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Reactions with Dimethylformamide-Dimethylacetal: Synthesis and Reactions of Several New Pyridine and Pyrazolo[3,4-*b*]pyridine Derivatives

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ABSTRACT: *6-Aminopyridine-2(1H)-thiones* **1a,b** *reacted with dimethylformamide-dimethylacetal (DMF-DMA) to give the corresponding 6-{[(N,N-dimethylamino)methylene]amino}pyridine derivatives* **2a,b**. *The latter compounds reacted with hydrazine hydrate to afford the 3,6-diamino-1H-pyrazolo[3,4-b]pyridine derivative* **4** *and 3-amino-5-hydrazino-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine derivative* **7**, *respectively. Compound* **4** *condensed with DMF-DMA to yield the 3,6-bis{[(N,N-dimethylamino)methylene]amino}-1H-pyrazolo-[3,4-b]pyridine derivative* **10**, *which reacted with malononitrile to give the corresponding pyridopyrazolopyrimidine derivative* **15**. © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:399–404, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20312

INTRODUCTION

Synthesis and characterization of pyridines and pyrazolo[3,4-*b*]pyridines became the main target of this research group. Several publications demonstrated this research effort [1–9]. This is because these derivatives possess diverse biological activities and are widely used in pharmaceutical and medicinal preparations. The pyridine ring found in acetylcholine, enhancement useful in the treatment of Alzheimer disease [10], and has antitummer [11], antiaminesic [12], and antimicrolial [7] activities. Moreover, pyridine-3-carbonitriles were used as cardiotonic [13,14] and antiviral [15] agents, and pyridine-3,5-dicarbonitriles were reported to have antiproliferative activity on human cancer cell lines [16]. On the other hand, pyrazolo[3,4-*b*]pyridines were used as antimicrobials [5,7,17], inhibitors of cyclin-dependent kinases [18], antimalarial [19], and antiproliferative [20]. The above findings stimulated the interest for the synthesis of additional new numbers of these derivatives that are required in medicinal chemistry programs.

RESULTS AND DISCUSSION

It has been found that 6-amino-4-(4-methoxyphenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1a**) [21] reacted with dimethylformamide-dimethylacetal (DMF-DMA) in dry xylene to afford a reaction product of molecular

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formula $C_{17}H_{15}N_5OS$ corresponding to equimolecular addition of **1a** to the reagent followed by loss of two molecules of methanol. The IR spectrum of this reaction product showed the absence of the band of the amino group. The newly introduced *N*,*N*-dimethylaminomethylene group was detected in the ^{1}H NMR spectrum of the reaction product as a singlet signal at $\delta = 3.17$ (two CH_3) and 8.91 (N=CH) ppm. Based on the above data, together with the data of elemental analysis, this reaction product could be formulated as 6-{[(*N*,*N*-dimethylamino)methylene]amino}-4-(4-methoxyphenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**2a**).

Analogously, 6-amino-4-(2-furyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1b**) [22] reacted with the same reagent to give the corresponding 6-{[(*N*,*N*-dimethylamino)methylene]amino}-4-(2-furyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**2b**), whose structure was established on the basis of elemental and spectral backgrounds as previously reported for **2a** (cf. Scheme 1 and the Experimental section).

The synthetic potential of each of **2a,b** was demonstrated via their reaction with hydrazine hydrate under reflux to give different reaction products. The product of the reaction of **2a** with hydrazine hydrate showed among its signals those of two amino, one imino (3451, 3339, 3216, 3153 cm^{-1}), and one nitrile (2200 cm^{-1}) functions in its IR spectrum. Its ^{1}H NMR spectrum revealed the presence of D_2O exchangeable two NH_2 ($\delta = 4.35$, 6.75 ppm) and one NH ($\delta = 11.86$ ppm) groups. This reaction product could then be formulated as the 3,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine derivative **4**.

On the contrary, the IR spectrum of the product of the reaction of **2b** with hydrazine hydrate showed the complete disappearance of the absorption bands of the nitrile functions. Instead new absorption bands of two NH_2 and two NH groups were detected. The signals of the NH_2 and NH protons ($\delta = 4.99$, 6.68, 7.55, and 11.69 ppm) were D_2O exchanged in the ^{1}H NMR spectrum, which also revealed the signal of 7H-pyrimidine at $\delta = 8.85$ ppm. Based on the above data this reaction product could be formulated as the 3-amino-5-hydrazino-1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivative **7** (cf. Scheme 1 and the Experimental section).

An unequivocal support for the structure of each of **4** and **7** was achieved via their synthesis through other routes as follows:

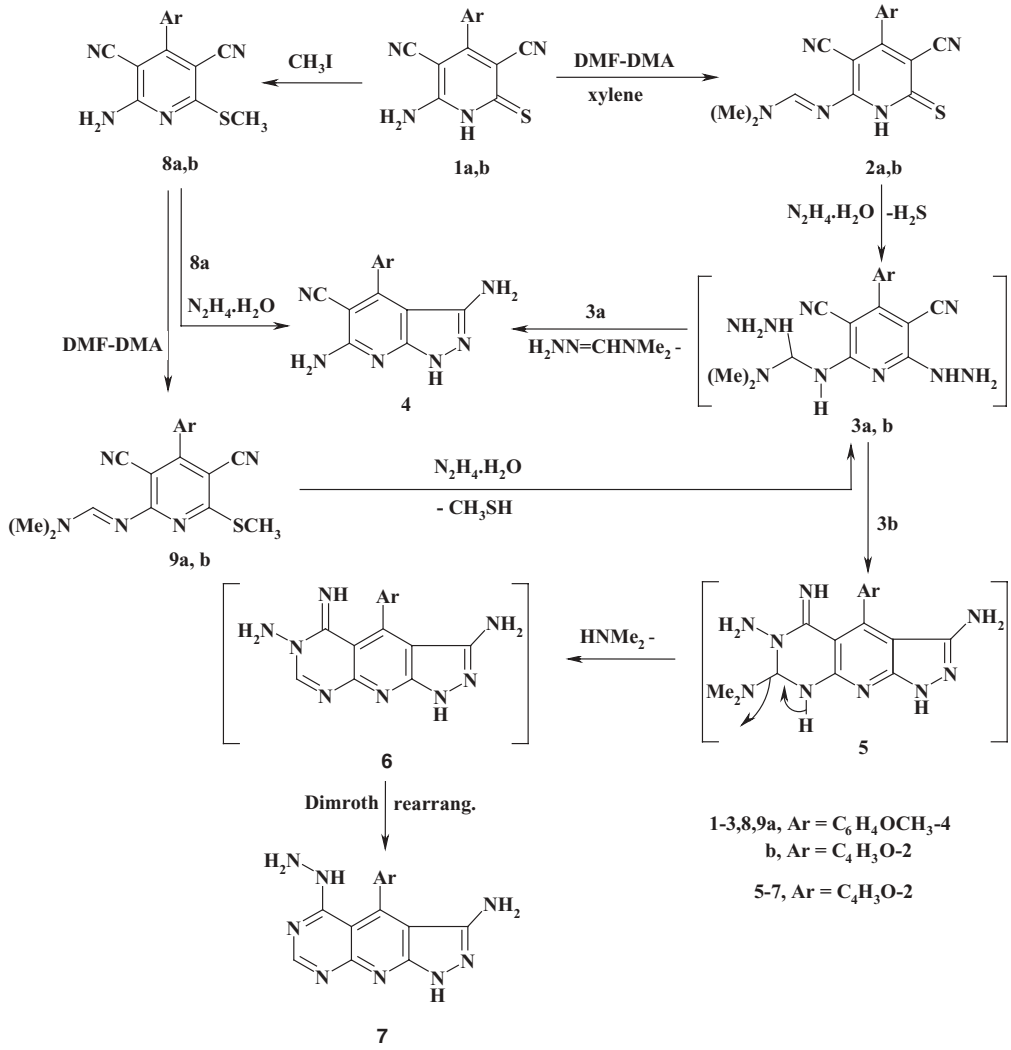
(a) Compounds **1a,b** were reacted each with one molecule of methyl iodide in DMF/potassium hydroxide solution to give the corresponding 6-amino-4-aryl-2-methylthiopyridine-3,5-dicarbonitriles **8a,b**, which in turn reacted with one molecule of DMF-DMA to give the corresponding 6-{[(*N*,*N*-dimethylamino)-methylene]amino}-4-aryl-2-methylthiopyridine-3,5-dicarbonitriles **9a,b**. The structure of each of **8a,b** and **9a,b** was established on the basis of elemental analysis, and IR and ^{1}H NMR spectral data studies (cf. the Experimental section).

(b) Compound **4** could be prepared directly by reacting **8a** with boiling hydrazine hydrate.

(c) Compound **9a** reacted with boiling hydrazine hydrate to give directly compound **4** with the same analytical and spectral data as those of **4** obtained by the other two methods described before. The formation of **4** in this reaction is assumed to proceed via the first formation of the nonisolable hydrazino derivative **3a** which could then be cyclized via addition to the nitrile function at position 3 and *N*,*N*-dimethylaminomethylene exchange of the hydrazino at position 6 under the applied reaction conditions leading to regeneration of the amino group [23] at that position and hence formation of **4** (cf. Scheme 1).

(d) Compound **9b** reacted also with boiling hydrazine hydrate to give directly compound **7** with the same analytical and spectral data as those of **7** obtained by the other method described before. The formation of **7** in this reaction is assumed to proceed via the first formation of the nonisolable hydrazino derivative **3b** that undergoes two cyclization steps which are both addition to the nitrile functions at positions 3 and 5 leading to the formation of the corresponding nonisolable 6-amino-5-iminopyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivative **5**. Compound **5** could then lose one molecule of dimethylamine to give the nonisolable intermediate **6**. Compound **6** underwent Dimroth rearrangement [24] to give the corresponding final isolable product 3-amino-5-hydrazinopyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivative **7** (cf. Scheme 1).

Several interesting reactions took place starting from the diamino-pyrazolopyridine derivative **4**. Thus, it has been found that **4** reacted with two molecules of DMF-DMA in boiling dry xylene to give a reaction product of molecular formula $C_{20}H_{22}N_8O$ corresponding to the addition of two molecules of the reagent to one molecule of **4** followed by the loss of four molecules of methanol. The IR spectrum of this reaction product

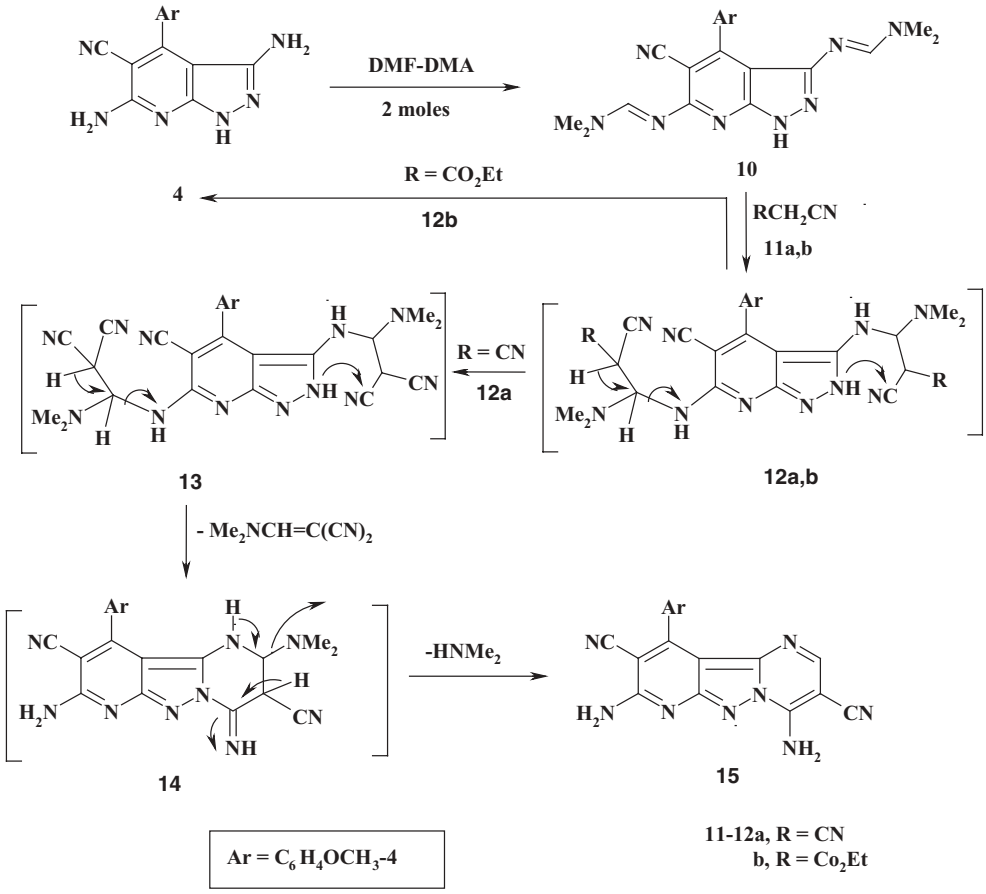


SCHEME 1

showed the presence of the bands of one NH (3185 cm^{-1}) and one CN (2215 cm^{-1}) group only. Its ^1H NMR spectrum revealed the presence of one NH (12.14 ppm) (D_2O exchangeable), two $-N(CH_3)_2$ (3.09 and 3.18 ppm), and two $-N{=}CH$ (8.59 ppm) groups. On the above backgrounds, this reaction product could be formulated as the 3,6-bis{[(*N*,*N*-dimethylamino)methylene]amino}-1*H*-pyrazolo[3,4-*b*]pyridine derivative **10** (cf. Scheme 2 and the Experimental section).

Compound **10** reacted with malononitrile (**11a**) to give a reaction product of molecular formula $C_{18}H_{12}N_8O$ corresponding to the addition of two molecules of **11a** to one molecule of **10** followed by loss of one molecule of *N*,*N*-dimethylaminodicyanoethylene and one molecule of dimethylamine. The IR spectrum of this reaction product showed the presence of two NH_2 (3442, 3351, 3211 cm^{-1}) and two CN (2213 cm^{-1}) groups. While the ^1H NMR spectrum revealed only signals of two NH_2 protons at $\delta = 4.74$, 6.77 ppm, a new singlet signal at $\delta = 8.40$ ppm corresponds to the 2H-pyrimidine ring and OCH_3 group in addition to the aromatic protons. The reaction product was thus formulated as 4,8-diamino-10-(4-methoxyphenyl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]-pyrimidine-3,9-dicarbonitrile (**15**) most likely formed via the intermediacy of the nonisolable adducts **12, 13**, and **14**, respectively (cf. Scheme 2 and the Experimental section).

In contrast to the behavior of **10** toward malononitrile **(11a)**, it reacted with ethyl cyanoacetate **(11b)** under practically the same reaction conditions to undergo *N*,*N*-dimethylaminomethylene



SCHEME 2

exchange reaction [23] to give back the original compound **4** with almost the same analytical, physical (mp and mixed mp), and spectral data as for **4** previously reported (cf. Scheme 2 and the Experimental section).

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra in KBr discs were recorded on a Bruker Vector 22 FT-IR spectrophotometer. ^{1}H NMR spectra were determined in DMSO-d_6 and $CDCl_3$ at 300 MHz on a Varian Mercury VX spectrometer using TMS as an internal standard. Chemical shifts are expressed as δ ppm and J as Hz units. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Compounds **1a** [21] and **1b** [22] were prepared according to the literature procedures.

In all the ^{1}H NMR spectra* = Lost after D_2O exchange.

Reactions with DMF-DMA in Dry Xylene: General Procedure

To a solution of the appropriate **1a,b, 8a,b** (0.01 mol) or **4** (0.02 mol) in dry xylene (30 mL), DMF-DMA (0.012 mol or 0.024 mol) was added and the reaction mixture was then heated under reflux for 3–5 h. The solid so obtained after cooling was collected by filtration and crystallized from the proper solvent to yield **2a,b**, **9a,b**, or **10**, respectively.

*6-{[(N,N-Dimethylamino)methylene]amino}-4-(4-methoxyphenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**2a**).* Yellow crystals from dioxan (63%), mp 280–282°C; IR (cm^{-1}) ν 3148 (NH), 2221, 2209 (two CN), 1624 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.17 (s, 6H, $N(CH_3)_2$), 3.86 (s, 3H, OCH_3), 7.11–7.55 (m, 5H, NH* & Ar–H), 8.91 (s, 1H, N=CH). Anal. For $C_{17}H_{15}N_5OS$ (337) Calcd: C, 60. 52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.80; H, 4.80; N, 21.00; S, 9.20%.

*6-{[(N,N-Dimethylamino)methylene]amino}-4-(2-furyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**2b**).* Brown crystals from dioxan (58%), mp 180°C; IR (cm^{-1}) ν 3145 (NH), 2212 (CN), 1625 (N=C). Anal. For $C_{14}H_{11}N_5OS$ (297) Calcd: C, 53.79; H, 3.47; N, 28.95; S, 5.52. Found: C, 54.00; H, 3.70; N, 28.70; S, 5.30%.

*6-{[(N,N-Dimethylamino)methylene]amino}-4-(4-methoxyphenyl)-2-methylthiopyridine-3,5-dicarbonitrile (**9a**).* Yellow crystals from DMF (67%), mp 305–306°C; IR (cm^{-1}) ν 2209 (CN), 1625 (N=C). Anal. For $C_{18}H_{17}N_5OS$ (351) Calcd: C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.80; H, 4.50; N, 20.20; S, 8.80%.

*6-{[(N,N-Dimethylamino)methylene]amino}-4-(2-furyl)-2-methylthio-pyridine-3,5-dicarbonitrile (**9b**).* Pale yellow crystals from dioxan (63%), mp 230–231°C; IR (cm^{-1}) ν 2212 (CN), 1625 (N=C); ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H, CH_3), 3.27 (s, 6H, $N(CH_3)_2$), 6.64 (2d, 1H, 4H-furyl), 7.56 (d, $J = 3.6$ Hz, 1H, 3H-furyl), 7.72 (d, $J = 2.0$ Hz, 1H, 5H-furyl), 8.77 (s, 1H, N=CH). Anal. For $C_{15}H_{13}N_5OS$ (311) Calcd: C, 57.86; H, 4.88; N, 22.49; S, 10.30. Found: C, 58.20; H, 4.50; N, 22.20; S, 10.00%.

*3,6-Bis{[(N,N-Dimethylamino)methylene]amino}-4-(4-methoxy-phenyl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**10**).* Orange crystals from dioxan (58%), mp 300–302°C; IR (cm^{-1}) ν 3185 (NH), 2215 (CN), 1625 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.09 (s, 6H, $N(CH_3)_2$), 3.18 (s, 6H, $N(CH_3)_2$), 3.84 (s, 3H, OCH_3), 7.14 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.46 (d, $J = 8.0$ Hz, 2H, Ar—H), 8.59 (s, 2H, two N=CH), 12.14 (s, 1H, NH*). Anal. For $C_{20}H_{22}N_8O$ (390) Calcd: C, 61.52; H, 5.68; N, 28.70. Found: C, 61.80; H, 5.30; N, 28.50%.

Reaction of **1a,b** *with Methyliodide*

A solution of the appropriate **1a,b** (0.01 mol) in DMF (20 mL) containing 0.01 mol of KOH was treated with methyl iodide (0.01 mol). The reaction mixtures were stirred at room temperature for 2 h, poured onto ice-cold water, and neutralized with dilute HCl (10%). The precipitates that formed were collected by filtration and crystallized from ethanol to yield **8a,b**, respectively.

*6-Amino-4-(4-methoxyphenyl)-2-methylthiopyridine-3,5-dicarbonitrile (**8a**).* White crystals from ethanol (78%), mp 230–232°C; IR (cm^{-1}) ν 3468, 3363 (NH_2), 2212 (CN), 1614 (N=C); ^{1}H NMR (DMSO-d_6) δ 2.71 (s, 3H, SCH_3), 3.86 (s, 3H, OCH_3), 5.30 (s, 2H, NH_2^*), 7.16 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.45 (d, $J = 8.0$ Hz, 2H, Ar—H). Anal. For $C_{15}H_{12}N_4OS$ (296) Calcd: C, 60.79; H, 4.08; N, 18.91; S, 10.82. Found: C, 61.00; H, 4.30; N, 18.60; S, 11.00%.

*6-Amino-4-(2-furyl)-2-methylthiopyridine-3,5-dicarbonitrile (**8b**).* Brown crystals from ethanol (75%), mp 215°C ; IR (cm^{-1}) ν 3388, 3305 (NH_2), 2216 (CN), 1617 (N=C). Anal. For $C_{12}H_8N_4OS$ (256) Calcd: C, 56.24; H, 3.15; N, 21.86; S, 12.51. Found: C, 56.60; H, 3.50; N, 21.60; S, 12.70%.

Reactions with Hydrazine Hydrate: General Procedure

A solution of the appropriate **2a,b**, **8a**, or **9a,b** (0.01 mol) in hydrazine hydrate (20 mL) was heated under reflux for 6 h and then cooled. The solid so obtained was collected by filtration and crystallized from the proper solvent to yield **4** or **7**, respectively.

*3,6-Diamino-4-(4-methoxyphenyl)-1H-pyrazolo-[3,4-b]pyridine-5-carbonitrile (**4**).* Orange crystals from ethanol (65%), mp 320–322°C; IR (cm^{-1}) ν 3451, 3339, 3216, 3153 (two NH_2, NH), 2200 (CN), 1610 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H, OCH_3), 4.35 (s, 2H, NH_2^*), 6.75 (s, 2H, NH_2^*) 7.13 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.45 (d, $J = 8.0$ Hz, 2H, Ar—H), 11.86 (s, 1H, NH*). Anal. For $C_{14}H_{12}N_6O$ (280) Calcd: C, 59.99; H, 4.32; N, 29.98. Found: C, 59.60; H, 4.60; N, 30.20%.

*3-Amino-4-(2-furyl)-5-hydrazino-1H-pyrazolo-[4′,3′:5,6]pyrido[2,3-d]pyrimidine (**7**).* Pale yellow crystals from DMF (66%), mp >350°C; IR (cm^{-1}) ν 3419, 3324, 3218, 3122 (two NH_2, two NH), 1634 (N=C); ^{1}H NMR (DMSO-d_6) δ 4.99 (s, 2H, NH_2^*), 6.68 (s, 2H, NH_2^*) 6.90–7.50 (m, 3H, furyl), 7.55 (s, 1H, NH*), 8.85 (s, 1H, 2H-pyrimidine), 11.59 (s, 1H, NH*). Anal. For $C_{12}H_{10}N_8O$ (282) Calcd: C, 51.06; H, 3.57; N, 39.70. Found: C, 51.30; H, 3.30; N, 40.00%.

Reaction of **10** *with* **11a,b**

A solution of **10** (0.01 mol) in glacial acetic acid (20 mL) was treated with **11a,b** (0.02 mol). The reaction mixture was heated under reflux for 4 h and then cooled. The solid products obtained were collected by filtration and crystallized from the proper solvent to yield **15** and **4**, respectively.

*4,8-Diamino-10-(4-methoxyphenyl)pyrido-[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3,9-dicarbonitrile (**15**).* Orange crystals from AcOH (57%), mp 260–261°C; IR (cm^{-1}) ν 3442, 3351, 3211 (two NH_2),

2213 (CN), 1610 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H, OCH_3), 4.74 (s, 2H, NH_2^*), 6.77 (s, 2H, NH_2^*) 7.13 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.50 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.40 (s, 1H, 2H-pyrimidine). Anal. For $C_{18}H_{12}N_8O$ (356) Calcd: C, 60.67; H, 3.39; N, 31.45. Found: C, 60.40; H, 3.60; N, 31.20%.

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