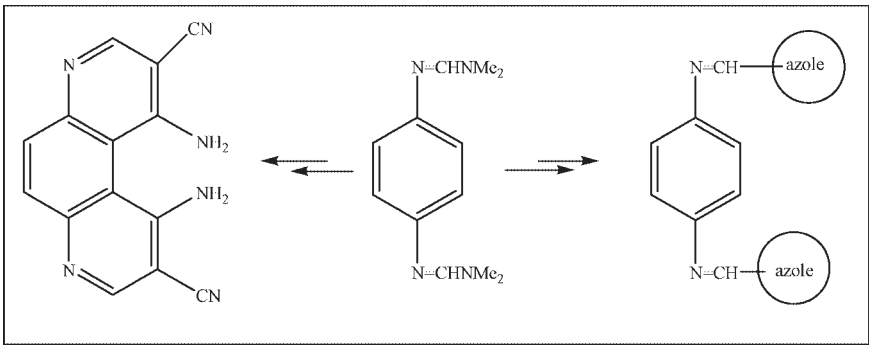
Utility of *p*-Phenylenediformamidine in the Synthesis of Bisazoles and Phenanthroline

Saleh M. Al-Mousawi[a] and Abdel-Zaher A. Elassar[b]*

[a]Department of Chemistry, Faculty of Science, University of Kuwait, Safat 13060, Kuwait
[b]Chemistry Department, Faculty of Science Helwan University, Cairo, Egypt
*E-mail: aelassar@yahoo.com

Received June 21, 2008
DOI 10.1002/jhet.157
Published online 25 August 2009 in Wiley InterScience (www.interscience.wiley.com).



p-Phenylenediformamidine **1** is readily obtained upon treating *p*-phenylenediamine with dimethylformamide dimethyl acetal (DMFDMA) by heating or by microwave irradiation. Compound **1** was treated with active methylene nitriles followed by hydrazine hydrate derivatives to give bisaminopyrazole derivatives. Other bisazoles can be obtained by reacting **1** with aminoazole derivatives. Cyclization of Bis [2-(*p*-phenelyeneimino)malononitrile] to 1,10-diaminophenanthroline-2,9-dicarbonitrile is also reported.

J. Heterocyclic Chem., **46**, 837 (2009).

INTRODUCTION

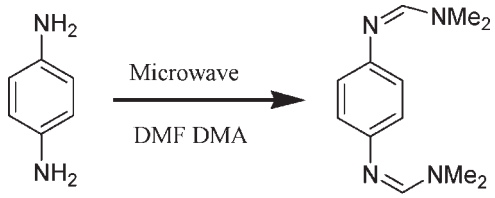
Heterocyclic compounds have attracted considerable interest. A lot of attention has been directed toward the synthesis of polyfunctionally substituted azoles because of their biological and pharmaceutical activities. For example, pyrazoles have shown many interesting biological and pharmacological properties such as inhibitors of p 38 MAP kinase [1] anti-tumor CDK inhibitors [2], potent inhibitors of type II topoisomerases [3]. Thiazolediamides are used as potent g-secretase [4], also as vanilloid receptor 1 (TRPV 1) antagonists [5]. Both imidazole and triazole potent CB_1 receptor antagonists related to SR141716 [6]. 4-Triazole-modified zanamivir analogs exert moderate inhibition against AIV (H5N1) [7]. Carroll *et al.* [8] reported that the heterocyclic replacement on substituted benzene ring showed a progressive loss of P2X-, potency in the order tetrazole > triazole > imidazole > pyrazole. He rationalized this result to overall electron density of the core heterocycle and P2X-, potency. Furthermore, phenylenediformamidine showed good acaricidal and insecticidal activity [9]. A combination of phenylenediformamidine and azoles in one system seemed to be useful. Thus, design of a simple and an efficient approach to the polyfunctionally substituted heterocycles on benzene ring is one of our goals. In conjugation with our previous work [10], here we report on the synthesis of bisazole using *p*-phenylenediformamidine as starting material.

RESULTS AND DISCUSSION

p-Phenylenediamine readily reacts with dimethylformamide dimethylacetal, DMFDMA, to give *N.N'-p*-phenylenediformamidine **1**, which agree with the literature in this data [11]. Formamidine, **1** could also be obtained by Vilsmeier reaction [12,13]. Synthesis of *p*-phenylenediformamidine **1** using microwave irradiation has not been described before. In this article, we have obtained *p*-phenylenediformamide **1** in an excellent yield and short time upon irradiating a mixture of *p*-phenylenediamine, DMFDMA, and xylene at 160°C (cf. Scheme 1). The reaction product was established based on mass spectrometry which showed *m/z* 260 (M^+). ^1H NMR revealed the presence of NMe_2 and aromatic protons as a singlet at d 3.49 and d 6.78 ppm, respectively. This NMR data confirm the symmetry in the molecule. Furthermore, the CH protons appeared at d 7.64 ppm.

Chemical reactivity of *p*-phenylenediformamidine **1** toward different active methylene has been investigated. Thus, compound **1** reacted with **2a–c** in glacial acetic acid to give the same reaction product **3**. This result prompted us to investigate the behavior of **1** in acetic

Scheme 1



1

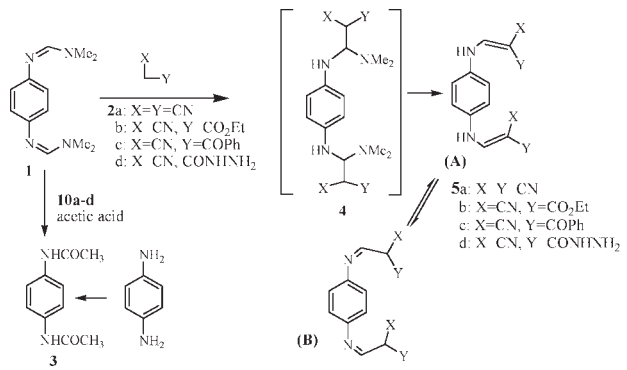
acid as a blank experiment. We also obtained here the same result as that obtained from its reaction with each of compounds **2a–c**. This supported our believing that the acetylation reaction had taken place between the solvent (acetic acid) and *p*-phenylenediformamidine **1**. This result was confirmed by refluxing *p*-phenylenediamine in glacial acetic acid which afforded the acetylated product **3**. Thus, the reaction of **2a–d** with *p*-phenylenediformamidine **1** in pyridine afforded the target products **5a–d**. The formation of these products are believed to proceed *via* addition of active methylene to the imine double bond to give the nonisolable intermediate **4** followed by loss of two molecules of dimethylamine. ^{1}H NMR spectrum of structure **5a** showed the low field signals as a doublet at d 8.45 ppm corresponding to CH protons, while aromatic protons appeared as a singlet at d 7.44 ppm. These data confirm the symmetry in the molecule. Signal at d 11.13 ppm was assigned to the NH protons. This signal underwent a facile hydrogen deuterium exchange upon addition of deuterium oxide. The NOE experiment showed the irradiation of NH protons enhancing the CH protons while the aromatic protons was not affected revealing the special proximity of NH and CH protons. The ^{13}C NMR spectrum revealed a low field signal at d 156.41 ppm and a high field signal at d 52.52 ppm corresponding to the imine carbon and ethylenic carbon, respectively. Other carbons appeared at expected positions. On the other hand, a structure of compound **5b** was established based on ^{1}H NMR which showed a triplet at d 1.27 ppm (J = 7.2 Hz) and quartet at d 4.21 ppm (J = 7.2 Hz) corresponding to methyl group and methylene group, respectively. Aromatic protons appeared at d 7.52 ppm as a singlet. Other synthetic method for **5b** [14] and **5a** [15] had been described *via* condensation of ethoxymethylene-malononitrile or ethoxymethylenethyl cyanoacetate with *p*-phenylenediamine. Similarly **5c** and **d** were elucidated (Scheme 2).

Enamine of **5a–d** (form A) may be tautomerized to the corresponding imine (form B). Thus, phenylenimino derivatives **5a–c** reacted with nucleophilic reagent, hydrazine hydrate, or phenyhydrazine, to afford the intermediate **6.** This could be formed *via* addition of the amino group of the hydrazine hydrate to the cyano function followed by further addition in case of **5a** and condensation in case of **5b** and **5c** to loss ethanol or water molecule, respectively, to give the final isolated product **7**, **8**, and **9.** An independent method for preparation of **9** took place through heating of **5d** for a long time in a basic medium. The obtained product was confirmed by mixing melting point and IR spectrum. The reaction product **9** is believed to proceed through intramolecular cyclization of **5d** through addition of amino group to cyano function. Reaction of **5a** and **5b** with phenylhydrazine produce the corresponding compounds **10** and **11**, respectively. The compounds **10** and **11** formed through addition of amino group of phenylhydrazine to the cyano function followed by addition to the second cyano group in case of **5a** or lose of ethanol in case of **5b** to cyclized to **10** and **11**, respectively. The structure of the reaction products are established based on the elemental analysis and spectral data. IR spectra in all cases revealed the absence of the cyano group and the presence of amino group. ^{1}H NMR confirms the presence of the imine protons, amino group, and NH. In addition, the absence of ethyl group was observed. Phenyl protons in **10** and **11** appeared at high field than those of corresponding **7** and **8** reflecting shielding effect of sp^3 nitrogen on aromatic protons (cf. experimental part) (Scheme 3).

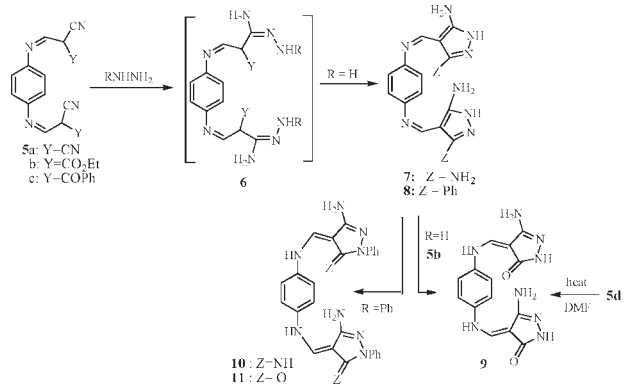
Moreover, bisazole derivatives **12–16** could be synthesized by direct treatment of *p*-phenylenedi-formamidine **1** with different heteroamines, for example, aminotriazole, aminoimidazole, aminothiazole, and aminobenzimidazole. The reaction products are believed to be formed through the addition of the nucleophilic amino group to the imine double bond to give the nonisolated intermediate **A** followed by loss of two molecules of dimethylamine to afford the final isolated products **B**, **12–16** (Scheme 4). The structure of the reaction products were confirmed by elemental analysis and spectral data as indicated in the experimental section.

Trials to cyclize **5a** to phenanthrolinedicarbonitrile derivative **17** or **18** in polyphosphoric acid or ionic

Scheme 2

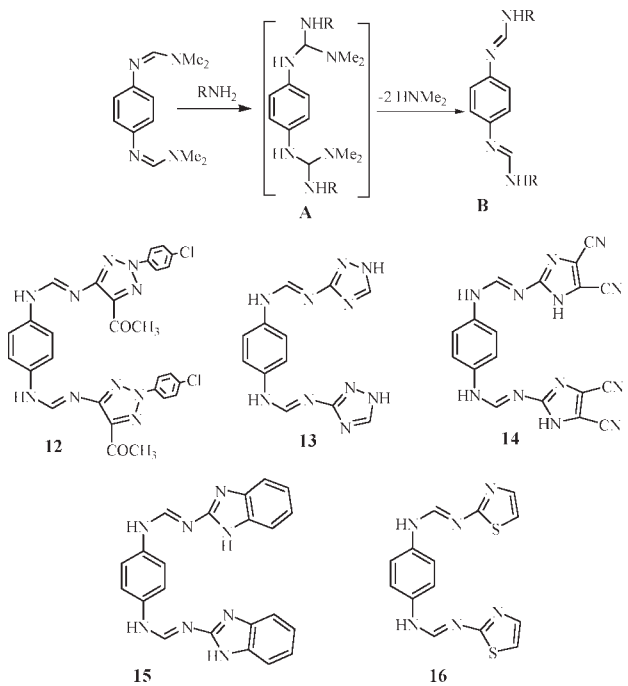


Scheme 3

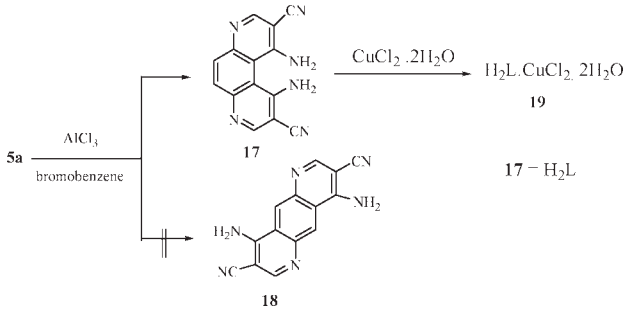


liquid (pyridinium hydrochloride) or by microwave irradiation for a long time has failed. An extension of Gould-Jacobs reaction [16–21] approach for cyclization of **5a** to **17**, a mixture of compound **5a** and anhydrous aluminum chloride has been heated under reflux in bromobenzene to give a product characterized **17** or **18**. The latter compound **18** is ruled out based on the NOE experiment which showed the protons of amino groups in opposite to the benzene protons. Where the irradiation of NH_2 protons has no effect on benzene ring protons which agree with compound **17**. In addition, the reaction product was established as 1,10-diaminophenanthroline-2,9-dicarbo-nitrile **17** based on elemental analysis and spectral data. ^{1}H NMR reveals the presence of

Scheme 4



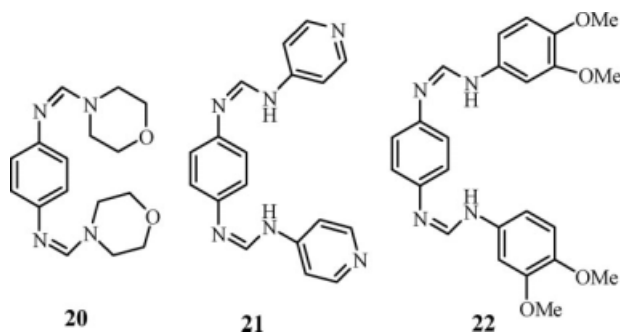
Scheme 5



amino protons at 11.12 ppm (D_2O-exchange), two protons of pyridine rings at 8.45 ppm, and a singlet proton at 7.47 ppm represent the symmetrical two protons of benzene ring. Bidentate **17** (H_2L) could also be confirmed by using as a ligand. Thus, compound **17** was uptake Cu(II) from its solution, which support that the two amino groups are in the same side, to give the complex **19**. Complex product **19** was established based on its elemental analysis and spectral data. IR reveals the presence of a broad band at 3440 cm^{-1} refers to presence of water molecules. IR also reveals the presence of amino and cyano bands at 3297, 3219, and 2215 cm^{-1}, respectively. In continuation of complex structure elucidation, energy-dispersive spectroscopy (EDS) reveals the presence of Cu(II). In addition to chlorine, carbon, hydrogen, and oxygen appeared clearly in the EDS chart. Furthermore, the electron spin resonance (ESR) confirmed the formation of the complex, where the π-band ESR spectrum of the Cu(II) complex at room temperature is of axial type consistent with d_{x2}-d_{y2} ground state (Scheme 5).

Investigation of reactivity of **1** toward aliphatic, heteroaromatic, and aromatic amines was also studied. Thus, compound **1** reacted with morpholine, 4-aminopyridine, and 3,4-dimethoxyaniline in pyridine to give the N-substituted amine derivatives **20–22**, respectively (Scheme 6). This reaction is believed to be proceed through loss of two dimethylamine molecules.

Scheme 6



EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker DPX 400, 400MHz super-conducting NMR spectrometer in DMSO-d_6 as solvent and TMS as internal standard; chemical shifts are reported in d units (ppm). Mass spectra were measured on a VG Autospec-Q (high resolution, high performance, tri-sector GC/MS/MS). Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer. Microwave experiments were conducted using a microwave oven DAEWOO, edition II (KOR-8667).

Preparation of *N,N'*-Phenylenediformamidine (1). ***Method A.*** To a solution of *p*-pheneylenediamine 1.08 g (0.01 mol) in xylene (30 mL), dimethylformamide dimethylacetal (DMFDMA), 1.19 g (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product so formed after cooling was collected by filtration and crystallized from xylene.

Method B. To a solution of *p*-pheneylenediamine 1.08 g (0.01 mol) in xylene (5 mL), dimethylformamide dimethylacetal (DMFDMA), 1.19 g (0.01 mol) was added. The reaction mixture was irradiated for 15 min in microwave at 160°C. The solid product so formed was collected by filtration and crystallized from xylene. Melting point 116–119°C (ref. [14] mp 119–120°C; ref. [12,13] mp 120.5–121°C).

Compound **1** was obtained as yellowish white crystals 1.8 g (82%), while in case of microwave synthesis 1.98 g (91%) was obtained, from xylene, mp 116–119°C; ir: 1655 cm^{-1} (C=N); ^{1}H NMR: δ 7.64 (s, 2H, CH=), 6.78 ppm (s, 4H, C_6H_4), 3.49 (s, 12H. 4Me) ^{13}C NMR: δ 153.74 (=CH=), 147.52, 121.76 (aromatic carbons), 39.86 (Me); ms: *m*/*z* 218 (M^+, 100%). Anal. Calcd. for $C_{12}H_{18}N_4$ (218.30): C, 66.02; H, 8.31; N, 25.67. Found: C, 65.98; H, 8.06; N, 25.76.

General procedure for ylidene synthesis (5a–d). ***Method A.*** To a solution of (**1**) 2.18 g (0.01 mol) in ethanol (30 mL), active methylene compound (**2a**) or (**2b**) or (**2c**) or (**2d**) (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The obtained product after cooling was collected by filtration and crystallized from the proper solvent.

Method B. To a solution of (**1**) 2.18 g (0.01 mol) in DMF (5 mL), active methylene compound (**2a**) or (**2b**), (0.01 mol), was added. The reaction mixture was irradiated for 30 min in microwave at 160°C in the case of (**2a**) and 155°C in the case of (**2b**). The obtained product after cooling was collected by filtration and crystallized from the proper solvent.

Bis [2-(*p*-phenelyeneimino)malononitrile] (5a). This compound was obtained as yellow crystals 1.62 g (62%) while in case of microwave synthesis 2.16 g (83%) was obtained), from acetone, mp > 300°C; ir: 3299, 3224 (2NH), 2223, 2210 (CN), 1655 cm^{-1} (C=N); ^{1}H NMR: δ 11.15 (br, 2H, 2NH), 8.49 (d, 2H, CH=), 7.44 ppm (s, 4H, C_6H_4). ^{13}C NMR: δ 156.41 (=CH=), 137.21, 119.81 (aromatic carbons), 117.37, 115.12 (CN), 52.52 (ethylenic carbon); ms: *m*/*z* 260 (M^+, 100%). Anal. Calcd. for $C_{14}H_8N_6$ (260.25): C, 64.61; H, 3.10; N, 32.29. Found: C, 64.95; H, 3.06; N, 31.99.

Bis[(Ethyl 2-cyano-2-(*p*-phenyleneimino) acetate] (5b). This compound was obtained as yellow crystals 1.77 g (50%) from acetone, mp > 300°C; ir: 3337 (br, 2NH), 2209 (CN), 1667 cm^{-1} (C=N); ^{1}H NMR: δ 10.77 (br, 2H, 2NH), 8.47 (d, 2H, CH=), 7.52 ppm (s, 4H, C_6H_4), 4.21 (q, 4H, 2CH_2=, J = 7.2 Hz), 1.27 (t, 6H, 2Me, J = 7.2 Hz). ^{13}C NMR: δ 167.15, 165.58 (2CO), 153.32 (2=CH=), 137.82, 136.51, 119.93, 119.84, 119.74, 119.16 (aromatic carbons), 117.00 (CN), 75.01, 74.19 (ethylenic carbons); 61.31 (CH_2), 15.22 (Me); ms: *m*/*z* 354 (M^+, 100%). Anal. Calcd. for $C_{18}H_{18}N_4O_4$ (354.36): C, 61.01; H, 5.12; N, 15.81. Found: C, 61.36; H, 5.42; N, 16.18.

Bis[(3-oxo-3-phenyl-2-(*p*-pheneyleneimino) propanenitrile] (5c). This compound was obtained as red crystals 2.72 g (65%) from acetone, mp > 300°C; ir: 3449, 3349 (NH), 2204 (CN), 1703 cm^{-1} (CO); ^{1}H NMR: δ 10.52 (br, 2H, 2NH), 8.40 (d, 2H, CH=), 7.51–6.59 ppm (m, 14H, C_6H_4, 2C_6H_5). ^{13}C NMR: δ 190.54 (CO), 153.65, 152.96, 147.98, 140.19, 130.70, 128.44, 128.22, 126.54, 121.22, 119.08 (aromatic carbons), 114.57 (CN), 87.15 (ethylenic carbons); ms: *m*/*z* 446 (M^+, 10%). Anal. Calcd. for $C_{26}H_{18}N_4O_2$ (418.45): C, 74.63; H, 4.34; N, 13.39. Found: C, 74.63; H, 4.01; N, 13.77.

Bis[2-cyano-2-(*p*-pheneyleneimino)acetamide] (5d). This compound was obtained as red crystals 1.79 g (55%) from acetone, mp > 300°C; ir: br, 3343 (NH & NH_2), 2210 (CN), 1670 cm^{-1} (CO). ^{1}H NMR: δ 10.93, 5.59 (br, 8H, 4NH, 2NH_2), 8.45 (d, 2H, 2CH=), 7.39 ppm (s, 4H, C_6H_4); ms: *m*/*z* 296. (M^+, 10%). Anal. Calcd. for $C_{14}H_{14}N_8O_2$ (326.31): C, 51.53; H, 4.32; N, 34.34. Found: C, 51.78; H, 4.53; N, 34.34.

General procedure for synthesis of bisazoles (7, 8, 10, 11). To a solution of (**5a**) or (**5b**) or (**5c**), (0.01 mol), in DMF (30 mL) an equivalent amount of hydrazine hydrate or phenyl hydrazine was added. The reaction mixture was heated under reflux for 3 h. The obtained product after cooling was collected by filtration and washed by ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

***N*^{1},*N*^{4}-Bis[(3,5-diamino-4*H*-pyrazol-4-ylidene)methyl)benzene-1,4-diamine (7).** This compound was obtained as yellow crystals 2.10 g (65%) from acetone, mp 150–151°C; ir: 3164, 3112 cm^{-1} (NH & NH_2). ^{1}H NMR: δ 10.06 (br, 8H, 4NH_2), 8.15 (s, 2H, 2CH=), 8.01 (s, 2H, 2NH), 7.91 ppm (m, 4H, C_6H_4); ms: *m*/*z* 324 (M^+, 6%). Anal. Calcd. for $C_{14}H_{16}N_{10}$ (324.34): C, 51.84; H, 4.97; N, 43.18. Found: C, 52.01; H, 5.12; N, 43.44.

***N*^{1},*N*^{4}-Bis[(3-amino-5-phenyl-4*H*-pyrazol-4-ylidene)methyl] benzene-1,4-diamine (8).** This compound was obtained as brown crystals 2.45 g (55%) from acetone, mp > 300°C; ir: 3211, 3114 (NH & NH_2); 1617 cm^{-1} (C=N). ^{1}H NMR: δ 10.14 (br, 4H, 2NH_2), 9.44 (br, 2H, 2NH), 8.16 (s, 2H, 2CH=), 7.56–8.01 ppm (m, 14H, C_6H_4, 2C_6H_5); ms: *m*/*z* 446 (M^+, 12%). Anal. Calcd. for $C_{26}H_{22}N_8$ (446.51): C, 69.94; H, 4.97; N, 25.10. Found: C, 70.11; H, 5.12; N, 24.98.

Synthesis of *N*^{1},*N*^{4}-bis(3-amino-4-methylidene-1*H*-pyrazol-5(4*H*)-one)benzene-1,4-diamine (9). ***Method A.*** To a solution of (**5b**) 3.54 g (0.01 mol) in DMF (30 mL), hydrazine hydrate 0.75 g (0.015 mol) was added. The reaction mixture was heated under reflux for 3 h. The obtained product after cooling was collected by filtration and washed by cold ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

Method B. A solution of (**5d**) 3.26 g (0.01 mol) was heated under reflux in DMF (30 mL) for 3 h. The obtained product after cooling was collected by filtration and washed by cold ethanol (3 × 10 mL). This compound was obtained as brown crystals 1.96 g (60%) from acetone, mp 163–164°C; ir: 3211, 3114 (NH & NH_2); 1668 (CO), 1617 cm^{-1} (C=N). ^{1}H NMR:

δ 10.04 (br, 2H, 2NH), 9.45 (br, 2H, 2NH), 8.14 (d, 2H, 2CH=), 8.01 (br, 4H, $2NH_2$), 8.01 ppm (s, 4H, C_6H_4). Anal. Calcd. for $C_{14}H_{14}N_8O_2$ (326.31): C, 51.53; H, 4.32; N, 34.34. Found: C, 51.38; H, 4.03; N, 34.54.

***N*^{1},*N*^{4}-Bis[(3-amino-5-imino-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)methyl]benzene-1,4-diamine (10).** This compound was obtained as brown crystals 3.38 g (71%) from DMF/EtOH (1:1), mp > 300°C; ir: 3435, 3224 (br, NH & NH_2); 1667 cm^{-1} (C=N). ^{1}H NMR: δ 10.90 (br, 4H, $2NH_2$), 10.60 (br, 2H, 2NH), 8.58 (m, 10H, $2C_6H_5$), 7.09,7.07 (d, 2H, J = 8 Hz, C_6H_4), 6.54, 6.52 (d, 2H, J = 8 Hz, C_6H_4), 6.65 (d, 2H, 2CH=), 5.17 (br, 2H, 2NH). Anal. Calcd. for $C_{26}H_{24}N_{10}$ (476.54): C, 65.53; H, 5.08; N, 29.39. Found: C, 65.35; H, 4.97; N, 29.53.

***N*^{1},*N*^{4}-Bis[(3-amino-5-oxo-1-phenyl-1,4*H*-pyrazol-4(5*H*)-ylidene)methyl]benzene-1,4-diamine (11).** This compound was obtained as brown crystals 3.45 g (72%) from DMF/EtOH (1:1), mp > 300°C; ir: 3274, 3182 (br, NH & NH_2); 1696, 1666 cm^{-1} (CO). ^{1}H NMR: δ 10.83, 10.77, 10.73 (br, 6H, 2NH & $2NH_2$), 8.47–8.28, 7.54–7.49 (m, 10H, $2C_6H_5$), 7.40 (s, 4H, C_6H_4), 7.95 (d, 2H, 2CH=). Anal. Calcd. for $C_{26}H_{22}N_8O_2$ (478.51): C, 65.26; H, 4.63; N, 23.42. Found: C, 65.04; H, 4.57; N, 23.56.

General procedure for synthesis bisazoles (12–16). To a solution of (**1**) 2.18 g (0.01 mol) in pyridine (20 mL), heteroamines (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The reaction mixture was poured on ice-cold water. The obtained product was collected by filtration and washed by ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

***N*^{1},*N*^{4}-Bis(5-acetyl-2-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-yl) phenylenediformamidine (12).** This compound was obtained as yellow crystals 3.91 g (65%) from DMF/EtOH (1:1), mp > 300°C; irir: 3480, 3382 (NH); 1617 cm^{-1} (C=N). ^{1}H NMR: δ 8.00, 7.98 (d, 4H, C_6H_4, J = 8.0 Hz), 7.67, 7.66 (d, 4H, C_6H_4, J = 8.4 Hz), 7.64 (s, 4H, C_6H_4), 6.75 (d, 2H, 2CH=), 6.36 (s, 2H, 2NH), 2.59 ppm (s, 6H, 2Me). ^{13}C NMR: δ 193.40, 154.91 (triazole carbons), 146.00, 137.95, 132.62, 132.37, 130.16, 120.29 (Ar-carbons), 27.17 (Me); ms: *m*/*z* 601 (M^+, 30%). Anal. Calcd. for $C_{28}H_{22}Cl_2N_{10}O_2$ (601.45): C, 55.92; H, 3.69; N, 23.29. Found: C, 56.11; H, 3.92; N, 23.63.

***N*^{1},*N*^{4}-Bis(1*H*-1,2,4-triazol-3-yl)phenylenediformamidine (13).** This compound was obtained as yellowish brown crystals 1.96 g (66%) from acetic acid, mp 262–263°C; ir: 3439, 3288, 3259 (NH), 1684, 1663 cm^{-1} (C=N). ^{1}H NMR: δ 13.34, 11.51 (s, 4H, 4NH); 7.70 (s, 1H, triazole-H), 7.52 (d, 2H, 2CH=), 7.47 (S, 4H, C_6H_4). ^{13}C NMR: δ 168.70 (CH=N), 160.09, 149.39 (triazole carbons), 135.46, 120.19 (aromatic carbons); ms: *m*/*z* 296 (M^+, 30%). Anal. Calcd. for $C_{12}H_{12}N_{10}$ (296.29): C, 48.64; H, 4.08; N, 47.27. Found: C, 48.43; H, 3.92; N, 47.42.

***N*^{1},*N*^{4}-Bis(4,5-dicyano-1*H*-imidazole-2-yl)phenylenediformamidine (14).** This compound was obtained as brown crystals 2.17 g (55%) from acetone, mp > 300°C; ir: 3434, 3248 (NH); 2231 (CN), 1666 cm^{-1} (C=N). ^{1}H NMR: δ 11.59 (s, 2H, 2 imidazole-NH), 10.21 (br, 2H, 2NH) 7.97 (d, 2H, 2CH=), 7.59 (s, 4H, C_6H_4). ^{13}C NMR: δ 160.83, 168.70 (2CH=N), 133.92, 117.60 (Ar-carbons), 135.71, 135.05, 121.74, 121.31, 121.22, 121.16 (imidazole carbons), 119.97, 119.93, 119.63, 119.03 (4CN); ms: *m*/*z* 394 (M^+, 8%). Anal. Calcd. for $C_{18}H_{10}N_{12}$ (394.35): C, 54.82; H, 2.56; N, 42.62. Found: C, 54.78; H, 2.72; N, 42.63.

***N*^{1},*N*^{4}-Bis(1*H*-benzo[*d*]imidazol-2-yl)phenylenediformamidine (15).** This compound was obtained as yellow crystals 2.72 g (69%) from DMF, mp 296–298°C; ir: 3381, 3178 (NH), 1664 cm^{-1} (C=N). ^{1}H NMR: δ 11.87 (br, 2H, 2NH), 10.14 (br, 2H, 2NH), 8.58, 8.57 (d, 4H, 2benzimidazole-H) 7.38, 7.36 (m, 4H, 2 benzimidazole-H), 7.92 (d, 2H, 2CH=), 7.04 (s, 4H, C_6H_4). ^{13}C NMR: δ 158.69 (CH=N), 152.14, 143.72, 121.51, 110.68 (benzimidazole carbons), 134.75, 117.63 (Phenyl carbon); ms: *m*/*z* (M^+, 72%). Anal. Calcd. for $C_{22}H_{18}N_8$ (394.43): C, 66.99; H, 4.60; N, 28.41. Found: C, 66.88; H, 4.78; N, 28.63.

***N*^{1},*N*^{4}-Bis(thiazol-2-yl)phenylenediformamidine (16).** This compound was obtained as brown crystals 1.98 g (60%) from acetone, mp > 300°C; ir: 3248 (NH); 1665 cm^{-1} (C=N). ^{1}H NMR: δ 10.16 (br, 2H, 2NH) 7.75, 7.73 (d, 2H, J = 8Hz, thiazole-H), 7.40(d, 2H, 2CH=), 7.16 (s, 4H, C_6H_4), 6.53, 6.51 ppm (d, 2H, J = 8 Hz, thiazole-H). ^{13}C NMR: δ 159.66 (2CH=N), 169.67, 139.46, 118.11 (thiazole carbons), 134.74, 117.56 ppm (phenyl carbons); ms: *m*/*z* 328 (M^+, 64%). Anal. Calcd. for $C_{14}H_{12}N_6S_2$ (328.42): C, 51.20; H, 3.68; N, 25.59; S, 19.53. Found: C, 51.01; H, 3.44; N, 25.84; S, 19.78.

Synthesis of 1,10-diaminophenanthroline-2,9-dicarbo-nitrile (17). A mixture of (**5a**) 2.6 g (0.01 mol) in bromobenzene and resublimed aluminum chloride (0.01 mol) was heated under reflux for 6 h. After cooling, the reaction mixture was poured onto cold water (40 mL) containing 2 mL of concentrated hydrochloric acid, and left to stand for 2 h. The obtained product was collected by filtration and washed by water (3 × 30 mL) and ethanol (3 × 10 mL). NOE experiment has been done via irradiation of amino protons at δ 11.04 ppm enhanced the pyridine protons at δ 8.38 ppm and vice versa while, the aromatic protons was not affected. This compound was obtained as pale green crystals 1.95 g (75%), from DMF/EtOH, mp > 300°C; ir: 3320, 3224 (NH_2), 2211, 2210 cm^{-1} (CN); ^{1}H NMR: δ 11.04 (br, 4H, $2NH_2$, D_2O-exchange), 8.38 (s, 2H, pyridine-H), 7.47 ppm (s, 2H, C_6H_2). ^{13}C NMR: δ 136.74, 131.15, 121.51 (aromatic carbons), 117.00, 117.21(CN), 155.65, 149.98, 87.78 (pyridine carbons); ms: *m*/*z* 260 (M^+, 100%). Anal. Calcd. for $C_{14}H_8N_6$ (260.25): C, 64.61; H, 3.10; N, 32.29. Found: C, 64.65; H, 3.11; N, 32.01.

General procedure for synthesis of bisazoles (19–21). To a solution of (**1**) 2.18 g (0.01 mol) in pyridine (20 mL), morpholine or 4-aminopyridine or 3,4-dimethoxyaniline (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h. The reaction mixture was poured onto ice-cold water. The obtained product was collected by filtration and washed by ethanol (3 × 10 mL). The obtained product was crystallized from the proper solvent.

Preparation of complex (19). To a solution of (**17**) 2.6 g (0.01 mol) in DMF (20 mL), $CuCl_2 \cdot 2H_2O$, 4.12g (0.01 mol) solution was added. The reaction mixture was heated under reflux for 5 h. The solvent was evaporated and the solid product, so formed, after cooling and water addition was collected by filtration and washed by ether (3 × 10 mL) and crystallized from DMF. Compound **19** was obtained as brown crystals 3.75 g (87%), mp > 250°C; ir: 3440 (OH, water), 3297, 3219 (NH_2), 2215 cm^{-1} (CN). ^{1}H NMR: δ 11.15, 11.12 (s, 4H, $2NH_2$), 8.48, 8.46 (s, 2H, pyridine-H), 7.43 (s, 2H, C_6H_4). Anal. Calcd. for $C_{14}H_{12}Cl_2Cu\ N_6O_2$

(430.74) C, 39.04; H, 2.81; N, 19.51. Found: C, 39.14; H, 2.96; N, 19.46.

***N*^{1},*N*^{4}-Bis(*N*-morpholino)phenylenediformamidine (20).** This compound was obtained as pale white crystals 1.97 g (65%) from ethanol, mp 234–236°C; ir: 2984, 2962, 2901 (CH-aliphatic), 1625 cm^{-1} (C=N). ^{1}H NMR: δ 7.72 (s, 2H, 2CH=), 6.81 (s, 4H, C_6H_4), 3.43 (t, 8H, morpholine-H), 2.50 (t, 8H, morpholine-H). ^{13}C NMR: δ 159.70 (CH=N), 145.46, 121.19 (aromatic carbons), 61.21, 49.45 (morphiline carbons); ms: *m*/*z* 302 (M^+, 60%). Anal. Calcd. for $C_{16}H_{22}N_4O_2$ (302.37) C, 63.55; H, 7.33; N, 18.53. Found: C, 63.52; H, 7.30; N, 18.60.

***N*^{1},*N*^{4}-Bis(pyridin-4-yl)phenylenediformamidine (21).** This compound was obtained as brown crystals 2.06 g (65%) from ethanol, mp 174–177°C; ir: 3170 (NH), 1660 cm^{-1} (C=N). ^{1}H NMR: δ 10.10 (br, 2H, 2NH); 8.76, 7.15 (m, 8H, 2 pyridine-H), 8.20 (d, 2H, 2CH=), 7.54 (s, 4H, C_6H_4). ^{13}C NMR: δ 162.70 (CH=N), 156.61, 149.36 110.01 (pyridine carbons), 145.30, 121.19 (aromatic carbons); ms: *m*/*z* 316 (M^+, 6%). Anal. Calcd. for $C_{18}H_{16}N_6$ (316.36) C, 68.34; H, 5.10; N, 26.56. Found: C, 68.29; H, 5.09; N, 26.51.

***N*^{1},*N*^{4}-Bis(3,4-dimethoxyphenyl)phenylenediformamidine (22).** This compound was obtained as pale white crystals 2.74 g (63%) from ethanol, mp > 300°C; ir: 3300 (NH), 1662 cm^{-1} (C=N). ^{1}H NMR: δ 10.71 (br, 2H, 2NH), 7.52 (d, 2H, 2CH=), 7.31 (s, 4H, C_6H_4), 6.10–6.72 (m, 6H, $2C_6H_3$), 3.62 (s, 12H, 4MeO); ms: *m*/*z* 434 (M^+, 60%); Anal. Calcd. for $C_{24}H_{26}N_4O_4$ (434.49) C, 66.34; H, 6.03; N, 12.89. Found: C, 66.44; H, 5.98; N, 12.60.

Acknowledgment. The authors are grateful to Kuwait University Research Administration for financial support of project SC10/06 and for SAF facilities project GS01/01 and GS03/01.

REFERENCES AND NOTES

[1] Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tong, L.; Torcellini, C. J Med Chem 2002, 45, 2994.

[2] Lin, R.; Chin, G.; Yu, Y.; Connolly, P. J.; Li, S.; Lu, Y.; Adams, M.; Fuentes-Pesquera, A. R.; Emanuel, S. L.; Greenberger, L. M. Bioorg Med Chem Lett 2007, 17, 4557.

[3] Gomez, L.; Hack, M. D.; Wu, J.; Wiener, J. J. M.; Venkatesan, H.; Santillan, A., Jr.; Pippel, D. J.; Mani, N.; Morrow, B. J.; Motley, S. T.; Shaw, K. J.; Wolin, R.; Grice, C. A.; Jones, T. K. Bioorg Med Chem Lett 2007, 17, 2723.

[4] Chen, Y. L.; Cherry, K.; Corman, M. L.; Ebbinghaus, C. F.; Gamlath, C. B.; Liston, D.; Martin, B.-A.; Oborski, C. E.; Sahagan, B. G. Bioorg Med Chem Lett 2007, 17, 5518.

[5] Xi, N.; Bo, Y.; Doherty, E. M.; Fotsch, C.; Gavva, N. R.; Han, N.; Hungate, R. W.; Klionsky, L.; Liu, Q.; Tamir, R.; Xu, S.; Treanor, J. J. S.; Norman, M. H. Bioorg Med Chem Lett 2005, 15, 5211.

[6] Dyck, B.; Goodfellow, V. S.; Phillips, T.; Gery, J.; Haddach, M.; Rowbottom, M.; Naeve, G. S.; Brown, B.; Saunders, J. Bioorg Med Chem Lett 2004, 14, 1151.

[7] Li, J.; Zheng, M.; Tang, W.; He, P.-L.; Zhu, W.; Li, T.; Zuo, J.-P.; Liu, H.; Jaing, H. Bioorg Med Chem Lett 2006, 16, 5009.

[8] Carroll, W. A.; Kalvin, D. M.; Medrano, A. P.; Florjancic, A. S.; Wang, Y.; Donnelly-Roberts, N. M. T.; Grayson, G.; Honore, P.; Jarvis, M. F. Bioorg Med Chem Lett 2007, 17, 4044.

[9] Jozef, D.; Emst, B.; Manfred, B. D. D.; Kurt, R. Ger Offen DE,1978,77–2755481,19771213.

[10] Elassar, A. A. Heteroatom Chem 2004, 15, 293.

[11] Meth-Cohn, O.; Narine, B.; Tamowski, B. J Chem Soc Perkin Trans 1 1981, 5, 1520.

[12] Bredereck, H.; Effenberger, F.; Botsch, H. Chem Ber 1964, 97, 3397.

[13] Bredereck, H.; Bredereck, K. Chem Ber 1961, 94, 2278.

[14] Kristen, H.; Hamann, O. Pharmazie 1976, 31, 222.

[15] Abdel-Ghany, H.; El-Sayed, A. M.; El-Shafei, A. K. Synth Commun 1995, 25, 1119.

[16] Albrecht, R. Prog Res 1977, 21, 9.

[17] Spencer, C. F.; Snyder, H. R., Jr.; Alaimo, R. J Heterocycl Chem 1975, 12, 1319.

[18] Milata, V.; Ilavsky, D. Collect Czechoslovak Chem 1987, 52, 2918.

[19] Renault, J.; Chaoui, M.; Giorgi-Renault, S.; Cavier, R.; Delage, N. Ann Pharm Fr 1982, 40, 81.

[20] Hao Dong, P. L.; Coquelet, C.; Bastide, J.-M.; Lebecq, J.-C. Eur J Med Chem Chim Ther 1980, 15, 119.

[21] Gewald, K.; Schafer, H.; Sattler, K. Monatsh Chem 1979, 110, 1189.