A MILD AND EFFICIENT SYNTHESIS OF NEW BENZIMIDAZOLE DERIVATIVES *VIA* A ONE-POT REACTION. AN ADDITION VERSUS CONDENSATION REACTION

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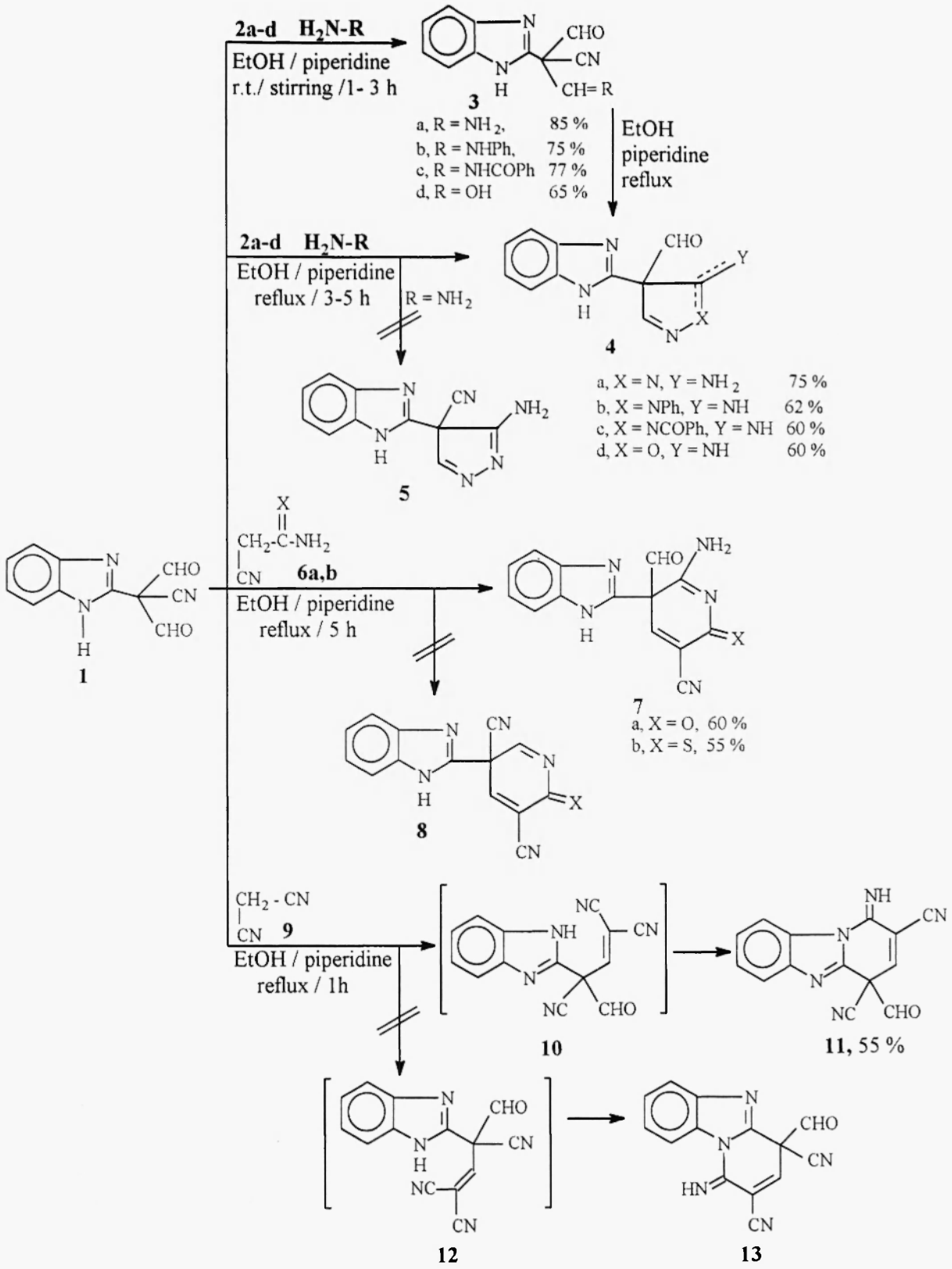
Abstract: New polyfunctional benzimidazole derivatives of pharmaceutical interest were prepared starting from 2-cyanomethylbenzimidazole-2,2-dicarboxaldehyde which reacts easily with different active methylene compounds and some of nucleophilic reagents. The addition predominantly lead to the cyclic products in competition with the condensation reaction.

Introduction: The synthesis of benzimidazole derivatives[1-5] has found considerable interest as a component of biological active compounds,[6-8] and in vitro anti-HIV.[7] As an extension of our recent work on the synthesis of such expected important biological active components,[9-12] we report herein on the synthesis of new polysubstituted benzimidazole derivatives starting with 2-cyanomethylbenzimidazole-2,2-dicarboxaldehyde.[13]

Results and Discussion: Thus, the α-cyanoaldehyde[13] **1** reacts easily with hydrazine hydrate **2a** in ethanol at room temperature to yield the Schiff base **3a** in 85% yield. However, in the presence of piperidine at reflux temperature the pyrazole derivative **4a** was obtained in 75 % yield. On the other hand, the Schiff base **3a** was cyclized to **4a** in 65 % yield by reflux in ethanolic piperidine solution, (Scheme 1). The **IR** spectrum of **3a** showed the presence of absorption bands at ν 1642-1690, 2204, 3217 and 3313-3422 cm^{-1} due to CHO, CN, NH and NH_2 groups. The **^{1}H NMR** spectrum ($CDCl_3$) of **3a** showed signals at δ 6.3, 7.0-7.5 and 8.3 ppm assigned for NH_2, aromatic, NH and CHO protons. However, the **IR** spectrum of **4a** showed the absence of the characteristic absorption of the CN function. The **MS** of **3a** showed *m/z* at 229 (M + 2, 18), 212 (M-NH, 100), 199 (M-CO, 33), 170 (M-H_2-CO-HCN, 82), 157 (31) and 143 (30%). The **MS** of **4a** showed *m/z* at 227 (M^+, 37), 199 (M-CO, 15), 157 (199-N_3, 33) and 111 (34%). The **^{1}H NMR** spectrum (DMSO)of **4a** showed signals at δ6.5, 7.1-7.8, 8.9 ppm assigned for NH_2, aromatic, NH and CHO protons, respectively. From the above spectroscopic data, it seems that the addition to the cyano function is highly like than the condensation reaction would afford **5**, as shown in Scheme 1. Similarly, compound **1** reacts directly with substituted hydrazine **2b-d** under the same reaction conditions to yield **3b-d** and **4b-d**, (*c.f.* Scheme 1)


2a-d H2N-R
EtOH / piperidine
r.t./ stirring /1- 3 h
3
a, R = NH2, 85 %
b, R = NHPh, 75 %
c, R = NHCOPh 77 %
d, R = OH 65 %
EtOH
piperidine
reflux
2a-d H2N-R
EtOH / piperidine
reflux / 3-5 h
R = NH2
4
a, X = N, Y = NH2 75 %
b, X = NPh, Y = NH 62 %
c, X = NCOPh, Y = NH 60 %
d, X = O, Y = NH 60 %
5
1
6a,b
EtOH / piperidine
reflux / 5 h
7
a, X = O, 60 %
b, X = S, 55 %
8
9
EtOH / piperidine
reflux / 1h
10
11, 55 %
12
13

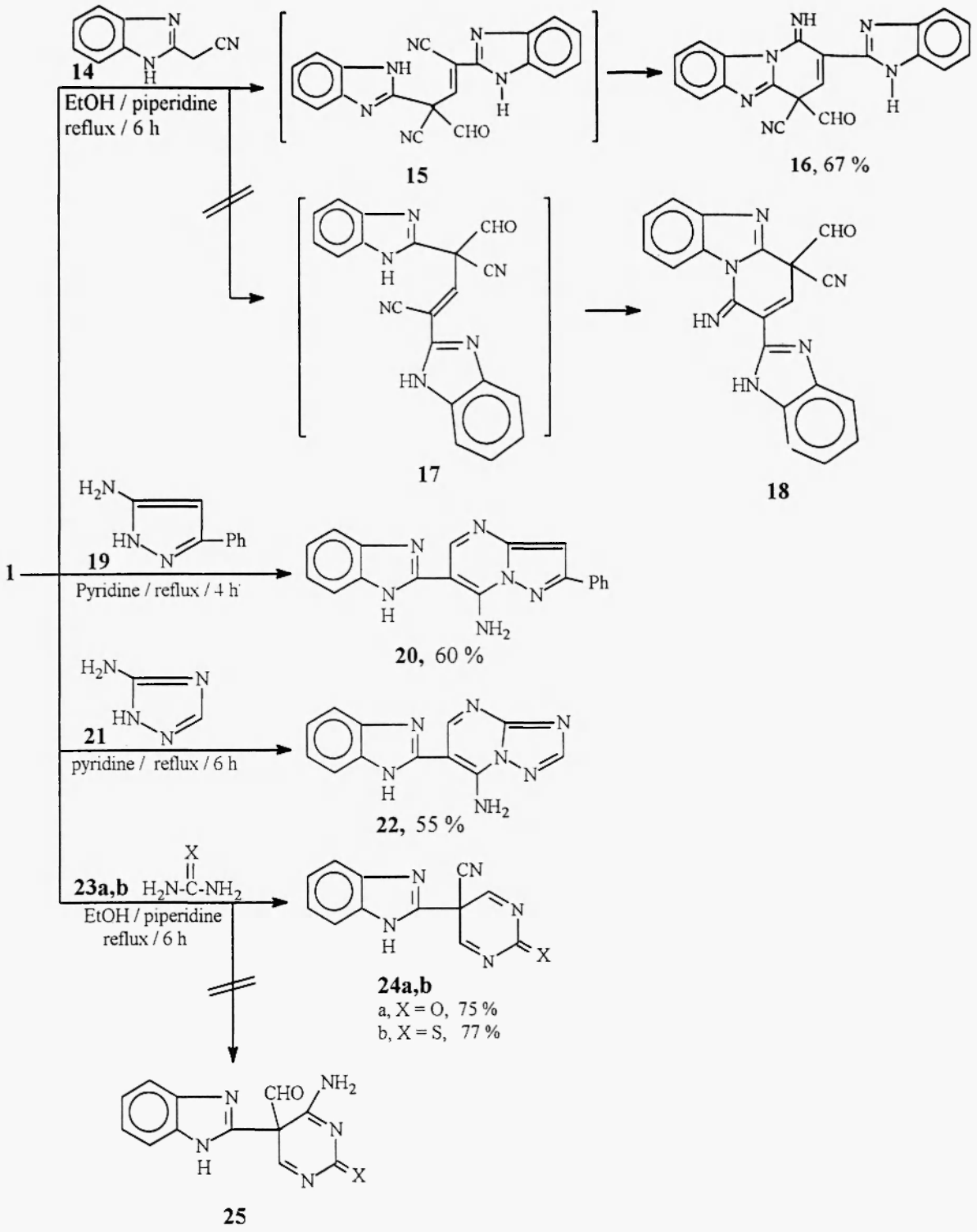
Scheme 1

Likewise, compound **1** reacts directly with cyanoacetamides **6a,b** in ethanolic piperidine solution at reflux to give the pyridine derivatives **7a,b**. The formation of 7 was assumed to be formed *via* a condensation reaction, followed by a nucleophilic addition to the cyano function. The **IR** spectrum of **7a** revealed bands at ν 3345, 3215, 2201, 1695 and 1675-1648 cm^{-1} assigned to NH_2, CN, C=O and CHO groups. The **MS** of **6a** showed *m/z* at 278 (M-1, 7), 263 (278-NH, 11), 251 (M-CO, 11), 235 (263-CO, 9), and 208 (235-HCN, 17 %). Again, the possible structure **8** was ruled out based on the spectral analysis. However, compound **1** reacts smoothly with malononitrile **9** in ethanolic piperidine solution to yield the planer pyrido[1,2-a] benzimidazole **11** in 55 % yield *via* the formation of the plausible acyclic intermediate **10** rather than the possible trigonal structure **13**, (Scheme 1). The **IR** spectrum of **11** showed absorption bands at ν 1650-1685, 2218, 2220, 3321-3125 cm^{-1} assigned to CHO, CN and NH groups. The **MS** of **11** showed *m z* at 260 (M-1, 11), 235 (M-CN, 9), 207 (M-CN-CO, 8), 182 (M-2CN-CO, 9), 170 (16), 149 (42). It worth that the reaction with ethyl cyanoacetate was unsuccessful under otherwise identical conditions. However, the aldehyde **1** reacts with 2-cyanomethylbenzimidazole **14** in ethanolic piperidine at reflux to give the planer pyrido[1,2-a]benzimidazole **16** in 67 % yield *via* the intermediate **15**. The structure was assigned based on IR, ^1H NMR and mass spectra. The **MS** of **16** showed *m/z* at 353 (M+1, 14), 339 (M-N, 11), 313 (M-N-CN, 26), 285 (14), 252 (15), 212 (59) and 170 (61%). The pyrimidines **20** and **22** were obtained *via* the reaction of **1** with **19** and **21** in pyridine at reflux for 4-6 h. The **IR** spectra of **20** and **22** revealed absorption bands at ν 1648-1685, 3225-3120 cm^{-1} due to CHO and NH functions. The **MS** of **20** showed *m/z* at 355 (M +1, 5), 250 (M-CO-Ph, 100), 222 (250-N_2, 22), 194 (222-C_2H_4, 20), 170 (48) and 157 (19 %). In contrast, the aldehyde **1** condensed directly with thiourea **23a** and urea **23b** in ethanolic piperidine solution to yield the pyrimidines **24a,b** *via* losing two moles of water (*c. f.* Scheme 2). The **IR** spectra of **24a,b** showed absorption bands due to the CN function at ν 2204 and at 3215 cm^{-1} (NH) with the disappearance of the aldehyde absorption. The **^1H NMR** spectrum (DMSO) of **24a** showed signals at δ 7.1-7.9 assigned to aromatic and NH protons. The **MS** of **20b** showed *m/z* at 253 (M + 1, 4), 252 (M^+, 17), 212 (M-CN-N, 81), 198 (M-CN-N_2, 40) and 170 (100 %).

Experimental: All melting points are uncorrected. The **IR** spectra were recorded (KBr, ν – cm^{-1}) on a Shimadzu 408 and a Pye Unicam Spectrophotometer. The **^1H NMR** spectra ($CDCl_3$, DMSO-d_6, δ = ppm) were recorded on a Varian EM 390 90 MH_Z Spectrometer and TMS was used as internal reference. Mass spectra were recorded on a mass Spectrometer MS 9 (AET) EI Mode. Elemental analysis were carried out at Microanalytical Center, Cairo University, Egypt. 2-Cyanomethylbenzimidazole-2,2-dicarboxaldehyde **1** was prepared in analogy to literature.[13]

Preparation of the Schiff bases (3a-d).

General procedure: A mixture of **1** (1.0 g, 0.01 mol) and hydrazine hydrate **2a** (0.24 g, 0.01 mol) in 40 ml of absolute ethanol was stirred at room temperature for 1 h. The colourless product so formed (**3a**) was filtered, washed with ethanol and recrystallised from DMF. Analogously, the aldehyde **1** was reacted in ethanol with phenylhydrazine **2b** (0.5 g), benzoic acid hydrazide **2c** (0.64 g) to give the Schiff bases **3b,c**. However, hydroxyamine hydrochloride (0.37 g) reacted in the presence of 0.1 ml of piperidine. The physical, spectral and analytical data were listed in Table I.


14
EtOH / piperidine
reflux / 6 h
15
16, 67 %
17
18
1
19
Pyridine / reflux / 4 h
20, 60 %
21
pyridine / reflux / 6 h
22, 55 %
23a,b
EtOH / piperidine
reflux / 6 h
24a,b
a, X = O, 75 %
b, X = S, 77 %
25

Scheme 2

Table I: The physical, analytical and spectral data

Comp. No.	Mp (^{0}C) Solvent	Yield %	Molecular. Formula (M. Wt.)	Analysis % Calcd./ Found C H N	Spectral Data ^{1}H NMR (δ, ppm)	MS *m/z* (M %)
3a	210-12 EtOH	85	$C_{11}H_7N_5$ (221.23)	58.14 3.99 30.82 58.03 3.88 30.70	6.3 (s, 2H, NH_2), 7.4 (s, 1H, CH=N), 7.0-7.8 (m, 4H, Ar-H), 8.3 (s, 1H, NH).	229 (M + 2, 18)
3b	260-62 EtOH	75	$C_{17}H_{12}N_5$ (303.16)	67.35 4.32 23.10 67.22 4.19 23.01	7.1-8.1 (m, 12H, Ar-H + CH=N, 2 NH), 8.6 (s, 1H, CHO).	303 (M^+, 15)
3c	238-40 EtOH	77	$C_{18}H_{13}N_5O$ (331.34)	65.25 3.95 21.14 65.06 3.80 21.00	7.1-7.9 (m, 12H, Ar-H + CH=N, 2 NH +), 8.5 (s, 1H, CHO)	331 (M^+, 15)
4a	280-82 MeOH	65	$C_{11}H_7N_5$ (221.23)	58.14 3.99 30.82 58.08 3.89 30.66	6.5 (s, 2H, NH_2), 7.1-7.8 (m, 6H, Ar-H + NH), 8.6 (s, 1H, CHO).	227 (M^+, 37)
4b	210-12 DMF	62	$C_{17}H_{12}N_5$ (303.16)	67.35 4.32 23.10 67.18 4.11 23.00	7.5 (s, 1H, NH), 7.1-7.8 (m, 11H, Ar-H + NH), 8.5 (s, 1H, CHO).	303 (M^+,22)
4c	100-02 MeOH	60	$C_{18}H_{13}N_5O$ (331.34)	65.25 3.95 21.14 65.12 3.82 21.04	6.6 (s, 1H, NH), 7.1-7.8 (m, 11H, Ar-H + NH), 8.6 (s, 1H, CHO).	331 (M^+, 22)
6a	200-02 EtOH	60	$C_{14}H_9N_5O$ (279.26)	60.21 3.25 25.08 60.11 3.16 25.26	6.6 (s, 2H, NH_2), 7.1-7.6 (m, 5H, Ar-H), 7.8 (s, 1H, NH), 8.9 (s, 1H, CHO).	278 (M - 1, 7)
6b	130-32 EtOH	55	$C_{14}H_9N_4S$ (295.26)	56.95 3.07 23.71 56.83 3.19 23.56	6.7 (s, 2H, NH_2), 7.1-7.8 (m, 5H, Ar-H + NH), 8.5 (s, 1H, CHO)	295 (M^+,12)
8	255-57 DMF	70	$C_{14}H_7N_5$ (261.24)	64.36 2.70 26.81 64.21 2.56 26.67	7.0-7.8 (m, 6H, Ar-H + NH), 8.0 (s, 1H, CHO).	261 (M-1, 10)

Continued Table 1:

10	355-57 DMF	67	$C_2H_{16}N_6$ (352.36)	68.05 3.43 23.85 68.05 3.31 23.73	7.0-7.6 (m, 10H, Ar-H + NH), 7.9 (s, 1H, CHO), 12.0 (s. 1H, NH).	353 (M + 1, 14)
12	255-57 EtOH	60	$C_{21}H_{14}N_6$ (354.17)	67.82 3.98 23.73 67.67 3.83 23.61	7.0-7.7 (m, 11H, Ar-H + NH), 7.9 (s, 1H, CHO), 11.9 (s. 1H, NH).	355 (M + 1. 5)
14	248-50 EtOH	55	$C_{13}H_{13}N_7$ (279.12)	55.94 3.25 35.13 55.82 3.14 35.04	7.1-8.2 (m, 7H, Ar-H + NH), 8.7 (s. 1H, CHO), 11.8 (s. 1H, NH).	279 (M^+. 8)
16a	255-57 DMF	75	$C_{12}H_{13}NO$ (237.22)	60.76 2.97 29.52 60.64 2.84 29.40	7.1-7.9 (m, 7H, Ar-H + NH).	237 (M^+. 5)
16b	240-42 DMF	77	$C_{12}H_{11}N_5S$ (253.28)	56.91 2.79 27.63 56.78 2.65 27.50	7.1-7.8 (m, 7H, Ar-H + NH).	253 (M + 1, 4)

Preparation of 5-amino-4-(benzimidazole-2-yl)pyrazole-4-carboxaldehyde (4a) and its derivatives (4b-d).

General procedure: A mixture of **1** (1.0 g, 0.01 mol) and hydrazine hydrate **2a** (0.24 g, 0.01 mol) in 40 ml of absolute ethanol containing 0.1 ml of piperidine was refluxed for 3-5 h. The reaction mixture was concentrated under reduce pressure and the residue washed with acidified cold water and then triturated with methanol. The colourless product formed (**4a**) was filtered, washed with ethanol and recrystallised from ethanol. Analogously, the aldehyde **1** was reacted with phenyl hydrazine **2b** (0.5 g), benzoic acid hydrazide **2c** (0.64 g) and hydroxylamine hydrochloride **2d** (0.37 g) to yield **4b-d**.

Preparation of 2-amino-5-cyano-6-oxo-3-(benzimidazole-2-yl)pyridine-3-carboxaldehyde (7a) and the pyridine-6-thione (7b).

General procedure: A mixture of **1** (0.5 g, 0.01 mol) and cyanoacetamide **6a** (0.2 g, 0.01 mol) in 20 ml of ethanol was refluxed in the presence of 0.1ml of piperidine for 5 h. The solution was concentrated under vacuum and the residue washed with acidified cold water, then treated with methanol. The colourless solid product formed was filtered and recrystallised from ethanol to afford **6a** in 60 % yield. In analogy, the aldehyde **1** was reacted with cyanothioacetamide **6b** (0.1 mol for each) to yield the pyridine-6-tluone **7b** in 55 % yield. The physical, spectral and analytical data were listed in Table I.

Preparation of benzimidazo[1,2-a]pyridine (11)

A mixture of **1** (0.5 g, 0.01 mol), malononitrile **9** (0.15 g, 0.01 mol) and 0.1 ml of piperidine was boiled in 20 ml of ethanol on a water bath. After 20 min. a green solid was formed, and the mixture was refluxed for additional 1h. The green solid product **11** was filtered, washed with methanol and recrystallised from DMF in 55 % yield. The spectral, physical and analytical data were listed in Table I.

Synthesis of 5-cyano-2-imino-3-(benzimidazole-2-yl)pyrido[1,2-a]benzimidazole-5-carboxaldehyde (16)

A mixture of **1** (0.5 g, 0.01 mol), 2-cyanomethylbenzimidazole **14** (0.37 g, 0.01 mole) and 0.1 ml of piperidine in 30 ml ethanol was refluxed for 6h. The solvent was evaporated under vacuum, the residue washed by acidified cold water and then by methanol. The solid product was filtered and recrystallised from DMF.

Preparation of pyrazolo[5,1-a]pyrimidine (20) and 1,2,4-triazolo[5,1-a]pyrimidine (22)

General procedure: A mixture of **1** (0.5 g, 0.01 mol), 5-amino-3-phenyl-1*H*-pyrazoline **19** (0.37g, 0.01 mol) or 5-amino-1*H*-1,2,4-triazole **21** (0.2 g, 0.01 mol) and 0.1 ml of piperidine was refluxed in 20 ml of ethanol for 4-6 h. The solvent was evaporated under vacuum, the residue was poured to 30 mL acidified cold water and then with methanol. The solid products were filtered and recrystallised from ethanol.

Preparation of 3-cyano-3-(benzimidazole-2-yl)pyrimidine-6-one (24a) and 3-cyano-3-(benzimidazole-2-yl) pyrimidine-6-thione (24b).

General procedure: A mixture of **1** (0.5g, 0.01 mol), urea **23a** (0.14 g, 0.01 mol) or thiourea **23b** (0.18 g, 0.01 mol) and 0.1 ml of piperidine was refluxed for 6 h in 30 ml of ethanol. The solid products formed during the reflux were filtered, washed with methanol and recrystallised from DMF, (Table I).

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