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Silica sulfuric acid/ethylene glycol as an efficient catalyst for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives

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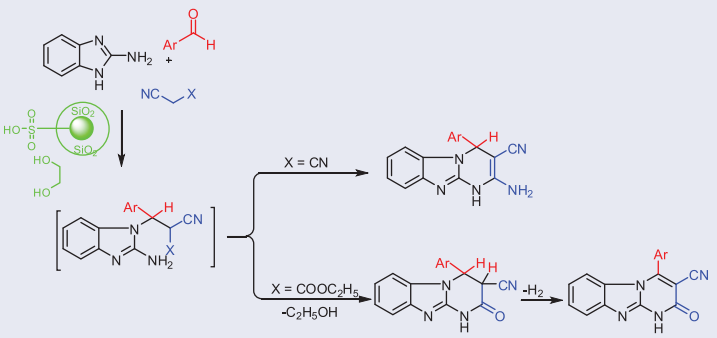
ABSTRACT

A simple and efficient eco-friendly method was developed for the synthesis of new benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives in excellent yields. The synthesis was achieved through the reaction of 2-aminobenzimidazole, aldehydes and active nitriles (malononitrle or ethyl cyanoacetae) in the presence of silica sulfuric acid/ethylene glycol. This protocol offers very short reaction times (in some cases, reaction times were reduced to five minutes), high yields and low cost. This method thus provides an improvement over the existing methods.

GRAPHICAL ABSTRACT



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2-Aminobenzimidazole; benzo[4,5]imidazo[1,2-a]pyrimidine; nitrile compounds; silica sulfuric acid

Introduction

Most of natural and synthetic heterocyclic compounds have been identified as potential drug candidates with a wide range of biological activities.[1–6] Therefore, the organic chemistry was interested in the synthetic community of medicinal chemistry, combinatorial chemistry and diversity oriented synthesis was directed to develop new and an efficient synthetic methods for heterocyclic compounds.[7–11]

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Upon a comprehensive survey for the methods of preparation of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives, we found that the most methods are the one-pot three-component condensation reactions of aminobenzimidazole, aldehydes and dicarbonyl compounds (or active nitrles) in the presence of catalysts.[12–15] However, some of these methodologies suffer from disadvantages, such as low yields, use of high boiling solvents, excess of catalyst or special apparatus. Also, to our knowledge, ethyl cyanoacetate was not used as active nitrle in this one-pot three-component reaction. Thus, we decided to investigate a new, efficient, and an convenient method for building new types of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives.

Recently, there are interesting for the development of efficient methodologies that are environmentally benign. The usage of catalysts has received great interest in the various organic syntheses. Solid supported reagents are useful technique to improve the activity and selectivity of the individual reagents, because this technique increase the surface area of the reagent to manifold.[16] Silica sulfuric acid as solid acid is a versatile catalyst. They make reaction processes more economic, more convenient and environmentally benign.

Silica sulfuric acid (SSA) successfully used as efficient heterogeneous catalysts for many organic transformations due to different factors such as ease of preparation, low cost, recycling and eases of handling. Owing to the numerous advantages associated with this cheap and nonhazardous catalyst, under mild conditions, silica sulfuric acid has been explored as a powerful catalyst for various organic transformations.[17]

We are reported the development of silica sulfuric acid as a simple and efficient catalyst for the synthesis of tricyclic and tetarcyclic dihydropyrimidine derivatives,[18] highly substituted piperidines[19] and 3,4,5-trisubstituted 2(5 H)-furanone derivatives[20] by a one-pot multicomponent reaction under mild conditions. This reaction can be regarded as an efficient approach for the preparation of synthetically and pharmaceutically important compounds. This one-pot reaction has some important advantages such as easy workup procedure, simple and readily available precursors, nontoxic and inexpensive catalyst, and good to excellent yields.

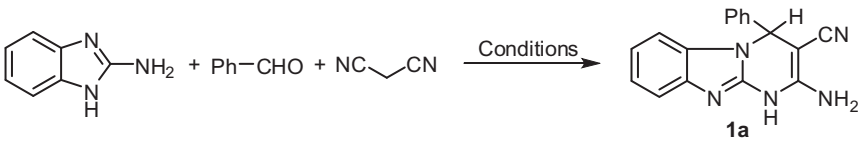
This solid acid has also been used in synthesis of synthesis of substituted pyrroles,[21] synthesis of 2,3-dihydroquinazolin-4(1H)-ones,[22] oxazolines and imidazolines,[23] deprotection of oxime to carbonyls[24] and chemoselective detritylation of 5′-tritylated nucleosides.[25]

On the other hand, in modern organic synthesis, traditional volatile organic reaction solvents are continuously replaced by environmentally benign solvents or used solvent-free techniques for the syntheses of various heterocyclic compounds.[26–28]

In view of these facts and as a continuation of our previous efforts to develop new synthetic methodologies, development of synthetic method that afforded high yields of the target products by investigating new, convenient and efficient method for building new types of benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives was aimed to investigate.

Result and discussion

In order to optimize the reaction conditions, 2-aminobenzimidazole, benzaldehyde, and malononitrile were taken as model substrates (Scheme 1). In the initial study, when



Scheme 1. Optimization of reaction conditions for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile **1a**.

Table 1. Results of benzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carbonitrile **1a** with different catalysts and solvents.

Entry	Catalyst (mol)	Solvent/ °C	Time (min)	Yield (%)
1	None	$(CH_2OH)_2$/120	90	50
2	PPA/SiO_2 (0.11)	$(CH_2OH)_2$/120	10	84
3	$HClO_4/SiO_2$ (0.11)	$(CH_2OH)_2$/120	10	90
4	**SSA (0.11)**	**$(CH_2OH)_2$/120**	**5**	**97**
5	SSA (0.11)	H_2O/ reflux	30	72
6	SSA (0.11)	MeOH/reflux	60	77
7	SSA (0.11)	EtOH/reflux	10	84
8	SSA (0.11)	$CHCl_3$/reflux	10	74
9	SSA (0.11)	DMF	90	77
10	SSA (0.15)	$(CH_2OH)_2$/120	5	90
11	SSA (0.05)	$(CH_2OH)_2$/120	5	84
12	SSA (0.025)	$(CH_2OH)_2$/120	5	87

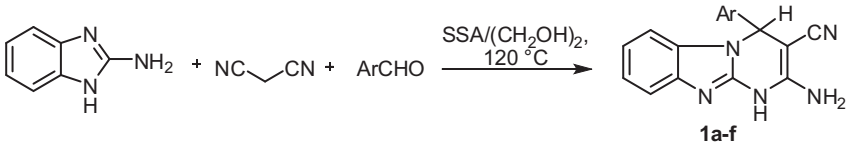
2-aminobenzimidazole was left to react with benzaldehyde and malononitrile in ethylene glycol without catalyst (Table 1, entry 1); it was found that, the desired product benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (**1a**) was obtained in low yield (50%) even at prolonged reaction time.

As shown in Table 1, different catalysts and solvents were investigated with regard to the best yield and low reaction times for the synthesize 2-amino-4-phenyl-1,4-dihydrobenzo[4,5]-imidazo[1,2-*a*]pyrimidine-3-carbonitrile **(1a)**. The reaction was carried out by using various catalysts (namely PPA/SiO_2, $HClO_4/SiO_2$ and SSA) alone to set up standard reaction conditions in order to obtain the best catalyst as shown in Table 1. From the obtained results, it was found that, the best catalyst in terms of yield and reaction time was silica sulfuric acid (Table 1, entry 4). The attention was then focused toward the effect of solvents on the yield of the one-pot assembly of the model. Replacing ethylene glycol by H_2O, CH_3OH, C_2H_5OH, $CHCl_3$, or DMF (Table 1, entry 5-9, respectively) produced the model **1a** in yields lower than that of entry 4. Moreover, upon studying the efficacy of the ratio of the catalyst (0.11, 0.15, 0.05, 0.025 mol) it was noticed that 0.11 mol of the catalyst was the optimum ratio (Table 1, entry 4). Optimized condition was established in ethylene glycol as a solvent, it gave the best result with 97% yield of the required benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile **1a** (Table 1, entry 4). This remarkable activation in reaction rate prompted us to explore the potential of this protocol for the synthesis of other 2-amino-4-aryl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carbonitrile derivatives.

Under optimized reaction conditions, the reusability of silica sulfuric acid was examined. The silica sulfuric acid is exists in the solid state and easily separated from reaction mixture simply by filtration. The catalyst was washed with ethyl acetate and diethyl

Table 2. The effect of reusability of SSA catalyst on the benzo[4,5] imidazo[1,2-a]-pyrimidine-3-carbonitrile **1a** yield.

Number of uses	Time (min)	Yield (%)
1	5	97
2	5	97
3	6	95
4	8	93



Scheme 2. Reaction of 2-aminobenzimidazole and aldehydes with malononitrile.

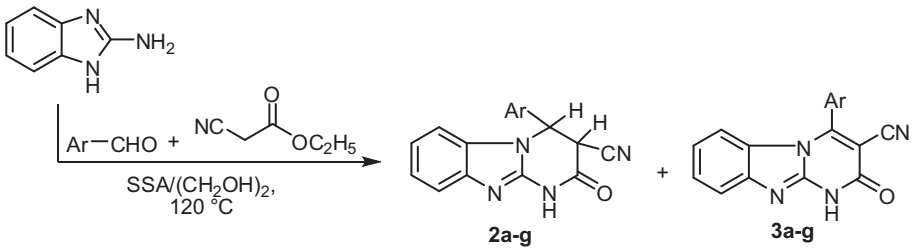
Table 3. Reaction times and yields of the synthesis of 2-amino-benzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carbonitriles **1a–f**.

			Found		Reported	
Entry	Compd. No.	Ar	Time (min)	Yield %	Time (min)	Yield %
1	**1a**	Ph	5	97	6	90[29]
					2	92[15]
					3	91[30]
2	**1b**	4-FC_6H_4	5	86	3	87[29]
					5	90[15]
					3	91[30]
3	**1c**	4-OHC_6H_4	15	83		
4	**1d**	3-$OCH_3C_6H_4$	10	83		
5	**1e**	2,5-$(OCH_3)_2$-C_6H_3	15	97		
6	**1f**	naphthalen-2-yl	15	97	3	92[29]
					3	92[30]

ether and a fresh reaction was then performed under the same condition. The silica sulfuric acid could be used for at least four times without significant loss in product yield (Table 2).

The scope and limitations of the present three-component reaction under optimized conditions were explored using a variety of aldehydes. Thus, 2-aminobenzimidazole and malononitrile were reacted with different aldehydes to afford the corresponding 2-amino-4-aryl-1,4-dihydro benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **1a-f** in good yields (83–97%) as shown in Scheme 2 and Table 3. Under identical conditions, heterocyclic aldehydes such as 5-methylfuranal and 2-thiophene aldehyde gave none of the corresponding 2-amino-4-hetrocycles-1,4-dihydro benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives.

Structure of the synthesized products **1a–f** was deduced on the basis of IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analyses. Thus, their IR spectra exhibited characterized absorption bands in 3480–3137 cm^{-1} region corresponding to NH & NH_2 functional groups. Moreover, IR spectra exhibited strong absorption band around 2180 cm^{-1} due to cyano functional group. ^{1}H NMR spectrum of **1e** as representative example exhibited two singlet signals at: $\delta = 3.60$ and 3.66 ppm for two methoxy protons, signal



Scheme 3. Reaction of 2-aminobenzimidazole and aldehydes with ethyl cyanoacetate.

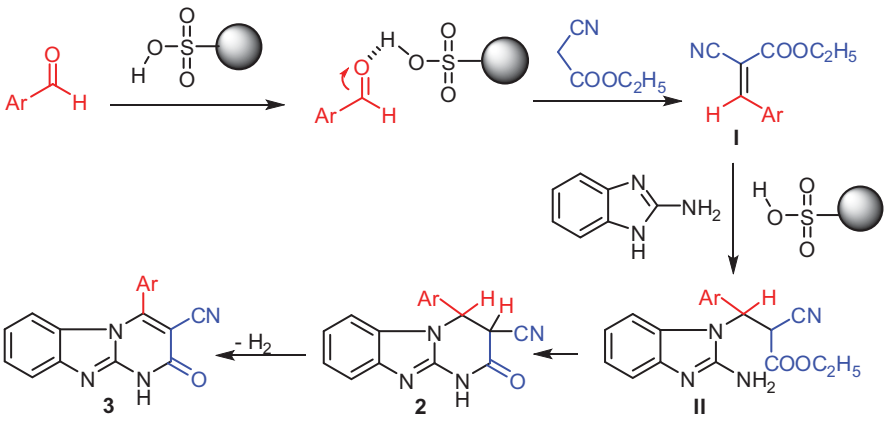
Table 4. Reaction times and yields of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **2a–g** and **3a–g**.

Entry	Ar	Time (min)	Compd. No.	Yield %
1	Ph	35	**2a**	50
			3a	18
2	4–FC_6H_4	35	**2b**	44
			3b	19
3	3–ClC_6H_4	35	**2c**	0
			3c	83
4	3–$OCH_3C_6H_4$	50	**2d**	47
			3d	16
5	2,5–$(OCH_3)_2$–C_6H_3	80	**2e**	51
			3e	0
6	3–$NO_2C_6H_4$	10	**2f**	58
			3f	37
7	naphthalen-2-yl	60	**2g**	73
			3g	9

at: $\delta = 5.34$ ppm for CH proton of the pyrimidine ring (H-4). Also, the spectrum revealed the presence of two broad signals at: $\delta = 6.73$ and 8.28 ppm for the NH_2 and NH protons, respectively. ^{13}C NMR spectrum supported these assignments and added a strong evidence for these interpretations; where, ^{13}C NMR spectrum revealed signals at: 55.7 and 56.3 ppm assigned to two methoxy carbons and signal at 49.5 ppm assigned to CH carbon of pyrimidine ring (H-4).

Regarding to the effect of the aromatic aldehydes: The presence of 2,5-dimethoxyphenyl moiety (Table 3, entry 5) resulted the higher yield of the product (**1e**; 97%) with compared to other aryl moieties followed by phenyl moiety (entry 2, **1a**; 96%). 3-methoxyphenyl moiety (**1d**, entry 4) had the same behavior of 4-hydroxyphenyl moiety (**1c**, entry 3) towards this reaction (83%). 4-Fluorophenyl moiety (**1b**, entry 2) showed result (86%). Naphthyl moiety (**1f**, entry 6) had the same behavior of 2,5-dimethoxyphenyl moiety towards this reaction (97%).

A plausible reaction mechanism was suggested in which silica sulfuric acid can serve as a Lewis acidic catalyst for Knoevenagel condensation of activated aldehyde with malononitrile which leads to the formation of 2-arylidenemalononitrile intermediates. 2-Amino benzimidazole was reacted with the latter intermediates in the Michael way to generate intermediates, which subjected to cyclization, leading to the formation of the desired 2-amino-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **1a–f** (Table 4).



Scheme 4. A plausible mechanism for the one-pot synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **2a–g** and **3a–g**.

After the successful application of silica sulfuric acid/ethylene glycol in the synthesis of 2-amino-4-aryl-1,4-dihydrobenzo[4,5]- imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **1a–f**, this catalyst was also applied in the three-component condensation of ethyl cyanoacetate with 2-aminobenzimidazole and different aldehydes, leading to two products, as shown in Scheme 3. Structures of the obtained products were elucidated by careful inspection of their spectral data. IR spectra showed bands for cyano group. ^{1}H NMR spectra showed absence of the ester and amino groups. The obtained products were confirmed as 1,2,3,4-tetrahydrobenzo [4,5]imidazo[1,2-*a*]-pyrimidine-3-carbonitrile derivatives **2a–g** and their oxizied form 1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine-3-carbonitrile derivatives **3a–g**. In all cases (except 3-chlorobenzaldehyde), the majority products were the 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **2** while 1,2-dihydrobenzo[4,5]imidazo [1,2-*a*]pyrimidine-3-carbonitrile derivatives **3** were observed as a sole product in case of product **3c**. Under identical conditions, heterocyclic aldehydes such as 5-methylfuranal and 2-thiophene aldehyde gave none of the corresponding benzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives.

Structures of products **2a–g** and **3a–g** were deduced on the basis of IR, ^{1}H & ^{13}C NMR spectroscopy and correct elemental analyses. IR spectrum of **2d**, as representative example, exhibited the absorption bands at 3432, 2232 and 1675 cm^{-1} for imino, cyano and carbonyl functional groups, respectively. ^{1}H NMR spectrum of **2d** as representative example exhibited singlet signal at: $\delta = 3.83$ ppm for methoxy protons. CH protons of pyrimidine ring (H-3 and H-4) were observed as two doublet signals at: $\delta = 5.89$ and 7.49 ppm while in ^{1}H NMR spectrum of **3d**, CH proton signals of pyrimidine ring were not observed. ^{13}C NMR spectra for the products **2** and **3** supported these assignments and added a strong evidence for these interpretations.

The plausible reaction mechanism (Scheme 4) was suggested in which silica sulfuric acid can serve as a Lewis acidic catalyst for Knoevenagel condensation of the aldehyde with ethyl cyanoacetate which lead to the formation of arylidene ethyl cyanoacetate intermediates **I**. The imino-group of the 2-aminobenzimidazole was reacted with the latter intermediates in the Michael way, leading to generate the intermediates **II**, which

subjected to loss a molecule of ethanol (from reacting the amino- group with the ester- group) to form the intermediates which undergoes cyclization, leading to formation of the desired products 2-oxo-4-aryl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **2a–g** which underwent dehydrogenation afforded the 2-oxo-4-aryl-1,2-dihydrobenzo[4,5]- imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives **3a–g**.

Conclusion

In conclusion, the present investigation demonstrated a novel catalyst (Silica sulfuric acid/ethylene glycol) for the synthesis of benzo[4,5] imidazo[1,2-*a*]pyrimidine-3-carbonitrile. Silica sulfuric acid/ethylene glycol catalyst was able to modify the reaction protocol and successfully benzo[4,5] imidazo[1,2-*a*]pyrimidine-3-carbonitrile derivatives were obtained in high yield and high purity with short reaction times *via* the three-component condensation reactions of 2-aminobenzimidazole, aldehydes and active nitriles (malononitrle or ethyl cyanoacetae). Silica sulfuric acid/ethylene glycol catalyst offer several advantages such as simplicity, mild reaction conditions, high yields, and little environmental impact. Hence, it can be applied for the synthesis of other heterocyclic compounds.

Experimental section

General procedure for synthesis of the 2-amino-benzo [4,5]imidazo[1,2-a] pyrimidine-3-carbonitrile derivatives 1a-f

To the mixture of 2-aminobenzimidazole (1 mmol), malononitrile (1 mmol) and the desired aldehyde (namely benzaldehyde, 4-fluorobenzaldehyde, 4-hydroxybenzaldehyde, 3-methoxybenzaldehyde, 2,5-dimethoxybenzadehyde and 2-naphthaldehyde) (1 mmol) in ethylene glycol (5 mL), SSA (42.6 mg, 0.11 mol %) was added. The mixture was heated at 120 °C for an appropriate time (Table 2). After completion of the reaction (TLC), 10 mL EtOAc was added to the reaction mixture and the catalyst was recovered by filtration. The organic layer was dried over Na_2SO_4; the solvent was evaporated and purified by recrystallization from ethanol to give compounds **1a–g**

2-Amino-4-(4-hydroxyphenyl)-1,4-dihydrobenzo[4,5] imidazo[1,2-a]pyrimidine-3-carbonitrile (1c)

Yield 83%; m.p. 222 °C; IR: ν/cm^{-1}: 3481, 3382, 3326 (OH, NH_2 & NH), 2911 (CH_{-aliph}), 2188 (C≡N), 1679 (C = N); ^{1}H NMR (400 MHz, DMSO): δ/ppm = 5.13 (s, 1H, CH), 6.75 (m, 3H, Ar-H & NH_2), 6.94 (m, 1H, Ar-H), 7.00 (t, 1H, Ar-H), 7.11 (d, 2H, Ar-H), 7.21 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 7.85 (d, 1H, Ar-H), 8.58 (br, 1H, OH); ^{13}C NMR (101 MHz, DMSO): 53.5, 63.1, 112.8, 115.8 (2C), 116.5, 119.7, 120.3, 123.8, 127.8 (2C), 129.8, 133.6, 144.1, 149.4, 152.3, 157.6; Anal. calcd for $C_{17}H_{13}N_5O$ (303.32): C, 67.32; H, 4.32; N, 23.09; Found: C, 67.46; H, 4.29; N, 22.98%

General procedure for the synthesis of the 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile derivatives 2a-g and 1,2-dihydrobenzo[4,5]imidazo[1,2-a] pyrimidine-3-carbonitrile derivatives 3a-g

To the mixture of 2-aminobenzimidazole (1 mmol), ethyl cyanoacetate (1 mmol) and the desired aldehyde (namely benzaldehyde, 4-fluorobenzaldehyde, 3-chlorobenzaldehyde, 3-methoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, 3-nitrobenzaldehyde or 2-naphthaldehyde) (1 mmol) in ethylene glycol (5 mL), SSA (42.6 mg, 0.11 mol %) was added. The mixture was heated at 120 °C for an appropriate time (Table 3). After completion of the reaction (TLC), 10 mL EtOAc was added to the reaction mixture and the catalyst was recovered by filtration. The organic layer was dried over Na_2SO_4; the solvent was evaporated. The mixture of two products was separated by column chromatography on silica-gel using pet. ether/ethyl acetate (60/40) as eluent.

4-(3-Methoxyphenyl)-2-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a] pyrimidine-3-carbonitrile (2d)

Yield 47%; m.p.323 °C; IR: ν/cm^{-1}: 3432 (NH), 2923 ($CH\text{-}_{aliph}$), 2232 (CN), 1675 (C=O), 1601 (C=N); ^1H NMR (400 MHz, DMSO): δ/ppm = 3.83 (s, 3H, OCH_3), 5.89 (d, 1H, $J = 8.2$ Hz, CH), 6.96 (t, 1H, $J = 7.7$ Hz,), 7.10–7.40 (m, 7H, Ar-H + NH), 7.49 (d, 1H, $J = 7.8$ Hz, CH), 7.67 (t, 1H, $J = 7.8$ Hz, Ar-H); ^{13}C NMR (101 MHz, DMSO): 56.0, 113.2, 114.1, 115.2, 117.8, 120.5, 122.2, 126.2, 127.9, 130.9, 131.6, 148.9, 155.8, 160.2; Anal. Calcd for $C_{18}H_{14}N_4O_2$ (318.33): C, 67.91; H, 4.43; N, 17.60; Found: C, 68.07; H, 4.39; N, 17.72%.

4-(3-Methoxyphenyl)-2-oxo-1,2-dihydropyrimido[1,2-a]benzimidazole-3-carbonitrile (3d)

Yield 16%; m.p. 294 °C; IR: ν/cm^{-1}: 3301 (NH), 2204 (C≡N), 1694 (C=O), 1637 (C=N); ^1H NMR (400 MHz, DMSO): δ/ppm = 3.83 (s, 3H, OCH_3), 7.11 (m, 2H, Ar-H), 7.20–7.30 (m, 2H, Ar-H), 7.37–7.50 (m, 2H, Ar-H), 7.61 (d, 1H, $J = 7.9$ Hz, Ar-H), 8.03 (br, 1H, NH), 8.41 (d, 1H $J = 7.9$ Hz, Ar-H); ^{13}C NMR (101 MHz, DMSO): 55.7, 80.0, 111.8, 114.3, 115.6, 116.1, 119.5, 121.3, 122.5, 125.4, 127.9, 129.8, 132.3, 140.0, 152.2, 153.3, 159.4, 161.0, 166.6; Anal. Calcd for $C_{18}H_{12}N_4O_2$ (316.31): C, 68.35; H, 3.82; N, 17.71; Found: C, 68.43; H, 3.78; N, 17.58%.

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