Chemoselective Synthesis of 4-Oxo-2-aryl-4,10-dihydropyrimido [1,2-*a*][1,3]benzimidazol-3-yl Cyanides *via* [3+3] Atom Combination of 2-Aminobenzimidazole with Ethyl-α-Cyanocinnamoates

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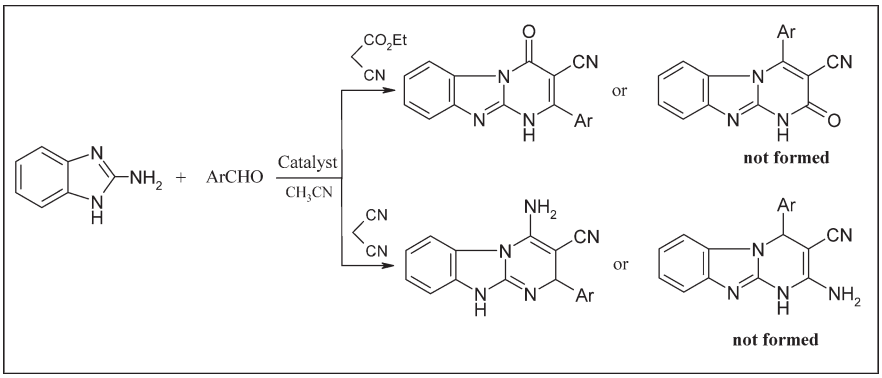
This article is dedicated in the memory of Mr. Alireza Afzalipour, founder of Kerman University, on the occasion of the centenary of his birth.



Chemoselective synthesis of 4-oxo-2-aryl-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanides from three-component reactions of 2-aminobenzimidazole, aldehydes, and ethyl cyanoacetate *via* [3+3] atom combination is reported. The effect of different base catalysts such as sodium acetate, triethylamine, and magnesium oxide MgO on the product yield has also been investigated under conventional heating.

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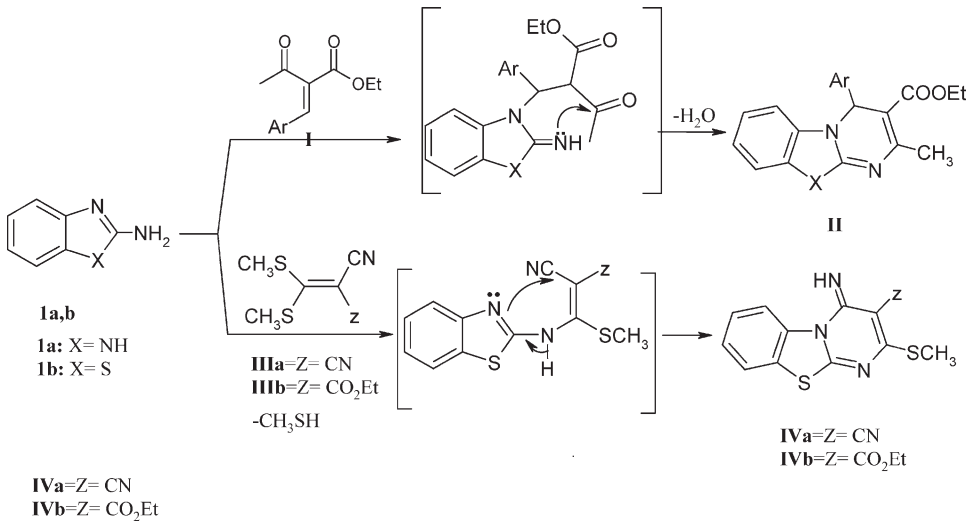
INTRODUCTION

2-Aminobenzimidazole **1a** or 2-aminobenzothiazole **1b** have three sites of electron rich sites, at the nitrogen and sulfur atoms. Nucleophilic reactions on these compounds can take place on either of the exocyclic or the endocyclic nitrogen centre, depending on the nature of the electro phile and the reaction conditions [1,2]. Benzimidazole derivatives are known as intermediates for the synthesis of molecules exhibit a number of important pharmacological properties, such as antihistaminic [3], antiallergic [4], and antipyretic [5]. In addition, these compounds are effective against the human cytomegalovirus (HCMV) [6] and several viruses such as HIV [7,8], herpes (HSV-1) [9], RNA [10], influenza [11], and human cytomegalovirus (HCMV) [8].

The widespread interest in benzimidazole containing systems has promoted extensive studies of their syntheses. Substituted 2-aminobenzimidazoles are useful intermediates for the syntheses of fused heterocyclic ring systems [12]. Nucleophilic reactions of 2-aminobenzimidazole **1a** can take place on either of the exocyclic or the endocyclic nitrogen centre, depending on the nature of the electrophile and the reaction conditions [1,2]. The conjugate addition of 2-aminobenzothiazole **1a** to the acetylenic acids in butanol, followed by cyclocondensation, gave the corresponding 2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones, which is due to Michael addition of the endocyclic nitrogen centre on acetylenic carbon. More recently, we have reported nucleophilic addition of 2-minobenzimidazole **1a** to an enone type of 3-benzylidene-2,4-pentane-dione **I** in the presence of catalysts such as magnesium oxide MgO and 12-tungstophosphoric acid (PW) followed by cyclization, leads to 4*H*-pyrimido[2,1-*b*]benzimidazole derivatives **II**. In this case, the endocyclic nitrogen of the 2-minobenzimidazole **1a** is the most reactive [13]. However, in the case of Michael addition of 2-aminobenzothiazole **1b** on bis (methylthio)methyllene malononitrile nitrile **IIIa** or ethyl-2-cyano-3,3-bismethyl thioacrylate **IIIb** afforded 3-cyano-4-imino-2-methyl-thio-*4H*-pyrimido [2,1-*b*] [1,3] benzothiazoles **IVa** and 4H-pyrimido[2,1-b]benzothiazole-2-thiome-thyl-3-cyano-4-one derivatives **IVb**, respectively, the exocyclic nitrogen being the most reactive for these reactions (Scheme 1) [14,15].

Ethyl-α-cyanocinnamoates have three electron deficient centers at C_β and carbons of nitryl and carboxylate

Scheme 1



groups. Thus, they can react with binucleophiles to prepare heterocyclic compounds. These processes are highly regioselective, and chemoselective synthesis of these compounds depend on the reactivity of binucleophiles [16–18].

RESULTS AND DISCUSSION

To study the regioselectivity of the 2-aminobenzothiazole **1a** with ethyl-α-cyanocinnamoates, we have investigated three-component reaction of 2-aminobenzimidazole **1a**, aldehydes **2a–c** and ethyl cyanoacetate or malononitrile **3** in the presence of base catalysts such as sodium acetate, triethylamine, and magnesium oxide [commercial MgO (CM-MgO) and high surface area MgO (HSA-MgO)]. We have found that 2-aminobenzothiazole **1a** acts as a binucleophile toward the deficient centers at C_β and nitryl group of ethyl-α-cyanocinnamoates to release 4-oxo-2-aryl1,4-dihydropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanides as only product. This fact represents a distinct advantage in terms of chemoselectivity synthesis of these compounds (Scheme 2).

To optimize the reaction conditions for preparing compounds **3** and **4**, the effect of base catalyst for preparing compounds **3** and **4** under different reaction conditions were investigated.

First, we examined three-component reactions of 2-aminobenzimidazole **1a**, aldehydes **2a–f**, and ethyl cyanoacetate or malononitrile in an organic solvent (toluene) at reflux in the presence of triethylamine as base catalyst. The reactions were too slow, and the yields

Scheme 2

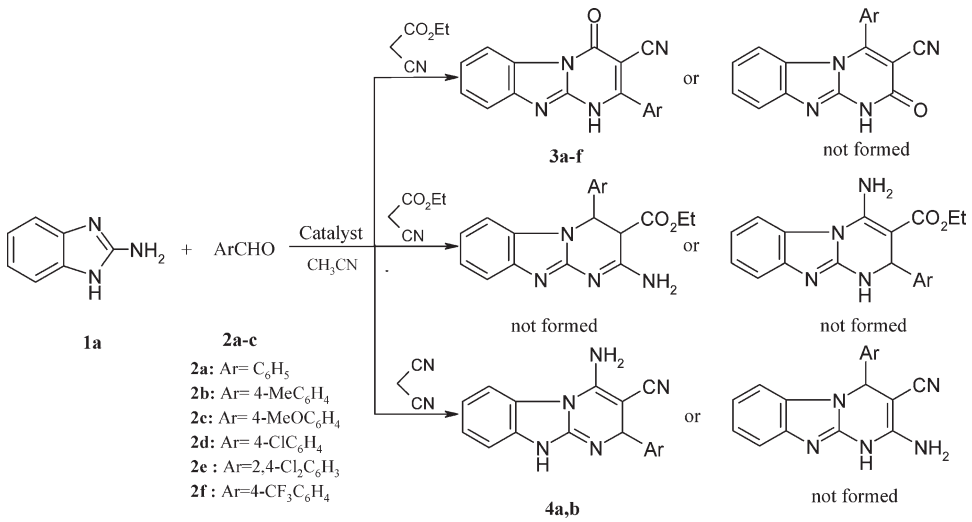


Table 1

Synthesis of compounds **3a-f and 4a,b** in the presence of base catalysts.

		Base catalyst: triethylamine		Base catalyst: sodium acetate		Base catalyst: CM[a]/HSA[b] (MgO)	
Compound Number	R	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (min)	Yield (%)
3a	C_6H_5	10	58	9	70	73/40	36/96
3b	4-MeC_6H_4	18	36	12	42	90/57	28/72
3c	4-$MeOC_6H_4$	16	35	11	36	98/85	26/60
3d	4-ClC_6H_4	11	40	10	44	90/80	26/64
3e	2,4-ClC_6H_3	15	47	10	53	80/64	25/78
3f	4-$CF_3C_6H_4$	12	52	10	68	50/45	34/92
4a	C_6H_5	10	65	8	80	90/10	80/92
4b	4-ClC_6H_4	8	75	6	85	45/5	75/95

[a] Commercial MgO.
[b] High surface area MgO.

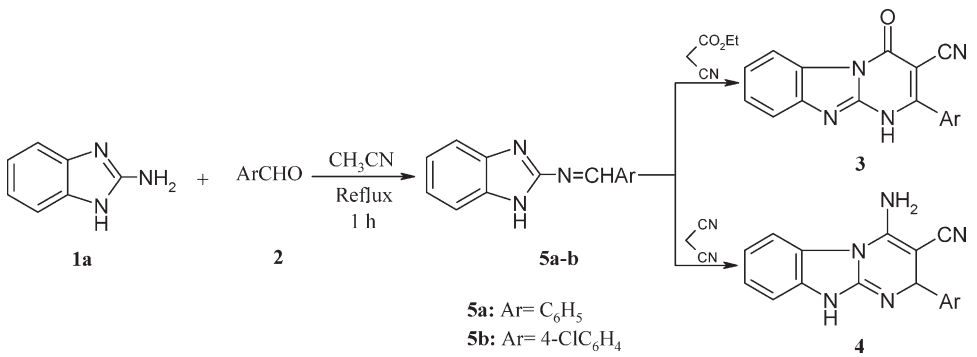
were not high. Second, other reactions were performed in water and ethanol at reflux and in the presence of an equivalent amount of sodium acetate. Finally, the three-component reaction was carried out in the presence of two types of magnesium crystals [commercial MgO (CM-MgO) and high surface area MgO (HSA-MgO)]. High surface area MgO was found to be more active than CM-MgO, and the results of these methods are presented in Table 1.

2-Aminobenzimidazole **1a** and ethyl-α-cyanocinnamoates or α-cyanocinnamonitrile have several sites of electron rich sites or electron defision sites, respectively. Thus these reaction are highly regioselective, leading to only one of the some possible isomers that can be formed in different conditions [19]. To confirm the structure of products **3** and **4**, reaction of *N*-(1,3-benzoimidazol-2-yl)-*N*-(alkylidene)-amines **5a,b** (which prepared by reaction of aldehydes with **1a**) with ethyl cyanoacetate or malononitrile were studied, which afforded the same product of 4-oxo-2-aryl-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanid es (**3a,b**) or 4-amino-2-aryl-2*H*-pyrimido[1,2-*b*][1,3]benzi midazol-3-yl cyanide derivatives (**4a,b**) respectively in the presence of high surface area MgO (Scheme 3).

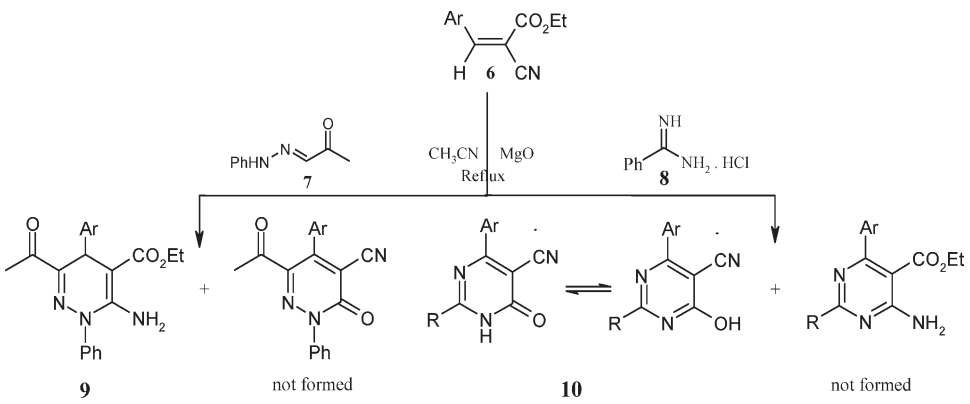
We have recently reported the three-component reaction of malononitrile or ethyl cyanoacetate with (phenylhydrazono)-propan-2-one **7** or amidine systems as1,3-dinucleophile and aldehydes in the presence of MgO afforded only 3-amino-2,5-dihydropyridazine and 4-amino-5-pyrimidine carbonitrile or pyrimidinone derivatives respectively [20,21]. In these protocols as exhibited in Scheme 4, we have investigated reactions of ethyl-α-cyanocinnamoates **6** which have three electron deficient centers at carbons of nitryl and carboxylate groups and carbon of C_β with 1,3-dinucleophile such as (phenylhydrazono)propan-2-one **7** or phenylamidine **8** afforded only 2,5-diaryl ethyl -6-acetyl-3-amino-2,5-dihydro-4-pyridazinecarboxylate and 4-diaryl-6-oxo-1,6-dihydro-5-pyrimidinecarbonitrile derivatives, respectively, in the presence of magnesium oxide MgO as a highly effective heterogeneous base catalyst in excellent yields. In these reactions 1,3-dinucleophiles act *via* regioselective on C_β and carbon of carboxylate group of ethyl-α-cyanocinnamoates which have three electron deficient centers (Scheme 4).

The structures of compounds **3a–f** and **4a,b** were elucidated and assigned from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. The IR

Scheme 3



Scheme 4



spectra of compounds **3a–f** and **4a,b** showed the presence of CN at a region of 2240–2230 cm^{-1}, and a sharp band at 1700–1650 cm^{-1} which is due to the amide groups.

In summary, we have described chemoselective synthesis of 4-oxo-2-aryl-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanides from three-component reactions of 2-aminobenzimidazole, aldehydes, and ethyl cyanoacetate in the peresence of base catalysts such as triethylamine, sodium acetate, and magnesium oxide (MgO). The advantage of these procedures reported here are: high selectivity, high purity of products, and easy workup.

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FTIR spectrometer. The proton and carbon NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Preparation of high surface area MgO. The catalysts used in this study were obtained by calcinations of rehydrated $Mg(OH)_2$. The experimental results showed that an optimal calcination temperature in the range 400–500°C gives poorly crystalline, high surface area MgO that can be regenerated by washing, and then reused. After separation of the product by filtration, the recovered solvent containing MgO was reused twice without loss of activity of the catalyst [22].

General procedure for the preparation of 4-oxo-2-aryl-1,4-dihydropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanides (3a–f) and 4-amino-2-aryl-2*H*-pyrimido[1,2-*b*][1,3] benzimidazol-3-yl cyanides (4a,b). ***Method I*** A mixture of the 2-aminobenzimidazole **1a** (2 mmol), aldehyde **2** (2 mmol) and ethyl cyanoacetate or malononitrile (2 mmol) and sodium acetate (2 mmol) in H_2O (50 mL) and ethanol (5 mL) was refluxed with stirring for the time reported in Table 1 (the progress of the reaction being monitored by TLC and unsing *n*-hexane/ethyl acetate as an eluent). The product **3** precipitated from the reaction mixture after cooling and the solid was filtered and recrystallized from ethanol.

Method II. A mixture of the 2-aminobenzimidazole **1a** (2 mmol), aldehyde **2** (2 mmol), and ethyl cyanoacetate or malononitrile (2 mmol) in ethanol (25 mL) was refluxed with stirring in the presence of triethylamine (0.5 mL). The reactions were continued until completion, as monitored by TLC. After completion of the reaction, the product was purified as in method **I**.

Method III. A mixture of the 2-aminobenzimidazole **1a** (2 mmol), aldehyde (2 mmol), and ethyl cyanoacetate or malononitrile (2 mmol) in CH_3CN (25 mL) was refluxed with stirring in the presence of commercial MgO or high surface area MgO (0.25 g). The reactions were continued until completion, as monitored by TLC. After completion of the reaction, the catalyst was removed by filtration, and the filtrate was concentrated to obtain the crude product. The crude product was crystallized from ethanol.

4-Oxo-2-phenyl-4,10-dihydropyrimido[1,2-*a*][1,3] benzimidazol-3-yl cyanide (3a). Pale yellow crystals. mp 300–303°C. IR (KBr, ν_{max}/cm^{-1}): 3295 (broud, NH), 2207 (CN), 1695 (C=O), 1641 (C=N), 1603 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): 8.37 (d, 1H, Ar); 7.86 (d, 2H, Ar); 7.76 (s, 1H, NH);7.58–7.07 (m, 6H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) 166.3 (C), 160.5 (C), 152.0 (C), 138.3 (C), 129.8 (CH), 128.4(CH), 128.0 (CH), 127.4 (C), 124.8 (CH), 121.7 (CH), 120.7 (CH), 115.5 (CH), 115.0 (C), 111.0 (CH), 79.0 (C3). MS (*m/z*): 286 (10) (M^+), 277(35), 236 (15), 207 (20), 186 (23), 133 (100), 115 (18),105 (80), 97 (27),91 (40), 83 (34),77 (45), 69(42),63 (29),55 (61), 43 (92). Anal. Calcd. For $C_{17}H_{10}N_4O$: C, 71.32; H, 3.52; N, 19.57%. Found: C, 71.15; H, 3.21; N,19.19.

2-(4-Methylphenyl)-4-oxo-4,10-dihydropyrimido [1,2-*a*] [1,3]benzimidazol-3-yl cyanide (3b). Yellow crystals. mp 300–302°C. IR (KBr, ν_{max}/cm^{-1}): 3291–2770 (broud, NH), 2208 (CN), 1698 (C=O), 1637 (C=N), 1605 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): 8.37 (d, 1H, Ar); 7.77 (d, 1H, Ar); 7.73 (s, 1H, NH); 7.56(d, 1H, Ar); 7.38(t, 1H, Ar); 7.32(d, 1H, Ar); 7.26–7.06 (m, 2H, Ar) 2.38 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) 166.3 (C), 160.5 (C), 162.7 (C), 152.2 (C), 139.7 (C), 135.4 (C), 128.6 (CH), 128.4 (CH), 124.8 (CH), 121.5 (CH), 120.8 (C), 115.3 (C), 115.0 (CH),

111.3 (CH), 75.4 (C3), 20.9 (CH_3). MS (*m/z*): 300 (25) (M^+), 272(20), 234 (8), 133 (100), 105 (80), 90 (15), 79 (35), 63 (20), 52 (28), 43 (18). Anal. Calcd. For $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66%. Found: C, 71.67; H, 4.15; N, 18.28.

2-(4-Methoxyphenyl)-4-oxo-4,10-dihydropyrimido[1, [1,2-*a*][1,3]benzimidazol-3-yl cyanide (3c). Yellow crystals. mp 291–294°C. IR (KBr, ν_{max}/cm^{-1}): 3303–2773 (broud, NH), 2206 (CN), 1698 (C=O), 1640 (C=N), 1606 (C=C). ^1H NMR (500 MHz, DMSO-d_6): 8.37 (d, 1H, Ar); 7.87 (d, 2H, Ar); 7.56 (s, 1H, NH); 7.62(d, 1H, Ar); 7.36(t, 1H, Ar); 7.24–7.04 (m, 3H, Ar); 3.83 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d_6) 165.5 (C), 160.6 (C), 152.85 (C), 152.55 (C), 130.04 (CH), 127.38 (C), 124.59 (CH), 121.13 (CH), 120.51 (C), 119.38 (C), 115.42 (C), 114.88 (CH), 113.38 (CH), 111.28 CH), 78.45 (C3), 55.22 (CH_3). MS (*m/z*): 316 (12) (M^+), 301(5), 133 (100), 105 (90), 90 (18), 79 (42), 63 (28), 50 (35), 43 (40). Anal. Calcd. For $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71%. Found: C, 68.09; H, 3.55; N, 17.34.

2-(4-Chlorophenyl)-4-oxo-4,10-ihydropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanide (3d). Pale yellow crystals. mp 304–306°C. IR (KBr, ν_{max}/cm^{-1}): 3295–2769 (broud, NH), 2207 (CN), 1700 (C=O), 1639 (C=N),1604 (C=C). ^1H NMR (500 MHz, DMSO-d_6): 8.37 (d, 1H, Ar); 7.87 (d, 2H, Ar); 7.80 (s, 1H, NH); 7.57(d, 2H, Ar); 7.37(t, 1H, Ar); 7.26–7.09 (m, 2H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) 164.8 (C), 160.5 (C), 162.9 (C), 151.8 (C), 137.2 (C), 134.5 (C), 130.3 (CH), 128.1 (CH), 124.7 (C), 121.8 (CH), 120.7 (CH), 115.8 (C), 114.9 (CH), 111.3 (CH), 79.0 (C3). MS (*m/z*): 322 (5) (M+2), 320 (9) (M^+), 316 (15), 282 (50), 277 (100), 201 (27), 183 (30), 152 (20), 77 (37), 51 (30). Anal. Calcd. For $C_{17}H_9ClN_4O$: C, 63.66; H, 2.83; Cl, 11.05; N, 17.47 %. Found: C, 63.30; H, 2.52; Cl, 10.73; N, 17.05.

2-(2,4-Dichlorophenyl)-4-oxo-4,10-dropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanide (3e). Yellow crystals. mp 298–300°C. IR (KBr, ν_{max}/cm^{-1}): 3282–2726 (broud, NH), 2218 (CN), 1698 (C=O), 1661 (C=N), 1604 (C=C). ^1H NMR (500 MHz, DMSO-d_6): 8.38 (d, 1H, Ar); 8.13 (s, 1H, NH); 7.76 (s, 1H, Ar); 7.61–7.14 (m, 5H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) 164.3 (C), 159.8 (C), 153.3 (C), 151.3 (C), 137.0 (C), 134.2 (C), 131.4 (CH), 128.9 (CH), 127.3 (CH), 124.6 (C), 122.3 (CH), 120.6 (CH), 116.4 (C), 114.9 (C), 111.3 (CH), 80.7 (C3). MS (*m/z*): 355 (8) (M^+), 354 (29), 277 (38), 264 (32), 148 (20), 133 (100), 105 (90), 91 (30), 79 (60), 69 (43), 57 (66), 43 (84). Anal. Calcd. For $C_{17}H_8Cl_2N_4O$: C, 57.49; H, 2.27; Cl, 19.96; N, 15.77 %. Found: C, 57.18; H, 2.05; Cl, 19.58; N, 15.43.

4-Oxo-2-[4-(trifluoromethyl)phenyl]-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazol-3-yl cyanide (3f). Yellow crystals. dc 310°C. IR (KBr, ν_{max}/cm^{-1}): 3414–3200 (broud, NH), 2206 (CN), 1694 (C=O), 1638 (C=N), 1605 (C=C). ^1H NMR (500 MHz, DMSO-d_6): 8.38 (d, 1H, Ar); 8.04 (d, 2H, Ar); 7.96 (s, 1H, NH); 7.87(d, 2H, Ar); 7.59(d, 1H, Ar); 7.38(t, 1H, Ar); 7.28–7.08 (m, 1H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) 164.5 (C), 160.6 (C), 153.3 (C), 142.4 (C), 132.1 (C), 129.6 (q, $^2J_{C-F}$ 32.50 Hz, C), 129.6 (CH), 127.66 (C), 126.32 (q, $^1J_{C-F}$ 287.50 Hz, CF3), 125,2 (CH), 124.53 (CH), 121.85 (CH), 120.54 (C), 114.96 (CH), 111.29 (CH), 78.42 (C3). MS (*m/z*): 354 (80) (M^+), 326(15), 300 (15), 159 (25), 133 (100), 105 (38), 90 (25), 79 (18), 63 (15), 51 (15), 43 (24). Anal. Calcd. For $C_{18}H_9F_3N_4O$: C, 61.02; H, 2.56; N, 15.81%. Found: C, 60.79; H, 2.25; N, 15.45.

4-Amino-2-phenyl-2,10-dihydropyrimido[1,2-*a*][1,3] [1,3] benzimidazol-3-yl-cyanide (4a). White crystals, mp 201–203°C; ν_{max}(KBr): 3350, 3110 (broad, NH2, NH), 2175 (CN), 1650, 1620(C=N) cm^{-1}; δ_H (500 MHz, DMSO -d_6): 8.57(1H, s, NH), 8.07–6.99(9H, m, Ar), 6.78(2H, s, NH2), 5.20(1H, s, CH). δ_C (125 MHz, DMSO-d_6): 151.7 (C), 149.1(C), 143.6 (C), 142.8 (CH), 129.3 (C), 128.6 (CH), 127.8 (CH), 125.8 (CH), 123.3 (C), 119.8 (CH), 119.1(C), 116.0 (CH), 112.3 (CH), 61.9 (C3), 53.2 (C2). MS, *m/z* (%): 287 (M^+, 30), 286 (30), 210 (base beak, 100), 133 (90), 105 (17), 90(20), 77(28), 51(18), 43(27). Anal.Calcd. For $C_{17}H_{13}N_5$: C, 71.07; H, 4.56; N, 24.37 %. Found: C, 70.75; H, 4,38; N, 24.06.

4-Amino-2-(4-chlorophenyl)-2,10-dihydropyrimido [1,2-*a*][1,3]benzimidazol-3-yl cyanide (4b). White crystals, mp 209–210°C; ν_{max}(KBr): 3438, 3336, 3100 (broad, NH2, NH), 2187(CN), 1676, 1651(C=N) cm^{-1}; δH (500 MHz, DMSO-d_6):8.58(1H, s, NH), 7.64–6.98 (8H, m, Ar), 6.83(2H, s, NH2), 5.25(1H, s, CH). δ_C (125 MHz, DMSO-d_6): 151.5 (C), 149.2(C), 143.5 (C), 141.7 (C), 132.4 (CH), 129.2 (CH), 128.6 (CH), 127.9 (C), 123.3 (CH), 119.9 (CH), 118.9 (C), 118.1 (CH), 112.4 (C), 61.5 (C3), 52.6 (C2). MS, *m/z* (%): 321(M+, 8), 306(12), 230(32), 216(30), 188(35), 171(15), 119(23), 105(base beak, 100), 91(85), 77(45), 57(27), 51(18), 43(84), 41(19). Anal.Calcd. For $C_{17}H_{12}ClN_5$: C, 63.46; H, 3.76; N, 21.77 %. Found: C, 63.20; H, 3.39; N, 21.43.

General procedure for the preparation of *N*-(1,3-benzoimidazol-2-yl)-*N*-(alkylidene)amines (5a,b). The reactions were carried out in a standard round bottom glass flask equipped with a vertical condenser under thermal conditions. Reactions were performed with arylaldehydes **2** (2 mmol), 2-aminobenzoles **1a, b** (2 mmol) in acetonitrile (40 mL) under stirring at refluxing temperature for 1 hr. The final reaction mixture was cooled, the precipitate was filtered and recrystallized from ethanol to afford desired product **5** [23].

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