Monatshefte für Chemie 126, 1391–1400 (1995)

Monatshefte für Chemie
Chemical Monthly

Reaction of 3-Phenyl-5-aminopyrazole with Carbon Disulfide: A Novel Synthesis of 3-(3′-Phenylpyrazol-5′-yl)-4-phenylpyrazol-2-thione as well as of Pyrazolo[3,4-*d*]thiazole and Pyrano[2,3-*d*]thiazole Derivatives

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Summary. 3-Phenyl-5-aminopyrazole (**1**) reacts with carbon disulfide, followed by *in situ* reaction with α-haloketones **3a–c**, to afford **5**, **7a**, and **7b**, respectively. Compounds **5** and **7** were further utilized for the formation of heterocycles and their fused derivatives.

Keywords. Aminopyrazole; Pyrazolo[3,4-*d*]thiazole; Pyrano[2,3-*d*]thiazole.

Reaktion von 3-Phenyl-5-aminopyrazol mit Schwefelkohlenstoff: Ein neue Synthese von 3-(3′-Phenylpyrazol-5′-yl)-4-phenylprazol-2-thion sowie von Pyrazolo[3,4-*d*]thiazol- und Pyrano[2,3-*d*]thiazolderivaten

Zusammenfassung. 3-Phenyl-5-aminopyrazol (**1**) reagiert mit Schwefelkohlenstoff und anschließend *in situ* mit den α-Halogenketonen **3a–c** zu **5**, **7a** und **7b**. Die Verbindungen **5** und **7** wurden weiter zu Heterocyclen und ihren kondensierten Derivaten umgesetzt.

Introduction

Many pyrazole derivatives have been reported to be of use as antipyretic and analgesic drugs [1–3], bactericides, and fungicides [4]. On the other hand, thiazoles are known to be highly biologically active reagents [5–8]. Therefore, compounds containing both the pyrazole and thiazole moities are expected to posses potential biological activities. Thus we report herein the synthesis of heterocyclic compounds containing the two mentioned rings *via* the readily available 3-phenyl-5-amino-pyrazole (**1**) as starting material.

Results and Discussion

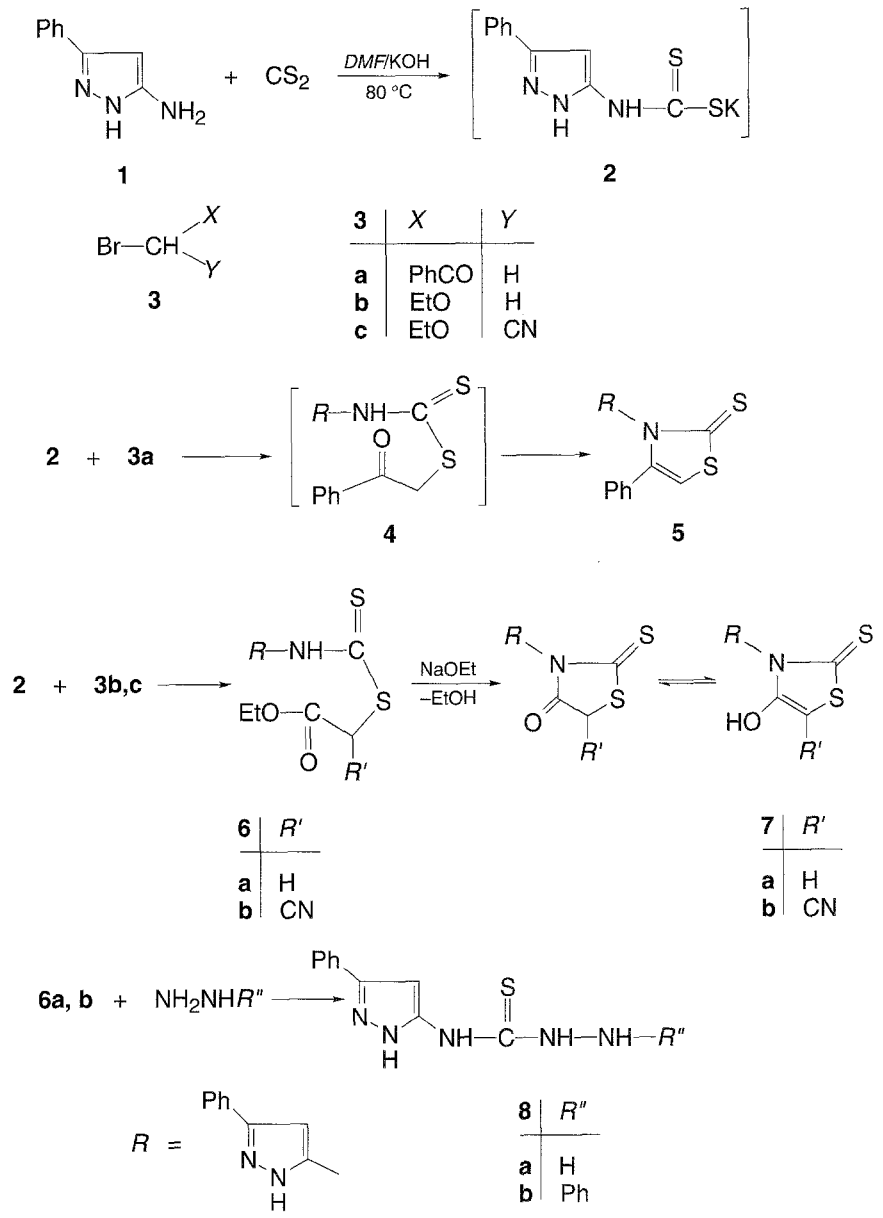
3-Phenyl-5-aminopyrazole (**1** [9]) reacts with carbon disulfide in dry *DMF* containing potassium hydroxide at 80 °C to give the nonisolable potassium thiocarbamate **2** [10]. Treatment of **2** with phenacylbromide **3a** afforded 4-phenyl-3-(3′-phenyl-

pyrazol-5′-yl)-thiazole-2-thione (**5**). Its structure was confirmed on the basis of analytical and spectroscopic data. Thus, the IR spectrum of compound **5** showed a week absorption band at $\nu = 1200–1190\,cm^{-1}$ (C=S stretching). Moreover, the ^1H NMR spectrum revealed the presence of three singlets at $\delta = 6.41$, 6.75, and 8.42 (D_2O exchangeable) ppm (pyrazole H-4, thiazole H-5, NH) and two multiplets at 7.33–7.49 ppm (phenyl protons).

When the thiocarbamate salt **2** was treated with ethyl bromoacetate (**3b**) and ethyl α-bromocyanoacetate (**3c**), it afforded the thioester derivatives **6a** and **6b**, respectively. Upon heating in sodium ethoxide solution, compounds **6a** and **6b** were cyclized to afford the thiazole derivatives **7a** and **7b**, respectively. Structure **7** was established on the basis of analytical and spectroscopic data (see Experimental). Compound **6a** reacted with hydrazine hydrate to afford 4-(3′-phenyl-5′-yl)-3-thiosemicarbazide (**8a**). Its structure was established on the basis of analytical and spectroscopic data and through its independent synthesis. Thus, the ^1H NMR spectrum of **8a** revealed, in addition to the aromatic multiplet at $\delta = 7.32–7.41$ ppm, the presence of two singlets at $\delta = 4.48$ (NH_2) and 6.89 (pyrazole H-4) ppm and three D_2O exchangeable singlets at $\delta = 8.23$, 8.41, and 8.50 ppm (three NH groups). Compound **6b** also reacted with hydrazine hydrate to afford a product identical in all aspects (spectroscopic data, m.p., and mixed m.p.) to **8a**. In a similar manner, compounds **6a** and **6b** reacted with phenyl hydrazine to afford an identical product (1-phenyl- 4-(3′-phenyl-5′-yl)-3-thiosemicarbazide, **8b**; (Scheme 1).

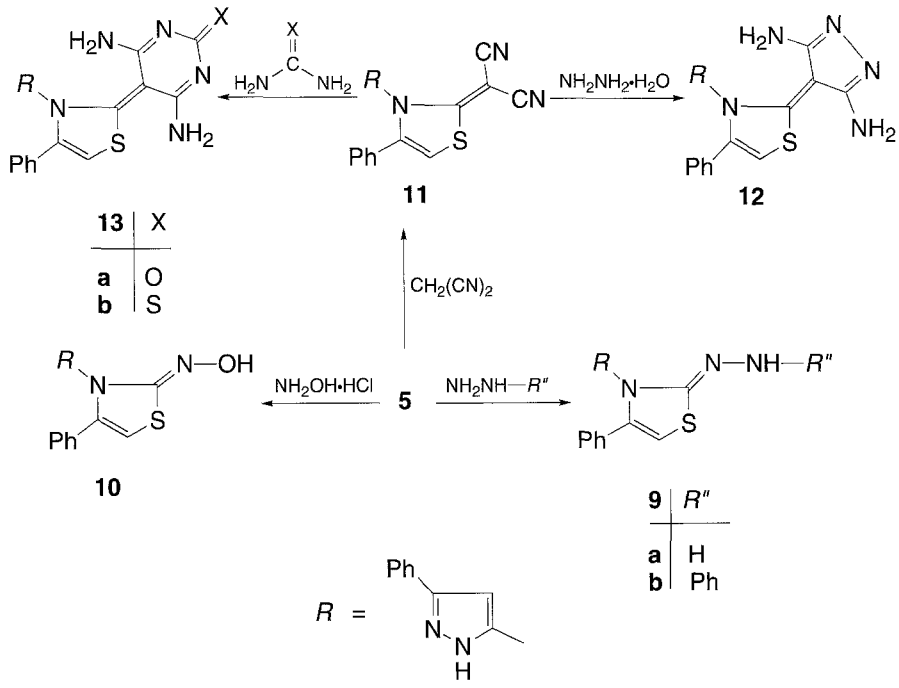
The potential reactivity of compound **5** towards chemical reagents to afford heterocycles and fused heterocycles was demonstrated. Thus, the reaction of **5** with hydrazine hydrate and phenyl hydrazine gave the hydrazone derivatives **9a** and **9b**, respectively. The formation of **9a** and **9b** takes place *via* loss of hydrogen sulfide. In a similar manner, compound **5** reacted with hydroxylamine hydrochloride to afford the oxime derivative **10**. The reaction of **5** with malononitrile in dioxane containing piperidine gave the dicyanomethino derivative **11**. Structure **11** was confirmed on the basis of analytical and spectroscopic data. Thus, the IR spectrum of the reaction product revealed the presence of two cyano group absorption bands at $\nu = 2225$ and $2220\,cm^{-1}$, whereas its mass spectrum showed the molecular ion at $m/e = 367$. Compound **11** reacted with hydrazine hydrate to afford almost quantitatively the pyrazolidenothiazole derivative **12.** Structure **12** was confirmed on the basis of spectroscopic data. The IR spectrum of compound **12** revealed absorption bands at $\nu = 3480–3365\,cm^{-1}$ due to the NH_2 and NH groups; no absorption was observed in the $\nu = 2250–2150\,cm^{-1}$ region, thus excluding the presence of a cyano function. The ^1H NMR spectrum showed, beside the expected signals for rest of the molecule, the presence of two D_2O exchangeable singlets at $\delta = 4.67$ and 5.34 ppm attributable to the two NH_2 groups. A similar formation of 3,5-diaminopyrazoles from dicyanomethino derivatives has been reported [11]. In similar way, compound **11** also reacted with urea and thiourea in sodium ethoxide solution, yielding the pyrimidine derivatives **13a** and **13b**, respectively (Scheme 2).

On the other hand, the reaction of compound **7a** with benzaldehyde in refluxing *DMF* containing a catalytic amount of piperidine afforded the benzal derivative **14** which subsequently reacted with malononitrile to give the pyrano[2,3-*d*]thiazole derivative **15**. Its structure was established on the basis of analytical and spectral



Scheme 1

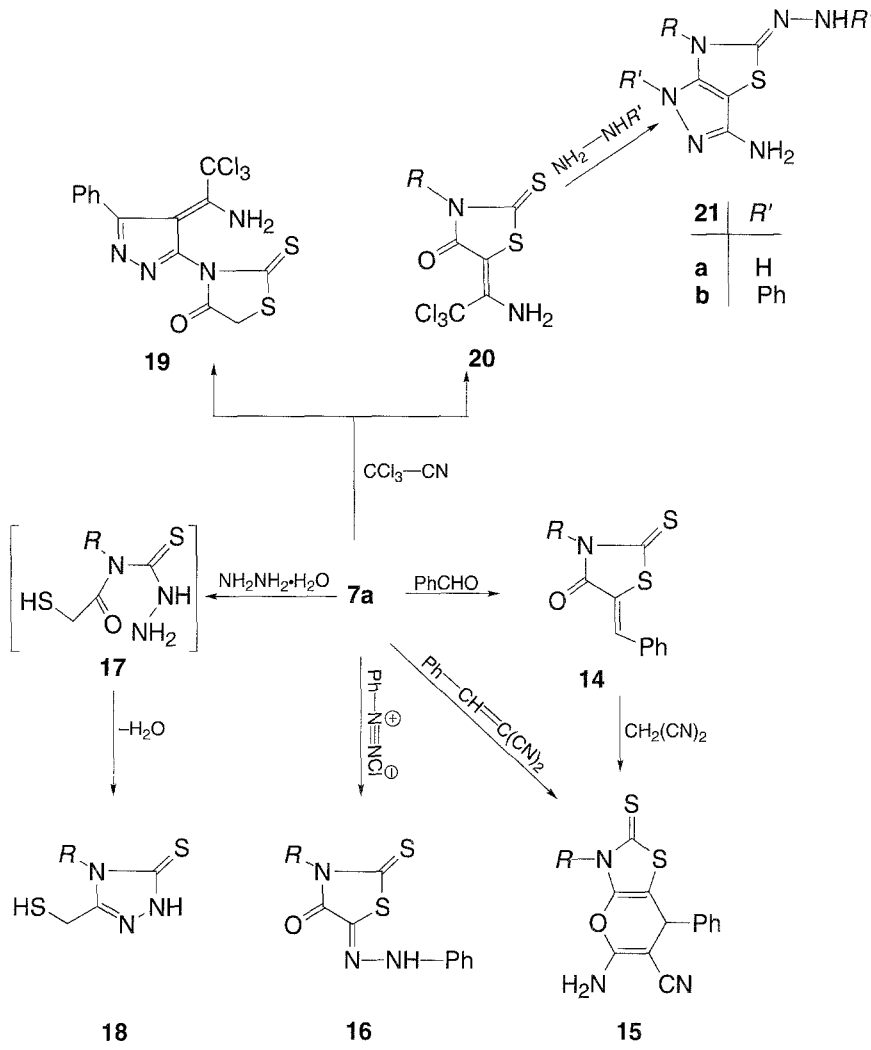
data and through the independent synthesis of compound **15**. The IR spectrum of **15** showed the presence of NH_2 and NH absorption bands at 3460–3375 cm^{-1}, a CN absorption band at 2220 cm^{-1}, and a C=S absorption band at 1205 cm^{-1}. The ^1H NMR spectrum revealed the presence of two D_2O exchangeable singlets at 3.89 and 8.26 ppm (NH_2 and NH protons), two singlets at 6.67 and 6.84 ppm (pyrazole H-4 and pyran H-4), and a multiplet at 7.32–7.54 ppm (two phenyl protons). Furthermore, the reaction of compound **7a** with benzalmalononitrile in refluxing dioxan containing a catalytic amount of triethylamine afforded a product



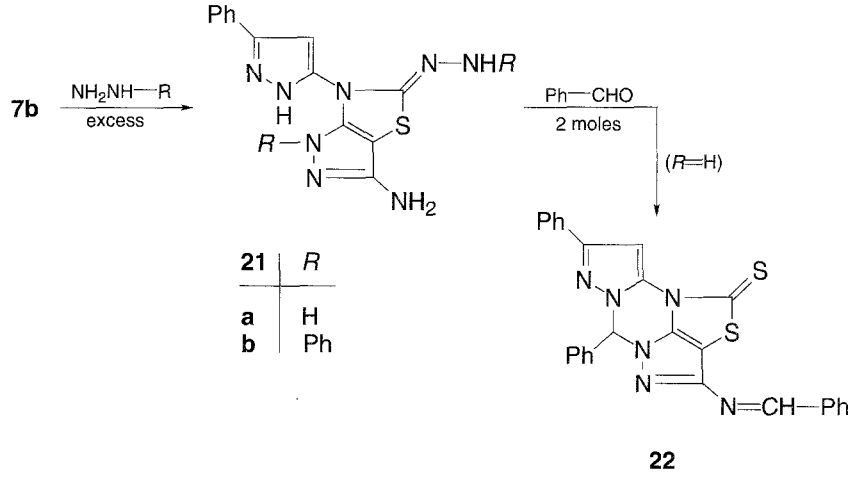
Scheme 2

identical in all aspects (m.p., mixed m.p., and spectroscopic data) to compound **15** (Scheme 3).

The reactivity of **7a** with respect to coupling reactions with diazonium salts was studied. The reaction of **7a** with an equivalent amount of benzenediazonium chloride gave the phenylhydrazone derivative **16**. Moreover, the reaction of **7a** with hydrazine hydrate gave the triazole derivative **18**. Formation of **18** is believed to proceed through the intermediate formation of **17** [12]. The reaction of **7a** with trichloroacetonitrile afforded a single product with a molecular formula of $C_{14}H_9Cl_3N_4OS_2$. Two possible isomeric structures were proposed (**19** and **20**). Structure **19** was ruled out on the basis of the ^{1}H NMR spectrum of the reaction product which revealed the existence of the pyrazole H-4 in its usual position at $\delta = 6.80$ ppm together with the absence of the thiazole CH_2 protons signal (around 4.0 ppm). Moreover, the reaction product **20** was readily cyclized upon reaction with hydrazine hydrate and phenylhydrazine to form the pyrazolo[3,4-*d*]thiazole derivatives **21a** and **21b**, respectively. The formation of **21** is believed to proceed *via* nucleophilic substitution of the CCl_3 group by the hydrazine molecule followed by cyclization through water elimination (see Scheme 3). The reaction of **7b** with a two fold amount of hydrazine hydrate or phenyl hydrazine afforded the identical pyrazolo[3,4-*d*]thiazole derivatives **21a** and **21b**, respectively (m.p.). Furthermore, compound **21a** reacted with two equivalents of benzaldehyde in *DMF* containing a catalytic amount of piperidine to afford the annelated compound **22**. The structure of **22** was established on the basis of analytical and spectroscopic data (see Experimental and Scheme 4).



Scheme 3



Scheme 4

Experimental

M.p.s and uncorrected. IR spectra (KBr: Pye Unicam SP-1000; MS(*m/z*): 70 eV; ^{1}H NMR spectra (*DMSO*-d_6): Varian EM-300 (300 MHz, *TMS* as internal standard, δ (ppm); microanalytical data: Micro Analytical Data Unit at Cairo University.

Preparation of **5**, **6a**, *and* **6b** *(general procedure)*

To a solution of **1** (0.01 mol) in *DMF* (30 ml), a solution of KOH (0.01 mol in 10 ml H_2O) was added followed by (0.01 mol). The reaction mixture was heated in a water bath at 80 °C for 2 h and then left to cool to 20 °C. After addition of the appropriate halogen compound **3a**, **3b**, or **3c** (0.01 mol), the reaction mixture was stirred at 20 °C for 1 h and the solid product formed upon pouring onto ice containing few drops of hydrochloric acid ($pH = 6$) was collected by filtration.

3-(3′-Phenylpyrazol-5′-yl)-4-phenylthiazol-2-thione (**5**)

Yellow crystals from EtOH, yield 90%, m.p. 190 °C; $C_{18}H_{13}N_3S_2$ (335.4); calc.: C 64.4; H 3.9, N 12.5, S 19.1; found: C 64.3; H 4.2, N 12.2, S 19.3; IR: 3420–3345 (NH), 3060 (CH aromatic), 1650 (C=N), 1640 (C=C), 1200–1190 (C=S); ^{1}H NMR: 6.41, 6.75 (2s, 2H, pyrazole H-5, thiazole H-5), 7.33–7.49 (2m, 10H, $2C_6H_5$), 8.42 (s, 1H, NH); MS: 335 (M^+).

5-(Ethyl acetatothiocarbamato)-3-phenylpyrazole (**6a**)

Pale yellow crystals from ethanol, yield 78%, m.p. 195 °C; $C_{14}H_{15}N_3O_2S_2$ (321.4); calc.: C 52.3, H 4.7, N, 13.1, S 19.9; found: C 52.2, H 4.8, N 12.9, S 19.7; IR: 3460–3325 (2 NH), 3060 (CH aromatic), 2980, 2875 (CH_3, CH_2), 1690 (C=O), 1660 (C=N), 1635 (C=C); ^{1}H NMR: 1.36 (t, 3H, $J = 8.02$ Hz, CH_3), 3.23 (s, 2H, $J = 8.02$ Hz, CH_2), 4.42 (q, 2H, CH_2), 6.87 (s, 1H, pyrazole H-4), 7.32–7.45 (m, 5H, C_6H_5), 8.44, 8.67 (2s, 2H, NH).

5-(Ethyl cyanoacetatothiocarbamato)-3-phenylpyrazole (**6b**)

Orange crystals from ethanol, yield 69%, m.p. 212 °C; $C_{15}H_{14}N_4O_2S_2$ (346.4); calc.: C 52.0, H 4.1, N 16.2, S 18.5; found: C 52.3, H 3.8, N 16.4, S 18.2; IR: 3450–3385 (2 NH), 3055 (CH aromatic), 2985 (CH_3), 2870 (CH_2), 2220 (CN), 1695 (C=O), 1665 (C=N), 1640 (C=N), 1205–1900 (C=S); ^{1}H NMR: 1.37 (t, 3H, $J = 8.23$ Hz, CH_3), 4.29 (q, 2H, $J = 8.23$ Hz, CH_2), 4.87 (s, 1H, CH), 6.88 (s, 1H, pyrazole H-4), 7.33–7.47 (m, 5H, C_6H_5), 8.28, 8.47 (s, 2H, 2 NH).

Cyclization of **6a** *and* **6b**

A solution of **6a** (0.01 mol) or **6b** (0.01 mol) in ethanol (50 ml) containing sodium hydroxide (0.5 g) was heated under reflux for 12 h. The solid product formed upon pouring onto ice/water containing hydrochloric acid ($pH = 6$) was collected by filtration.

4-Hydroxy-3-(3′-phenylpyrazolo-5′-yl)-thiazole-2-thione (**7a**)

Yellow crystals from dioxane, yield 72%, m.p. 250–252 °C; $C_{12}H_9N_3OS_2$ (275.3); calc.: C 52.3, H 3.3, N 15.3, S 23.3; found: C 52.0, H 3.4, N 15.0, S 23.5; IR: 3520–3460 (OH, NH), 3060 (CH aromatic), 1650 (C=N), 1635 (C=C), 1230 (C=S); ^{1}H NMR: 6.63, 6.78 (2s, 2H, pyrazole H-4, thiazole H-5), 7.32–7.36 (m, 5H, C_6H_5), 8.34 (s, 1H, NH), 10.36 (s, 1H, OH).

5-Cyano-3-(3′-phenylpyrazolo-5′-yl)-4-hydroxythiazole-2-thione (**7b**)

Orange crystals from dioxane, yield 59%, m.p. 113 °C; $C_{13}H_8N_4OS_2$ (300.3); calc.: C 52.0, H 2.7, N 18.6, S 21.3; found: C 51.8, H 3.0, N 18.9, S 21.0; IR: 3540–3365 (OH, NH), 3060 (CH aromatic), 2220 (CN),

1650 (C=N), 1635 (C=C), 1230 (C=S); ^{1}H NMR: 6.35 (s, 1H, pyrazole H-4), 7.25–7.39 (m, 5H, C_6H_5), 8.56 (s, 1H, NH), 10.45 (s, 1H, OH).

Preparation of the thiosemicarbazide derivatives **8a, b** *(general procedure)*

To a solution of **6a** (0.01 mmol) or **6b** (0.01 mol) in ethanol, hydrazine hydrate (0.01 mol) or phenylhydrazine (0.01 mol) was added. The reaction mixture was heated under reflux for 12 h. The solid product formed upon pouring onto ice/water containing few drops of HCl was collected by filtration.

4-(3′-Phenylpyrazolo-5′-yl)-thiosemicarbazide (**8a**)

White crystals from dioxane, yield 77%, m.p. 179 °C; $C_{10}H_{11}N_5S$ (233.3); calc.: C 51.5, H 4.7, N 30.0, S 13.7; found: C 51.7, H 4.4, N 29.8, S 13.9; IR: 3460–3370 (NH_2, 3 NH), 3050 (CH aromatic), 1655 (C=N), 1635 (C=C), 1230 (C=S); ^{1}H NMR: 4.48 (s, 2H, NH_2), 6.89 (s, 1H, pyrazole H-4), 7.32–7.41 (m, 5H, C_6H_5), 8.23, 8.41, 8.50 (3s, 3H, 3 NH).

4-(3′-Phenylpyrazolo-5′-yl)-1-phenylthiosemicarbazide (**8b**)

Yellow crystals from *DMF*, yield 63%, m.p. 212 °C; $C_{16}H_{15}N_5S$ (309.37); calc.: C 62.1, H 4.9, N 22.6, S 10.4; found: C 62.0, H 5.1, N 22.4, S 10.4; IR: 3460–3380 (3 NH), 3060 (CH aromatic), 1650 (C=N), 1635 (C=C), 1250 (C=S); ^{1}H NMR: 6.78 (s, 1H, pyrazole H-4), 7.32–7.41 (m, 10H, 2 C_6H_5), 8.37, 8.40–8.43 (4s, 4H, 4 NH).

4-Phenyl-3-(3′-phenylpyrazolo-5′-yl)-2-ylidinomalononitrilothiazole (**11**)

To a solution of **5** (0.01 mol) in dioxane (30 ml) containing piperidine (0.5 ml), malononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 5 h and then evaporated *in vacuo*. The remaining product was triturated with ethanol and the formed solid product was collected by filtration and crystallized from *DMF*. Yield 68%, m.p. 167 °C; $C_{21}H_{13}N_5S$ (367.4); calc.: C 68.6, H 3.6, N 19.1, S 8.7; found: C 68.4, H 3.7, N 19.2, S 8.9; IR: 3460–3320 (NH), 3060 (CH aromatic), 2225, 2220 (2 CN), 1655 (C=N), 1640 (C=C); ^{1}H NMR: 6.56, 6.89 (2s, 2H, pyrazole H-4, thiazole H-2), 7.32–7.40 (m, 10H, 2 C_6H_5), 8.45 (s, 1H, NH); MS: 367 (M^+).

Preparation of **9a**, **9b**, **12**, *and* **18** *(general procedure)*

The same experimental procedure described before for the synthesis of **8a** and **8b** was carried out except for the use of **5** (0.01 mol) to form **9a** and **9b** instead of **6a**, the use of **11** (0.01 mol) to form **12**, and the use of **7a** (0.01 mol) to form **18**.

2-Hydrazono-4-phenyl-3-(3′-phenylpyrazolo-5′-yl)-thiazole (**9a**)

Orange crystals from dioxane, yield 65%, m.p. 234 °C; $C_{18}H_{15}N_5S$ (333.4); calc.: C 64.8, H 4.5, N 21.0, S 9.6; found: C 64.6, H 4.6, N 20.8, S 9.5; IR: 3455–3365 (NH_2, NH), 3060 (CH aromatic), 1675 (exocyclic C=N), 1640 (C=C); ^{1}H NMR: 4.79 (s, 2H, NH_2), 6.75, 6.89 (2s, 2H, pyrazole H-4, thiazole H-5), 7.34–7.46 (m, 10H, 2 C_6H_5), 8.69 (s, 1H, NH).

2-Phenylhydrazono-4-phenyl-3-(3′-phenylpyrazolo-5′-yl)-thiazole (**9b**)

Orange crystals from dioxane, yield 74%, m.p. 179 °C; $C_{24}H_{19}N_5S$ (409.5); calc.: C 70.4, H 4.7, N 17.1, S 7.8; found: C 70.6, H 4.7, N 16.9, S 8.0; IR: 3465–3365 (2 NH), 3060 (CH aromatic), 1670 (exocyclic C=N), 1645 (C=C); ^{1}H NMR: 6.67, 6.89 (2s, 2H, pyrazole H-4, thiazole H-5), 7.29–7.43 (m, 15H, 3 C_6H_5), 8.47, 8.71 (2s, 2H, 2 NH).

2-(2',3'-Diaminopyrazol-4'-ylideno)-4-phenyl-3-(3''-phenylpyrazolo-5''-yl)-thiazole (**12**)

Yellow crystals from *DMF*, yield 79%, m.p. >300 °C; $C_{21}H_{17}N_7S$ (399.4); calc.: C 63.1, H 4.3, N 24.5, S 8.0; found: C 63.2, H 4.5, N 24.7, S 8.4; IR: 3480–3365 (2 NH_2, NH), 3060 (CH aromatic), 1660 (C=N), 1640 (C=C); ^{1}H NMR: 4.67, 5.34 (2s, 4H, 2 NH_2), 6.61, 6.79 (2s, 2H, pyrazole H-4, thiazole H-5), 7.34–7.49 (m, 10H, 2 C_6H_5).

4-(3'-Phenylpyrazolo-5'-yl)-3-methylmercapto-1H-1,2,4-triazole-5-thione (**18**)

Yellow crystals from dioxane, yield 80%, m.p. >300 °C; $C_{12}H_{11}N_5S_2$ (289.3); calc.: C 49.8, H 3.8, N 24.2, S 22.1; found: C 49.7, H 3.6, N 24.0, S 22.3; IR: 3460–3365 (2 NH), 3320 (SH), 3060 (CH aromatic), 1660 (C=N), 1640 (C=C), 1230 (C=S); ^{1}H NMR: 4.24 (s, 2H, CH_2), 6.67 (s, 1H, pyrazole H-4), 7.24–7.45 (m, 5H, C_6H_5), 7.59 (s, br, 1H, SH), 8.45, 8.79 (2s, 2H, 2 NH).

4-Phenyl-3-(3'-phenylpyrazolo-5'-yl)-2-oximothiazole (**10**)

To a solution of **5** (0.01 mol) in ethanol containing sodium acetate (0.01 mol), hydroxylamine hydrochloride (0.01 mol) was added. The reaction mixture was heated under reflux for 9 h and then poured into water. The formed solid product was collected by filtration. Yellow crystals from ethanol, yield 56%, m.p. 194 °C; $C_{18}H_{14}N_4OS$ (334.4); calc.: C 64.6, H 4.2, N 16.7, S 9.6; found: C 64.5, H 4.0, N 16.8, S 9.7; IR: 3560–3375 (OH, NH), 3050 (CH aromatic), 1650 (C=N), 1635 (C=C); ^{1}H NMR: 6.56 (s, 1H, NH), 6.68, 6.92 (2s, 2H, pyrazole H-4, thiazole H-5), 7.32–7.48 (m, 10H, 2 C_6H_5), 10.43 (s, 1H, OH).

Preparation of the pyrimidine derivatives **13a** *and* **13b** *(general procedure)*

To a solution of **11** (0.01 mol) in sodium ethoxide solution (0.01 mol, prepared by adding sodium metal (0.01 g-atom) to absolute ethanol (30 ml)), urea (0.01 mol) or thiourea (0.01 mol) was added. The reaction mixture was heated in a boiling water bath for 7 h and then poured onto ice/water containing hydrochloric acid ($pH = 6$). The formed solid product was collected by filtration.

4,6-Diamino-2-oxo-5-(4'-phenylthiazolo-3'-(3''-phenylpyrazolo-5''-yl)-2-ylideno)-pyrimidine **13a**

Orange crystals from *DMF*, yield 87%, m.p. 134 °C; $C_{22}H_{17}N_7OS$ (427.5); calc.: C 61.8, H 4.0, N 22.9, S 7.5; found: C 61.5; H 3.7, N 23.1, S 7.4; IR: 3460–3365 (2 NH_2, NH), 1700 (C=O), 1660 (C=N), 1645 (C=C); ^{1}H NMR: 4.78, 5.64 (2s, 4H, 2 NH_2), 6.56, 6.89, (2s, 2H, pyrazole H-4, thiazole H-5), 7.34–7.47 (m, 10H, 2 C_6H_5), 8.59 (s, 1H, NH).

4,6-Diamino-5-(4'-phenylthiazolo-3'-(3''-phenylpyrazolo-5''-yl)-2-ylideno)-pyrimidine-2-thione **13b**

Orange crystals from *DMF*, yield 67%, m.p. 189 °C; $C_{22}H_{17}N_7S_2$ (443.5); calc.: C 59.6, H 3.8, N 22.1, S 14.4; found: C 59.3, H 3.7, N 22.0, S 14.5; IR: 3450–3360 (2 NH_2, NH), 3060 (CH aromatic), 1650 (C=N), 1640 (C=C), 1205 (C=S); ^{1}H NMR: 4.74, 5.70 (2s, 4H, 2 NH_2), 6.57, 6.92 (2s, 2H, pyrazole H-4, thiazole H-5), 7.30–7.45 (m, 10H, 2 C_6H_5), 8.34 (s, 1H, NH).

5-Benzal-3-(3'-phenylpyrazolo-5'-yl)-4-oxothiazole-2-thione (**14**)

Equimolar quantities (0.01 mol) of **7a** and benzaldehyde in absolute ethanol (40 ml) containing piperidine (0.5 ml) were heated under reflux for 5 h and then evaporated *in vacuo*. The remaining product was triturated with diethyl ether and the formed solid product was collected by filtration. Orange crystals from ethanol, yield 69%, m.p. 201–203 °C; $C_{19}H_{13}N_3OS_2$ (363.4); calc.: C 62.8, H 3.6,

N 11.6, S 17.6; found: C 62.6, H 3.8, N 11.7, S 17.8; IR: 3450–3385 (NH), 3060 (CH aromatic), 1695 (C=O), 1660 (C=N), 1640 (C=C), 1250 (C=S); ^{1}H NMR: 6.56 (pyrazole H-4), 6.99 (s, 1H, CH=C), 7.23–7.46 (m, 10H, 2 C_6H_5), 8.78 (s, 1H, NH); MS: 363 (M^+).

5-Amino-6-cyano-7-phenyl-3-(3'-phenylpyrazolo-5'-yl)-pyrano[2,3-d]thiazole-2-thione (**15**)

Method A: To a solution of **14** (0.01 mol) in *DMF* (30 ml) containing triethylamine (0.5 ml), malononitrile (0.01 mol) was added and the reaction mixture was heated under reflux for 10 h. The solid product formed upon pouring onto ice/water was collected by filtration.

Method B: To a solution of **7a** (0.01 mol) in *DMF* (25 ml) containing triethylamine (0.5 ml), benzalmalononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 4 h and then evaporated *in vacuo*. The remaining product was triturated with ethanol and the formed solid product was collected by filtration.

Brown crystals from dioxane, yield 82% (*Method A*), 77% (*Method B*), m.p. 233 °C; $C_{22}H_{15}N_5OS_2$(429.5); calc.: C 61.5, H 3.5, N 16.3, S 14.9; found: C 61.2, H 3.7, N 16.0, S 15.3; IR: 3460–3375 (NH_2, NH), 2220 (CN), 1205 (C=S); ^{1}H NMR: 3.89 (s, 2H, NH_2), 6.67, 6.84 (pyrazole H-4, pyran H-4), 7.32–7.54 (m, 10H, 2 C_6H_5), 8.26 (s, 1H, NH).

4-Oxo-5-phenylhydrazono-3-(3'-phenylpyrazolo-5'-yl)-thiazole-2-thione (**16**)

To a cold solution (0–5 °C) of **7a** (0.01 mol) in ethanol containing sodium hydroxide (0.02 mol), benzenediazonium chloride (0.01 mol, prepared by adding sodium nitrite solution (0.01 mol) to a cold solution (0–5 °C) of aniline (0.01 mol) containing the appropriate quantity of hydrochloric acid with continuous stirring) was added with stirring. The reaction mixture was left at 0–5 °C for 4 h and the formed solid product was collected by filtration.

Red crystals from ethanol, yield 80%, m.p. 156 °C; $C_{18}H_{13}N_5OS_2$ (379.4); calc.: C 65.9; H 3.4, N 18.4, S 16.9; found: C 56.6, H 3.6, N 18.7, S 17.2; IR: 3460–3410 (2 NH), 3055 (CH aromatic), 1700 (C=O), 1650 (C=N), 1645 (C=C), 1220 (C=S); ^{1}H NMR: 6.58 (s, 1H, pyrazole H-4), 7.27–7.48 (m, 10H, 2 C_6H_5), 8.34, 8.72 (2s, 2H, 2 NH); MS: 379 (M^+).

5-(α-Amino-β-trichloroethanylidino-3-(3'-phenylpyrazolo-5'-yl)-4-oxothiazole-2-thione (**20**)

A solution of **7a** (0.01 mol) in absolute ethanol (50 ml) containing sodium acetate (0.01 mol) was treated with trichloroacetonitrile (0.01 mol). The whole reaction mixture with stirred at room temperature (25 °C) for 24 h. The solid product formed upon dilution with water was collected by filtration.

White crystals from dioxane, yield 81%, m.p. 253–255 °C; $C_{14}H_9Cl_3N_4OS_2$ (419.7); calc.: C 40.1, H 2.1, Cl 25.3, N 13.3, S 15.3; found: C 39.8, H 2.0, Cl 24.9, N 13.6, S 15.5; IR: 3460–3360 (NH_2, NH), 3060 (CH aromatic), 1695 (C=O), 1650 (C=N), 1640 (C=C), 1250 (C=S); ^{1}H NMR: 4.45 (s, 2H, NH_2), 6.80 (s, 1H, pyrazole H-4), 7.32–7.42 (m, 5H, C_6H_5), 8.36 (s, 1H, NH).

Preparation of **21a** *and* **21b** *(general procedure)*

To a solution of **20** (0.01 mol) or **7b** (0.01 mol) in *DMF* (30 ml), hydrazine hydrate (0.02 mol) or phenylhydrazine (0.02 mol) was added. The reaction mixture was heated under reflux for 12 h. The solid product formed upon pouring onto ice/water containing few drops of hydrochloric acid was collected by filtration.

6-Amino-7H-2-hydrazono-3-(3'-phenylpyrazolo-5'-yl)-pyrazolo[3,4-d]thiazole (**21a**)

Yellow crystals from dioxane, yield 55% (from **20**), 62% (from **7b**), m.p. 125 °C; $C_{13}H_{12}N_8S$ (312.3); calc.: C 50.0, H 3.8, N 35.9, S 10.3; found: C 50.1, H 4.1, N 35.7, S 10.6; IR: 3460–3340 (2 NH_2, 2 NH),

3060 (CH aromatic), 1675 (exocyclic C=N), 1645 (C=C); ^{1}H NMR: 4.45, 5.37 (2s, 4H, 2 NH_2), 6.78 (s, 1H, pyrazole H-4), 7.34–7.48 (m, 5H, C_6H_5), 8.35, 8.42 (2s, 2H, 2 NH); MS: 312 (M^+).

6-Amino-7H-2-phenylhydrazono-3-(3'-phenylpyrazolo-5'-yl)-pyrazolo[3,4-d]thiazole (**21b**)

Yellow crystals from *DMF*, yield 51% (from **20**), 68% (from **7b**), m.p. 184 °C; $C_{25}H_{20}N_8S$ (464.5); calc.: C 64.6; H 4.3, N 24.1, S 6.9; found: C 64.6, H 4.4, N 24.0, S 6.8; IR: 3460–3335 (NH_2, 2 NH), 3060 (CH aromatic), 1670 (exocyclic C=N), 1640 (C=C); ^{1}H NMR: 4.56 (s, 2H, NH_2), 6.79 (s, 1H, pyrazole H-4), 7.34–7.46 (m, 10H, 2 C_6H_5), 8.41, 8.48 (2s, 2H, 2 NH).

Synthesis of the annelated derivative **22**

To a solution of **21a** (0.01 mol) in *DMF* (30 ml) containing piperidine (0.5 ml), benzaldehyde (0.01 mol) was added. The reaction mixture was heated under reflux for 10 h. The solid product formed upon pouring onto ice/water was collected by filtration.

Orange crystals from dioxane, yield 62%, m.p. 289–293 °C; $C_{27}H_{20}N_8S$ (488.5); calc.: C 66.4, H 4.1, N 22.9, S 6.6; found: C 66.1, H 3.8, N 23.2, S 6.5; IR: 3470–3345 (NH_2), 3050 (CH aromatic), 1660 (exocyclic C=N), 1645 (C=C); ^{1}H NMR: 4.49 (s, 2H, NH_2), 6.81 (s, 1H, pyrazole H-4), 6.99 (s, 1H, CH=C), 7.02 (s, H, triazine H-2) 7.30–7.49 (m, 15H, 3 C_6H_5); MS: 488 (M^+).

Acknowledgements

R. M. Mohareb is greatly indebted to the *Alexander von Humboldt Foundation*, Germany, for a fellowship.

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Received June 1, 1995. Accepted June 12, 1995

Verleger: Springer-Verlag KG, Sachsenplatz 4–6, A-1201 Wien. – Herausgeber: Österreichische Akademie der Wissenschaften, Dr.-Ignaz-Seipel-Platz 2, A-1010 Wien und Gesellschaft Österreichischer Chemiker, Eschenbachgasse 9, A-1010 Wien. – Redaktion: Währinger Straße 38, A-1090 Wien. – Satz und Umbruch: Thomson Press Ltd., New Delhi, India. – Offsetdruck: Eugen Ketterl Gesellschaft m.b.H., Schopenhauerstraße 45, A-1180 Wien. – Verlagsort: Wien. – Herstellungsort: Wien. – Printed in Austria.