68.6; H, 5.3; N, 14.0.

5-Ethylamino-1-(4-fluorophenyl)-3-methylpyrazole (3k).

(**3k**) was obtained in 85% yield from (**2k**); oil; IR (neat) 3200, 1570, 1510 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}FN_3$: C, 65.74; H, 6.44; N, 19.16. Found: C, 65.7; 6.3; N, 19.2.

5-Benzylamino-1-(4-fluorophenyl)-3-methylpyrazole (3l).

(**3l**) was obtained in 90% yield from (**2l**); mp 56-59°C; IR (KBr) 3300, 1570, 1530, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (s, 3H), 3.96 (br, 1H), 4.25 (d, J=6.5Hz, 2H), 5.38 (s, 1H), 7.07-7.53 (m, 9H). Anal. Calcd. for $C_{17}H_{16}FN_3$: C, 72.58; H, 5.73; N, 14.94. Found: C, 72.4; H, 5.5; N, 14.9.

5-Ethylamino-1-(3-fluorophenyl)-3-methylpyrazole (3m).

(**3m**) was obtained in 86% yield from (**2m**); oil; IR (neat) 3200, 1615, 1600, 1570, 1525 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}FN_3$: C, 65.74; H, 6.44; N, 19.16. Found: C, 65.7; H, 6.2; N, 19.3.

5-Benzylamino-1-(3-fluorophenyl)-3-methylpyrazole (3n).

(**3n**) was obtained in 89% yield from (**2n**); oil; IR (neat) 3240, 1620, 1600, 1570, 1520, 1490 cm^{-1}. Anal. Calcd. for $C_{17}H_{16}FN_3$: C, 72.58; H, 5.73; N, 14.94. Found: C, 72.6; H, 5.7; N, 14.8.

5-Ethylamino-1-(2-fluorophenyl)-3-methylpyrazole (3o).

(**3o**) was obtained in 86% yield from (**2o**); oil; IR (neat) 3260, 1590, 1570, 1540, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, J=7Hz, 3H), 2.20 (s, 3H), 3.1 (m, 2H), 3.5 (br, 1H), 5.35 (s, 1H), 7.2-7.6 (m, 4H). Anal. Calcd. for $C_{12}H_{14}FN_3$: C, 65.74; H, 6.44; N, 19.16. Found: C, 65.6; H, 6.3; N, 19.2.

5-Benzylamino-1-(2-fluorophenyl)-3-methylpyrazole (3p).

(**3p**) was obtained in 82% yield from (**2p**); oil; IR (neat) 3200, 1570, 1530, 1500 cm^{-1}. Anal. Calcd. for $C_{17}H_{16}FN_3$: C, 72.58; H, 5.73; N, 14.94. Found: C, 72.5; H, 5.8; N, 15.0.

General Procedure for the Preparation of 1-Alkyl/aryl-5-alkylamino-3-methyl-4-nitroso-pyrazoles (4a-p)[19].

5-Ethylamino-3-methyl-4-nitroso-1-phenylpyrazole (4c).

Five drops of an aqueous solution of hydrochloric acid (20%) and amyl nitrite (2.69 mL, 20 mmol) were added dropwise to a solution at 0°C of (**3c**) (4.02 g, 20 mmol) in ethanol (20 mL). After 1 h stirring at room temperature, the solvent was removed under reduced pressure to give a solid which was purified by crystallisation from water: violet crystals of (**4c**), 3.25 g, 70% yield, mp 112-114°C, IR (KBr) 3240, 1615, 1550, 1505, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, J=8 Hz, 3H), 2.7 (s, 3H), 2.8 (m, 2H), 7.45 (s, 5H), 10.1 (br, 1H, D_2O exchangeable). Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.6; H, 6.2; N, 24.2.

The same procedure was applied for the synthesis of the following compounds:

1,3-Dimethyl-5-ethylamino-4-nitrosopyrazole (4a).

(**4a**) was obtained in 70% yield from (**3a**); mp 97-98°C (ether-light petroleum); IR (KBr) 3260, 3200, 3120, 1640, 1550, 1260, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, J=7Hz, 3H), 2.6 (s, 3H), 3.55 (m, 2H), 3.75 (s, 3H), 10.9 (br, 1H, D_2O exchangeable). Anal. Calcd. for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 50.2; H, 7.4; N, 33.2.

5-Benzylamino-1,3-dimethyl-4-nitrosopyrazole (4b).

(**4b**) was obtained in 72% yield from (**3b**); mp 140-142°C (ether); IR (KBr) 3200 br, 1635, 1550, 1525, 1500, 1230, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (s, 3H), 3.63 (s, 3H), 4.67 (d, J=8Hz, 2H), 7.2-7.5 (m, 5H), 10.3 (br, 1H, D_2O exchangeable). Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.6; H, 6.3; N, 24.3.

5-Benzylamino-3-methyl-4-nitroso-1-phenylpyrazole (4d).

(**4d**) was obtained in 54% yield from (**3d**); mp 119-120°C (separated as violet crystals from the reaction mixture); IR (KBr) 3200, 1615, 1550, 1500, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (s, 3H), 4.05 (d, J=8Hz, 2H), 6.8-7.5 (m, 10H), 10.3 (br, 1H, D_2O exchangeable). Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.16. Found: C, 70.0; H, 5.4; N, 19.1.

1-(4-Chlorophenyl)-5-ethylamino-3-methyl-4-nitrosopyrazole (4e).

(**4e**) was obtained in 71% yield from (**3e**); mp 133-134°C (ether); IR (KBr) 3160, 3080, 1610, 1540, 1500, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, J=8Hz, 3H), 2.7 (s, 3H), 2.9 (m, 2H), 7.4, 7.5 (A_2B_2, J=8Hz, 4H), 10.1 (br, 1H, D_2O exchangeable). Anal. Calcd. for $C_{12}H_{13}ClN_4O$: C, 54.45; H, 4.95; N, 21.16. Found: C, 54.6, H, 4.9; N, 21.1.

5-Benzylamino-1-(4-chlorophenyl)-3-methyl-4-nitrosopyrazole (4f).

(**4f**) was obtained in 64% yield from (**3f**); mp 133-134°C (separated as violet crystals from the reaction mixture); IR (KBr) 3200, 1615, 1550, 1510, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7 (s, 3H), 4.1 (d, J=8Hz, 2H), 6.9-7.5 (m, 9H), 10.5 (br, 1H, D_2O exchangeable). Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.14. Found: C, 62.4; H, 4.6; N, 17.1.

1-(3-Chlorophenyl)-5-ethylamino-3-methyl-4-nitrosopyrazole (4g).

(**4g**) was obtained in 75% yield from (**3g**); mp 104-105°C (ether-light petroleum); IR (KBr) 3200 br, 1640, 1560, 1510, 1250 cm^{-1}. Anal. Calcd. for $C_{12}H_{13}ClN_4O$: C, 54.45; H, 4.95; N, 21.16. Found: C, 54.7; H, 4.9; N, 20.9.

5-Benzylamino-1-(3-chlorophenyl)-3-methyl-4-nitrosopyrazole (4h).

(**4h**) was obtained in 68% yield from (**3h**); mp 114-115°C (ether-light petroleum); IR (KBr) 3200 br, 1620, 1550, 1520, 1240 cm^{-1}. Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.14. Found: C, 62.6; H, 4.5; N, 17.3.

1-(2-Chlorophenyl)-5-ethylamino-3-methyl-4-nitrosopyrazole (4i).

(**4i**) was obtained in 66% yield from (**3i**); mp 116-117°C (ether-light petroleum); IR (KBr) 3200, 1610, 1550, 1510, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, J=7Hz, 3H), 2.7 (s, 3H), 2.8 (q, J=7Hz, 2H), 7.5-7.7 (m, 4H), 10.3 (br, 1H). Anal. Calcd. for $C_{12}H_{13}ClN_4O$: C, 54.45; H, 4.95; N, 21.16. Found: C, 54.2; H, 4.9; N, 21.3.

5-Ethylamino-1-(4-fluorophenyl)-3-methyl-4-nitrosopyrazole (4k).

(**4k**) was obtained in 61% yield from (**3k**); mp 113-114°C (ether-light petroleum); IR (KBr) 3200 br, 1620, 1550, 1510, 1220 cm^{-1}. Anal. Calcd. for $C_{12}H_{13}FN_4O$: C, 58.06; H, 5.28; N, 22.57. Found: C, 58.4; H, 5.4; N, 22.4.

5-Benzylamino-1-(4-fluorophenyl)-3-methyl-4-nitrosopyrazole (4l).

(**4l**) was obtained in 62% yield from (**3l**); mp 105-108°C (separated as violet crystals from the reaction mixture); IR (KBr) 3200 br, 1625, 1550, 1510, 1220 cm^{-1}. Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.8; H, 4.87; N, 18.05. Found: C, 65.9; H, 4.6; N, 18.1.

5-Ethylamino-1-(3-fluorophenyl)-3-methyl-4-nitrosopyrazole (4m).

(**4m**) was obtained in 42% yield from (**3m**); mp 88-89°C (ether-light petroleum); IR (KBr) 3200 v. br, 1620, 1550, 1510, 1270, 1190 cm^{-1}. Anal. Calcd. for $C_{12}H_{13}FN_4O$: C, 58.06; H, 5.28; N, 22.57. Found: C, 58.7; H, 5.3; N, 22.4.

5-Benzylamino-1-(2-fluorophenyl)-3-methyl-4-nitrosopyrazole (4p).

(**4p**) was obtained in 60% yield from (**3p**); mp 76-79°C (ether-light petroleum); IR (KBr) 3200 v. br, 1620, 1550, 1510, 1250 cm^{-1}. Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.8; H, 4.87; N, 18.05. Found: C, 65.7; H, 5.0; N, 18.0.

Table I. Imidazo[4,5-*c*]pyrazoles (5): Physical Properties and Analytical Data.

Compd	yield %	mp,°C (*)	Formula		C%	H%	N%	Cl%	F%
5a	88	90	$C_7H_{10}N_4+0.5\ H_2O$	Calcd.	52.82	6.96	35.19		
		(A,E)		Found	53.0	6.9	34.9		
5b	71	190-196	$C_{12}H_{12}N_4+H_2O$	Calcd.	62.59	6.13	24.33		
		(A)		Found	62.5	6.0	24.2		
5c	82	217	$C_{12}H_{12}N_4$	Calcd.	67.91	5.70	26.40		
		(C)		Found	68.0	5.4	26.2		
5d	62	273	$C_{17}H_{14}N_4+H_2O$	Calcd.	69.85	5.52	19.16		
		(D)		Found	69.6	5.6	18.9		
5e	86	250-251	$C_{12}H_{11}ClN_4$	Calcd.	58.42	4.49	22.71	14.37	
		(A)		Found	58.5	4.5	22.7	14.5	
5f	78	214	$C_{17}H_{13}ClN_4+H_2O$	Calcd.	62.48	4.63	17.14	10.85	
		(B)		Found	62.6	4.5	17.3	10.7	
5g	65	189-190	$C_{12}H_{11}ClN_4$	Calcd.	58.42	4.49	22.71	14.37	
		(A)		Found	58.5	4.6	22.8	14.1	
5h	67	256-258	$C_{17}H_{13}ClN_4+H_2O$	Calcd.	62.48	4.63	17.14	10.85	
		(B,A)		Found	62.6	4.7	17.4	10.5	
5i	65	175-176	$C_{12}H_{11}ClN_4$	Calcd.	58.42	4.49	22.71	14.37	
		(A,E)		Found	58.2	4.4	23.0	14.6	
5j	59	174-175	$C_{17}H_{13}ClN_4$	Calcd.	66.13	4.24	18.14	11.48	
		(B)		Found	65.9	4.3	18.3	11.7	
5k	76	248-249	$C_{12}H_{11}FN_4$	Calcd.	62.60	4.82	24.33		8.25
		(A)		Found	62.4	4.8	24.5		8.2
5l	68	194-195	$C_{17}H_{13}FN_4+H_2O$	Calcd.	65.80	4.87	18.05		6.12
		(D)		Found	65.7	4.8	17.8		5.9
5m	65	188-189	$C_{12}H_{11}FN_4+H_2O$	Calcd.	58.06	5.28	22.57		7.65
		(A)		Found	58.3	5.2	22.8		7.6
5n	74	276-277	$C_{17}H_{13}FN_4+0.5\ H_2O$	Calcd.	67.76	4.68	18.59		6.31
		(B,A)		Found	67.9	4.6	18.5		6.2
5o	58	194	$C_{12}H_{11}FN_4$	Calcd.	62.60	4.82	24.33		8.25
		(A,D)		Found	62.4	4.8	24.6		8.1
5p	80	204-206	$C_{17}H_{13}FN_4$	Calcd.	69.85	4.48	19.17		6.50
		(B)		Found	69.9	4.5	19.2		6.4

*All products were obtained in good purity by a simple washing with small amounts of ether. Further purification was achieved by column chromatography on silica gel using the following solvents as eluent: A: AcOEt; B: AcOEt-light petroleum (1:1, by volume); C: AcOEt-light petroleum (4:1, by volume); D: AcOEt-light petroleum (3:7, by volume); E: EtOH. Only fractions reactive to a 4% aqueous solution of sodium hypochlorite (yellow spot) were collected.

General Procedure for the Preparation of Imidazo[4,5-*c*]pyrazoles (5a-p).

5-Methyl-1-phenylimidazo[4,5-*c*]pyrazole (5c).

A solution of (**4c**) (3.55 g, 15 mmol) in pyridine (180 mL) was heated under reflux for 15 min; the solvent was removed under reduced pressure and the residue was purified by column chromatography (eluent: ethyl acetate-light petroleum 4:1). Fractions containing only the product reactive to a 4% aqueous solution of sodium hypochlorite (yellow spot, R_f =0.39) were pooled and evaporated to dryness: colourless crystals of (**5c**), 2.68 g, 82% yield, mp 217°C.

The same procedure was applied for the synthesis of all the homologues (**5**), except for compound (**5c**) which required a heating time of 90 min. Physical properties, analytical and spectral data are reported in Tables I and II.

Table II. Imidazo[4,5-*c*]pyrazoles (5): IR and ^{1}H NMR Data.

Compd	IR ν [cm^{-1}][a]	^{1}H NMR δ values[b]
5a	3100v.br., 1560	2.3 (s, 3H), 2.42 (s, 3H), 3.8 (s, 3H), 11.5* (br, 1H)
5b	3050v.br., 1560	2.35 (s, 3H), 3.8 (s, 3H), 7.4-8.2 (m, 5H), 12.3* (br, 1H)
5c	3050v.br., 1550	2.4 (s, 3H), 2.5 (s, 3H), 7.8-8.1 (m, 5H), 11.9* (br, 1H)
5d	3050v.br., 1550	2.5 (s, 3H), 7.4-8.2 (m, 10H), 12.3* (br, 1H)
5e	3000v.br., 1555	2.4 (s, 3H), 2.5 (s, 3H), 7.45-8.1 (A_2B_2, J=9Hz, 4H), 12.0* (br, 1H)
5f	3080v.br., 1545	2.5 (s, 3H), 7.3-8.2 (m, 9H), 12.2* (br, 1H)
5g	3100v.br., 1550	2.4 (s, 3H), 2.5 (s, 3H), 7.1-8.1 (m, 4H), 12.1* (br, 1H)
5h	3080v.br., 1550	2.45 (s, 3H), 7.2-8.2 (m, 9H), 12.8* (br, 1H)
5i	3050v.br., 1550	2.35 (s, 3H), 2.40 (s, 3H), 7.3-7.7 (m, 4H), 12.0* (br, 1H)
5j	3080v.br., 1550	2.45 (s, 3H), 7.35-8.2 (m, 9H), 12.7* (br, 1H)
5k	2950v.br., 1555	2.4 (s, 3H), 2.5 (s, 3H), 7.2-8.2 (m, 4H), 12.1* (br, 1H)
5l	3050v.br., 1550	2.45 (s, 3H), 7.25-8.3 (m, 9H), 12.8* (br, 1H)
5m	3080v.br., 1550	2.35 (s, 3H), 2.45 (s, 3H), 6.9-8.0 (m, 4H), 12.2* (br, 1H)
5n	3080v.br., 1560	2.45 (s, 3H), 7.0-8.3 (m, 9H), 12.8* (br, 1H)
5o	3050v.br., 1550	2.35 (s, 3H), 2.40 (s, 3H), 7.3-7.9 (m, 4H), 12.0* (br, 1H)
5p	3080v.br., 1560	2.45 (s, 3H), 7.3-8.2 (m, 9H), 12.7* (br, 1H)

[a] KBr; [b] Solvent: $CDCl_3$-DMSO-d_6 1:1 for compounds (**5a-f**), DMSO-d_6 for compounds (**5g-p**);

* Exchanges with D_2O in about 3'.

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References and Notes

1. a) P. Giori, A.C. Veronese, C.B. Vicentini, M. Guarneri, *J. Heterocyclic Chem.*, **1985**, *22*, 1093; b) P. Giori, A.C. Veronese, T. Poli, C.B. Vicentini, M. Manfrini and M. Guarneri, *J. Heterocyclic Chem.*, **1986**, *23*, 585; c) P. Giori, T. Poli, A.C. Veronese, C.B. Vicentini, M. Manfrini and M. Guarneri, *J Heterocyclic Chem*, **1986**, *23*, 1661; d) C.B. Vicentini, A.C. Veronese, T. Poli, M. Guarneri, P.Giori, V. Ferretti, *J. Heterocyclic Chem.*, **1989**, *26*, 797.
2. a) G. Vertuani, P.Giori, M.Guarneri, G.P. Sarto, *J. Pharm. Sci.*, **1985**, *74*, 1013; b) P.Giori, T.Poli, C.B. Vicentini, M. Manfrini, M. Guarneri, V. Brandolini, *Il Farmaco, Ed. Sc.*, **1985**, *40*, 795; c) C.B. Vicentini, T. Poli, M. Guarneri, V. Brandolini, M. Manfrini, P. Giori, *Italian Patent*, **A/87** 21121; d) C.B. Vicentini, T. Poli, M. Manfrini, M. Guarneri, P. Giori, V. Brandolini, *Il Farmaco, Ed. Sc.*, **1987**, *42*, 133; e) T. Poli, C.B. Vicentini, V. Brandolini, A.C. Veronese, M. Manfrini, M. Guarneri and P. Giori, *Pestic. Sci.*, **1989**, *25*, 161; f) C.B. Vicentini, T. Poli, A.C. Veronese, V. Brandolini, M. Manfrini, M. Guarneri and P. Giori, *Pestic. Sci.*, **1989**, *27*, 77.
3. C.B. Vicentini, A.C. Veronese, M. Guarneri, *Italian Patent*, **A/85**, 19418; C.B. Vicentini, A.C. Veronese, P. Giori and M. Guarneri, *Tetrahedron Lett.*, **1988**, *29*, 6171.
4. A. Dornow, E. Hinz, *Chem. Ber.*, **1958**, *91*,1834.
5. M. Lange, R. Quell, H. Lettau, H. Schubert, *Z.Chem.* **1977**, *17*, 94.
6. I.I. Grandberg, G.V. Klyuchko, *Zh. Obshch. Khim.*, **1962**, *32*, 1898; *C.A.*, **1963**, 4537f.
7. a) V. Sudarsanam, K. Nagarajan, K. Rama Rao, S.J. Shenoy, *Tetrahedron Lett.*, **1980**, *21*, 4757; b) K. Nagarajan, V. Sudarsanam, S.J. Shenoy, K. Rama Rao, *Indian J. Chem., Sect. B*, **1982**, *21B*, 997.
8. E.C. Wagner, *Org. Synth.*, **1943**, 2, 65.
9. J. Clark, J.H. Lister, *J.Chem.Soc.*, **1961**,5048.
10. J. Elguero, *Comprehensive Heterocyclic Chemistry*, K.T. Potts ed., Pergamon Press, Oxford, **1984**, *5*, 272.
11. E.C. Taylor, E.E. Garcia, *J. Am. Chem. Soc.*, **1964**, *86*, 4720.
12. A.C. Veronese, G. Cavicchioni, G. Servadio, G. Vecchiati, *J. Heterocyclic Chem.*, **1980**, *17*, 1723.
13. H. Fuchs, M. Gottlieb, W. Pfleiderer, *Chem. Ber.*, **1978**, *111*, 982.
14. O. Meth-Cohn, H. Suschitzky, *Adv. Heterocyclic Chem.*, **1972**, *14*, 211.
15. G. Gilli, V. Bertolasi, A.C. Veronese, *Acta Cryst.*, **1983**, *B39*, 450.
16. A. Michaelis, *Liebigs Ann. Chem.*, **1905**, *339*, 141.
17. A. Michaelis, A. Schäfer, *Liebigs Ann. Chem.*, **1913**, *397*, 141.
18. D. E. Butler, H. A. DeWald, *J. Org. Chem.*, **1975**, *40*, 1353.
19. The derivatives (**4j**), (**4n**) and (**4o**) were not isolated and cyclised rapidly during the nitrosation to the imidazo-pyrazoles (**5j**), (**5n**) and (**5o**).