

Novel synthesis of new symmetrical bis-heterocyclic compounds: synthesis of bis-thiazolo, bis-pyrazolo-, bis-benzotriazolo, bis-indolo- and bis-pyrazolyl thiazolo-2,6-diamino pyridine derivatives

N. I. Abdel-Sayed

Chemistry Department, Faculty of Women for Arts, Science and Education, Ain Shams University, Heliopolis, P.O. Box 11757, Cairo, A. R. Egypt

Received December 25, 2008; Revised June 8, 2009

The reaction of 2,6-diaminopyridine with chloroacetyl chloride yielded 2,6-bis-(2-chloroacetamido-N-yl) pyridine. The later reacted with KCN, KSCN, indole and benzotriazole separately to give 2,6-bis-(cyanoacetamido-N-yl)pyridine [which on coupling with benzenediazonium chloride yielded the bis-cyanophenyl hydrazone derivative and by refluxing the later compound with chloroacetonitrile afforded 2,6-diamido-bis-(4-amino-5-cyano-1-phenylpyrazol-3-yl)pyridine], 2,6-bis-(thiocyanate acetamido-N-yl)pyridine, 2,6-bis-[2-(1[H]-indol-3-yl)acetamido-N-yl] pyridine and 2,6-bis-[2-(1,2,3-benzotriazol-1-yl)acetamido-N-yl]pyridine, respectively. Acetylation of 2,6-diaminopyridine with acetic anhydride afforded 2,6-bis-(acetamido-N-yl) pyridine which on coupling with benzenediazonium chloride yielded the bis-phenylhydrazone derivative. By reacting the later with chloroacetonitrile afforded 2,6-diamino-bis-(5-cyano-1-phenylpyrazol-4-yl)pyridine. Under basic conditions the reaction of 2,6-diaminopyridine with CS₂ followed by ethyl- α -bromocanoacetate and phenacyl bromide separately afforded 2,6-bis-(5-cyano-4-hydroxythiazol-3-yl-2-thione)pyridine and 2,6-bis-(4-phenyl thiazol-3-yl-2-thione)pyridine respectively. Condensation of the later compounds separately with malononitrile yielded the dicyanomethinthiazole derivatives. The reaction of either hydrazine hydrate or phenyl hydrazine with the thiazolyl thione derivatives or with the dicyanomethinthiazole derivatives afforded the hydrazone-thiazole and the pyrazole derivatives respectively.

Key words: 2,6-diaminopyridine; bis-(thiazolo)pyridine; bis-(pyrazolo)pyridine; bis-(hydrazonopyrazolo)pyridine.

INTRODUCTION

The incorporation of two moieties increases biological activity of both and thus it was of value to synthesize some new heterocyclic derivatives having two moieties in the same molecules. In continuation to our programme [1–10], this research has been devoted to the development of new classes of bis-heterocycle systems which incorporate the bis-thiazolo-, bis-pyrazolo-, bis-benzotriazolo-, bis-indolo-, bis-triazolo- and bis-pyrazolyl thiazolo- pyridine derivatives moiety. The importance of such compounds lies in their diverse pharmaceutical activities namely antibacterial [11, 12], antidiabetic [13], anti HIV [14], antiviral [15, 16] and analgesic activities.

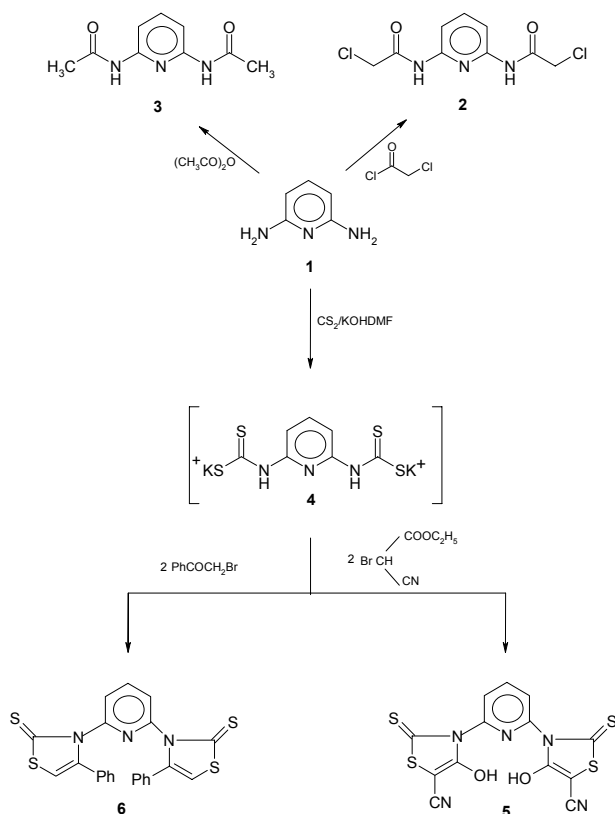
RESULTS AND DISCUSSION

Mixing 2,6-diaminopyridine with chloroacetylchloride in dioxane afforded the 2,6-bis-(2-chloroacetamido)pyridine **2** (Scheme 1). Compound **2** could be converted into **7** on treatment with potassium cyanide and into **8** on treatment with potassium thio-

cyanate. Treatment of **2** with indole and with benzotriazole separately in toluene/triethylamine afforded **9** and **10**, respectively. The ¹H NMR of **10** revealed non identity of all four benzotriazolyl protons.

Compound **11** is symmetrical and should have shown only two signals for these protons (Scheme 2). Compound **7** coupled readily with benzene diazonium chloride to yield the bis-aryl hydrazone derivative **12** which on refluxing in DMF with chloroacetonitrile afforded the bis-pyrazolyl diaminopyridine derivative **14** (Scheme 2). On the other hand acetylation of compound **1** yielded the 2,6-bis-(acetamido)pyridine **3** (Scheme 1). Coupling of **3** with benzene diazonium chloride afforded the bis-hydrazone derivative **15**. Thus, reacting **15** with chloroacetonitrile in a mixture of DMF and triethylamine has afforded **17** in excellent yield. Intermediacy of **16** is most likely (Scheme 2). Further, the reaction of **1** with carbon disulphide under basic conditions in KOH/DMF solution affords the non isolable intermediate, the N-potassium thiocarbamate salt **4** [17]. Thus, the reaction of **4** with ethyl- α -bromocanoacetate and with phenacyl bromide separately afforded the thiazole derivatives **5** and **6** respectively (Scheme 1).

* To whom all correspondence should be sent:
E-mail: nadia_iskandar@yahoo.com



Scheme 1.

Confirmation of the structures of **5** and **6** were obtained through studying their reactivity towards chemical reagents. The reaction of compounds **5** or **6** with either hydrazine hydrate or phenyl hydrazine afforded the corresponding hydrazone derivatives **18a,b** and **22a,b** respectively (Scheme 3). Formation of the latter compounds took place through elimination of hydrogen sulphide. Their structures were confirmed by analytical and spectral data. The reaction of **5** and **6** with malononitrile gave the condensed products the dicyanomethino derivatives **19** and **23** respectively (Scheme 3); their formation took place *via* elimination of hydrogen sulphide. The reaction of **19** and **23** with either hydrazine hydrate or phenylhydrazine afforded the pyrazole derivatives **20**, **21**, **24** and **25** (Scheme 3). The structures of the latter compounds were confirmed by analytical and spectral data.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye Unicam SP-100 spectrophotometer. ^1H and ^{13}C NMR spectra (DMSO- d_6 as a solvent) were obtained on a Varian Gemini 200 and on a Bruker AC200 and AC600 MHz spectrometers respectively, TMS as internal standard, chemical shifts in δ (ppm); mass spectra: AEI MS 30 mass spectrometer operating at 70 eV; elemental analysis were obtained from Microanalytical Data

Unit at Cairo University, Egypt.

2,6-Bis-(2-chloroacetamido-N-yl) pyridine (2): A mixture of **1** (1.09 g, 10 mmol) and chloroacetylchloride (2.30 g, 20 mmol) in 20 ml of dioxane was refluxed for 45 min. The mixture was allowed to cool to room temperature then poured onto cold water. The obtained solid was collected by filtration and crystallized from methanol to give pale pink crystals (93% yield), m.p. 105°C; IR (KBr) ν (cm^{-1}): 3118 (NH) and 1700 (C=O); ^1H NMR (DMSO- d_6) δ (ppm): 4.58 (s, 4H, 2CH₂), 8.10–8.30 (m, 3H, pyr-H), 8.50 (s, 2H, 2NH); ^{13}C NMR (DMSO- d_6) δ (ppm): 190.5 (2CO), 154.2 (C-2 and C-6 pyridine), 149.3 (C-3 and C-5 pyridine), 138.5 (C-4 pyridine), 53.23 (CH₂); MS: $m/z = 262$ [M^+]; Anal. Calcd. for C₉H₉N₃Cl₂O₂ (262.09): C, 41.24; H, 3.46; N, 16.03; Cl, 27.05. Found: C, 41.35; H, 3.47; N, 16.25; Cl, 27.35.

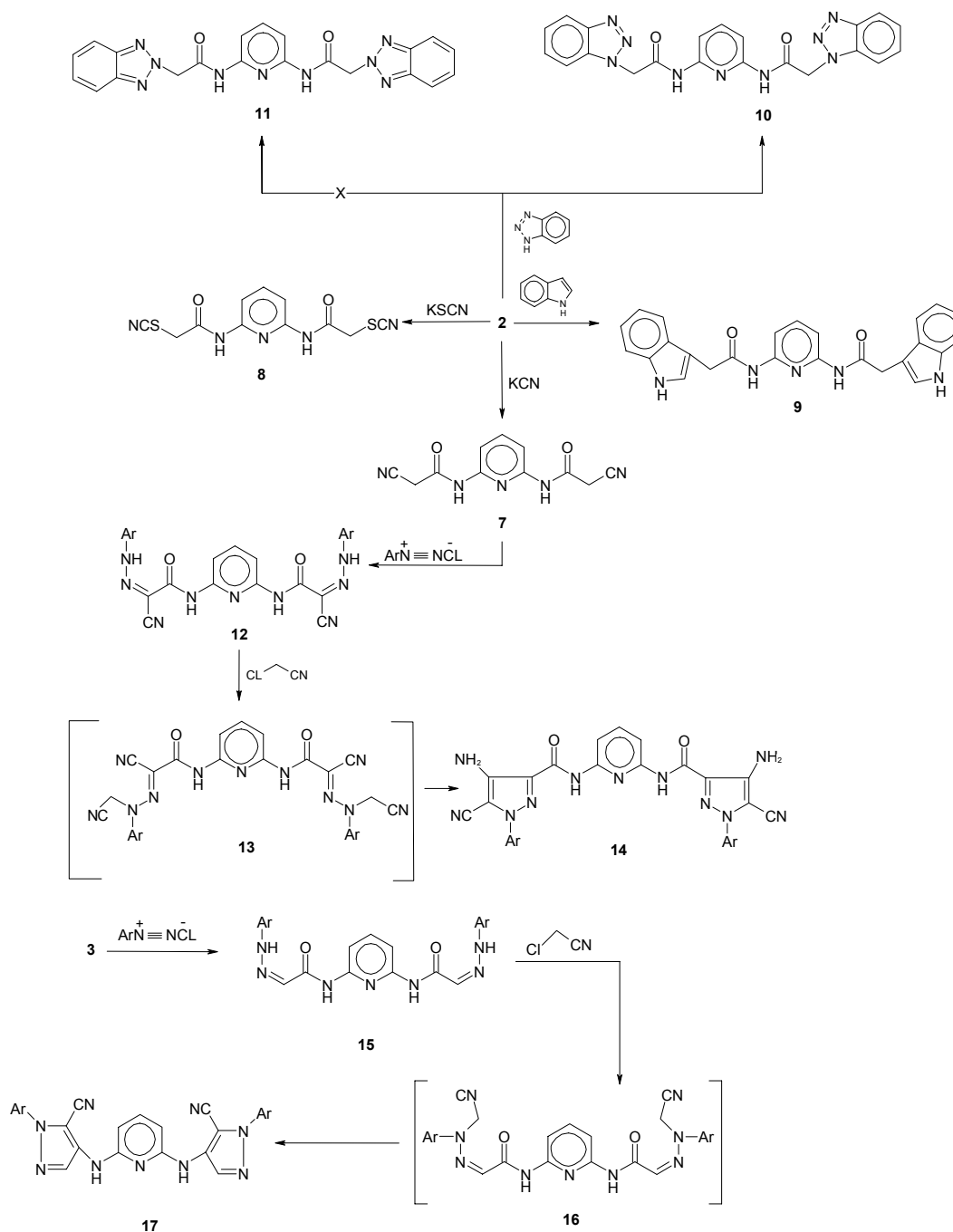
2,6-Bis-(acetamido-N-yl) pyridine (3): Reflux gently 1 g of **1** and 3 ml of acetic anhydride for 15 min. Pour in 20 ml of cold water then boil to destroy any excess of acetic anhydride. Filter the precipitate, wash with a little cold water and dry in air. Crystallization from ethanol afforded 0.18 g of a creamy crystals (95% yield), m.p. 95°C; IR (KBr) ν (cm^{-1}): 3225 (NH), 1700 (C=O); ^1H NMR (DMSO- d_6) δ ppm: 1.5 (s, 6H, 2CH₃), 8.10–8.30 (m, 3H, pyr-H), 8.55 (s, 2H, 2NH); ^{13}C NMR (DMSO- d_6) δ (ppm): 184.5 (2CO), 153.5 (C-2 and C-6 pyridine), 148.4 (C-3 and C-5 pyridine), 138.7 (C-4 pyridine), 24.15 (CH₃); MS: $m/z = 193$ [M^+]; Anal. Calcd. for C₉H₁₁N₃O₂ (193.21): C, 55.95; H, 5.74; N, 21.75. Found: C, 55.90; H, 5.76; N, 21.90.

2,6-Bis (5-cyano-4-hydroxythiazol-3-yl-2-thione) pyridine (5): To a solution of **1** (1.09 g, 0.01 mol) in 30 ml of DMF, carbon disulphide (1.52 g, 0.02 mol) and potassium hydroxide (1.12 g, 0.02 mol) in 10 ml of water were added. The whole reaction mixture was heated in a boiling water bath for 1 h then left to cool till 20°C. To a cold solution of the reaction mixture (3.84 g, 0.02 mol) of ethyl α -bromocynoacetate was added. The reaction mixture was stirred at room temperature for one night. The solid product, formed upon acidification with hydrochloric acid, was collected by filtration and crystallized from dioxane to give orange crystals (87% yield), m.p. 150°C; IR (KBr) ν (cm^{-1}): 3480–3340 (OH), 2225 (2 CN), 1210–1195 (2 C=S); ^1H NMR (DMSO- d_6) δ (ppm): 7.90–8.25 (m, 3H, pyr-H), 10.33 (s, 2H, 2OH); ^{13}C NMR (DMSO- d_6) δ (ppm): 164.5 (2C=S), 153.2 (C-2 and C-6 pyridine), 150.2 (C-4 and C-4' thiazole), 148.1 (C-3 and C-5 pyridine), 140.8 (C-5 and C-5' thiazole), 138.1 (C-4 pyridine), 119.7 (2CN); MS: $m/z = 391$ [M^+]; Anal. Calcd. for C₁₃H₅N₅S₄O₂

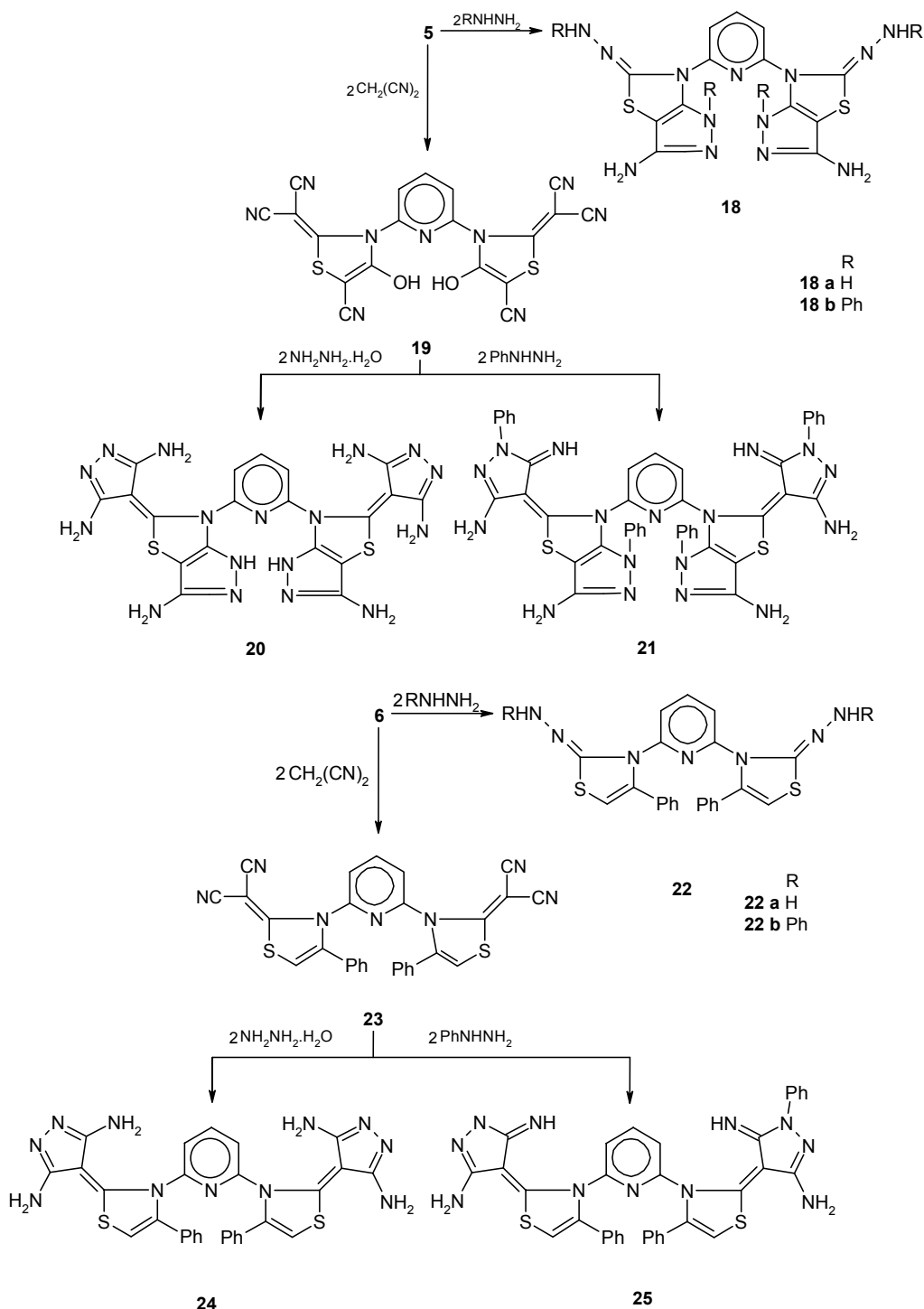
(391.47): C, 39.89; H, 1.29; N, 17.89; S, 32.76. Found: C, 39.95; H, 1.31; N, 18.01; S, 32.80.

2,6-Bis-(4-phenylthiazol-3-yl-2-thione)pyridine (6): To a solution of **1** (1.09 g, 0.01 mol) in 30 ml of DMF, (1.52 g, 0.02 mol) of carbon disulphide and (1.12 g, 0.02 mol) of potassium hydroxide in 10 ml of water were added. The whole reaction mixture was heated in boiling water bath for 1 h then left to cool down to 20°C; (3.96 g, 0.02 mol) of phenacyl-bromide was added to this cold solution. The reaction mixture was stirred at room temperature for one night. The solid product formed upon acidification with hydrochloric acid was collected by filtration.

Crystallization from dioxane gave red crystals (80% yield), m.p. 99°C; IR (KBr) ν (cm⁻¹): 3060 (CH aromatic), 1200–1190 (C=S); ¹H NMR (DMSO-d₆) δ (ppm): 6.95 (s, 2H, thiazole H-5), 7.32–7.55 (m, 10H, 2C₆H₅), 7.95–8.30 (m, 3H, pyr-H); ¹³C NMR (DMSO-d₆) δ (ppm): 180.4 (C-5 and C-5' thiazole), 164.1 (2C=S), 153.4 (C-2 and C-6 pyridine), 148.8 (C-3 and C-5 pyridine), 146.5 (C-4 and C-4' thiazole), 138.5 (C-4 pyridine), 152.1, 143.2, 132.1, 129.5, 128.5, 126.2 (C-arom.); MS: m/z = 461 [M⁺]; Anal. Calcd. for C₂₃H₁₅N₃S₄ (461.65): C, 59.84; H, 3.28; N, 9.10; S, 27.78. Found: C, 59.80; H, 3.27; N, 9.11; S, 27.82.



Scheme 2.



Scheme 3.

2,6-Bis-(cyanoacetamido-N-yl) pyridine (7): To a warmed solution of **2** (1.31 g, 5 mmol) in 10 ml benzene, were added (0.78 g, 12 mmol) of potassium cyanide in 10 ml of water. The reaction mixture was stirred at 50°C (bath temperature) for 1 h, then the aqueous layer was separated and poured onto acidified cooled water. The product, so formed, was collected by filtration and dried. Crystallization from acetic acid gave creamy crystals (95% yield), m.p. 235°C; IR (KBr) ν (cm⁻¹): 2252 (CN), 3220 (NH),

1638 (C=O); ¹H NMR (DMSO-d₆) δ (ppm): 4.48 (s, 4H, 2 CH₂), 8.10–8.30 (m, 3H, pyr-H), 9.45 (s, 2H, 2NH); MS: $m/z = 243$ [M⁺]; Anal. Calcd. for C₁₁H₉N₅O₂ (243.23): C, 54.32; H, 3.73; N, 28.79. Found: C, 54.37; H, 3.74; N, 28.84.

2,6-Bis-(thiocyanate acetamido-N-yl)pyridine (8): To a warmed solution of **2** (1.13 g, 5 mmol) in 10 ml acetonitrile, were added (0.92 g, 12 mmol) of potassium thiocyanate. The reaction mixture was stirred at 50°C (bath temperature) for 1 h, then

poured onto ice cold water. The product, so formed, was collected by filtration, crystallized from ethanol to give faint pink crystals (95% yield), m.p. 130°C; IR (KBr) ν (cm⁻¹): 3220 (NH), 2157 (SCN), 1696 (C=O); ¹H NMR (DMSO-d₆) δ (ppm): 4.48 (s, 4H, 2CH₂), 8.10–8.30 (m, 3H, pyr-H), 9.20 (s, 2H, 2NH); MS: m/z = 307 [M⁺]; Anal. Calcd. for C₁₁H₉N₅S₂O₂ (307.35): C, 42.99; H, 2.95; N, 22.79; S, 20.86. Found: C, 43.01; H, 2.98; N, 23.01; S, 20.88.

General procedure for the synthesis of compounds 9 and 10

A mixture of **2** (2.62 g, 10 mmol), (2.34 g, 20 mmol) of indole or (2.38 g, 20 mmol) of benzotriazole and 2 ml triethylamine (20 mmol) in 15 ml of toluene was refluxed for 2 h. The solvent was removed in vacuum and the remaining residue was triturated with 5% sodium hydroxide. The solid product, so formed, was collected by filtration.

2,6-Bis-[2-(1[H]-indol-3-yl)acetamido-N-yl] pyridine (9): Crystallization from ethanol gave white crystals (78% yield), m.p. 162°C; IR (KBr) ν (cm⁻¹): 3225 (NH), 1700 (C=O); ¹H NMR (DMSO-d₆) δ (ppm): 4.60 (s, 4H, 2CH₂), 7.38–7.75 (m, 8H, 2C₆H₄), 8.10–8.30 (m, 3H, pyr-H), 8.44 (d, 2H, two indole H-2), 9.43 (s, 2H, 2NH), 11.92 (br s, 2H, two indole NH); MS: m/z = 423 [M⁺]; Anal. Calcd. for C₂₅H₂₁N₅O₂ (423.48): C, 70.91; H, 4.99; N, 16.54. Found: C, 70.94; H, 4.98; N, 16.78.

2,6-Bis-[2-(1,2,3-benzotriazol-1-yl)acetamido-N-yl] pyridine (10): Crystallization from ethanol gave white solid (75% yield), m.p. 175°C; IR (KBr) ν (cm⁻¹): 3225 (NH), 1700 (C=O); ¹H NMR (DMSO-d₆) δ (ppm): 4.58 (s, 4H, 2CH₂), 7.33–7.80 (m, 8H, 2C₆H₄), 8.10–8.30 (m, 3H, pyr-H), 9.33 (s, 2H, 2NH); MS: m/z = 427 [M⁺]; Anal. Calcd. for C₂₁H₁₇N₉O₂ (427.43): C, 59.01; H, 4.01; N, 29.49. Found: C, 59.05; H, 4.00; N, 29.55.

General procedure for the synthesis of compounds 12 and 15

To a stirred solution of (0.01 mol) of **7** or **3** in 20 ml of dioxane containing 10 g of sodium acetate, was added benzene diazonium salt (prepared from 20 mmol of aniline and the appropriate quantities of sodium nitrite and hydrochloric acid). The solid product separated on standing was collected by filtration.

2,6-Bis-(2-cyano-2-phenylhydrazonocetamido-N-yl)pyridine (12): Crystallization from dioxane gave yellow crystals (75% yield), m.p. 261°C; IR (KBr) ν (cm⁻¹): 3440, 3234 (NH), 2215 (CN), 1700 (C=O); ¹H NMR (DMSO-d₆) δ (ppm): 7.11–7.25 (m, 10H, 2C₆H₅), 8.10–8.30 (m, 3H, pyr-H), 9.35 (s, 2H, 2NH), 12.04 (br, 2H, hydroazonyl NH); MS: m/z =

451 [M⁺]; Anal. Calcd. for C₂₃H₁₇N₉O₂ (451.451): C, 61.19; H, 3.79; N, 27.92. Found: C, 61.23, H, 3.77; N, 28.15.

2,6-Bis-(1-oxo-2-phenylhydrazonoethanoneamido-N-yl)pyridine (15): Crystallization from dioxane gave yellow crystals (78% yield), m.p. 255°C; IR (KBr) ν (cm⁻¹): 3440, 3230 (NH), 1700 (C=O); ¹H NMR (DMSO-d₆) δ (ppm): 7.11–7.45 (m, 10H, 2C₆H₅), 7.56 (s, 2H, olefinic CH), 8.10–8.30 (m, 3H, pyr-H), 9.30 (s, 2H, 2NH), 12.04 (br, 2H, two hydrazone NH); MS: m/z = 401 [M⁺]; Anal. Calcd. for C₂₁H₁₉N₇O₂ (401.43): C, 62.83; H, 4.77; N, 24.42. Found: C, 62.85; H, 4.74; N, 24.46.

General procedure for the synthesis of compounds 14 and 17

To a solution of (5 mmol) of **12** or **15** in a 2 ml of DMF and 10 ml of triethylamine, was added (1.3 ml, 20 mmol) of chloroacetonitrile. The reaction mixture was refluxed for 1 h and then left to cool to room temperature. The obtained residual product was triturated with ethanol to give a solid product that was collected by filtration, washed with water and crystallized from the proper solvent.

2,6-Diamido-bis-(4-amino-5-cyano-1-phenylpyrazol-3-yl) pyridine (14): Crystallization from ethanol gave faint brown crystals (75% yield), m.p. 268–270°C; IR (KBr) ν (cm⁻¹): 1700 (C=O), 3450 (NH₂), 3200 (NH), 2220 (CN), 1650 (C=N); ¹H NMR (DMSO-d₆) δ (ppm): 6.52 (s, 4H, 2NH₂), 7.31–7.65 (m, 10H, 2C₆H₅), 8.10–8.30 (m, 3H, pyr-H), 8.90 (s, 2H, 2NH); MS: m/z = 529 [M⁺]; Anal. Calcd. for C₂₇H₁₉N₁₁O₂ (529.53): C, 61.24; H, 3.62; N, 29.10. Found: C, 61.25; H, 3.61; N, 29.40.

2,6-Diamino-bis-(5-cyano-1-phenylpyrazol-4-yl) pyridine (17): Crystallization from ethanol gave faint brown crystals (85% yield), m.p. 230°C; IR (KBr) ν (cm⁻¹): 3200 (NH), 2220 (CN), 1600 (C=C), 1650 (C=N); ¹H NMR (DMSO-d₆) δ (ppm): 7.30 (s, 2H, pyrazolyl H-3), 7.41–7.65 (m, 10H, 2C₆H₅), 8.10–8.30 (m, 3H, pyr-H), 8.35 (s, 2H, 2NH); MS: m/z = 443 [M⁺]; Anal. Calcd. for C₂₅H₁₇N₉ (443.48): C, 67.71; H, 3.86; N, 28.43. Found: C, 67.72; H, 3.84; N, 28.44.

2,6-Bis-(5-cyano-2-dicyanomethino-4-hydroxythiazol-N-yl)pyridine (19): A solution of **5** (3.91g, 0.01 mol) in 40 ml of DMF containing piperidine 0.5 ml, (1.32 ml, 0.02 mol) of malonitrile was added. The reaction mixture was heated under reflux for 10 h, then evaporated *in vacuo*. The remaining product was triturated with ethanol and the formed solid product was collected by filtration. Crystallization from dioxane gave brown crystals (75% yield), m.p. > 360°C; IR (KBr) ν (cm⁻¹): 3490 (OH), 2225, 2220, 2215 (CN), 1655 (C=C); ¹H NMR

(DMSO- d_6) δ (ppm): 8.10–8.30 (m, 3H, pyr-H), 10.44 (s, 2H, 2OH); MS: m/z = 455 [M^+]; Anal. Calcd. for $C_{19}H_5N_9S_2O_2$ (455.44): C, 50.11; H, 1.11; N, 27.68; S, 14.08. Found: C, 50.15; H, 1.09; N, 27.72; S, 14.12.

General procedure for the synthesis of compounds 18a, b; 20, 21 and 22a, b

To a solution of **5**, **19** or **6** (0.01 mol) in 30 ml of DMF, hydrazine hydrate or phenylhydrazine (0.04 mol) or (0.02 mol) were added, respectively. The reaction mixture was heated under reflux for 6–8 h then poured into ice/water mixture containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

2,6-Bis-(3-amino-1[H]-5-hydrazonopyrazolo[4,5-d]thiazol-N-yl) pyridine (18a): Crystallization from ethanol gave pale yellow crystals (68% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3465–3365 (NH, NH₂), 1660 (exocyclic C=N), 1645 (C=C); ¹H NMR (DMSO- d_6) δ (ppm): 4.46, 5.35 (2s, 8H, 4NH₂), 8.10–8.30 (m, 3H, pyr-H), 8.44 (s, 2H, 2NH); MS: m/z = 415 [M^+]; Anal. Calcd. for $C_{13}H_{13}N_{13}S_2$ (415.46): C, 37.58; H, 3.15; N, 43.83; S, 15.44. Found: C, 37.56; H, 3.16; N, 43.85; S, 15.43.

2,6-Bis-(3-amino-1-phenyl-5-phenylhydrazono-pyrazolo[4,5-d]thiazol-N-yl)pyridine (18b): Crystallization from dioxane gave yellow crystals (70% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3450–3370 (NH₂, NH), 1665 (exocyclic C=N), 1650 (C=C); ¹H NMR (DMSO- d_6) δ (ppm): 5.32 (s, 4H, 2NH₂), 7.36–7.48 (m, 20H, 4C₆H₅), 8.10–8.30 (m, 3H, pyr-H), 8.45 (s, 2H, 2NH); MS: m/z = 719 [M^+]; Anal. Calcd. for $C_{37}H_{29}N_{13}S_2$ (719.86): C, 61.74; H, 4.06; N, 25.29; S, 8.91. Found: C, 61.75; H, 4.04; N, 25.3; S, 8.90.

2,6-Bis[3-amino-1[H]-5-(3',5'-diaminopyrazolo-4'-ylidino) pyrazolo [4,5-d]thiazol-N-yl] pyridine (20): Crystallization from ethanol gave white crystals (68% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3460–3370 (NH₂, NH), 1660 (C=N), 1655 (C=C); ¹H NMR (DMSO- d_6) δ (ppm): 5.31, 5.36, 7.42 (3s, 12H, 6NH₂), 8.10–8.30 (m, 3H, pyr-H), 8.41 (s, 2H, 2NH); MS: m/z = 547 [M^+]; Anal. Calcd. for $C_{19}H_{17}N_{17}S_2$ (547.59): C, 41.68; H, 3.13; N, 43.48; S, 11.71. Found: C, 41.65; H, 3.14; N, 43.52; S, 11.69.

2,6-Bis-[3-amino-1-phenyl-5-(3'-amino-5'-imino-1'-phenylpyrazolo-4'-ylidino) pyrazolo[4,5-d] thiazol-N-yl] pyridine (21): Crystallization from dioxane gave pale brown crystals (74% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3460–3365 (NH₂, NH), 1670 (exocyclic C=N), 1660 (C=N), 1645 (C=C); ¹H NMR (DMSO- d_6) δ (ppm): 4.82, 5.45 (2s, 8H, 4NH₂), 7.30–7.46 (m, 20H, 4C₆H₅), 8.10–8.30 (m,

3H, pyr-H), 8.33 (s, 2H, 2NH); MS: m/z = 851 [M^+]; Anal. Calcd. for $C_{43}H_{33}N_{17}S_2$ (851.94): C, 60.62; H, 3.90; N, 27.95; S, 7.53. Found: C, 60.60; H, 3.91; N, 27.99; S, 7.50.

2,6-Bis-(2-hydrazono-4-phenylthiazol-N-yl)pyridine (22a): Crystallization from dioxane gave buff crystals (75% yield), m.p. 125°C; IR (KBr) ν (cm^{-1}): 3460 (NH₂), 1665 (exocyclic C=N), 1650 (C=C); ¹H NMR (DMSO- d_6) δ (ppm): 6.35 (s, 4H, 2NH₂), 6.37 (s, 2H, thiazolyl H-5), 7.32–7.37 (m, 10H, 2C₆H₅), 8.10–8.30 (m, 3H, pyr-H); MS: m/z = 457 [M^+]; Anal. Calcd. for $C_{23}H_{19}N_7S_2$ (457.59): C, 60.37; H, 4.19; N, 21.43; S, 14.01. Found: C, 60.39; H, 4.17; N, 21.55; S, 13.89.

2,6-Bis-(2-phenylhydrazono-4-phenylthiazol-N-yl) pyridine (22b): Crystallization from dioxane gave pale yellow crystals (73% yield), m.p. 120°C; IR (KBr) ν (cm^{-1}): 3460–3375°C (NH), 1665 (exocyclic C=N), 1650 (C=C); ¹H NMR (DMSO- d_6) δ (ppm): 6.37 (s, 2H, thiazolyl H-5), 7.32–7.48 (m, 20H, 4C₆H₅), 8.10–8.30 (m, 3H, pyr-H), 8.33 (s, 2H, 2NH); MS: m/z = 609 [M^+]; Anal. Calcd. for $C_{35}H_{27}N_7S_2$ (609.78): C, 68.94; H, 4.46; N, 16.08; S, 10.52. Found: C, 68.97; H, 4.44; N, 16.10; S, 10.49.

2,6-Bis-(2-dicyanomethino-4-phenylthiazol-N-yl) pyridine (23): To a solution of **6** (4.61 g, 0.01 mol) in 30 ml of DMF, (1.32 ml, 0.02 mol) of malononitrile was added. The mixture was heated under reflux for 6 h (till the evolution of H₂S was ceased). The solid product formed upon pouring into water was collected by filtration. Crystallization from dioxane gave brown crystals (80% yield), mp 145°C; IR (KBr) ν (cm^{-1}): 2225–2220 (CN), 1655 (C=C); ¹H NMR (DMSO- d_6) δ (ppm): 6.34 (s, 2H, thiazolyl H-5), 7.34–7.45 (m, 10H, 2C₆H₅), 8.10–8.30 (m, 3H, pyr-H); MS: m/z = 525 [M^+]; Anal. Calcd. for $C_{29}H_{15}N_7S_2$ (525.62): C, 66.27; H, 2.88; N, 18.65; S, 12.20. Found: C, 66.28; H, 2.87; N, 18.66; S, 12.19.

General procedure for the synthesis of compounds 24 and 25

To a solution of **23** (5.01 g, 0.01 mol) in 40 ml of dioxane, hydrazine hydrate or phenyl hydrazine (0.02 mol) was added. The reaction mixture was heated under reflux for 3–4 h, then left to cool. The solid product formed upon standing was collected by filtration.

2,6-Bis-[2-(3',5'-diaminopyrazolo-4'-ylidino)-4-phenyl thiazol-N-yl] pyridine (24): Crystallization from DMF gave white crystals (70% yield), m.p. 323°C; IR (KBr) ν (cm^{-1}): 3465 (NH₂), 1645 (C=C), 1660 (C=N); ¹H NMR (DMSO- d_6) δ (ppm): 4.44, 5.03 (2s, 8H, 4NH₂), 6.42 (s, 2H, thiazolyl H-5), 7.35–7.58 (m, 10H, 2C₆H₅), 8.10–8.30 (m, 3H, pyr-H); MS: m/z = 589 [M^+]; Anal. Calcd. for

C₂₉H₂₃N₁₁S₂ (589.71): C, 59.07; H, 3.93; N, 26.13; S, 10.87. Found: C, 59.05; H, 3.94; N, 26.17; S, 10.84.

2,6-Bis-[2-(3'-amino-5'-imino-1'-phenylpyrazolo-4'-ylidino)-4-phenylthiazol-N-yl] pyridine (25): Crystallization from ethanol afforded pale yellow crystals (65% yield), m.p. > 360°C; IR (KBr) ν (cm⁻¹): 3465, 3390 (NH₂, NH), 1660 (C=N), 1645 (C=C); ¹H NMR (DMSO-d₆) δ (ppm): 4.43 (s, 4H, 2NH₂), 6.43 (s, 2H, thiazolyl H-5), 7.30–7.64 (m, 20H, 4C₆H₅), 8.10–8.30 (m, 3H, pyr-H), 8.37 (s, 2H, 2NH); MS: m/z = 741 [M⁺]; Anal. Calcd. for C₄₁H₃₁N₁₁S₂ (741.91): C, 66.38; H, 4.21; N, 20.77; S, 8.64. Found: C, 66.40; H, 4.20; N, 20.80; S, 8.60.

REFERENCES

1. R. M. Mohareb, S. M. Sherif, F. A. M. Abdel-Aal, N. I. Abdel-Sayed, *Leibigs Ann. Chem.*, 1143 (1990).
2. N. I. Abdel-Sayed, *Women's College Ann. Rev.*, **16**, 12 (1991).
3. R. M. Mohareb, N. I. Abdel-Sayed, S. M. Sherif, *Phosphorus, Sulfur and Silicon*, **63**, 119 (1991).
4. R. M. Mohareb, S. I. Aziz, N. I. Abdel-Sayed, H. Z. Shams, *J. Chin. Chem. Soc.*, **39**, 181 (1992).
5. R. M. Mohareb, N. I. Abdel-Sayed, *Collect. Czech. Chem. Commun.*, **57**, 1758 (1992).
6. R. M. Mohareb, S. M. Sherif, A. Habashi, N. I. Abdel-Sayed, S. S. Osman, *Collect. Czech. Chem. Commun.*, **60**, 1578 (1995).
7. S. M. Sherif, N. I. Abdel-Sayed, S. M. El Kousy, R. M. Mohareb, *Monatsh. Chem.*, **126**, 601 (1995).
8. R. M. Mohareb, Y. M. Elkholy, N. I. Abdel-Sayed, *Phosphorus, Sulfur and Silicon*, **106**, 193 (1995).
9. R. M. Mohareb, S. I. Aziz, N. I. Abdel-Sayed, A. H. El-Banna, *J. Chem. Res.*, (S) 10 (1999); *Ibid.*, (M) 0101 (1999).
10. N. I. Abdel-Sayed, *Egypt. J. Chem.*, **42**, 175 (1999).
11. P. Nussbaumer, G. Petranyi, A. Stutz, *J. Med. Chem.*, **34**, 65 (1991).
12. N. J. P. Broom, J. S. Elder, P. C. T. Hannan, J. E. Pons, P. J. O'Hanlon, G. Walker, J. Wilson, P. Woodall, *J. Antibiotic*, **48**, 1336 (1995).
13. M. Nakanishi, H. Imamura, Y. Maruyama, H. Hoshino, *J. Pharm. Soc. Jpn.*, **90**, 272 (1970).
14. D. Briel, *Pharmazie*, **45**, 236 (1995).
15. M. Yamaguchi, N. Maruyama, T. Koga, K. Kamei, M. Akima, T. Kuroki, M. Hamana, N. Ohi, *Chem. Pharm. Bull.*, **43**, 236 (1995).
16. R. E. Boyd, J. B. Press, C. R. Rasmussen, R. B. Raffa, E. E. Codd, C. D. Connelly, Q. S. Li, R. P. Martinez, M. A. Lewis, B. J. Almond, *J. Med. Chem.*, **44**, 863 (2001).
17. M. T. Cocco, C. Congiu, V. Onnis, *J. Heterocyclic Chem.*, **32**, 463 (1995).

НОВИ СИНТЕЗИ НА НОВИ СИМЕТРИЧНИ БИС-ХЕТЕРОЦИКЛЕНИ СЪЕДИНЕНИЯ: СИНТЕЗ НА БИС-ТИАЗОЛ-, БИС-ПИРАЗОЛ-, БИС-БЕНЗОТРИАЗОЛ-, БИС-ИНДОЛ- И БИС-ПИРАЗОЛИЛТИАЗОЛ-2,6-ДИАМИНПИРИДИНОВИ ПРОИЗВОДНИ

Н. И. Абдел-Сайед

*Департамент по химия, Девически факултет по изкуства, наука и образование, Университет Айн Шамс,
Хелиополис, п.к. 11757, Кайро, АР Египет*

Постъпила на 25 декември 2008 г.; Преработена на 8 юни 2009 г.

При реакция на 2,6-диаминопиридин с хлорацетилхлорид се получава 2,6-бис-(2-хлорацетамид-N-ил)пиридин. Реакцията на продукта поотделно с KCl, KSCN, индол и бензотриазол води съответно до 2,6-бис-(цианацетамид-N-ил)пиридин (продуктът при купелуване с бензендиазониев хлорид дава бис-цианфенилхидразоновото производно и чрез дестилация на последното съединение с обратен хладник и хлорацетонитрил се получава 2,6-диамин-5-циан-1-фенилпиразол-3-ил)пиридин), 2,6-бис-(тиоцианат ацетамид-N-ил)пиридин, 2,6-бис-[2-(1-[H]-индол-3-ил)ацетамид-N-ил]пиридин и 2,6-бис-[2-(1,2,3-бензотриазол-1-ил)ацетамид-N-ил]пиридин. Ацетиране на 2,6-диаминопиридин с оцетен анхидрид води до 2,6-бис-(ацетамид-N-ил)пиридин, който при купелуване с бензендиазониев хлорид дава бис-фенилхидразоновото производно. При реакцията на последното с хлорацетонитрил се получава 2,6-диамино-бис-(5-циан-1-фенил-пиразол-N-ил)пиридин. В алкална среда реакцията на 2,6-диаминопиридин с CS₂ последвана поотделно с стил- α -бромцианоацетат и фенацилбромид дава съответно 2,6-бис-(5-циан-4-хидроксипиразол-3-ил-2-тионил)пиридин и 2,6-бис-(4-фенил-тиазол-3-ил-2-тионил)пиридин. При кондензация на получените съединения поотделно с малонитрил се получават дицианметинтиазолови производни. При реакция на хидразинхидрат или фенилхидразин с тиазолилтенови производни или с дицианметинтиазолови производни води съответно до хидразонтиазолови и пиразолови производни.