Synthesis of Pyrazolo[3,4-*d*]thiazoles†

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Synopsis. Several 5-substituted 1-phenylpyrazolo-[3,4-*d*]thiazole derivatives have been synthesized by reaction of 5-amino-3-methyl-1-phenylpyrazole-4-thiol with different reagents.

There is little information in the literature about pyrazolothiazoles although a good deal of work has been carried out on various other fused pyrazoles. This paper reports a convenient approach to the synthesis of pyrazolo[3,4-*d*]thiazoles.

Thiocyanation of 5-amino-3-methyl-1-phenylpyrazole (**1**) gave rise to the 4-thiocyanato derivative (**2**). The thiocyanato compound was readily hydrolyzed by acid to the amino thiol (**3**). This amino thiol proved to be an excellent precursor for the synthesis of pyrazolo-[3,4-*d*]thiazoles.

Reaction of the amino thiol (**3**) with acetic anhydride gave 3,5-dimethyl-1-phenylpyrazolo[3,4-*d*]thiazole(**4**). The structure of this product (**4a**) was established by its elemental analysis, mass spectrum (*m*/*z* at 229) and its NMR spectrum. The compound exhibited fluorescence in UV light. It was hoped that the introduction of an aromatic ring at the 5-position of the pyrazolothiazole would shift the fluorescence into the visible region.

Reaction of the amino thiol (**3**) with benzoic acid in polyphosphoric acid at high temperature gave rise to the 5-phenyl derivative (**5a**) as shown by its elemental analysis and mass spectrum (*m*/*z* at 291). However, this compound also exhibited fluorescence only in UV.

The amino thiol was therefore reacted with cinnamic acid in polyphosphoric acid and the expected 5-styryl derivative (**5b**) was obtained as shown by elemental analysis and infrared spectrum (absence of -NH and amide carbonyl peaks). The 5-styryl derivative (**5b**) showed pale green fluorescence in daylight.

The amino thiol (**3**) was reacted with ethyl cyanoacetate to give 5-cyanomethyl-3-methyl-1-phenylpyrazolo[3,4-*d*]thiazole (**4b**). The structure of this product was established by elemental analysis and infrared spectrum. (Chart I).

We have earlier[1] shown that *o*-cyanoarylamidines (**6**) readily cyclize with ammonium acetate to yield 4-aminoquinazoline derivative (**7**). It was therefore anticipated that a similar heterocyclization could be achieved by reacting the *o*-thiocyanato amidine (**8**) to yield the aminothiadiazepine derivative (**10**). Accordingly the 5-amino-4-thiocyanatopyrazole (**2**) was reacted with the Vilsmeier reagent (DMF/$POCl_3$) which gave the expected amidine (**8**). Hydrolysis of the amidine (**8**) under mild acidic or alkaline conditions gave mercapto amidine (**9**). Hydrolysis of the mercapto amidine with stronger acid or alkali gave rise to the amino thiol (**3**). Reaction of the thiocyanato amidine with ammonium acetate did not proceed as anticipated but gave rise to the mercapto amidine (**9**) identified by mixed mp and TLC comparison with the authentic sample. (Chart II).

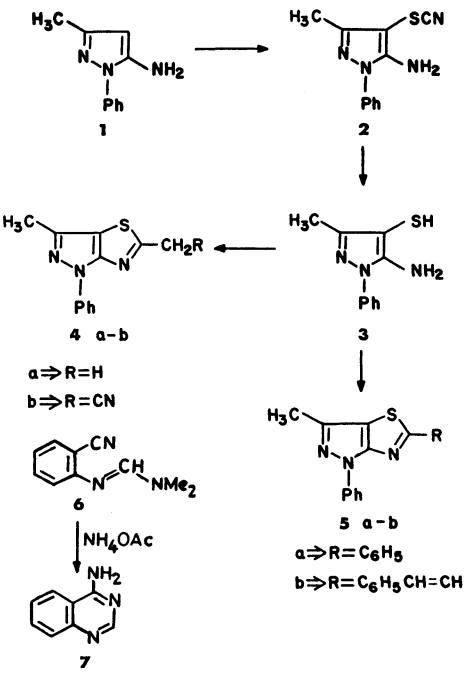

Chart I

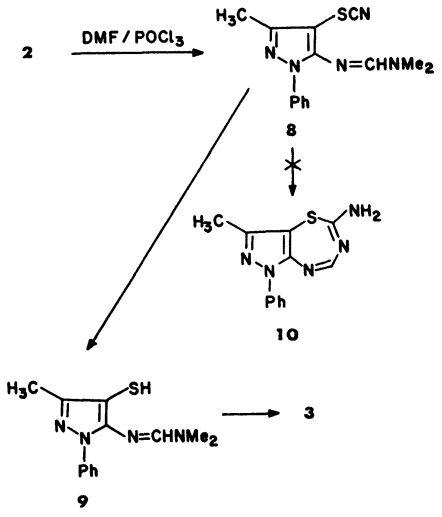

Chart II

Experimental

All melting points are uncorrected. The infrared spectra (in Nujol) were recorded on Perkin Elmer 395 spectrophotometer and ^{1}H-NMR spectra on a Varian EM-360 spectrometer. The mass spectra were recorded on Varian MAT II RS with Varian 100 e data system.

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5-Amino-3-methyl-1-phenyl-4-thiocyanatopyrazole (2). A mixture of aminopyrazole (**1**) (0.01 mol) and potassium thiocyanate(0.03 mol) in MeOH(10 ml) was cooled to 0 °C. Under stirring Br_2(0.01 mol) in MeOH(2 ml) was added dropwise maintaining the temperature below 5 °C. The mixture was stirred for 3 h at 0—5 °C. It was then poured into ice-cold water and neutralized with Na_2CO_3 to pH 9. The yellowish brown thiocyanato compound (**2**) that separated was filtered, washed with water, and dried. The thiocyanato compound (**2**) was obtained in 89% yield and was crystallized from ethanol: mp 115 °C. Found: C, 57.4; H, 4.0, N, 24.0, S, 14.3%. Calcd for $C_{11}H_{10}N_4S$: C, 57.4; H, 4.3; N, 24.3, S, 13.9%; IR: 3300 (NH_2) and 2300 cm^{-1} (SCN).

5-Amino-3-methyl-1-phenylpyrazole-4-thiol (3). A solution of thiocyanato compound (**2**) in dilute HCl (10 ml, 10%) was stirred at room temperature for 4—5 h. The reaction mixture was neutralized with Na_2CO_3 to pH 9 and the yellowish brown compound (**3**) that separated in quantitative yield was crystallized from aqueous ethanol: mp 178 °C. Found: N, 20.4; S, 15.7%; M^+, 205. Calcd for $C_{10}H_{11}N_3S$: N, 20.5; S, 15.6%; M, 205. IR: 3300 cm^{-1} (NH_2).

3,5-Dimethyl-1-phenylpyrazole[3,4-d]thiazole (4a). A mixture of mercaptopyrazole (**3**) and Ac_2O (5 ml) was refluxed for 3 h. After pouring the reaction mixture into ice water the product (**4a**) separated in 85% yield was crystallized from ethanol: mp 148 °C. Found: N, 18.5; S, 14.0%; M^+, 229. Calcd for $C_{12}H_{11}N_3S$: N, 18.3, S, 13.9%; M, 229; ^1H NMR (TFA) δ=2.2 (3H, d, 3-CH_3), 3.0(3H, d, 5-CH_3), 7.4 (5H, s, aromatic).

General Procedure for the Preparation of 5-Aryl-3-methyl-1-phenylpyrazolo[3,4-d]thiazole (5). To polyphosphoric acid (P_2O_5 7 g, H_3PO_4 3 ml) at room temperature, a mixture of 5-aminopyrazole-4-thiol (**3**) (0.005 mol) and aromatic acid (0.005 mol) was added. The reaction mixture was heated to 180 °C and maintained for 1 h. After the usual work up, the product that separated was filtered and washed with water. Thus, the 5-phenyl derivative (**5a**) was obtained in 75% yield and was crystallized from ethanol, mp 152 °C. Found: N, 14.6; S, 11.3; M^+, 291. Calcd for $C_{17}H_{13}N_3S$: N, 14.4; S, 11.0%; M, 291. Also the 5-styryl derivative (**5b**) was obtained in 80% yield and was crystallized from ethanol; mp 200 °C; Found: N, 13.5; S, 9.9%. Calcd for $C_{19}H_{15}N_3S$: N, 13.2, S, 10.1%.

5-Cyanomethyl-3-methyl-1-phenylpyrazolo[3,4-d]thiazole (4b). A mixture of 5-aminopyrazole-4-thiol (**3**) (0.005 mol) and ethyl cyanoacetate (0.005 mol) was heated in an oil bath at 150 °C for 30 minutes. The mixture was cooled, dumped into water, neutralized to pH 6 and filtered. The product was purified by passing through a short column of alumina. It was further crystallized from aqueous ethanol to give **4b** in 72% yield; mp 125 °C. Found, N, 22.1; S, 12.5%. Calcd for $C_{13}H_{10}N_4S$: N, 22.1; S, 12.5%. IR 2240 cm^{-1}(CN) and absence of NH and amide carbonyl peaks.

Vilsmeier Reaction on 5-Amino-4-thiocyanatopyrazole (2). To the Vilsmeier reagent from DMF (7 ml) and $POCl_3$(0.02 mol) at 0—5 °C, 5-amino-4-thiocyanatopyrazole(0.01 mol) was added. After half hour the temperature was raised to 70 °C and maintained for 3 h. After pouring the reaction mixture into ice water, the pH was adjusted to 9 with Na_2CO_3. The oil separated was extracted in C_6H_6 and solvent removed to obtain **8** in 80% yield. Found, N, 24.8; S, 11.2%; M^+, 260. Calcd for $C_{14}H_{15}N_5S$: N, 24.5; S, 11.2%; M^+, 260. IR 2250 cm^{-1}(SCN).

Hydrolysis of Thiocyanatoamidine (8). A mixture of thiocyanatoamidine (**8**) (1 g) and HCl (10 ml, 10%) or NaOH (10 ml, 10%) was stirred overnight. The solution was cooled and neutralized to pH 8—9, when an oil separated. The benzene extract of the oil when eluted with C_6H_6 over a neutral alumina column afforded **9** in 80% yield, crystallized as yellow crystals from ethanol; mp 110 °C. Found: N, 21.4; S, 12.4%. Calcd for $C_{13}H_{16}N_4S$: N, 21.5; S, 12.3%, IR: absence of SCN peak at 2250 cm^{-1} and presence of a weak band at 2500 cm^{-1} for SH function.

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References

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