

A NEW SYNTHESIS OF PYRAZOLO[3,4-*d*]THIAZOLES

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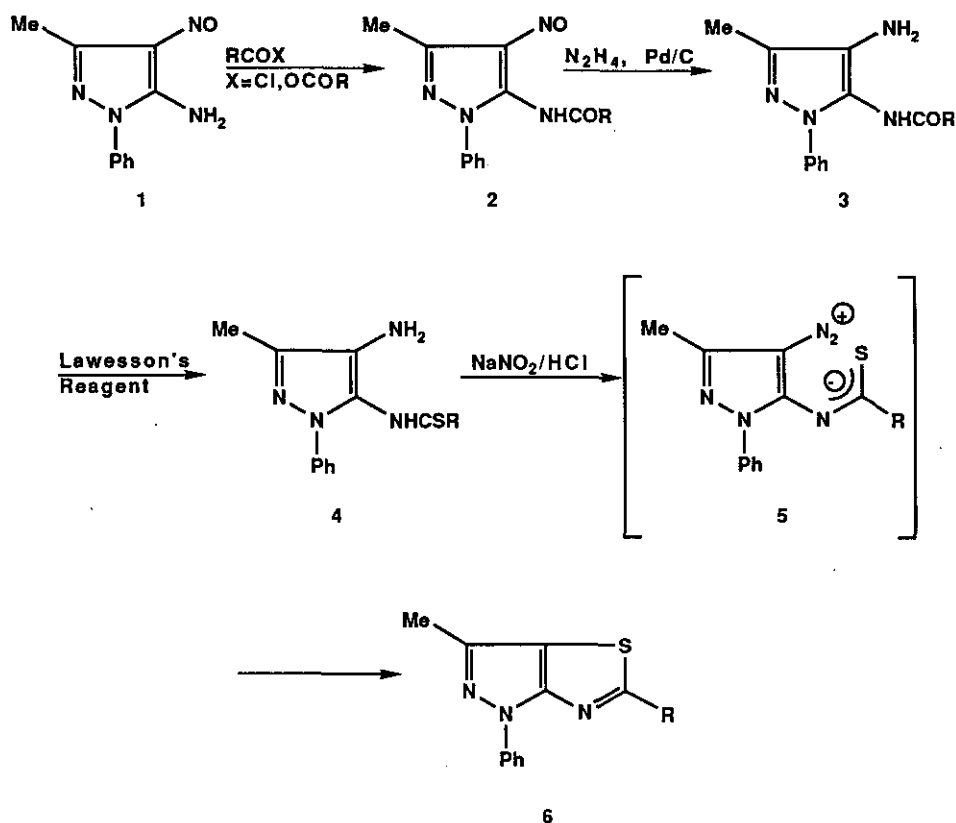
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Abstract- An efficient synthesis of pyrazolo[3,4-*d*]thiazoles (**6**) was achieved by treatment of *N*-(4-amino-5-pyrazolyl)thiocarboxamides (**4**) with sodium nitrite in acidic medium followed by irradiation with uv light.

Recent reports on antifungal-antibacterial properties of pyrazolo[3,4-*d*]thiazoles¹⁻³ have focused our interest toward an efficient synthetic procedure by which a series of homologues utilizable for structure-activity relationships studies could be prepared. A survey of the literature revealed that, beside a few methods consisting in the construction of the pyrazole ring on 4-thiazolidone derivatives,¹⁻⁴ the most general procedure involves the formation of the thiazole ring from difunctionalized pyrazoles. The following precursors are used: a) 5-amino-4-mercaptopyrazoles which are condensed with carbonyl compounds to afford 5-alkyl/arylpyrazolothiazoles;⁵ b) 5-amino-4-thiocyanatopyrazoles which under a variety of conditions are cyclized into 5-amino analogues;^{6,7} c) *N*-(4-bromo-5-pyrazolyl)thioureas⁶⁻⁸ and *N*-(4-bromo-5-pyrazolyl)thiocarboxamides^{9,10} which undergo an intramolecular displacement of the halogen to give 5-amino- and 5-alkyl/arylpyrazolothiazoles respectively. Furthermore the physical data of some of the reported pyrazolothiazoles don't agree between them.^{5,10}

Although the best leaving group is probably N₂ from the species RN₂⁺ readily achievable from primary amines, no example is reported in the literature concerning the use of *ortho*-dialzo-phenylthiocarboxamides as precursors for annulated thiazoles. Earlier work in our laboratory had shown that diazotization of *N*-alkyl/aryl-*N'*-(4-amino-5-pyrazolyl)ureas afforded the corresponding *N*-alkyl/aryl-*N'*-(4-dialzo-5-pyrazolyl)ureas which on irradiation with uv light furnished high yields of 5-aminopyrazolo[3,4-*d*]oxazoles.¹¹ Starting from these informations, we decided to investigate a new synthetic entry to the title compounds, based on the diazotization of *N*-(4-amino-5-pyrazolyl)thiocarboxamides.

The synthetic plan involves the use as starting materials of *N*-(4-nitroso-5-pyrazolyl)carboxamides (**2**) obtained by acylation of 5-amino-4-nitrosopyrazole (**1**). Reduction of **2** with hydrazine hydrate in the presence of palladized charcoal afforded *N*-(4-amino-5-pyrazolyl)carboxamides (**3**). Treatment of **3** with the Lawesson reagent^{12,13} in hexamethylenephosphoramidate at 80°C provided satisfactory yields of thiocarboxamides (**4**). Diazotization of **4** with one equivalent of sodium nitrite in acidic medium provided directly the required pyrazolo[3,4-*d*]thiazoles (**6**) without isolation of the diazo intermediates (**5**).



a: $\text{R} = \text{Me}$; b: $\text{R} = \text{PhCH}_2$; c: $\text{R} = \text{Ph}$

In spite of the fact that the cyclization process took place also when the reaction mixture was sheltered from light, the reaction rate and the yields of **6** were greatly increased by irradiation with uv light. This behavior is different from that of the parent compound *N*-(4-amino-5-pyrazolyl)benzamide,¹⁴ whose diazotization generates

a stable diazo derivative cyclizing into pyrazolo-oxazole only under uv irradiation. The greater instability of diazo-thiocarboxamides (5) in comparison with that of diazo-benzamides¹⁴ could be due to the higher nucleophilicity of the thiocarboxamido S-atom.

The proposed structures were confirmed by the spectral data (see Experimental). The key features of the ¹³C-nmr spectra of 6 are the absorptions near 115 ppm, attributable to C-3a carbon atom bonded to sulfur atom, and near 157 ppm attributable to C-6a carbon atom bonded to two nitrogen atoms. The absorption between 172 and 177 ppm was attributed to N=C-S carbon atom of the thiazole ring. Despite the fact that, at the best of our knowledge, no ¹³C-nmr spectra of structure (6) are available in the literature, our data are in accord with those reported for thiazole¹⁵ and benzothiazole derivatives.^{16,17}

It is worth noting that the melting point of compound (6a) prepared in our laboratory agrees with that reported by Moskalenko *et al.*,¹⁰ while the melting points of compounds (6a) and (6c) are quite different from those reported by other authors.¹⁸

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded from potassium bromide discs on a Perkin-Elmer 299B spectrophotometer. The ¹H-nmr and ¹³C-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 and coupling constants are in Hz. For column chromatography basic alumina (activity grade 1, 60-230 mesh ASTM, Merck) was used; for column flash chromatography silica gel (Kieselgel 60, 230-400 mesh ASTM, Merck) was employed. The irradiation of the samples was performed with the light of a T Q 120K Hanau mercury lamp.

Compounds (2a) and (2c) were prepared by the literature method.¹⁹

N-(3-Methyl-4-nitroso-1-phenylpyrazol-5-yl)phenylacetamide (2b).

A solution of phenylacetyl chloride (1.7 g, 11 mmol) in chloroform (25 ml) was added dropwise to a stirred mixture of 5-amino-3-methyl-4-nitroso-1-phenylpyrazole (1, 2.02 g, 10 mmol) in chloroform (50 ml) and of sodium hydrogen carbonate (0.92 g, 11 mmol) in water (25 ml). After 24 h stirring at room temperature, the organic phase was washed with 1N hydrochloric acid and then extracted with aqueous 5% sodium carbonate (6 x 50 ml). The combined extracts were acidified with 10% hydrochloric acid to pH 5 and the green precipitate was collected and washed with water. After being dried *in vacuo* over phosphorus pentoxide, the crude solid was crystallized from methanol. Yield 2.53 g (79%), mp 130-131°C (methanol); ir (KBr) cm^{-1} : 3200 (br), 1670, 1555, 1495, 1340; ¹H-nmr (CDCl₃) δ : 2.75 (s, 3H, Me), 3.61 (s, 2H, CH₂), 7.23-7.43 (m, 10H, 2Ph), 9.31 (br s, 1H, NH). *Anal.* Calcd for C₁₈H₁₆N₄O₂: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.32; H, 5.06; N, 17.38.

General procedure for N-(4-aminopyrazol-5-yl)carboxamides (3).

99% Hydrazine hydrate (1.1 g, 20 mmol) and 5% palladized charcoal (0.30 g) were added to a solution of **2** (4 mmol) in methanol (60 ml). After heating under reflux for 5 min, the catalyst was removed and the filtrate was evaporated to dryness *in vacuo*. The resulting colourless solid was purified by recrystallization from the indicated solvent.

N-(4-Amino-3-methyl-1-phenylpyrazol-5-yl)acetamide (3a).

Yield 78%, mp 145-146°C (toluene); ir (KBr) cm^{-1} : 3360, 3200 (br), 1660, 1620, 1500, 1365; $^1\text{H-nmr}$ (DMSO- d_6) δ : 1.98 (s, 3H, Me), 2.12 (s, 3H, Me), 3.74 (br, 2H, NH_2), 7.20-7.50 (m, 5H, Ph), 9.57 (s, 1H, NH). Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.70; H, 6.17; N, 24.28.

N-(4-Amino-3-methyl-1-phenylpyrazol-5-yl)phenylacetamide (3b).

Yield 87%, mp 115-116°C (toluene); ir (KBr) cm^{-1} : 3400, 3220 (br), 1650, 1590, 1520, 1490, 1365; $^1\text{H-nmr}$ (DMSO- d_6) δ : 2.12 (s, 3H, Me), 3.61 (s, 2H, CH_2), 3.68 (br s, 2H, NH_2), 7.10-7.50 (m, 10H, Ph), 9.81 (s, 1H, NH). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.62; H, 5.90; N, 18.37.

N-(4-Amino-3-methyl-1-phenylpyrazol-5-yl)benzamide (3c).

Yield 88%, mp 151-152°C (toluene); ir (KBr) cm^{-1} : 3380, 3240, 1660, 1600, 1505, 1480, 1365; $^1\text{H-nmr}$ (DMSO- d_6) δ : 2.16 (s, 3H, Me), 3.70 (br, 2H, NH_2), 7.10-7.70 (m, 8H, Ph), 7.94 (d, $J=7$ Hz, 2H, Ph), 10.00 (br, 1H, NH). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}$: C, 69.85; H, 5.52; N, 19.16. Found: C, 69.72; H, 5.57; N, 19.06.

General procedure for N-(4-amino-pyrazol-5-yl)thiocarboxamides (4).

A mixture of **3** (5 mmol) and of Lawesson reagent (2.02 g, 5 mmol) in hexamethylenephosphoramidate (15 ml) was heated at 80°C under stirring until no more of the starting material could be detected by tlc (4-6 h). After cooling to room temperature, the solution was poured into water (80 ml) and the mixture was extracted with ethyl acetate (2 x 50 ml). The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness. The crude residue was applied to an alumina column (eluent: methylene chloride/methanol/toluene 17:2:1 v/v) and the eluate was evaporated to a solid residue. Final purification was accomplished by flash chromatography using ethyl acetate/petroleum ether 4:1 v/v to elute the product ($R_f \cong 0.4$).

N-(4-Amino-3-methyl-1-phenylpyrazol-5-yl)thioacetamide (4a).

Colourless crystals, yield 85%, mp 189-190°C (toluene); ir (KBr) cm^{-1} : 3380, 2750 (br), 1590, 1540, 1500; $^1\text{H-nmr}$ (DMSO- d_6) δ : 2.13 (s, 3H, Me), 2.54 (s, 3H, Me), 3.39 (br, 2H, NH_2), 7.20-7.50 (m, 5H, Ph), 11.20 (br, 1H, NH). Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{S}$: C, 58.51; H, 5.73; N, 22.74; S, 13.01. Found: C, 58.63; H, 5.70; N, 22.54; S, 12.96.

N-(4-Amino-3-methyl-1-phenylpyrazol-5-yl)phenylthioacetamide (4b).

Colourless crystals, yield 61%, mp 136°C (toluene); ir (KBr) cm^{-1} : 3180 (br), 2920 (br), 1600, 1500, 1379; $^1\text{H-nmr}$ (DMSO- d_6) δ : 2.14 (s, 3H, Me), 3.71 (br, 2H, NH_2), 4.04 (s, 2H, CH_2), 7.10-7.40 (m, 10H, Ph), 11.66 (br, 1H, NH). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{S}$: C, 67.05; H, 5.63; N, 17.38; S, 9.94. Found: C, 67.15; H, 5.55; N, 17.47; S, 9.80.

N-(4-Amino-3-methyl-1-phenylpyrazol-5-yl)thiobenzamide (4c).

Yellow crystals, yield 66%, mp 209-211°C (toluene); ir (KBr) cm^{-1} : 3410, 3330, 3150 (br), 2920 (br), 1600, 1540, 1510, 1350; $^1\text{H-nmr}$ (DMSO- d_6) δ : 2.20 (s, 3H, Me), 3.90 (br, 2H, NH_2), 7.24-7.60 (m, 8H, Ph), 7.88 (d, $J=7$ Hz, 2H, Ph), 11.20 (br, 1H, NH). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{S}$: C, 66.21; H, 5.23; N, 18.17; S, 10.39. Found: C, 65.98; H, 5.23; N, 18.14; S, 10.28.

General procedure for pyrazolo[3,4-*d*]thiazoles (6).

A solution of sodium nitrite (0.15 g, 22 mmol) in water (5 ml) was added dropwise to an ice-cooled solution of 4 (2 mmol) in methanol (140 ml) and 1N hydrochloric acid (6 ml) under stirring. The mixture was allowed to warm to room temperature and irradiated for 3 h with uv light. After evaporation of the solvent, the crude residue was purified by flash chromatography (eluent: petroleum ether/ethyl acetate 96:4 v/v). Analytical samples of 6 were crystallized from the indicated solvent.

Alternatively, the reaction mixture was stirred for 24 h at room temperature sheltered from light and then worked up as above: in these conditions the yields were remarkably lower (20-40%) as compared with those recovered after uv irradiation for 3 h.

3,5-Dimethyl-1-phenylpyrazolo[3,4-*d*]thiazole (6a).

Colourless crystals, yield 62%; mp 92-93°C (ethanol) lit.,¹⁰ mp 90-91°C, lit.,⁵ mp 148°C; ir (KBr) cm^{-1} : 1600, 1520, 1430, 1380; $^1\text{H-nmr}$ (CDCl_3) δ : 2.46 (s, 3H, Me), 2.76 (s, 3H, Me), 7.16-7.24 (m, 1H, Ph), 7.40-7.48 (m, 2H, Ph), 8.13 (d, $J=7$ Hz, 2H, Ph); $^{13}\text{C-nmr}$ (CDCl_3) δ : 14.11 (q, $J=128$ Hz, Me), 20.91 (q, $J=130$ Hz, Me), 114.73 (s, C-3a), 118.53 (d, $J=161$ Hz, Ph), 125.19 (d, $J=162$ Hz, Ph), 129.14 (d, $J=160$ Hz, Ph), 139.37 (s, Ph and C-3), 158.00 (s, C-6a), 172.65 (s, C-5). Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{S}$: C, 62.86; H, 4.84; N, 18.33; S, 13.98. Found: C, 62.82; H, 4.88; N, 18.27; S, 14.06.

5-Benzyl-3-methyl-1-phenylpyrazolo[3,4-*d*]thiazole (6b).

Pale yellow needles, yield 85%; mp 83-84°C (methanol); ir (KBr) cm^{-1} : 1605, 1520, 1430, 1385; $^1\text{H-nmr}$ (CDCl_3) δ : 2.41 (s, 3H, Me), 4.34 (s, 2H, CH_2), 7.10-7.55 (m, 8H, Ph), 8.17 (d, $J=7$ Hz, 2H, Ph); $^{13}\text{C-nmr}$ (CDCl_3) δ : 14.06 (q, $J=127$ Hz, Me), 41.13 (t, $J=129$ Hz, Me), 115.07 (s, C-3a), 118.51 (d, $J=161$ Hz, CH, Ph), 125.20 (d, $J=160$, CH, Ph), 127.37 (d, $J=153$ Hz, CH, Ph), 128.80 (d, $J=153$ Hz, CH, Ph), 129.41

(d, $J=151$ Hz, CH, Ph), 136.82 (s, Ph), 139.35 (s, Ph), 139.49 (s, C-3), 157.89 (s, C-6a), 177.2 (s, C-5). Anal. Calcd for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76; S, 10.50. Found: C, 70.83; H, 4.89; N, 13.74; S, 10.54.

3-Methyl-1,5-diphenylpyrazolo[3,4-*d*]thiazole (6c).

Colourless crystals, yield 73%; mp $141^{\circ}C$ (ethanol) lit.,⁵ mp $152^{\circ}C$; ir (KBr) cm^{-1} : 1600, 1510, 1460, 1370; 1H -nmr($CDCl_3$) δ : 2.49 (s, 3H, Me), 7.10-7.25 (m, 1H, Ph), 7.40-7.50 (m, 5H, Ph), 7.96-8.02 (m, 2H, Ph), 8.23 (d, $J=8$ Hz, 2H, Ph); ^{13}C -nmr ($CDCl_3$) δ : 14.16 (q, $J=127$ Hz, Me), 114.41 (s, C-3a), 118.45 (d, $J=168$ Hz, CH, Ph), 125.21 (d, $J=161$ Hz, Ph), 126.68 (d, $J=158$ Hz, Ph), 128.93 (d, $J=160$ Hz, Ph), 129.13 (d, $J=163$ Hz, Ph), 130.88 (d, $J=160$ Hz, Ph), 133.97 (s, Ph), 139.37 (s, C-3), 139.85 (s, Ph), 158.87 (s, C-6a), 173.80 (s, C-5). Anal. Calcd for $C_{17}H_{13}N_3S$: C, 70.08; H, 4.50; N, 14.42; S, 11.00. Found: C, 69.94; H, 4.45; N, 14.53; S, 11.08.

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REFERENCES AND NOTES

1. V. N. Mehrotra and R. S. Achari, *J. Indian Chem. Soc.*, 1985, **62**, 306 (*Chem. Abstr.*, 1986, **105**, 78866t).
2. R. A. Pawar and A. P. Rajput, *Indian J. Chem, Sect. B*, 1989, **28B**, 866 (*Chem. Abstr.*, 1990, **112**, 158124j).
3. R. M. Abdel-Rahman, Z. El-Gendy, and M. B. Mahmoud, *J. Indian Chem. Soc.*, 1990, **67**, 61 (*Chem. Abstr.*, 1990, **113**, 97499g).
4. P. G. Sekachev, *Khim. Geterotsikl. Soedin*, 1973, 1351 (*Chem. Abstr.*, 1974, **80**, 27156u).
5. S. V. Thiruvikraman and S. Seshadri, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 785.
6. M. H. Elnagdi, S. M. Fahmy, M. R. H. Elmoghayar, and E. M. Kandeel, *J. Heterocycl. Chem.*, 1979, **16**, 61.
7. H. K. Gakhar, V. Parkash, and K. Bhushan, *J. Indian Chem. Soc.*, 1974, **51**, 941 (*Chem. Abstr.*, 1975, **83**, 58709t).
8. H. Eilingsfeld and R. Niess, *Ger. Offen.*, 2,429,195, 05 Feb 1976 (*Chem. Abstr.*, 1976, **84**, 135649y).

9. Z. I. Moskalenko and M. A. Al'perovich, U.S.S.R. 178,381 Jan. 22, 1966, (*Chem. Abstr.*, 1966, **64**, 19628g,h).
10. Z. I. Moskalenko and G. P. Shumelyak, *Khim. Geterotsikl. Soedin.*, **1974**, 932, (*Chem. Abstr.*, 1974, **81**, 120531t).
11. C. B. Vicentini, A. C. Veronese, T. Poli. M. Guarneri, and P. Giori, *Heterocycles*, 1991, **32**, 727.
12. S. Scheibye, B. S. Pedersen, and S. O. Lawesson, *Bull. Soc. Chim. Belg.*, 1978, **87**, 229.
13. A. A. El-Barbary and S. O. Lawesson, *Tetrahedron*, 1981, **37**, 2641.
14. F. De Sio, L. Cecchi, and F. Melani, *Heterocycles*, 1984, **22**, 2309.
15. N. Valls, V. M. Segarra, E. Alcade, A. Marin, and J. Elguero, *J. Prakt. Chem.*, 1985, **327**, 251.
16. J. Elguero, A. Martinez, S. P. Singh, and D. Kumar, *J. Heterocycl. Chem.*, 1991, **28**, 647.
17. G. L'abbé, N. Weyns, and I. Sannen, *J. Heterocycl. Chem.*, 1991, **28**, 405.
18. The method of these authors consists in the condensation of carbonyl compounds with 5-amino-4-mercapto-3-methyl-1-phenylpyrazole, in its turn obtained by acidic hydrolysis of 5-amino-3-methyl-1-phenyl-4-thiocyanatopyrazole⁵. In previous work,²⁰ we found that the acidic hydrolysis of the thiocyanatopyrazole affords the corresponding 4-pyrazolyldisulfide, exhibiting a melting point (178°C) identical to that attributed⁵ to the 4-mercapto intermediate. Therefore the difference in the physical data of compounds (6) reported by these authors and those prepared in our and in other¹⁰ laboratories could be due to a difference in the structure.
19. P. Giori, M. Guarneri, D. Mazzotta, and C.A. Benassi, *Gazz. Chim. Ital.*, 1974, **104**, 707.
20. M. Guarneri, P. Giori, and C. Branca, *Farmaco, Ed. Sc.*, 1971, **26**, 269.

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