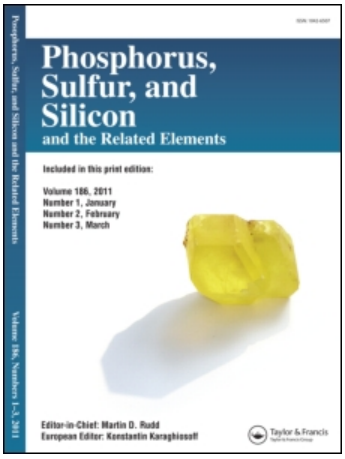

Phosphorus, Sulfur, and Silicon and the Related Elements

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One-Pot Synthesis of Thiazoles from Pyridazin-3-hydrazidic Acid Derivatives

Waganat W. Wardakhan[a]; Yehya M. Elkholy[b]
[a] National Organization for Drug Control and Research, Cairo, Egypt [b] Chemistry Department, Faculty of Science, Helwan University, Cairo, Egypt

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ONE-POT SYNTHESIS OF THIAZOLES FROM PYRIDAZIN-3-HYDRAZIDIC ACID DERIVATIVES

Waganat W. Wardakhan[a] *and Yehya M. Elkholy*[b]
National Organization for Drug Control and Research, Cairo, Egypt[a] *and Chemistry Department, Faculty of Science, Helwan University, Cairo, Egypt*[b]

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Several new thiazole derivatives have been synthesized; the reactivity of these compounds toward amines, aldehydes, and hydroxyl amine are reported. New syntheses of pyrimidino[5,4:3,4]pyrazolo[4,3:5,6]pyridazine derivatives also have been achieved.

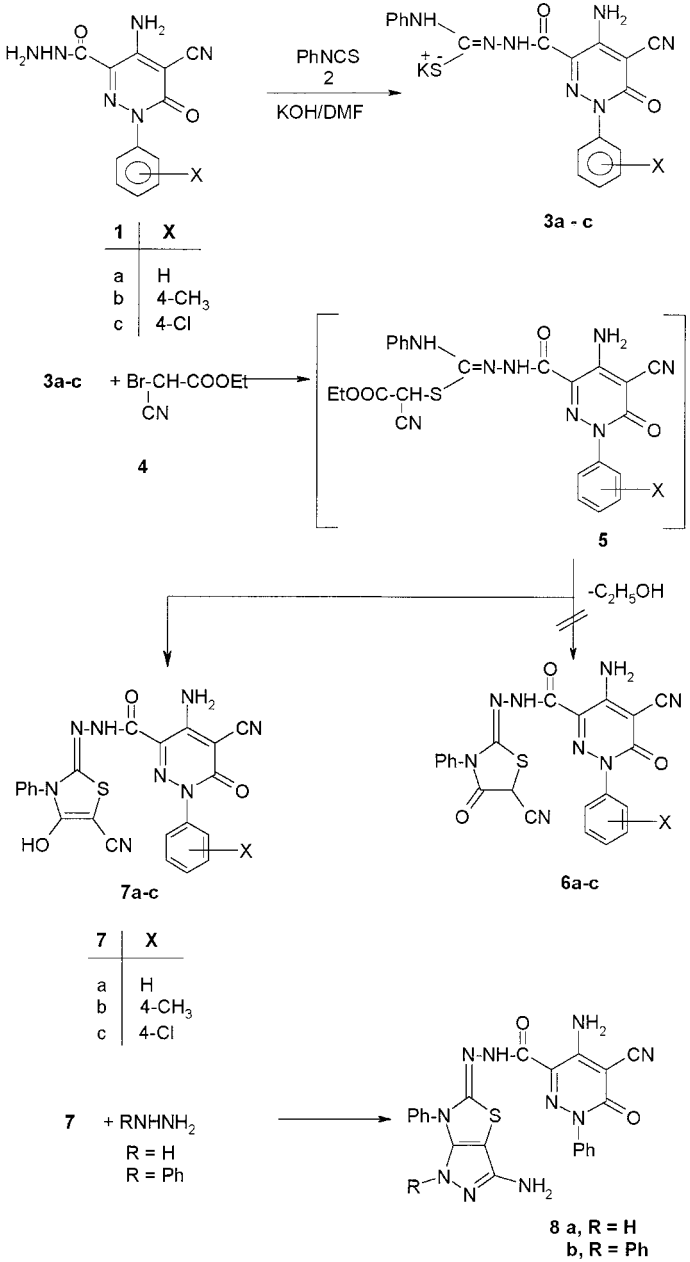
Keywords: Bromoethylcyanoacetate; phenylisothio cyanate; pyridazin-3-hydrazidic acid derivatives; thioglycollic acid

Pyridazine derivatives comprise a very interesting class of compounds because of their significant biological and pharmaceutical activities.[1–4] As part of our studies aimed at developing simple and efficient synthesis of polyfunctionally heteroaromatics from readily obtainable starting materials,[5–7] we report herein the synthesis of heterocyclic compounds containing both thiazole and pyridazine moieties through the use of the readily available 4-amino-5-cyano-6-oxo-1-arylpyridazine-3-hydrazidic acid derivatives[8] **1a–c** as the starting materials.

The reaction of 4-amino-5-cyano-6-oxo-1-arylpyridazine-3-hydrazidic acid derivatives **1a–c** with phenylisothiocyanate **2** in dimethyl fomamide containing potassium hydroxide at 70°C yielded the non-isolable potassium sulphide salts **3a–c** (Scheme 1). The latter reacted with bromoethyl cyanoacetate[9] to yield the 5-hydroxy thiazole-4-carbonitrile derivatives **7a–c**, not the thiazol-5-one derivatives **6a–c**.

The reaction probably took place via the intermediate formation of **5a–c** followed by ethanol elimination. Assignment of structures **7a–c** for the reaction products was based on analytical and spectral data.

Address correspondence to Y. M. Elkholy, Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt. E-mail: y_elkholy@yahoo.com



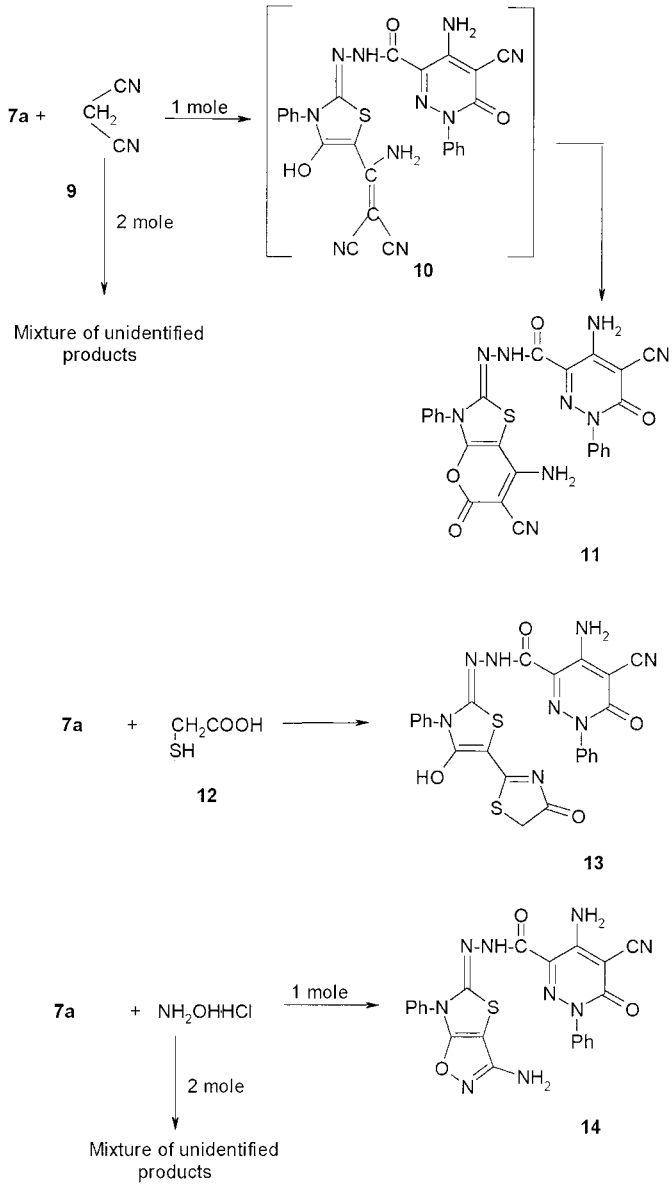
SCHEME 1

Thus, the IR spectrum of the reaction product showed OH, NH_2, NH stretchings at 3534–3490 cm^{-1} and two CN groups stretching at 2225 and 2220 cm^{-1}. The mass spectrum of **7a** shows m/z = 470 (M^+) for $C_{22}H_{14}N_8O_3S$. Moreover, the ^1H NMR spectrum showed no CH stretching for thiazole H-5 present in structures **6a–c** and the appearance of a broad singlet at 10.42 for one OH group also was indicative of the formation of **7a–c**, which was confirmed by studying their reactivity toward various chemical reagents. Thus, the ∝-hydroxy nitrile moiety present in **7a–c** showed greater reactivity over the enamino nitrile moiety as the latter exists in the nonactive anionic form. The reaction of **7a–c** with either hydrazine hydrate or phenyl hydrazine gave the pyrazolo[3,4-d]thiazole derivatives **8a** and **8b** respectively (cf. Scheme 1).

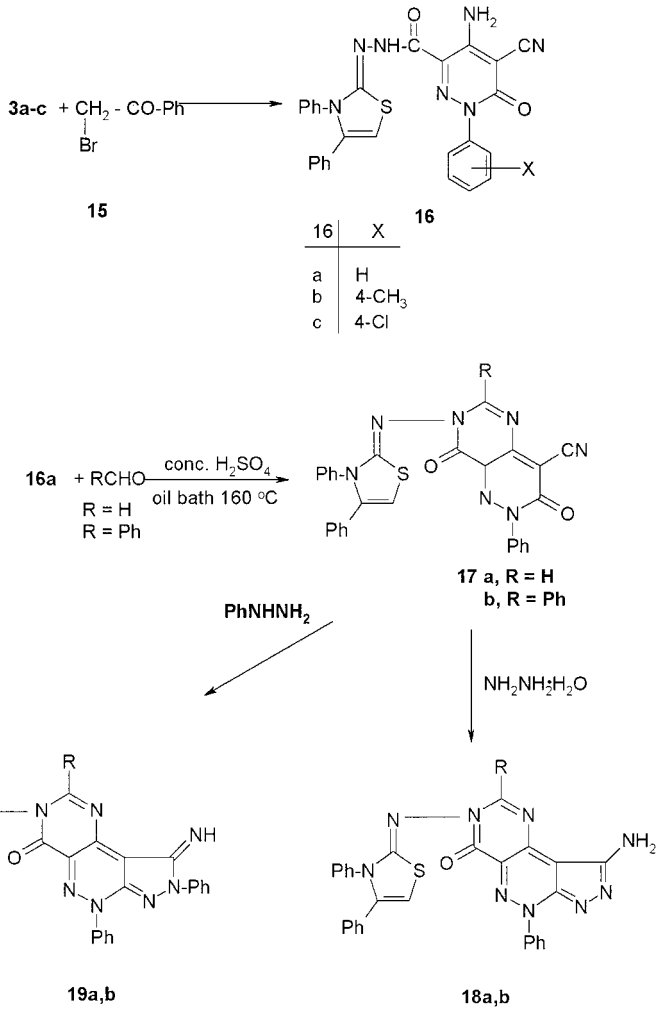
The reaction took place via first addition of NH_2 group of the hydrazine to CN group of thiazole followed by water elimination. The reaction of **7a** with malononitrile gave the 2-thiazolo[4,5-b]pyran-2-one derivative **11** (fingerprint IR, m.p., and mixed m.p.). The reaction likely took place through the intermediate formation of **10** followed by cyclization. Two pathways for cyclization are considered, in case of the reaction with malononitrile. The intermediate 2-iminothiazolo[4,5-b]pyran is formed followed by hydrolysis and ammonia liberation to give **11** (cf. Scheme 2).

The reaction of **7a** with thioglycollic acid **12** gave 5-thiazolylthiazole derivative **13** and the reaction of **7a** with hydroxylamine hydrochloride gave the isoxazolo[5,4-d]thiazole derivative **14** (Scheme 2). The use of excess amount of hydroxylamine hydrochloride gives a mixture of products.

The reaction of **3a–c** with phenacyl bromide **15** gave the thiazole derivatives **16a–c**, the structures of which were established based on analytical and spectral data (Scheme 3). Thus, the ^1H NMR spectrum of **16a** (as an example) showed a singlet (D_2O exchangeable) at 4.55 for one NH_2 group, a singlet at d 6.78 for thiazole H-5, a multiplet at 7.21–7.45 for three phenyl protons, and a singlet (D_2O exchangeable) at 8.97 for one NH group. Thus, the reaction of **16a** with formaldehyde or benzaldehyde gave a single product in each case with molecular formula $C_{28}H_{17}N_7O_2S$ and $C_{34}H_{21}N_7O_2S$, respectively, to which the structures of the pyrimidino[4,5-c]pyridazine derivatives **17a** and **17b**, respectively, were assigned (Scheme 3). The ^1H NMR spectrum of **17a**, showed beside the expected signals, two singlets at 6.89 and 7.02 corresponding to thiazole H-5 and pyrimidine H-2 respectively. The mass spectrum of **17a** shows m/z = 515 (M^+) for $C_{28}H_{17}N_7O_2S$. Thus, the reaction of **17a** and **17b** with hydrazine hydrate or phenylhydrazine gave the pyrimidino[5,4:3,4]-pyrazolo[4,3:5,6]pyridazine derivative **18a**,**b** and **19a**,**b** respectively. On the other hand, the reaction of

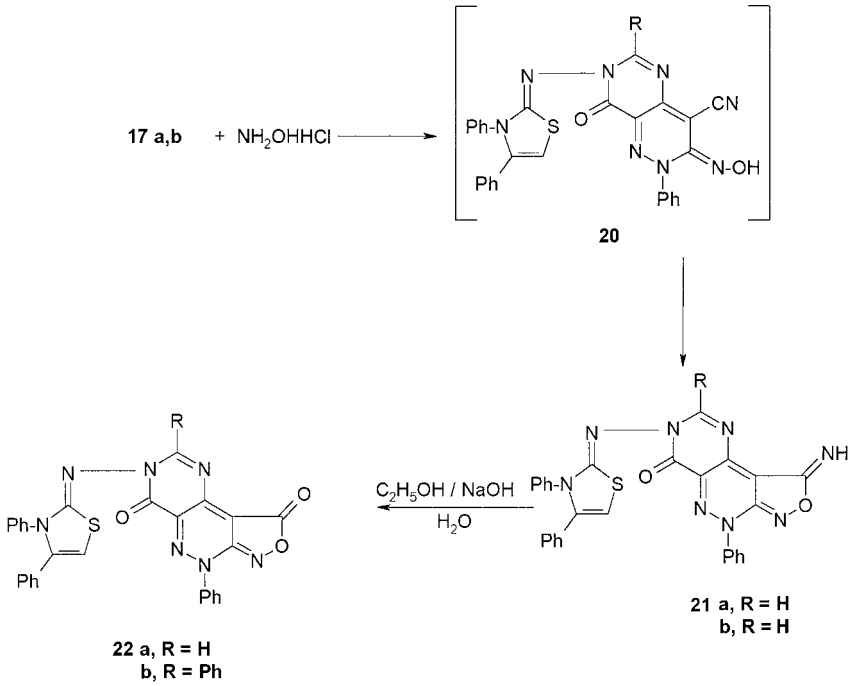


SCHEME 2



SCHEME 3

17a and **17b** with hydroxylamine hydrochloride gave the pyrimidino[5,4:3,4]isoxazolo[4,3:5,6]pyridazine derivatives **21a** and **21b** respectively (Scheme 4). Formation of the latter products can be explained in terms of the formation of the first intermediate **20a**,**b**, followed by nucleophilic addition of the OH group to the cyano group to form the final products **21a**,**b** respectively. The Imino function present in the latter products is hydrolyzed when these products were heated under reflux in ethanolic/NaOH solution to form the corresponding fused 3-oxoisoxazolo derivatives **22a**,**b** (Scheme 4). Structures



SCHEME 4

21a,**b** and **22a**,**b** were established based on analytical and spectral data.

EXPERIMENTAL

All melting points reported were uncorrected. IR spectra were recorded for KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were measured on a Varian EM 390-90 MHz in CD_3SOCD_3 as solvent using TMS as an internal standard. Chemical shifts are expressed as δ ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex massspectrometer at 70 eV. Analytical data were obtained from the Microanalytical Data Unit at Cairo University, Giza, Egypt.

Synthesis of compounds 7a–c and 16a–c

General Procedure

To a solution of either **la** (2.7 g, 0.01 mmol) or **lb** (2.8 g, 0.01 mmol) or **lc** (3.0 g, 0.01 mmol) in dimethylformamide (50 ml) containing potassium hydroxide (0.4 g, 0.01 mmol) was added phenylisothiocyanate.

The reaction mixture was heated in a boiling water bath at 70°C for 1 h and then left to cool. Bromoethyl cyanoacetate **4** (2.0 g, 0.01 mmol) or phenacyl bromide **15** (2.00 g, 0.01 mmol) were added to the reaction mixture, and the latter was stirred overnight and then poured into an ice-water mixture. The solid product, formed upon addition of hydrochloric acid (up to pH 6), was collected by filtration.

4-Amino-5-cyano-6-oxo-1-phenyl-3-carbohydrazido-N-(5-cyano-3-phenyl-4-hydroxythiazolidin-2-ylideno)pyridazine (7a)

7a: Yellow crystals (3.7 g, 78%), m.p. 125°C (from ethanol), ν max/cm^{-1} 3534–3490 (OH, NH_2, NH), 3060 (CH aromatic), 2225, 2220 (2 CN), 1705, 1695 (2 C=O), 1665 (exocyclic C=N), 1645 (C=C). ^{1}H NMR: δ 4.57 (s, 2H, NH_2), 7.30–7.45 (m, 10H, aromatic protons), 8.99 (s, 1H, NH), 10.42 (s, 1H, OH) MS (EI, 70 ev):m/z = 470 (M^+). Anal. requires for $C_{22}H_{14}N_8O_3S$ (470.4) C, 56.17; H, 3.00; N, 23.82; S, 6.82. Found: C, 56.34; H, 3.20; N, 23.62; S, 6.48.

4-Amino-5-cyano-6-oxo-1-(4-methylphenyl)-3-carbohydrazido-N-(-5-cyano-3-phenyl-4-hydroxythiazolidin-2-ylideno)pyridazine (7b)

7b: Orange crystals (3.2 g, 72%), m.p. 160°C (from ethanol), ν max/cm^{-1} 3585–3330 (OH, NH_2, NH), 3065 (CH aromatic), 2225, 2218 (2 CN), 1705, 1695 (2 C=O), 1667 (exocyclic C=N), 1643 (C=C). ^{1}H NMR: δ 2.29 (s, 3H, CH_3), 4.58 (s, 2H, NH_2), 7.25–7.45 (m, 9H, aromatic protons), 8.91 (s, 1H, NH), 10.45 (s, 1H, OH). Anal. requires for $C_{23}H_{16}N_8O_3S$ (484.43) C, 57.02; H, 3.30; N, 23.13; S, 6.62. Found: C, 57.24; H, 3.49; N, 23.21; S, 6.39.

4-Amino-5-cyano-6-oxo-1-(4-chlorophenyl)-3-carbohydrazido-N-(5-cyano-3-phenyl-4-hydroxythiazolidin-2-ylideno)pyridazine (7c)

7c: Orange crystals (2.9 g, 63%), m.p. 140°C (from 1,4-dioxane), ν max/cm^{-1} 3550–3336 (OH, NH_2, NH), 3065 (CH aromatic), 2225, 2220 (2 CN), 1706, 169O (2 C=O), 1663 (exocyclic C=N), 1643 (C=C). ^{1}H NMR: δ 4.57 (s, 2H, NH_2), 7.32–7.48 (m. 9H, aromatic protons), 8.97 (s, 1H, NH), 10.32 (s, 1H, OH). Anal. requires for $C_{22}H_{13}N_8O_3SCl$ (504.84): C, 57.83; H, 2.87; N, 24.52; S, 7.02. Found: C, 57.24; H, 3.49; N, 24.21; S, 6.39.

4-Amino-5-cyano-6-oxo-1-phenyl-3-carbohydrazido-N-(3,4-diphenylthiazolo 2-Ylideno)pyridazine (16a)

16a: Yellow crystals (3.2 g, 63%), m.p. 70°C (from ethanol), ν max/cm^{-1} 3450–3345 (NH_2, NH), 3050 (CH aromatic), 2225 (CN), 1695,

1689 (2 C=O), 1665 (exocyclic C=N), 1634 (C=C). ^{1}H NMR: δ 4.55 (s, 2H, NH_2), 6.78 (s, 1H, thiazole H-5), 7.21–7.45 (m, 15H, aromatic protons), 8.97 (s, 1H, NH). Anal. requires for $C_{27}H_{19}N_7O_2S$ (505.49): C, 64.15; H, 3.79; N, 19.40; S, 6.34. Found: C, 64.22; H, 3.64; N, 19.32; S, 6.39.

4-Amino-5-cyano-6-oxo-1-(4-methylphenyl)-3-carbohydrazido-N-(3,4-diphenylthiazol-2-ylideno)pyridazine (16b)

16b: Yellow crystals (3.5 g, 68%), m.p. l40°C (from ethanol), ν max/cm^{-1} 3455–3338 (NH_2, NH), 3065 (CH aromatic), 2220 (CN), 1695, 1680, (2 C=O), 1665 (exocyclic C=N), 1638 (C=C). ^{1}H NMR: δ 2.09 (s, 3H, CH_3), 4.58 (s, 2H, NH_2), 6.79 (s, 1H, thiazole H-5), 7.27–7.48 (m, 14H, aromatic protons), 8.99 (s, 1H, NH). Anal. requires for $C_{28}H_{21}N_7O_2S$ (519.51): C, 64.73; H, 4.07; N, 18.87; S, 6.17. Found: C, 64.53; H, 3.94; N, 19.19; S, 6.30.

4-Amino-5-cyano-6-oxo-1-(4-chlorophenyl)-3-carbohydrazido-N-(3,4-diphenylthiazol-2-ylideno)pyridazine (16c)

16c: Yellow crystals (2.8 g, 52%), m.p. 165°C (from ethanol), ν max/cm^{-1} 3520–3342 (NH_2, NH), 3058 (CH aromatic), 2222 (CN), 1693, 1687, (2 C=O), 1660 (exocyclic C=N), 1635 (C=C). ^{1}H NMR: δ 4.48 (s, 2H, NH_2), 7.02 (s, 1H, thiazole H-5), 7.20–7.55 (m, 14H, aromatic protons), 8.99 (s, 1H, NH). Anal. requires for $C_{27}H_{18}N_7O_2SCl$ (539.94): C, 60.04; H, 3.36; N, 18.15; S, 5.94. Found: C, 60.34; H, 3.51; N, 18.23; S, 6.20.

Synthesis of 8a,b Derivatives

General Procedure

To a solution of **7a** (4.7 g, 0.01 mmol) in dimethylformamide (5 ml), was added hydrazine hydrate or phenylhydrazine (0.01 mmol). The reaction mixture, in each case, was heated under reflux for 3 h, and then poured into an ice-water mixture containing few drops of hydrochloric acid. The solid product in each case was collected by filtration.

3-Amino-6-phenyl-5-[4-amino-5-cyano-1-phenyl-6-oxopyridazin-3-(carbohydrazido-N-ylideno)] Thiazolo[4,5-c]pyrazole (8a)

8a: Orange crystals (2.8 g, 58%), m.p. 165°C (from ethanol), ν max/cm^{-1} 3490–3360 (2 NH_2, 2 NH), 3050 (CH aromatic), 2222 (CN), 1695, 1683 (2 C=O), 1665 (exocyclic, C=N), 1640 (C=C). ^{1}H NMR:

δ 4.86, 5.48 (2s, 4H, $2NH_2$), 7.30–7.41 (m, 10H, aromatic protons) 8.88, 9.01 (2s, 2H, 2NH). Anal. requires for $C_{22}H_{16}N_{10}O_2S$ (484.45): C, 54.54; H, 3.33; N, 28.91; S, 6.82. Found: C, 54.60; H, 3.09; N, 28.90; S, 6.68.

3-Amino-l,6-diphenyl-5-[4-amino-5-cyano-l-phenyl-6-oxopyridazin-3-(carbohydrazido-N-ylideno)] Thiazolo[4,5-c]pyrazole (8b)

8b: Reddish brown crystals (3.3 g, 58%), m.p. 115°C (from ethanol), ν max/cm^{-1} 3475–3334 ($2NH_2$, NH), 3050 (CH aromatic), 2220 (CN), 1695, 1680 (2 C=O), 1660 (exocyclic C=N), 1645 (C=C). ^{1}H NMR: δ 4.79, 5.54 (2s, 4H, $2NH_2$), 7.28–7.39 (m, 15H, aromatic protons), 8.09 (s, 1H, 2NH). Anal. requires for $C_{28}H_{20}N_{10}O_2S$ (560.54): C, 59.36; H, 3.56; N, 24.72; S, 5.66. Found: C, 59.60; H, 3.09; N, 24.90; S, 5.98.

Synthesis of Compounds 14 and 21a,b

General Procedure

The solution of **7a** (4.7 g, 0.01 mmol), **17a** (5.16 g, 0.01 mmol) or **17b** (5.91 g, 0.01 mol) in ethanol (10 ml) containing sodium acetate (0.8 g, 0.01 mol), hydroxylamine hydrochloride (0.33 g, 0.01 mmol) was added. The reaction mixture was heated under reflux for 8 h then poured into water and the solid product in each case was collected by filtration.

3-Amino-6-phenyl-5-[4-amino-5-cyano-1-phenyl-6-oxopyridazin-3-(carbohydrazido-N-ylideno)]-isoxazolo[5,4-d]thiazole (14)

14: Yellowish white crystals (2.9 g, 40%), m.p. l40°C (from ethanol), ν max/cm^{-1} 3478–3343 ($2NH_2$, NH), 3050 (CH aromatic), 1690, 1685 (2 C=O), 1670 (exocyclic C=N), 1635 (C=C). ^{1}H NMR: δ 4.92, 5.51 (2s, 4H, $2NH_2$), 7.32–7.46 (m, 10H, aromatic protons), 8.69 (s, 1H, NH). Anal. requires for $C_{22}H_{15}N_9O_3S$ (485.47): C, 49.85; H, 3.11; N, 25.97; S, 6.60. Found: C, 49.52; H, 3.49; N, 25.52; S, 6.94.

7-Imino-3-oxo-4(3,4-diphenylthiazolidin-2-ylideno)-1-phenylpyrimidino[5,4:3,4]isoxazolo[4,3:5,6]pyridazine (21a)

21a: Yellow crystals (4.25 g, 80%), m.p. l65–168°C (from l,4- dioxane), ν max/cm^{-1} 3650–3375 (NH), 3055 (CH aromatic), 1700 (C=O), 1670 (exocyclic; C=N), 1640 (C=C). ^{1}H NMR: δ 6.99 (s, 1H, thiazole CH), 7.30–7.42 (m, 16H, aromatic protons, pyrimidine H-2), 9.00 (s, 1H, NH). Anal. requires for $C_{28}H_{18}N_8O_2S$ (530.48): C, 63.40; H, 3.42; N, 21.12; S, 6.04. Found: C, 63.39; H, 3.36; N, 21.07; S, 6.16.

1,5-Diphenyl-7-imino-3-oxo-4-(3,4-diphenylthiazolidin-2-ylideno)-pyrimidino[5,4:3,4]isoxazolo[4,3:5,6]-pyridazine (21b)

21b: Yellow crystals (4.98 g, 82%), m.p. 260–263°C (from,4-dioxane), ν max/cm^{-1} 3570–3340 (NH), 3060 (CH aromatic), 1700 (C=O), 1673 (exocydic C=N), 1642 (C=C). ^{1}H NMR: δ 6.99 (s, 1H, thiazole CH), 7.30–7.42 (m, 20H, aromatic protons), 9.01 (s, 1H, NH). Anal. requires for $C_{34}H_{22}N_8O_2S$ (606.58) C, 67.32; H, 3.66; N, 18.47; S, 5.29. Found: C, 67.39; H, 3.36; N, 18.07; S, 6.16.

Synthesis of Compound 11

To a solution of **7a** (4.7 g, 0.01 mmol) in dimethylformamide, malononitrile **9** (0.66 g, 0.01 mmol) was added. The reaction mixture was heated under reflux for 6 h then poured into an ice-water mixture, neutralized with dilute hydrochloric acid (pH-7), and the solid product was collected by filtration and crystallized from dioxane.

4-Amino-3-cyano-6-[1-phenyl-6-oxopyridazin-3-(carbonhydrazido-N-ylideno)]-2-oxo-7-phenyl Thiazolo [4,5-b]pyrane (11)

11: Orange crystals (3.8 g, 71%), m.p. 155°C (from l,4-dioxane), ν max/cm^{-1} 3480–3330 (2 NH_2, NH), 3050 (CH aromatic), 2225, 2220 (CN), 1720, 1685–1670 (3 C=O), 1666 (exocyclic C=N), 1638 (C=C). ^{1}H NMR: δ 4.67, 5.80 (s, 4H, 2NH_2), 7.33–7.39 (m, 10H, aromatic protons), 8.39 (s, 1H, NH). Anal. requires for $C_{25}H_{15}N_9O_4S$ (537.44) C, 55.86; H, 2.81; N, 23.45; S, 5.97. Found: C, 55.61; H, 3.11; N, 23.51; S, 6.29.

4-Amino-5-cyano-1-phenyl-3-carbohydrazido-N-ylidine-4-hydroxy-3-phenyl-5-(4-oxo-5H Thiazol-2-ylideno)]-6-oxopyridazine (13)

To a solution of **7a** (4.7 g, 0.01 mmol) in acetic acid (40 ml), thioglycollic acid **12** (0.92 g, 0.01 mmol) was added. The reaction mixture was heated under reflux for 2 h then left to cool. The solid product formed upon pouring into ice/water mixture was collected by filtration.

13: Orange crystals (3.8 g, 70%), m.p. 235°C (from l,4-dioxane), ν max/cm^{-1} 3520–3300 (OH, NH_2, NH), 3060 (CH aromatic), 2220 (CN), 1700, 1690, 1680 (3 C=O), 1668 (exocyclic; C=N),1640 (C=C). ^{1}H NMR: δ 4.77, 5.80 (s, 2H, NH_2), 6.89 (s, 2H, thiazole CH_2), 7.29–7.35 (m, 10H, aromatic protons), 8.34 (s, 1H, NH). 10.21 (s, 1H, OH) Anal. requires for $C_{24}H_{16}N_8O_4S_2$ (544.49): C, 52.94; H, 2.96; N, 20.58; S, 11.78. Found: C, 52.69; H, 3.01; N, 20.56; S, 11.34.

Synthesis of Compound 17a,b Derivatives

General Procedure

To a solution of **16a** (5.1 g, 0.01 mmol) in 1,4-dioxane (40 ml) containing piperdine (0.5 ml) was added either formaldehyde (0.3 g, 0.01 mmol) or benzaldehyde (1.06 g, 0.01 mmol). The reaction mixture, was heated under reflux for 4 h, then left to cool. The solid product so formed upon pouring into an ice-water mixture containing few drops of hydrochloric acid was collected by filtration.

7-Cyano-3,8-dioxo-4-N-(3,4-diphenylthiazolidin-2-ylideno)-1-phenylpyrimidino[4,5-c]pyridazine (17a)

17a: Yellow white crystals (3.5 g, 68%), m.p. 165°C (from dimethylformamide), ν max/cm^{-1} 3050 (CH aromatic), 2220 (CN) 1710, 1695, (2 C=O), 1660 (exocydic C=N), 1668 (C=N), 1632 (C=C). ^{1}H NMR: δ 6.89 (s, 1H, thiazole C—H), 7.23–7.39 (m, 16H, aromatic protons , pyrimidine H-2)- MS (EI, 70 ev): m/z = 515 (M^+) - Anal. requires for $C_{28}H_{17}N_7O_2S$ (515.49): C, 65.2; H, 3.32: N, 19.02; S, 6.22. Found: C, 65.12; H, 3.09 N, 19.50; S, 6.34.

7-Cyano-3,8-dioxo-4-N-(3,4-diphenylthiazolidin-2-ylideno)-1,5-diphenylpyrimidino[4,5-c]pyridazine (17b)

17b: Yellow white crystals (4.4 g, 74%), m.p. 178–180°C (dimethylformamide), ν max/cm^{-1} 3075 (CH aromatic), 2220 (CN), 1705, 1690 (2 C=O), 1665 (C=N), 1663 (exocyclic C=N), 1665 (C=C). ^{1}H NMR: δ 6.99 (s, 1H, thiazole C—H), 7.20–7.51 (m, 20H, aromatic protons) Anal. requires for $C_{34}H_{21}N_7O_2S$ (591.59): C, 69.02; H, 3.58 N, 16.57; S, 5.42. Found: C, 69.23; H, 3.39 N, 16.29; S, 5.39.

Synthesis of Compound 18a,b and 19a,b Derivatives

General Procedure

To a solution of either **17a** (5.16 g, 0.01 mmol) or **17b** (5.91 g, 0.01 mmol)in dimethylformamide (5 ml) was added either hydrazine hydrate (0.5 g, 0.01 mmol) or phenyl hydrazine (1.08 g, 0.01 mmol). The reaction mixture was heated under reflux for 4 h then pouring into an ice-water mixture containing few drops of hydrochloric acid. The solid product was collected by filtration.

7-Amino-3-oxo-4-N-(3,4-diphenylthiazolo-2-ylideno)-1-phenylpyrimidino[5,4:3,4]pyridazine-[4,3:5,6]pyridazine (18a)

18a: Yellow crystals (4.03 g, 76%), m.p. 300°C (from 1,4-dioxane), ν max/cm^{-1} 3455, 3338 (NH_2), 3065 (CH aromatic), 1695 (C=O), 1675

(exocyclic C=N), 1638 (C=C). ^{1}H NMR: δ 5.31 (s, 2H, NH_2), 6.99 (s, 1H, thiazole C–H), 7.26–7.39 (m, 16H, aromatic protons, pyrimidine H-2), Anal. requires for $C_{28}H_{19}N_9OS$ (529.53): C, 63.50; H, 3.62: N, 23.80; S, 6.05. Found: C, 63.29; H, 3.41 N, 23.76; S, 6.26.

7-Amino-3-oxo-4-N-(3,4-diphenylthiazolidin-2-ylideno)-1,4-diphenylpyrimidino[5,4:3,4]pyrazolo [4,3:5,6]pyridazine (18b)

18b: Yellow crystals (3.88 g, 64%), m.p. 230°C (from 1,4-dioxane), ν max/cm^{-1} 3474, 3337 (NH_2) 3060 (CH aromatic), 1689, (C=O), 1670, (exocyclic C=N), 1640 (C=C). ^{1}H NMR: δ (s, 2H, NH_2), 6.99 (s, 1H, thiazole CH), 7.23–7.75 (m, 20H, aromatic protons). Anal. requires for $C_{34}H_{23}N_9OS$ (605.63): C, 67.42; H, 3.83 N, 20.81; S, 5.29. Found: C, 67.43; H, 3.67 N, 20.69; S, 5.26.

7-Imino-3-oxo-4-N-(3,4-diphenylthiazolidin-2-ylideno)-1-phenylpyrimidino[5,4:3,4]pyrazolo [4,3:5,6]pyridazine (19a)

19a: Yellow crystals (4.42 g, 73%), m.p. 199–201°C (from 1,4-dioxane), ν max/cm^{-1} 3466–3335 (NH) 3066 (CH aromatic), 1680 (C=O), 1670 (exocyclic C=N), 1642 (C=C). ^{1}H NMR: δ 6.99 (s, 1H, thiazole CH), 7.29–7.48 (m, 21H, aromatic protons, pyrimidine H-2), 9,30 (s, 1H, NH). Anal. requires for $C_{34}H_{23}N_9OS$ (605.63): C, 67.42; H, 3.83: N, 20.81; S, 5.29. Found: C, 67.28; H, 3.80 N, 21.09; S, 5.08.

7-Imino-3-oxo-4-N-(3,4-diphenylthiazolidin-2-ylideno)-1,4-diphenylpyrimidino[5,4:3,4]pyrazolo [4,3:5,6]pyridazine (19b)

19b: Yellow crystals (4.43 g, 65%), m.p. 220°C (from 1,4-dioxane), ν max/cm^{-1} 3458–3300 (NH) 3060 (CH aromatic), 1688 (C=O), 1673 (exocyclic C=N), 1637 (C=C). ^{1}H NMR: δ 6.99 (s, 1H, thiazole CH), 7.31–7.59 (m, 25H, aromatic protons), 9.30 (s, 1H, NH). Anal. requires for $C_{40}H_{27}N_9OS$ (681.72): C, 70.47; H, 3.99: N, 18.49; S, 4.70. Found: C, 70.18; H, 4.21 N, 18.63; S, 4.98.

Synthesis of Compound 22a,b Derivatives

General Procedure

The solution of either **21a** (5.31 g, 0.01 mmol) or **21b** (6.07 g, 0.01 mmol) in ethanol (50 ml) containing solid sodium hydroxide (0.4 g, 0.01 mmol) was heated under reflux for 1 h, then poured into an ice-water mixture containing few drops of hydrochloric acid (till pH 6). The solid product formed upon stirring for 1 h was collected by filtration.

3,7-Dioxo-4-N-(3,4-diphenylthiazolidin-2-ylideno)-1-phenylpyrimidino[5,4:3,4]pyridazo[6,5:3,4]isoxazole (22a)

22a: Yellow crystals (3.62 g, 68%), m.p. 148°C (from 1,4-dioxane), ν max/cm^{-1} 3060 (CH aromatic), 1705, 1685 (2 C=O), 1673 (exocyclic C=N), 1645 (C=C). ^{1}H NMR: δ 6.89 (s, 1H, thiazole CH), 7.22–7.39 (m, 16H, aromatic protons, pyrimidine H-2). Anal. requires for $C_{28}H_{17}N_7O_3S$ (531.48): C, 63.27; H, 3.22: N, 18.45; S, 6.03. Found: C, 63.29; H, 3.41 N, 23.76; S, 6.26.

1,5-Diphenyl-3,7-dioxo-4-N-(3,4-diphenylthiazolidin-2-ylideno)-pyrimidino[4,5:3,4]pyridazo[6,5:3,4]isoxazole (22b)

22b: Yellow crystals (4.44 g, 73%), m.p. 204–206°C (from 1,4-dioxane), ν max/cm^{-1} 3060 (CH aromatic), 1703, 1690 (2 C=O), 1675 (exocyclic C=N), 1638 (C=C). ^{1}H NMR: δ 6.93 (s, 1H, thiazole CH), 7.30–7.42 (m, 20H, aromatic protons) Anal. requires for $C_{34}H_{21}N_7O_3S$ (607.58): C, 67.21; H, 3.48: N, 16.14; S, 5.28. Found: C, 67.41; H, 3.40 N, 16.06; S, 6.26.

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