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Imidazo[4,5-*c*]pyrazoles
Synthesis of 4-,5- and 6-Substituted Derivatives

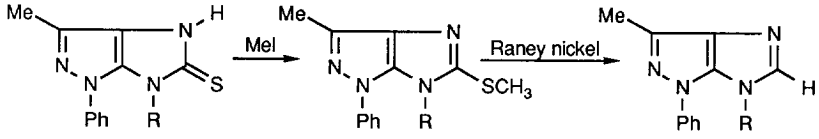
Chiara B. Vicentini,* Augusto C. Veronese,
Maurizio Manfrini and Mario Guarneri
Dipartimento di Scienze Farmaceutiche- Università di Ferrara 44100 - FERRARA, Italy

Abstract: The syntheses of 4-, 5-, and 6- substituted imidazo[4,5-c]pyrazoles, compounds of potential biological activity, are reported.

Pyrazoles and imidazoles play an important role among a wide variety of nitrogen heterocycles that have been used for developing useful agrochemicals and pharmacological agents, but, apart from a few patents that are claimed to provide particular derivatives employed as photographic couplers, there is a paucity of the literature[1] concerning the synthesis and biological activity of imidazo[4,5-*c*]pyrazoles.

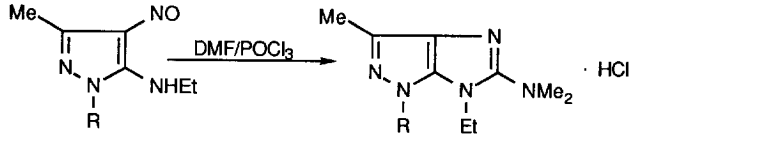
In previous researches in this area, we proved that the intramolecular cyclodehydration of 5-alkylamino-4-nitrosopyrazoles constitutes an efficient method for the synthesis of 5-substituted imidazo[4,5-*c*]pyrazoles, which in tests for biological evaluation showed interesting properties as CNS depressants.[2] Cyclization of 4-isothiocyanatopyrazoles gave imidazo[4,5-*c*]pyrazole-5-thiones[3] (**1**) in which the nitrogen atom in position 6 can be selectively linked to acyl, aryl and acylamino groups. As a part of our continuing studies of imidazopyrazole derivatives as promising agrochemicals and pharmacological agents, we report here the synthesis of imidazo[4,5-*c*]pyrazoles variously substituted in position 4, 5 and 6.

In order to obtain 5,6-disubstituted derivatives we reacted 6-substituted imidazo[4,5-*c*]pyrazole-5-thiones[3] (**1**) in sodium hydroxide with iodomethane to give 4-methylthio derivative (**2**). Compounds **2** were submitted to hydrogenolytic desulfurisation in the presence of Raney nickel to give **3**.



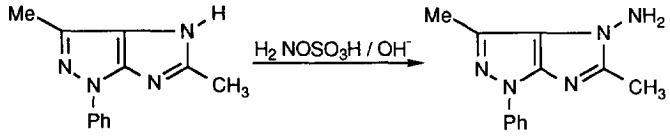
1 **2** **3** a: R=H; b: R=$CH_2C_6H_5$

As many attempts to replace the methylthiogroup with amines were unsuccessful, we reacted 5-amino-4-nitrosopyrazoles[2] (**4**) with the Vilsmeier-type reagent (dimethylformamide and phosphorus oxychloride) so obtaining 5-aminoimidazo[4,5-*c*]pyrazole derivatives (**5**).



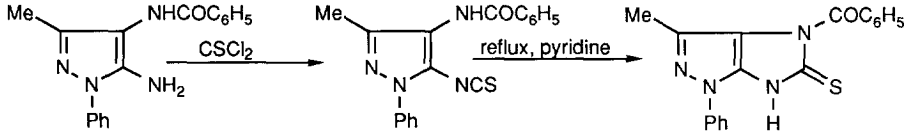
4 **5** a: R=Me; b: R=Ph

For the amination of position 4 we applied the Rees procedure.[4] 5-Methylimidazo[4,5-*c*]pyrazole[2] (**6**) was treated with hydroxylamine *O*-sulphonic acid in aqueous potassium hydroxide at 70-75°C to give 4-amino-5-methylimidazo[4,5-*c*]pyrazole (**7**).[5]



6 **7**

Furthermore the acylation of position 4 was obtained by treatment of 5-amino 4-benzamido pyrazole[6] (**8**) with thiophosgene to afford the 5-isothiocyanatopyrazole (**9**). Heating of **9** in pyridine gave 4-benzoyl-imidazo [4,5-*c*]pyrazole-5-thione (**10**).



8 **9** **10**

All these reactions gave the desired compounds in good yields. The spectral data of the compounds agree with the reported structures. Biological tests of the new compounds are in progress.

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus. The IR spectra were recorded from potassium bromide discs on a Perkin-Elmer 299B spectrophotometer. The ^1H NMR and ^{13}C 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. Column chromatography was performed using Merck silica gel (70-230 mesh); for flash chromatography technique silica gel (230-400 mesh) was employed.

3-Methyl-1-phenyl-5-methylthioimidazo[4,5-*c*]pyrazoles (2): General Procedure

Methyl iodide (0.71 g, 5 mmol) was added to a stirred solution of the appropriate imidazo[4,5-*c*]pyrazole-5-thione (**1**) (5 mmol) in 1M sodium hydroxide (25 ml). After 2h the reaction mixture was neutralized with 1M hydrochloric acid and then extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated. The resulting solid was purified by flash chromatography or by recrystallization from the indicated solvent.

3-Methyl-5-methylthio-1-phenylimidazo[4,5-*c*]pyrazole (2a)

Pale yellow crystals, 1.04 g, yield 85%, mp 218-219°C (ethanol); IR (KBr): 3100 br, 1600, 1550, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.39 (s, 3H, Me), 2.71 (s, 3H, SMe), 7.10-7.50 (m, 3H, Ph), 8.09 (d, J=8.0 Hz, 2H, Ph), 9.5 (br, 1H, NH). Anal. Calcd. for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.93; S, 13.12. Found: C, 58.8; H, 4.9; N, 22.8; S, 13.0.

6-Benzyl-3-methyl-5-methylthio-1-phenylimidazo[4,5-*c*]pyrazole (2b)

Pale yellow crystals from flash chromatography (eluent 1:1 ethyl acetate/light petroleum), 1.31 g, yield 78%, mp 86-87°C (ethyl acetate/light petroleum); IR (KBr): 1605, 1550, 1510, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.52

(s, 3H, Me), 2.67 (s, 3H, SMe), 5.19 (s, 2H, CH_2), 6.7-6.9 (m, 2H, Ph), 7.1-7.3 (m, 8H, Ph). Anal. Calcd. for $C_{19}H_{18}N_4S$: C, 68.24; H, 5.42; N, 16.75; S, 9.59. Found: C, 68.1; H, 5.4; N, 16.5; S, 9.5.

3-Methyl-1-phenylimidazo[4,5-*c*]pyrazoles (3): General Procedure

A solution of the appropriate 3-methyl-1-phenyl-5-methylthioimidazo[4,5-*c*]pyrazole (**5**) (2 mmol) in dioxane (30 ml) was added to a suspension of Raney nickel (freshly prepared from 6g of alloy) in dioxane (50 ml). After 1 h the catalyst was filtered off and the solvent was evaporated to dryness. The crude product was purified by silica gel column chromatography (eluent 17:2:1 dichloromethane/methanol/toluene).

3-Methyl-1-phenylimidazo[4,5-*c*]pyrazole (3a)

Colourless crystals, 0.32 g, yield 80%, mp 165-166°C (ethyl acetate/light petroleum); IR (KBr): 3150 br, 2890 br, 1620, 1570, 1525 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.39 (s, 3H, Me), 6.5-7.5 (1H, NH), 7.11 (t, J=7.9 Hz, 1H, Ph), 7.47 (t, J=8.0 Hz, 2H, Ph), 7.89 (s, 1H, CH), 8.04 (d, J=8.0 Hz, 2H, Ph). Anal. Calcd. for $C_{11}H_{10}N_4$: C, 66.65; H, 5.08; N, 28.26. Found: C, 66.5; H, 5.0; N, 28.1.

6-Benzyl-3-methyl-1-phenylimidazo[4,5-*c*]pyrazole (3b)

Colourless crystals; 0.45 g, yield 78%, mp 107°C (ethyl acetate/light petroleum); IR (KBr): 1610, 1550, 1505, 1455 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.35 (s, 3H, Me), 5.34 (s, 2H, CH_2), 6.70-6.80 (m, 2H, Ph), 7.10-7.45 (m, 8H, Ph), 7.90 (s, 1H, CH); ^{13}C NMR (DMSO-d_6) δ: 11.65 (q, J=126.9 Hz, Me), 48.62 (t, J=140.6 Hz, CH_2), 122.50 (d, Ph), 126.46 (d, Ph), 126.53 (d, Ph), 127.52 (d, Ph), 128.41 (d, Ph), 129.12 (d, Ph), 135.55 (s),136.24 (s), 136.38 (s), 138.52 (s), 138.68 (s), 143.12 (d, J=210.1 Hz, CH). Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.8; H, 5.6; N, 19.3.

5-Dimethylamino-3-methylimidazo[4,5-*c*]pyrazole hydrochlorides (5): General Procedure

A previously prepared mixture at 0°C of *N*-dimethylformamide (4 ml) and $POCl_3$ (0.4 ml, 4 mmol) was added to the appropriate 5-alkylamino-4-nitrosopyrazole (**4**) (4 mmol). After 2h stirring at room temperature, the reaction mixture was heated at 150°C for 1 h. The solution was evaporated and the residue was purified by column chromatography (eluent 17:2:1 dichloromethane/methanol/toluene).

5-Dimethylamino-1,3-dimethyl-6-ethylimidazo[4,5-*c*]pyrazole hydrochloride (5a)

Oil, 0.40 g, yield 48%; IR (neat): 1630, 1570, 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.40 (t, J=7.2 Hz, 3H, Me), 2.39 (s, 3H, Me), 2.84 (s, 6H, NMe_2), 2.90 (br, 1H, NH^+), 3.91 (s, 3H, NMe), 4.02 (q, J=7.2 Hz, NCH_2); ^{13}C NMR ($CDCl_3$) δ: 11.78 (q, J=126.8 Hz, Me), 16.22 (q, J=126.7 Hz, Me), 36.24 (q, J=138.4 Hz, Me), 38.77 (t, J=138.4 Hz, CH_2), 43.35 (q, J=131.4 Hz, Me), 128.08 (s), 134.30 (s, C-3), 139.23 (s), 157.39 (s). Anal. Calcd. for $C_{10}H_{18}ClN_5$: C, 49.28; H, 7.44; Cl, 14.55; N, 28.73. Found: C, 49.2; H, 7.5; Cl, 14.4; N, 28.7.

5-Dimethylamino-6-ethyl-3-methyl-1-phenylimidazo[4,5-*c*]pyrazole hydrochloride (5b)

Colourless crystals, 0.50 g, yield 46 %, mp 75-76°C (ethyl acetate/light petroleum); IR (KBr): 1630, 1580, 1520, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.89 (t, J=7.1 Hz, 3H, Me), 2.50 (s, 3H, Me), 2.87 (s, 6H, NMe_2), 3.40 (br, 1H, NH^+), 3.97 (q, J=7.1 Hz, 2H, CH_2), 7.1-7.5 (m, 5H, Ph). Anal. Calcd. for $C_{15}H_{20}ClN_5$: C, 58.91; H, 6.59; Cl, 11.59; N, 22.90. Found: C, 59.0; H, 6.7; Cl, 11.5; N, 23.0.

4-Amino-3,5-dimethyl-1-phenylimidazo[4,5-*c*]pyrazole (7)

3,5-Dimethyl-1-phenylimidazo[4,5-*c*]pyrazole (**6**) (5 mmol) was dissolved in 0.5N potassium hydroxide (40 ml) at 60°C. Solid hydroxylamine-*O*-sulphonic acid (10 mmol) was added portionwise during 1 h, the temperature being maintained at 70-75°C. The mixture was stirred for 1 h at *ca.* 70°C, cooled and filtered. The precipitate was washed with water and the residue was dissolved in ethyl acetate, washed with aqueous potassium hydroxide, dried and evaporated. The solid residue was purified by flash chromatography (eluent:

ethyl ether). White crystals, 0.66 g, yield 58 %, mp 133-134°C (ethyl acetate/light petroleum); IR (KBr): 3380, 3300, 1615, 1565, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.57 (s, 3H, Me), 2.58 (s, 3H, Me), 6.18 (br, 2H, NH_2), 7.24 (t, J=7.8, 1H, Ph), 7.57 (t, J=7.8, 2H, Ph), 8.15 (d, J=7.8 Hz, 2H, Ph); ^{13}C NMR (DMSO-d_6) δ: 11.97 (q, J=127.2 Hz, Me), 12.75 (q, J=125.7 Hz, Me), 115.77 (d, Ph), 123.28 (s), 123.44 (d, Ph), 129.17 (d, Ph), 129.94 (s, C-3), 139.62 (s, Ph), 147.35 (s), 153.35 (s, C-5). Anal. Calcd. for $C_{12}H_{13}N_5$: C, 63.42; H, 5.77; N, 30.81. Found: C, 63.3; H, 5.8; N, 30.8.

***N*-(5-Isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)benzamide (9)**

Thiophosgene (0.23 ml, 3 mmol) was added dropwise to a suspension of N-(5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)benzamide[6] (**8**) (0.87 g, 3 mmol) in water (15 ml). After 2 h stirring at room temperature, the pale yellow precipitate was collected, washed with water and dissolved in ethyl acetate. After drying over anhydrous magnesium sulfate, the solvent was removed to give a solid which was recrystallized from ethyl acetate/light petroleum. Colourless crystals, 0.70 g, yield 69%, mp 168-170°C (ethyl acetate/light petroleum); IR (KBr): 3280 br, 2080 br, 1670, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.25 (s, 3H, Me), 7.1-8.0 (m, 11H, Ph+NH). Anal. Calcd. for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75; S, 9.59. Found: C, 64.7; H, 4.3; N, 16.8; S, 9.5.

4-Benzoyl-3-methyl-1-phenylimidazo[4,5-*c*]pyrazole-5-thione (10)

A solution of *N*-(5-isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)benzamide (**9**) (0.33 g, 1 mmol) in pyridine (33 ml) was heated under reflux for 2h. The solvent was removed under reduced pressure to give a solid which was purified by flash chromatography (eluent: 1:1 ; 6:4 ethyl acetate/light petroleum). Colourless crystals, 0.21 g, yield 62%, mp 208-209°C (ethyl acetate/light petroleum); IR (KBr): 3300 br, 1670, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.18 (s, 3H, Me), 7.00-8.00 (m, 10H, Ph), 9.60 (br, 1H, NH). Anal. Calcd. for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75; S, 9.59. Found: C, 64.5; H, 4.2; N, 16.8; S, 9.5.

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