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One Pot Syntheses of Thiazol-2-hydrazone, Pyridino[2,3-*d*]pyridazine, Pyrazolo[3,4-*d*]pyridazine, and Isoxazolo[4,5-*d*]pyridazine Derivatives

Rafat M. Mohareb[1] and Daisy H. Fleita[2]

[1]*Department of Chemistry, University of California, Berkeley, California 94720-1460*

[2]*Chemistry Department, American University in Cairo, 113 Kaser El-Eini Street, Cairo, Egypt*

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ABSTRACT: *Reactions of the pyridazine derivatives* **1a–c** *with phenyl isothiocyanate followed by heterocyclization with ethyl chloroacetate gave the thiazolidinone derivatives* **6a–c**. *The reactivity of* **6a** *towards some chemical reagents was studied.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:258–262, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10026

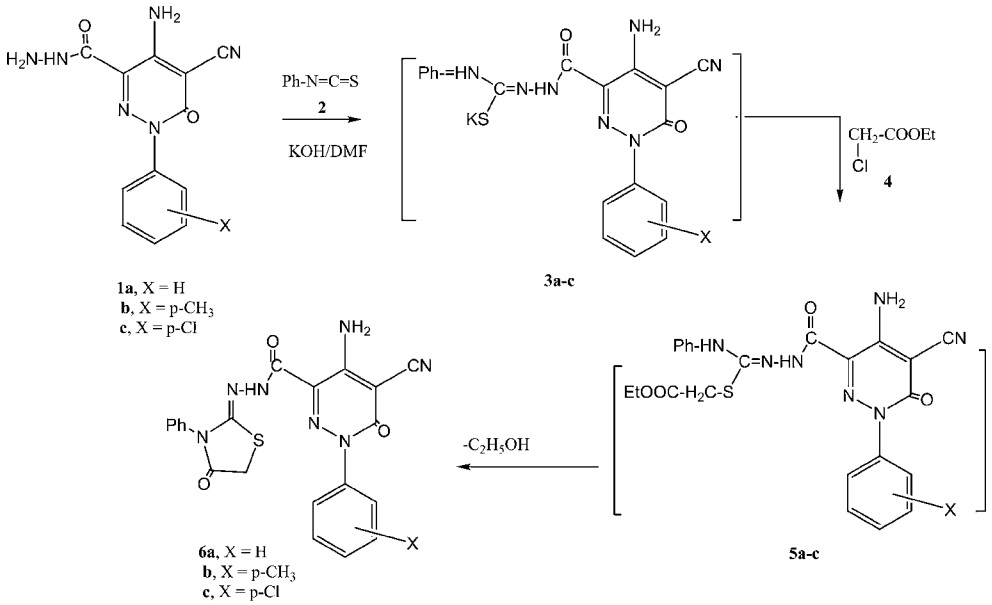
INTRODUCTION

Many pyridazine derivatives are reported to be useful as antiflammatory agents, herbicides, insecticides, and microbicides [1–4]. Also, thiazoles are known to be highly biologically active reagents [5–8]. Therefore, it seemed logical that compounds containing both the pyridazine and thiazole moieties would be expected to possess potential biological activities. Thus, we report herein the syntheses of heterocyclic compounds containing the two rings through the use of the readily available 4-amino-5-cyano-6-oxo-1-arylpyridazine-3-hydrazidic acid derivatives [9] **1a–c** as the key starting materials.

Correspondence to: Rafat M. Mohareb; e-mail: rmmohareb@hotmail.com.

RESULTS AND DISCUSSION

The reaction of 4-amino-5-cyano-6-oxo-1-arylpyridazine-3-hydrazidic acid derivatives **1a–c** with phenyl isothiocyanate (**2**) in dimethylformamide containing potassium hydroxide at 70°C gave the nonisolable intermediate potassium sulphide salts **3a–c**. The latter reacted with ethyl chloroacetate (**4**) to give the pyridazino-3-carbohydrazonothiazolidin-4-one derivatives **6a–c**. Formation of the latter products occurs via the intermediate formation of **5a–c**, followed by ethanol liberation (Scheme 1). The structures of the latter products were based on analytical and spectral data. Thus, the ^{1}H NMR spectrum of **6a** showed the presence of a singlet (D_2O exchangeable) at δ 4.58 for an NH_2 group, a singlet at δ 6.78 for the thiazole CH_2 group, a multiplet at δ 7.21–7.45 for two phenyl groups, and a singlet at δ 8.89 (D_2O exchangeable) for the NH group. Moreover, the ^{13}C NMR data showed δ 105.2, 128.6 (thiazole-C_5, C_2), 119.6 (CN), 122.0, 125.5, 127.7, 128.2, 129.5 (aromatic C), 132.6, 137.3, 140.9 (pyridazine C), 178.1, 179.5, 180.5 (3 C=O). Further confirmation for the structures of **6a–c** was obtained through a study of the chemical reactivity of **6a** towards several chemical reagents (Scheme 2). Variations in the sites of reaction have been observed previously [10]. Thus, the reaction of **6a** with benzaldehyde gave the benzal derivative **7**. On the other hand, with acetic acid/acetic anhydride mixture, the *N*-acetylpyridazine derivative **8** is formed. The structures of compounds **7** and **8**



SCHEME 1

were confirmed on the basis of analytical and spectral data (see Experimental section). The reaction of **6a** with benzenediazonium chloride gave the phenylhydrazone derivative **9**, not the phenylazo derivative **10**. The structure of compound **9** was established on the basis of its IR spectrum, which showed the presence of three C=O stretching bands at ν 1690, 1700, 1710 cm^{-1}. Also, the ^1H NMR spectrum which showed the presence of two D_2O exchangeable singlets at δ 8.78 and 9.24 for two NH groups. Moreover ^{13}C NMR data showed δ 119.9 (CN), 126.2, 128.3 (thiazole-C_5, C_1), 121.4, 123.3, 126.9, 127.8, 129.0, 129.9 (aromatic C), 132.3, 137.0, 140.5 (pyridazine C), 178.4, 179.0, 181.0 (3 C=O).

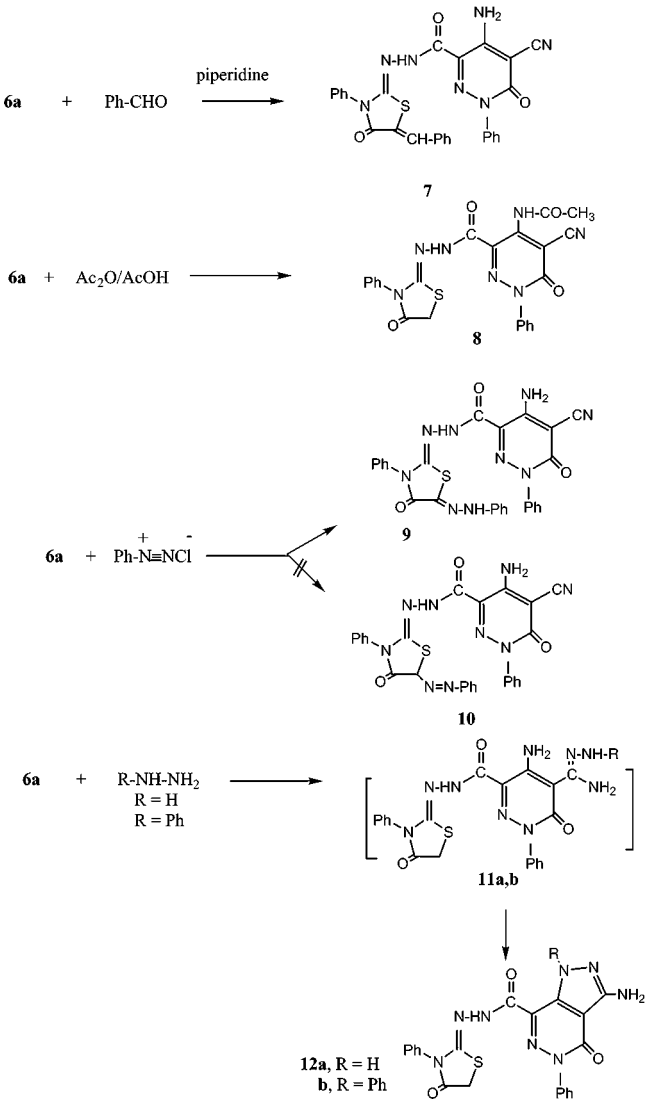
The reactivity of the enaminonitrile moiety present in **6a** towards some chemical reagents was then studied. Thus, the reaction of **6a** with each of hydrazine hydrate and phenylhydrazine gave the pyrazolo[3,4-*d*]pyridazine derivatives **12a** and **12b**, respectively. Structures of the latter products were confirmed on the basis of analytical and spectral data (see Experimental section). Moreover, the reactions of **6a** with hydroxylamine hydrochloride in refluxing 1,4-dioxane solution containing anhydrous sodium acetate gave the isoxazolo[5,4-*d*]pyridazine derivative **13**. The reactions of **6a** with cyanomethylene derivatives, namely malononitrile **14a** and ethyl cyanoacetate **14b**, were investigated in order to achieve the synthesis of fused azinoazine derivatives incorporating high biological activities [11]. Thus, the reaction of **6a** with either **14a** or **14b** gave, in each case, a single product with molecular formulae $C_{24}H_{17}N_9O_3S$ and $C_{24}H_{16}N_8O_4S$, respectively. Structures **16a** and **16b**, respectively, were assigned for these reaction products that were produced via the intermediate formation of **15a** and **15b** (Scheme 3). The IR spectrum of **16a** (as an example) showed one cyano group stretching at ν 2210 cm^{-1} and the ^1H NMR spectrum showed two singlets at δ 4.99 and 5.88 (D_2O exchangeable) due to two NH_2 groups.

EXPERIMENTAL

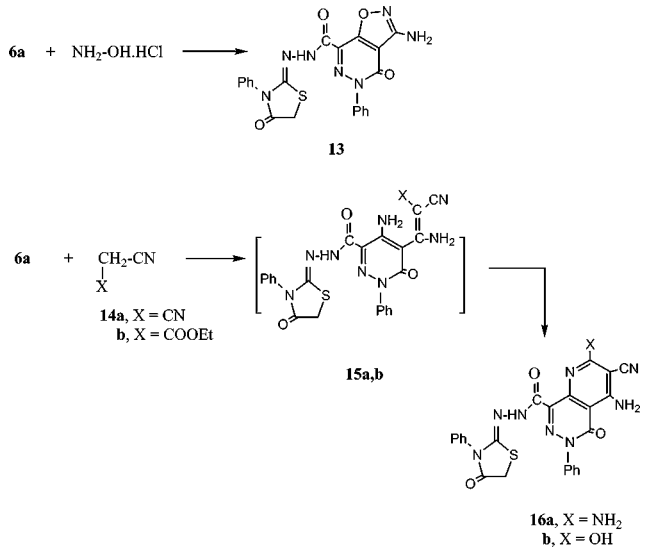
All melting points are uncorrected. IR spectra were recorded for KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^1H NMR spectra and ^{13}C NMR spectra were measured on a Varian EM390-90 MHz instrument in CD_3SOCD_3 as solvent with TMS as an internal standard, and chemical shifts are expressed as δ. Analytical data were obtained from the Microanalytical Data Unit at Cairo University, Giza, Egypt.

Synthesis of Compounds **6a–c***: General Procedure*

To a solution of either **1a** (2.7 g, 0.01 mol), **1b** (2.8 g, 0.01 mol), or **1c** (3.0 g, 0.01 mol) in dimethylformamide (50 ml) containing potassium hydroxide (0.4 g, 0.01 mol), phenyl isothiocyanate was added. The reaction mixture was heated in a hot water bath at 70°C for 1 h, then left to cool. Ethyl chloroacetate (**4**) (1.13 g, 0.01 mol) was added to the reaction mixture and the latter was stirred overnight, then poured into an ice/water mixture. The solid product formed upon addition of hydrochloric acid (to pH 6) was collected by filtration.



SCHEME 2



SCHEME 3

*4-Amino-5-cyano-6-oxo-1-phenyl-3-carbohydrazido-N-(3-phenyl-4-oxothiazolidin-2-ylidino)-pyridazine (***6a***).* Orange crystals (from 1,4-dioxane), yield 78% (3.4 g), m.p. 120°C. IR (ν/cm^{-1}) = 3460–3375 (NH_2, NH), 3065 (CH aromatic), 2220 (CN), 1695, 1680, 1670 (3 C=O), 1660 (exocyclic C=N), 1645 (C=C). ^{1}H NMR δ = 4.58 (s, 2H, NH_2), 6.78 (s, 2H, thiazole CH_2), 7.21–7.41 (m, 10H, 2Ar), 8.89 (s, 1H, NH). ^{13}C NMR δ = 105.2, 128.6 (thiazole-C_5, C_2), 119.6 (CN), 122.0, 125.5, 127.7, 128.2, 129.5 (aromatic C), 132.6, 137.3, 140.9 (pyridazine C), 178.1, 179.5, 180.5 (3 C=O). Calcd for $C_{21}H_{15}N_7O_3S$: C, 56.62; H, 3.39; N, 22.01; S, 7.20%. Found: C, 56.44; H, 3.29; N, 21.81; S, 6.96%.

*4-Amino-5-cyano-6-oxo-1-(4-methylphenyl)-3-N-(3-phenyl-4-oxothiazolidin-2-ylidino)-3-carbohydrazidopyridazine (***6b***).* Orange crystals (from ethanol), yield 66% (3.0 g), m.p. 210–213°C. IR (ν/cm^{-1}) = 3470–3370 (NH_2, NH), 3060 (CH aromatic), 2215 (CN), 1705, 1685, 1670 (3 C=O), 1663 (exocyclic C=N), 1645 (C=C). ^{1}H NMR δ = 2.01 (s, 3H, CH_3), 4.58 (s, 2H, NH_2), 6.88 (s, 2H, thiazole CH_2), 7.05, 7.29 (m, 9H, C_6H_4, C_6H_5), 8.91 (s, 1H, NH). ^{13}C NMR δ = 29.5 (CH_3), 105.3, 128.8 (thiazole-C_5, C_2), 120.1 (CN), 122.1, 127.2, 128.0, 132.2 (aromatic C), 132.2, 138.7, 140.2 (pyridazine C), 178.2, 179.2, 180.8 (3 C=O). Calcd for $C_{22}H_{17}N_7O_3S$: C. 57.52; H, 3.73; N, 21.34; S, 6.98%. Found: C, 57.34; H, 3.29; N, 21.66; S, 6.49%.

*4-Amino-5-cyano-6-oxo-1-(4-chlorophenyl)-3-carbohydrazido-N-(3-phenyl-4-oxothiazolidin-2-ylideno)-pyridazine (***6c***).* Orange crystals (from ethanol), yield 50% (2.4 g), m.p. 150°C. IR (ν/cm^{-1}) = 3480–3366 (NH_2, NH), 3078 (CH aromatic), 2225 (CN), 1700, 1695, 1670 (3 C=O), 1660 (exocyclic C=N), 1640 (C=C). ^{1}H NMR δ = 4.59 (s, 2H, NH_2), 6.90 (s, 2H, thiazole CH_2), 7.22–7.58 (m, 9H, C_6H_4, C_6H_5), 8.96 (s, 1H, NH). Calcd for $C_{21}H_{14}N_7O_3SCl$: C, 52.55; H, 2.94; N, 20.43; S, 6.68%. Found: C, 52.64; H, 3.20; N, 20.68; S, 6.59%.

*Synthesis of 4-Amino-5-cyano-6-oxo-1-phenyl-3-carbohydrazido-N-(5-benzal-3-phenyl-4-oxothiazolidin-2-ylidino)pyridazine (***7***)*

To a solution of **6a** (4.45 g, 0.01 mol) in 1,4-dioxane (40 ml) containing piperidine (0.5 ml), benzaldehyde (1.06 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h, then evaporated in a vacuum. The residual product was triturated with

ethanol and the formed solid product was collected by filtration.

Yellow crystals (from 1,4-dioxane), yield 58% (3.1 g), m.p. 138°C. IR: (ν/cm^{-1}) = 3490–3375 (NH_2, NH), 3065 (CH aromatic), 2220 (CN), 1705, 1690, 1675 (3 C=O), 1665 (exocyclic C=N), 1640 (C=C). ^{1}H NMR δ = 4.55 (s, 2H, NH_2), 6.99 (s, 1H, benzal CH), 7.19–7.48 (m, 15H, $3C_6H_5$), 8.99 (s, 1H, NH). ^{13}C NMR δ = 116.2 (CH=), 133.6, 126.4 (thiazole-C_5, C_2), 120.1 (CN), 122.3, 125.2, 128.0, 128.6, 129.4, 130.7, 131.1 (aromatic C), 132.2, 137.6, 140.4 (pyridazine C), 177.6, 179.9, 180.2 (3 C=O). Calcd for $C_{28}H_{19}N_7O_3S$: C, 63.03; H, 3.59; N, 18.38; S, 6.01%. Found: C, 63.14; H, 3.31; N, 18.48; S, 6.22%.

*Synthesis of 4-Acetylamino-5-cyano-6-oxo-1-phenyl-3-carbohydrazido-N-(3-phenyl-4-oxothiazolidin-2-ylidino)pyridazine (**8**)*

To a solution of **6a** (4.45 g, 0.01 mol) acetic acid/acetic anhydride mixture (50 ml, 5:1) was added, and the mixture was heated under reflux for 3 h, then evaporated in a vacuum. The residual product was triturated with diethyl ether and the formed solid product was collected by filtration.

Brown crystals (from 1,4-dioxane), yield 78% (3.8 g), m.p. 100°C. IR: (ν/cm^{-1}) = 3480–3365 (2NH), 3060 (CH aromatic), 2220 (CN), 1695, 1680, 1670, 1710 (4 C=O), 1660 (exocyclic C=N), 1645 (C=C). ^{1}H NMR δ = 2.25 (s, 3H, CH_3), 6.89 (s, 2H, thiazole CH_2), 7.23–7.42 (m, 10H, $2C_6H_5$), 8.95, 9.46 (2s, 2H, 2NH). ^{13}C NMR δ = 31.6 (CH_3), 105.0, 128.8 (thiazole-C_5, C_2), 120.0 (CN), 121.6, 122.3, 124.9, 126.6, 127.7, 129.5 (aromatic C), 130.9, 132.2, 137.1, 140.6 (pyridazine C), 178.8, 179.9, 180.1, 183.3 (4 C=O). Calcd for $C_{23}H_{17}N_7O_4S$: C, 56.67; H, 3.52; N, 20.11; S, 6.58%. Found: C, 56.61; H, 3.52; N, 19.89; S, 6.34%.

*Synthesis of 4-Amino-5-cyano-6-oxo-1-phenyl-3-carbohydrazido-N-(3-phenyl-5-N-phenylhydrazono-4-oxothiazolidin-2-ylideno)pyridine (**9**)*

To a cold solution of **6a** (4.45 g, 0.01 mol) in ethanol (50 ml), containing sodium hydroxide (0.4 g, 0.01 mole, in 7 ml water), benzenediazonium chloride (0.01 mol) was added with stirring. The solid product formed upon standing at room temperature for 1 h was collected by filtration.

Buff crystals (from 1,4-dioxane), yield 75% (4.13 g), m.p. 125°C. IR (ν/cm^{-1}) = 3479–3385 (NH_2, NH), 3065 (CH aromatic), 2220 (CN), 1710, 1700, 1690 (3 C=O), 1663 (exocyclic C=N), 1635 (C=C). ^{1}H NMR δ = 4.58 (s, 2H, NH_2), 7.30–7.52 (m, 15H, $3C_6H_5$), 8.78, 9.24 (2s, 2H, NH). ^{13}C NMR δ = 119.9 (CN), 126.2, 128.3 (thiazole-C_5, C_2), 121.4, 123.3, 126.9, 127.8, 129.0, 129.9 (aromatic C), 132.3, 137.0, 140.5 (pyridazine C), 178.4, 179.0, 181.0 (3 C=O). Calcd for $C_{27}H_{19}N_9O_3S$: 59.01; H, 3.49; N, 22.94; S, 5.83%. Found: C, 59.21; H, 3.42; N, 22.79; S, 5.63%.

*Synthesis of **12a,b**: General Procedure*

To a solution of **6a** (4.45 g, 0.01 mol) either hydrazine hydrate or phenylhydrazine (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h, then poured into an ice/water mixture containing a few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration.

*6-Amino-4-hydro-1-phenyl-3-N-carbohydrazido-(3-phenyl-4-oxothiazolidin-2-ylideno)-7-oxopyrazolo[3,4-d]pyridazine (**12a**).* Pale yellow crystals (from dimethylformamide), yield 70% (3.2 g), m.p. 180°C. IR (ν/cm^{-1}) = 3490–3370 (NH_2, 2NH), 3055 (CH aromatic), 1710, 1795, 1680 (3 C=O), 1667 (exocyclic C=N), 1640 (C=C). ^{1}H NMR δ = 5.68 (s, 2H, NH_2), 7.32–7.49 (m, 10H, $2C_6H_5$), 8.96, 9.33 (2s, 2H, 2NH). ^{13}C NMR δ = 105.7, 126.4 (thiazole-C_5, C_2), 122.1, 125.6, 127.6, 128.0, 129.9, 131.4, 132.0 (aromatic C), 132.2, 138.0, 139.3, 140.4 (pyridazine C, pyrazole C), 176.9, 178.8, 180.0 (3 C=O). Calcd for $C_{21}H_{16}N_8O_3S$: C, 54.78; H, 3.50; N, 24.34; S, 6.96%. Found: C, 54.99; H, 3.39; N, 24.39; S, 5.67%.

*6-Amino-1,4-diphenyl-3-N-carbohydrazido(3-phenyl-4-oxothiazolidin-2-ylideno)-7-oxopyrazolko[3,4-d]-pyridazine (**12b**).* Buff crystals (from dimethylformamide), yield 79% (4.3 g), m.p. 140°C. IR (ν/cm^{-1}) = 3480-3360 (NH_2, NH), 3066 (CH aromatic), 1700, 1690, 1675 (3 C=O), 1665 (exocyclic C=N), 1645 (C=C). ^{1}H NMR δ = 5.68 (s, 2H, NH_2), 7.30–7.46 (m, 15H, 3 C_6H_5), 9.36 (s, 1H, NH). Calcd for $C_{27}H_{20}N_8O_3S$: C, 60.44; H, 3.76; N, 20.88; S, 5.98%. Found: C, 60.55; H, 3.36; N, 20.69; S, 5.62%.

*Synthesis of 6-Amino-1-phenyl-3-N-catbohydrazido-(3-phenyl-4-oxothiazolidin-2-ylideno-7-oxoisoxazolo[3,4-d]pyridazine (**13**)*

To a solution of **6a** (4.45 g, 0.01 mol) in ethanol (10 ml) containing sodium acetate (0.8 g, 0.01 mol), hydroxylamine hydrochloride (0.33 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 8 h, then poured into water and the formed solid product was collected by filtration.

Yellowish white crystals (from ethanol), yield 70% (3.2 g), m.p. 130 °C. IR (ν/cm^{-1}) = 3480–3365 (NH_2, NH), 3060 (CH aromatic), 1705, 1695, 1675 (3 C=O), 1668 (exocyclic C=N), 1645 (C=C). ^{1}H NMR δ = 5.48 (s, 2H, NH_2), 6.78 (s, 2H, thiazole CH_2), 7.32–7.49 (m, 10H, $2C_6H_5$), 8.96 (s, 1H, NH). ^{13}C NMR δ = 105.8, 126.4 (thiazole-C_5, C_2), 122.4, 124.5, 128.3, 128.9, 129.2, 130.3, 132.0 (aromatic C), 132.4, 137.6, 139.6, 140.3 (pyridazine C, isoxazole C), 177.6, 179.9, 180.2 (3 C=O). Calcd for $C_{21}H_{15}N_7O_4S$: C, 54.66; H, 3.28; N, 21.25; S, 6.95%. Found: C, 54.89; H, 3.22; N, 21.30; S, 6.67%.

Synthesis of **16a,b***: General Procedure*

To a solution of **6a** (4.45 g, 0.01 mol) in dimethylformamide (30 ml) either malononitrile (**14a**) (0.66 g, 0.012 mol) or ethyl cyanoacetate (**14b**) (1.30 g, 0.01 mole) was added. The reaction mixture, in each case, was heated under reflux for 6 h, then poured into an ice/water mixture, neutralized with dilute hydrochloric acid (pH 7), whereby the solid product, so formed, was collected by filtration.

*5,7Diamino-1-phenyl-6-cyano-3-N-carbohydrazido(3-phenyl-4-oxothioazolidin-2-ylideno)-8-oxopyrido-[2,3-d]pyridazine (***16a***).* Buff crystals (from 1,4-dioxane), yield 70% (3.57 g), m.p. 155°C. IR: (ν/cm^{-1}) = 3495–3335 (2 NH_2, NH), 3066 (CH aromatic), 2210 (CN), 1700, 1690, 1680 (3 C=O), 1665 (exocyclic C=N), 1640 (C=C). ^{1}H NMR δ = 4.99, 5.88 (2s, 4H, $2NH_2$), 6.78 (s, 2H, thiazole CH_2), 7.30–7.46 (m, 10H, $2C_6H_5$), 8.96 (s, 1H, NH). Calcd for $C_{24}H_{17}N_9O_3S$: C, 56.36; H, 3.35; N, 24.65; S, 6.27%. Found: C, 56.69; H, 3.01; N, 24.56; S, 6.34%.

*7-amino-1-phenyl-6-cyano-5-hydroxy-3-N-carbohydrazido-(3-phenyl-4-oxothiazolidin-2-ylideno)-8-oxopyrido[2,3-d]pyridazine (***16b***).* Orange crystals (from 1,4-dioxane), yield 68% (3.40 g), m.p. 135°C. IR (ν/cm^{-1}) = 3490–3345 (NH_2, NH, OH), 3060 (CH aromatic), 2225 (CN), 1700, 1695, 1670 (3 C=O), 1662 (exocyclic C=N), 1632 (C=C). ^{1}H NMR δ = 5.88 (s, 2H, NH_2), 6.78 (s, 2H, thiazole CH_2), 7.30–7.46 (m, 10H, $2C_6H_5$), 8.96 (s, 1H, NH), 10.30 (s, 1H, OH). Calcd for $C_{24}H_{16}N_8O_4S$: C, 56.25; H, 3.15; N, 21.86; S, 6.26%. Found: C, 56.61; H, 3.31; N, 21.50; S, 6.58%.

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