Synthesis and Reactivity of 1-Amino-4-methyl-3,4-dihydro-5*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzoimidazolo-5-one

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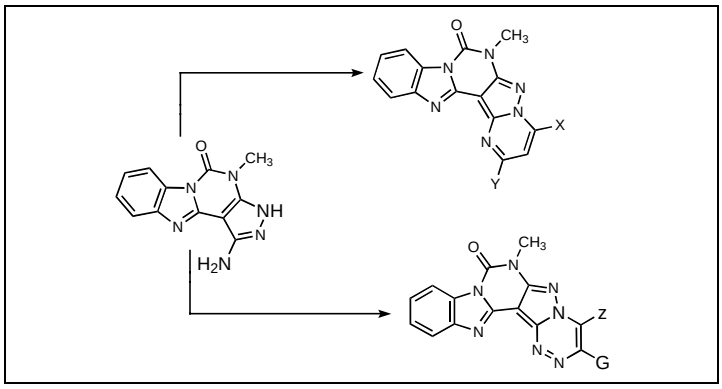

Pyrimido[2'',1'':5',6']pyrazolo[3',4':4,5]-pyrimido[1,6-*a*]benzoimidazoloe-2,8(1*H*,7*H*)-diones, and [1,2,4]-triazino-[3'',4'':5',6']pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazol-8(7*H*)-ones were synthesized in a good yields *via* 1-amino-4-methyl-3,4-dihydro-5*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzoimidazolo-5-one and the appropriate active methylene compounds. Structures of the newly synthesized compounds were elucidated on the basis of elemental analyses, spectral data, and alternative synthesis methods whenever possible.

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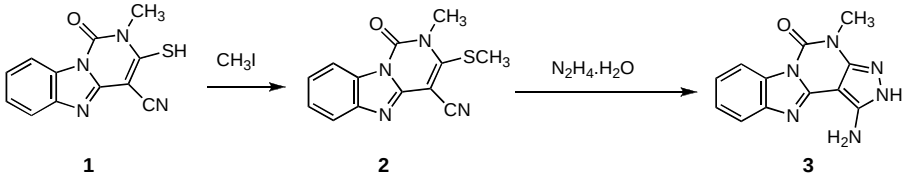
INTRODUCTION

Benzimidazoles are one of the most extensively studied classes of heterocyclic compounds owing partly to their biological activities such as anticonvulsant [1], sedative [1], immunosuppresant [1], antitumor [1], antihistaminic [1] and antifugal [2]. There is considerable interest in exploring new stereoselective synthesis [3] and biological evaluation of new benzimidazole derivatives [4] despite the existence of numerous synthetic methods of benzimidazole derivatives [5]. As an extension of our study [6,7] and as a part of our program aiming at the synthesis of different fused benzimidazoles, we report here the reactivity of 1-amino-4-methyl-3,4-dihydro-5*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzoimidazolo-5-one.

RESULTS AND DISCUSSION

Treatment of **1** with iodomethane [8] gave 2-methyl-3-(methylsulfanyl)-1-oxo-1,2-dihydropyrimido[1,6-*a*]-benzimidazo-4-carbonitrile (**2**). Structure **2** was confirmed by elemental analysis, its ^{1}H NMR spectrum and chemical transformations. When compound **2** is reacted with hydrazine hydrate in boiling ethanol under reflux 1-amino-4-methyl-3,4-dihydro-5H-pyrazolo-[3',4':4,5]pyrimido[1,6-*a*]benzoimidazolo-5-one (**3**) is obtained (Scheme 1).

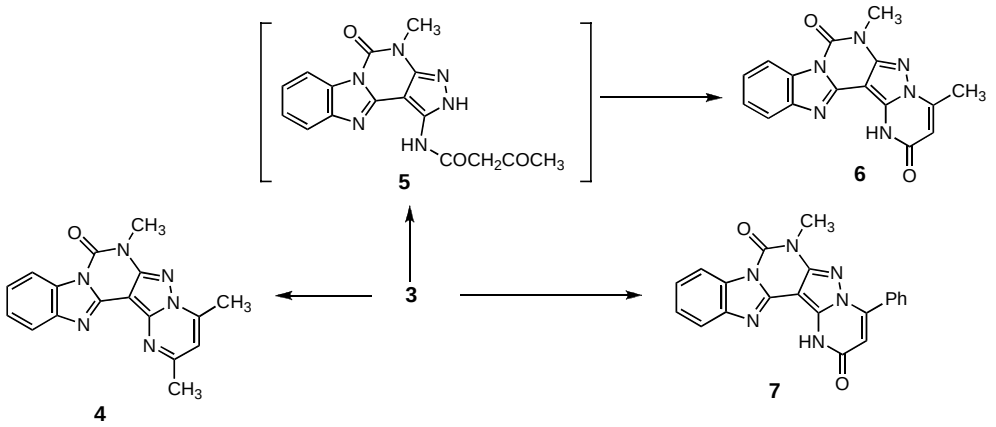
Structure **3** was confirmed by elemental analysis, ^{1}H NMR and IR spectra and chemical transformations. The IR spectrum of **3** revealed bands at 3340, 3312, 3280 (NH_2, NH), 1706 (CO) and 1580 (C=C). Its ^{1}H NMR spectrum showed signals at δ = 3.39 (s, 3H), 6.37 (s, br., 2H), 7.23-7.38 (m, 2H), 7.60-7.64 (d, 1H), 8.22-8.26 (d, 1H) and 11.8 (s, br., 1H).



1 **2** **3**

Scheme 1

Compound **3** reacted with 2,4-pentandione in boiling acetic acid under reflux afforded 2,4,6-trimethylbenz-imidazolo[1'',2'':1',6']pyrazolo[4',5':4,3]-pyrazolo[1,5-*a*]-pyrimidin-7-one (**4**) (Scheme 2).

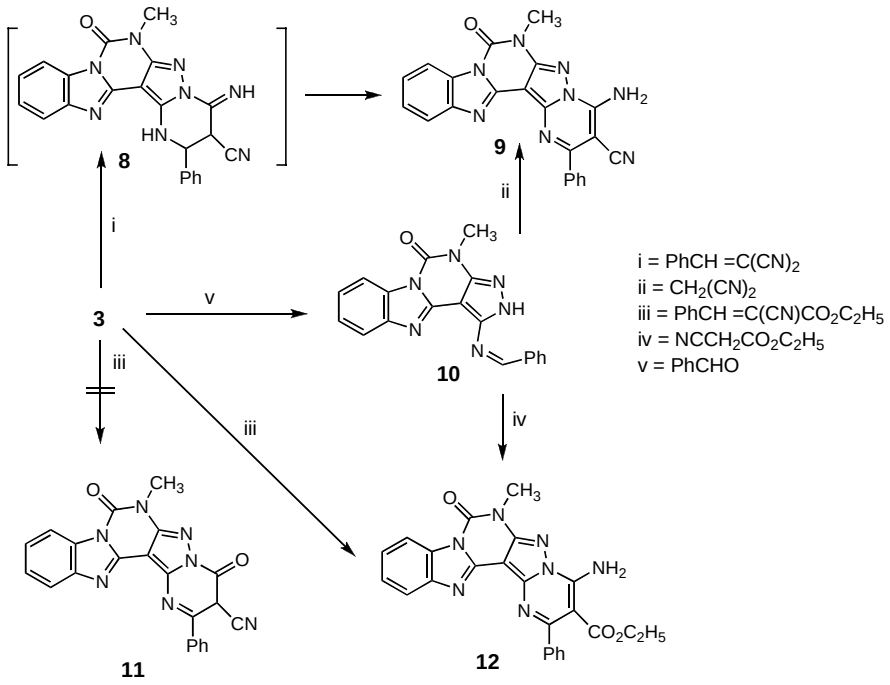


Scheme 2

Also, when **3** is reacted with ethyl 3-oxobutanoate in boiling acetic acid the product formulated as 4,6-dimethyl-1,6,4a,7a-tetrahyderobenzimidazolo[1'',2'':1',6']-pyrimidino [4',5':4,3]pyrazolo[1,5-*a*]pyrimidine-2,7-dione (**6**) was obtained. Also, when **3** is reacted with acetacetanilide the product obtained is identical in all respects (mp., mixed mp. and spectra) with **6**. This reaction seemed to proceed through the elimination of ethanol (or aniline) to give intermediate **5**, which underwent cyclization *via* elimination of a water molecule to afford the final product **6**.

Similarly, when **3** is reacted with each of ethyl 3-oxo-3-phenylpropanoate and 2-benzoylacetanilide the product obtained is 6-methyl-4-phenyl-1,6,4a,7a-tetrahydrobenz-imidazolo-[1'',2'':1',6']pyrimido[4',5':4,3]pyrazolo[1,5-*a*]-pyrimidine-2,7-dione (**7**), as shown by elemental analysis and spectral data.

However, treatment of **3** with α-cyanocinnamonitrile in boiling ethanol, containing catalytically amount of piperidine, under reflux gave 4-amino-7-methyl-8-oxo-2-phenyl-7,8-dihydropyrimido[2'',1'':5',6']pyrazolo[3',4':4,5]-pyrimido[1,6-*a*]benzimidazole-3-carbonitrile (**9**) (Scheme 3). Structure **9** was elucidated by elemental analysis, spectral data and alternative synthesis. Thus, ^{1}H NMR spectrum showed signals at δ = 3.55 (s, 3H), 6.52 (s, br., 2H), 7.35-7.42 (m, 7H), 7.71-7.74 (d, 1H) and 8.26-8.31 (d, 1H). Its IR spectrum revealed bands at 3305, 3244 (NH_2), 2187 (CN), 1721 (CO) and 1612 C=N). Also,



Scheme 3

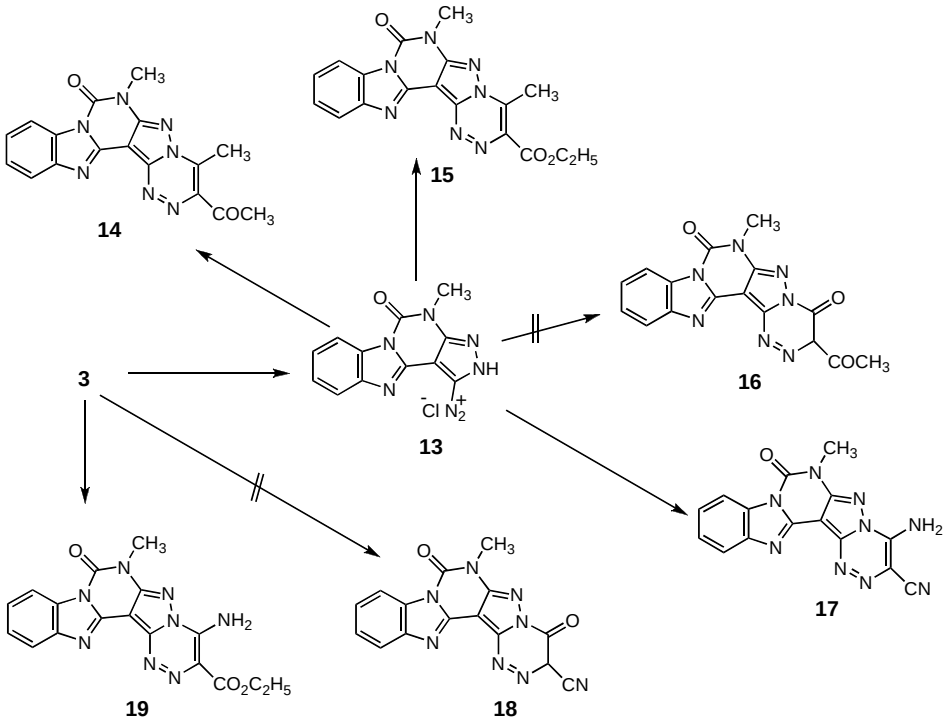
treatment of 5-(1-aza-2-phenylvinyl)-2-methyl-2,10b-dihydrobenzimidazolo[1,2-*e*]pyrazolo[3,4-*d*]pyrimid-in-1-one (**10**), which was prepared *via* reaction of **3** with benzaldehyde, with malononitrile in boiling ethanol in the presence of a catalytical amount of piperidine gave product identical in all respects (mp., mixed mp. and spectra) with **9**. The reaction seemed to be proceeding through Michael addition of active methylene to (-N=CHPh) to give the intermediate **8**, which underwent cyclization and autoxidation to give **9** (Scheme 3).

Similarly, ethyl 2-cyano-3-phenylacrylate reacted with **3** in boiling ethanol under reflux to give a product that seemed to correspond to structure **11** or isomeric structure **12**. The IR spectrum reveals bands at, 3313, 3177 (NH_2), 1704 (CO), 1622 (C=N), 1612 (C=C) and no absorption band in the region 2100-2300 cm^{-1} is observed thus verifying the absence of CN group. ^1H NMR spectrum showed signals at δ = 1.31 (t, J= 7.2 Hz, 3H), 3.62 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 6.52 (s, br., 2H), 7.31-7.72 (m, 7H), 7.76-7.82 (d, 1H) and 6.21-8.26 (d, 1H). Foregoing data the product was formulated as: ethyl 4-amino-7-methyl-8-oxo-2-phenyl-6,4a,7a-trihydropyrimido-[1",2":1',6']pyrimidino[4',5':4,3]-pyrazolo[1,5-*a*]pyrimid-ine-3-carboxylate (**12**).

[1,2,4]triazino[4",3":1',5']pyrazolo[3,4-*d*]pyrimidin-7-one (**14**).

Also, treatment of **13** with ethyl 3-oxobutanoate gave, one isolable product according to *tlc*, which seemed to correspond to **15** or isomeric **16**. Its IR spectrum revealed bands at 1720, 1663 (CO's) and 1604 (C=C); mass spectrum of the product showed peaks at m/z = 379 (3.3%, M+2), 378 (23.3%, M+1), 377 (100%, M), 348 (4%, M-C_2H_5), 332 (9.7%, M-OC_2H_5), 304 (11.9%, M-$C_2H_5CO_2$), 248 (15.7%), 182 (10.4%), 90 (43.2%) and 67 (18.4%). Based on this data the product was formulated as: ethyl 4,6-dimethyl-7-oxo-6,7a-dihydrobenzimidazolo-[1,2-*e*]-[1,2,4]triazino[4',3':1,5]-pyrazolo[3,4-*d*]pyrimidine-3-carboxylate (**15**) while isomeric structure **16** was ruled out (Scheme 4).

Similarly, **13** reacted with malononitrile in ethanolic sodium acetate at 0°C afford 4-amino-6-methyl-7-oxo-6,7a-dihydrobenzimidazolo[1,2-*e*][1,2,4]triazino-[4',3':1,5]-pyrazolo[3,4-*d*]pyrimidine-3-carbonitrile (**17**). Structure **17** was elucidated by elemental analysis and spectral data. Thus, the IR spectrum revealed bands at 3343, 3260 (NH_2), 2213 (CN), 1718 (CO's), 1641 (C=N) and 1605 (C=C). Its mass spectrum showed a peak at m/z 331 (100%, M).



Scheme 4

Next, treatment of diazonium chloride **13**, which was prepared by reaction of **3** with nitrous acid, with 2,4-pentandione in ethanolic sodium acetate solution gave 3-acetyl-4,6-dimethyl-6,7a-benzimidazolo[1,2-*e*]dihydro-

Finally, treatment of **13** with ethyl cyanoacetate in ethanolic sodium acetate solution gave a product formulated as ethyl 4-amino-6-methyl-87-oxo-6,7a-di-hydrobenz-imidazolo[1,2-*e*][1,2,4]triazino[4',3':1,5]py-

Table 1

Characterization data of the newly synthesized compounds.

Compound	Mp (°C)	ColourYield %	Molecular Formula	Analysis % Calcd./Found C	H	N	S
2	222-25	Yellow	$C_{13}H_{10}N_4OS$	57.76	3.73	20.73	11.86
	DMF	65		57.62	3.54	20.75	11.55
3	>300	Colorless	$C_{12}H_{10}N_6O$	56.69	3.96	33.05	-
	AcOH	73		56.90	3.68	32.90	
4	>300	Pale Yellow	$C_{17}H_{14}N_6O$	64.14	4.43	26.40	-
	DMF	45		64.20	4.30	26.30	
6	>300	Colorless	$C_{16}H_{12}N_6O_2$	60.00	3.78	26.24	-
	DMF	52		60.12	3.97	26.40	
7	>300	Pale Yellow	$C_{21}H_{14}N_6O_2$	65.96	3.69	21.98	-
	AcOH	60		65.82	3.65	21.80	
9	>300	Yellow	$C_{22}H_{14}N_8O$	65.02	3.47	27.57	-
	AcOH	55		65.12	3.51	27.70	
10	>300	Yellow	$C_{19}H_{14}N_6O$	66.66	4.12	24.55	-
	DMF	62		66.46	4.00	24.34	
12	>300	Pale Yellow	$C_{24}H_{19}N_7O_3$	63.57	4.22	21.62	-
	AcOH	49		63.92	4.24	21.90	
14	>300	Yellow	$C_{17}H_{13}N_7O_2$	58.79	3.77	28.23	-
	AcOH	72		58.90	3.60	28.10	
15	>300	Yellow	$C_{18}H_{15}N_7O_3$	57.29	4.01	25.98	-
	AcOH	82		57.00	3.90	25.91	
17	>300	Yellow	$C_{15}H_9N_9O$	54.38	2.74	38.05	-
	AcOH	67		54.36	2.79	37.85	
19	>300	Pale Yellow	$C_{17}H_{14}N_8O_3$	53.97	3.73	29.62	-
	AcOH	78		54.12	3.80	29.70	

Table 2

Spectra of the newly synthesized compounds.

Compound	Spectral data
2	^{1}HNMR ($CDCl_3$): δ = 2.77 (s, 3H), 3.76 (s, 3H), 7.42-7.57 (m, 2H), 7.80-7.84 (d, 1H) and 8.22-8.26 (d, 1H). IR: 2218 (CN) and 1711 (CO).
3	^{1}H NMR ($CDCl_3$): δ = 3.39 (s, 3H), 6.37 (s, br., 2H), 7.23-7.38 (m, 2H), 7.60-7.64 (d, 1H), 8.22-8.26 (d, 1H) and 11.8 (s, br., 1H). IR: 3340, 3312, 3280 (NH_2, NH), 1706 (CO) and 1580 (C=C).
4	^{1}H NMR ($CDCl_3$): δ = 2.71 (s, 6H), 3.75 (s, 3H), 6.71 (s, 1H), 7.27-7.42 (m, 2H), 7.82-7.87 (dd, 1H) and 8.34-8.39 (dd, 1H). IR: 3236 (NH), 1713, 1659 (CO's) and 1605 (C=C).
6	^{1}H NMR ($CDCl_3$): δ = 2.72 (s, 3H), 3.55 (s, 3H), 6.75 (s, 1H), 7.35-7.42 (m, 2H), 7.72-7.76 (d, 1H), 8.29-8.34 (d, 1H) and 13.37 (s, br., 1H). IR: 3252 (NH), 1709, 1657 (CO's), 1611 (C=N) and 1578 (C=C).
7	^{1}H NMR ($CD_3)_2$SO: δ = 3.55 (s, 3H), 6.52 (s, br., 1H), 7.35-7.42 (m, 7H), 7.71-7.74 (d, 1H), 8.26-8.31 (d, 1H) and 13.31 (s, br., 1H). IR: 3433, 3305, 3244 (NH, NH2), 2187 (CN), 1721 (CO) and 1612 C=N).
9	^{1}H NMR ($CD_3)_2$SO: δ = 3.62 (s, 3H), 6.52 (s, br., 2H), 7.31-7.72 (m, 7H), 7.76-7.82 (d, 1H) and 6.21-8.26 (d, 1H). IR: 3406, 3313, 3177 (NH, NH_2), 1704 (CO), 1622 (C=N) and 1612 (C=C).
10	IR: 1712, 1697, (CO's), 1660 (C=N) and 1602 (C=C). MS: 344 (18.6 %, M+2), 343 (100%, M+1), 342 (87%, M), 320 (10.7%), 304 (4.92), 254 (8.5%), 181 (10.1%), 90 (28%) and 67 (15%).
12	^{1}H NMR ($CDCl_3$): 1.31(t, J = 7.2 Hz, , 3H), 3.62 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 6.52 (s, br., 2H), 7.31-7.72 (m, 7H), 7.76-7.82 (d, 1H) and 8.21-8.26 (d, 1H). IR: 1720, 1663 (CO's) and 1604 (C=C). MS: 453 (100%, M^+), 424 (4%, M-C_2H_5), 408 (9.7%, M-OC_2H_5), 380 (11.9%, M- $C_2H_5CO_2$), 248 (15.7%), 182 (10.4%), 90 (43.2%) and 67 (18.4%).
14	^{1}H NMR: (insoluble) IR: 3443, 3260 (NH_2), 1718 (CO's), 1641 (C=N) and 1605 (C=C). MS: 347 (100%, M^+).
15	^{1}H NMR: (insoluble) IR: 3343, 3260 (NH_2), 1712, 1618 (CO's), 1641 (C=N) and 1605 (C=C). MS: 379 (3.3%, M+2), 380 (23.3%, M+1), 377 (100%, M), 380 (3.3%), 306 (17%), 254 (39.2%), 182 (17.5%) and 90 (16.8%).
17	^{1}HNMR ($CD_3)_2$SO: δ = 3.76 (s, 3H), 6.23 (s, br., 2H), 7.42-7.57 (m, 2H), 7.80-7.84 (d, 1H) and 8.22-8.26 (d, 1H). IR: 3343, 3260 (NH_2), 2213 (CN), 1718 (CO), 1641 (C=N) and 1605 (C = C). MS: 331 (100%, M).
19	^{1}H NMR ($CD_3)_2$SO: δ = 1.30 (t, J = 7.2, 3H), 3.62 (s, 3H), 4.22 (q, J = 7.2 Hz), 6.52 (s, br., 2H), 7.23-7.38 (m, 2H), 7.60-7.64 (d, 1H), 8.22-8.26 (d, 1H). IR: 3340, 3312, 3280 (NH_2, NH), 1706 (CO) and 1580 (C=C). MS: 380 (3.3%, M+2), 379 (23.3%, M+1), 378 (100%, M), 306 (17%), 254 (39.2%), 192 (17.5%), and 90 (16.8%)

razolo[3,4-*d*]-pyrimidine-3-carboxylate (**19**). Its mass spectrum showed peaks m/z at = 380 (3.3%, M+2), 379 (23.3%, M+1), 378 (100%, M), 306 (17%), 254 (39.2%), 182 (17.5%) and 90 (16.8%).

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of the Cairo University

Synthesis of 2-methyl-3-(methylsulfanyl)-1-oxo-1,2-dihydroyrimido[1,6-a]benzimidazo-4-carbonitrile (2). A mixture of 2-(1-ethoxycarbonoyl)benzimidazolylacetonitrile, methyl isothiocyanate, potassium hydroxide (5 mmol each) in *N,N*-dimethylformamide (15 mL) was stirred for 6 hrs. Iodomethane (0.72 g, 5 mmol) was added while stirring and the reaction mixture was stirred for 2 hrs. The resulting solid was collected and recrystallized from *N,N*-dimethylformamide to give **2** (Tables 1 and 2).

Synthesis of 1-amino-4-methyl-3,4-dihydro-5*H*-pyrazolo-[3',4':4,5]pyrimido[1,6-*a*]benzoimidazolo-5-one (3). A mixture of **2** (2.18 g, 5 mmol) and hydrazine hydrate (1 mL, 99%) in ethanol (20 mL) was boiled under reflux for 4 hrs. The resulting solid was collected and recrystallized from acetic acid to give **3** (Tables 1, 2).

Synthesis of 4, 6 and 7. Equimolar amounts aminopyrazole **3** and the appropriate 2,4-pentandione, ethyl acetoacetate (or aceto-acetanilide) or ethyl benzoylacetate (or benzoylacetanilide) (5 mmol) in acetic acid (20 mL) were heated under reflux for 3 hrs. The resulting solid was collected and recrystallized from *N,N*-dimethylformamide to give **4, 6** and **7**, respectively (Tables 1 and 2).

Synthesis of 9 and 12. Equimolar amounts of aminopyrazole **3** and the appropriate α-substituted cinnamonitrile (5 mmol each) in ethanol (20 mL) containing catalytical amount of piperidine (3 drops) was boiled under reflux for 2 hrs. The resulting solid was collected and recrystallized from *N,N*-dimethylformamide to give **9** and **12,** respectively (Tables 1 and 2).

5-(1-Aza-2-phenylvinyl)-2-methyl-2,10b-dihydrobenzimi-dazolo[1,2-*e*]pyrazolo[4,3-*d*]pyridine-1-one (10). Equimolar amounts of aminopyrazole **3** and the appropriate benzaldehyde (5 mmol each) in ethanol (20 mL) containing catalytical amount of piperidine (3 drops) was boiled under relux for 2 hrs. The resulting solid was collected and recrystallized from *N,N*-dimethylformamide to give **10** (Tables 1 and 2).

Synthesis of Benzimidazolo[1'',2'':1',6']pyrimidino[4',5': 4,3]-pyrazolo[1,5-*a*]pyrimidine derivatives 14, 15, 17and 19. Diazonium chloride **13** (which was prepared *via* addition sodium nitrite solution (0.35g, (5 mmol), 10 mL water) to a mixture of **3** (2.15 g, 5 mmol), acetic acid (1 mL) and hydrochloric acid (3 mL, 6 *M*)) at 0°C) was added dropwise to a cold solution of each of 2,4-pentandione, ethyl 3-oxobutanoate, malononitrile or ethyl cyanoacetate (5 mmol each), sodium acetate (1 g) in ethanol (50 mL) while stirring at 0-5°C. The reaction mixture was stirred 3 hrs the resulting solid was collected and recrystallized from acetic acid to give **14**, **15**, **17** and **19**, respectively (Tables 1 and 2).

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