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Silica Sulfuric Acid / ethylene Glycol: An Efficient Eco-friendly Catalyst for One-pot Synthesis of Tricyclic and Tetarcyclic Dihydropyrimidine Derivatives

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A SIMPLE and efficient eco-friendly chemical method was developed for the synthesis of series of tricyclic and tetarcyclic dihydropyrimidine derivatives in excellent yields using a one-pot, multi-component reaction in the presence of catalyst silica sulfuric acid / ethylene glycol. Tricyclic dihydropyrimidine derivatives (benzo[4,5]imidazo[1,2-*a*] pyrimidines derivatives) were synthesized in high yield and high purity in short reaction times by the reaction of 2-aminobenzimidazole, aldehydes and ethyl acetoacetate in the presence of silica sulfuric acid / ethylene glycol. Tetracyclic dihydropyrimidine derivatives (benzo[4,5]imidazo[1,2-*a*]pyrimido[4,5-*d*]pyrimidin-4(1*H*)-ones) were synthesized by the reaction of 2-aminobenzimidazole, aldehydes and cyanoacetamide in the presence of Silica sulfuric acid / ethylene glycol. This present new protocol offers shorter reaction time, high yields and low cost. This method provides much improved protocol over the already existing methods.

Keywords: Silica sulfuric acid/ethylene glycol, Dihydropyrimidine derivatives Benzo[4,5] imidazo[1,2-*a*]pyrimidine, 2-Aminobenzimidazole.

Introduction

Development of efficient, practical and environment friendly methods of synthesis is one of the main priorities for modern organic chemistry [1,2]. Recently, the silica sulfuric acid (SSA) catalyzed multi-component reaction has been applied [3-6].

Dihydropyrimidine derivatives have attracted much attention as important structural motifs in medicinal chemistry. They have significant therapeutic and biological activities, such as T cell activation [7], antineoplastic activity [8], as well as DNA-topoisomerase I [9], TIE-2 and VEGFR2 inhibitory activities [10]. Moreover, benzo[4,5]imidazo[1,2-a]pyrimidine derivatives have pharmacological and therapeutic properties [11,12].

Upon a comprehensive survey for the methods of preparation of benzo[4,5]imidazo[1,2-a] pyrimidine derivatives, we found that the their synthesis could be carried out in two ways. The first way involved the reaction of a ketoester with an aldehyde followed by condensation with 2-aminobenzimidazole to give the target products [13-15]. The second way was the most common and involved the one-pot three-component condensation reactions of dicarbonyl compounds, aldehydes and 2-aminobenzimidazole in the presence of ionic liquid [16-18], ionic liquid-supported nanoporous silica (SBA-IL) [19], thiamine hydrochloride [20], p-toluenesulfonic acid [21], N,N,N',N'-tetrabromobenzene-1,3-disulfonamide (TBBDA) [22], melamine trisulfonate [23], poly(vinylpyrrolidonium) perchlorate [24], N,N'-dichlorobis(2,4,6-

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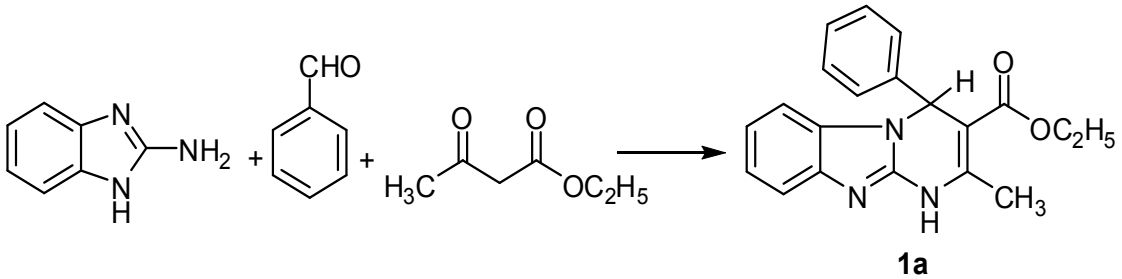
trichlorophenyl) urea [25], H_2NSO_3H [26], irradiation microwave [27,28], Fe_3O_4@silica sulfuric acid [29], $Zn(ClO_4)_2 \cdot 6H_2O$ [30], H_3BO_3 [31], zirconium sulfophenylphosphonate [32] and silica sulfuric acid [33]. This reaction can also be carried out under catalyst-free conditions [34]. However, some of these methodologies suffer from disadvantages, such as low yields, use of high boiling solvents, excess of catalyst or special apparatus. Thus, we decided to investigate a new, efficient, and a convenient method for building new important types of benzo[4,5]imidazo[1,2-a] pyrimidine derivatives.

Result and Discussion

As shown in Scheme 1, in order to optimize the reaction conditions, 2-aminobenzimidazole, benzaldehyde, and ethyl acetoacetate were taken as model reactants. In the initial study, when 2-aminobenzimidazole left to react with benzaldehyde and ethyl acetoacetate in ethylene glycol without catalyst (Table 1, entry 1); it was found that the synthesis of ethyl 2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a] pyrimidine-3-carboxylate (1a) was obtained at prolonged reaction time with low yield.

Different catalysts and solvents were investigated with regard to the best yield and low reaction times for the synthesis of ethyl 2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*] pyrimidine-3-carboxylate (**1a**). The reaction was carried out by using different catalysts, namely silica-supported polyphosphoric acid (PPA-SiO_2), perchloric acid adsorbed on silica-gel ($HClO_4SiO_2$) and silica sulfuric acid (SSA), to investigate the standard reaction conditions in order to find 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



Scheme 1. Optimization of reaction conditions for the synthesis ethyl 2-methyl-4-phenyl-1,4-dihydrobenzo[4,5] imidazo[1,2-a]pyrimidine-3-carboxylate (1a)

TABLE 1. Results of ethyl 2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a] pyrimidine-3-carboxylate (1a) with different catalyst and solvent

Entry	Catalyst (mmol)	Solvent/ °C	Time (min)	Yield (%)
1	None	$(CH_2OH)_2$/ 120	30	64
2	PPA/SiO_2	$(CH_2OH)_2$/ 120	30	69
3	$HClO_4SiO_2$	$(CH_2OH)_2$/ 120	30	67
4	**SSA (0.11)**	**$(CH_2OH)_2$/ 120**	**10**	**76**
5	SSA (0.11)	EtOH/ reflux	35	70
6	SSA (0.11)	MeOH/ reflux	60	67
7	SSA (0.11)	$CHCl_3$/ reflux	120	51
8	SSA (0.11)	H_2O/ reflux	60	51
9	SSA (0.11)	CH_3CN	60	63
10	SSA (0.15)	$(CH_2OH)_2$/ 120	10	67
11	SSA (0.05)	$(CH_2OH)_2$/ 120	10	75
12	SSA (0.025)	$(CH_2OH)_2$/ 120	10	71

solvents on the yield of the one-pot assembly of the model. Replacing ethylene glycol (EG) by water, methanol, ethanol or $CHCl_3$ (Table 1, entries 5, 6, 7, 8, respectively) produced the model **1a** in yields lower than that of EG. Moreover, upon studying the efficacy of the catalyst ratios (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 conditions were established in ethylene glycol as a solvent; this afforded the best result with 93% yield of the required ethyl 2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a] pyrimidine-3-carboxylate (**1a**) (Table 1, entry 4). Due to this remarkable activation, the potential of this protocol for the synthesis of other benzo[4,5] imidazo[1,2-*a*]pyrimidine derivatives were explored.

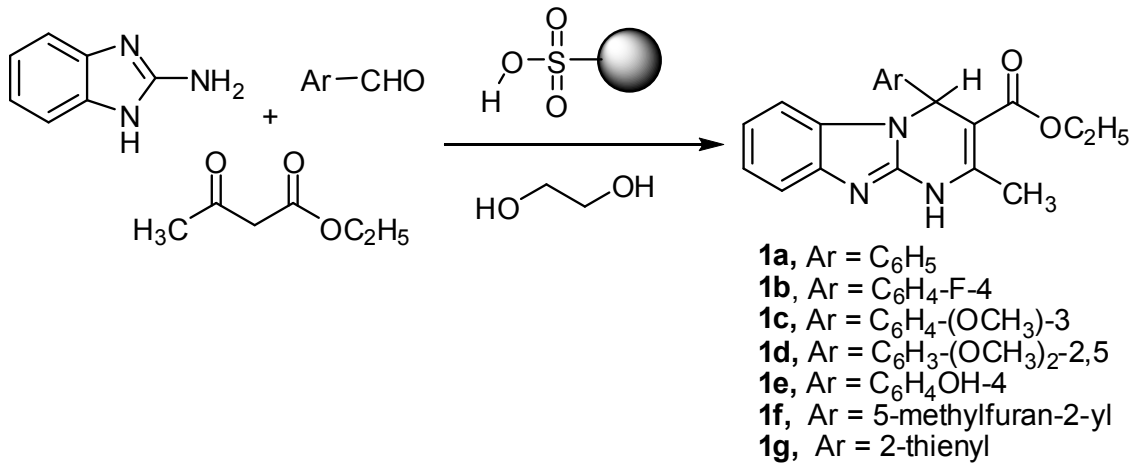
The scope and limitations of this three-component reaction under optimized conditions were explored using a variety of aromatic and heterocyclic aldehydes. Thus, 2-aminobenzimidazole and ethyl acetoacetate were reacted with different aldehydes in the presence of SSA/EG. The reactions were finished at the specified times and afforded the corresponding benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **1a-g** in good yields (70-94%) as shown in Scheme 2 and Table 2. Regarding the effect of the aromatic and heterocyclic aldehydes: the presence of 3-methoxyphenyl moiety (**1c**, Table 2, entry 3) afforded higher yield of product (94%) compared to other aryl moieties. The 2,5-dimethoxyphenyl moiety (**1d**, entry 4) and 4-hydroxyphenyl moiety (**1e**, entry 5) showed results 86 % and 88 %, respectively. Among substituted phenyl moiety, 4-fluorophenyl moiety (**1b**, entry 2) showed the lowest yield (71 %). 2-Thiophene aldehyde (**1g**, Table 2, entry 7) has the same behavior of 4-fluorophenyl moiety towards this reaction (about 70 %).

The structure of the obtained products was deduced on the basis of IR, ^{1}H & ^{13}C NMR spectroscopy and satisfactory elemental analyses. The ^{1}H NMR spectrum of **1f,** as a representative example, was characterized by the presence of triplet and quartet signals at δ: 1.28 and 4.24 ppm, respectively, due to ethyl protons, two singlet signals at δ = 2.18 and 2.75 ppm for the protons of two methyl groups. The CH proton of the pyrimidine ring (H-4) was observed as a singlet at δ = 6.52 ppm.

The attention was turned to a study the mechanistic aspect of this one-pot three component reaction. A plausible reaction mechanism (Scheme 3) was suggested in which SSA/EG can serve as a Lewis acidic catalyst for Knoevenagel condensation of activated aldehyde and with the tautomerized ethyl acetoacetate which lead to the formation of intermediate [**I**]. 2-Aminobenzimidazole was reacted with the latter intermediate by Michael addition, leading to generate the intermediate [**II**], which undergoes dehydration and cyclization by losing a molecule of water, giving the of desired benzo[4,5] imidazo[1,2-*a*]pyrimidine derivatives **1**.

In order to explore our method further, ethyl aetoacetate was replaced by cyanoacetamide. The 2-aminobenzimidazole, 4-fluorobenzaldehyde, and cyanoacetamide were taken as model reactants. As shown in Scheme 4, the product 2-amino-4-fluorophenyl -1,4-dihydrobenzo[4,5] imidazo[1,2-*a*]pyrimidine-3-carboxamide **2** was not obtained while in contrast, the product 2,5-bis(4-fluorophenyl)-2,3,5,12-tetrahydrobenzo[4,5] imidazo[1,2-a]pyrimido[4,5-d]pyrimidin-4(1*H*)-one **3a** was obtained. The probable reason for this phenomenon was that under these reaction conditions, compound **2** was able to easily react with another aldehyde to form **3a**.

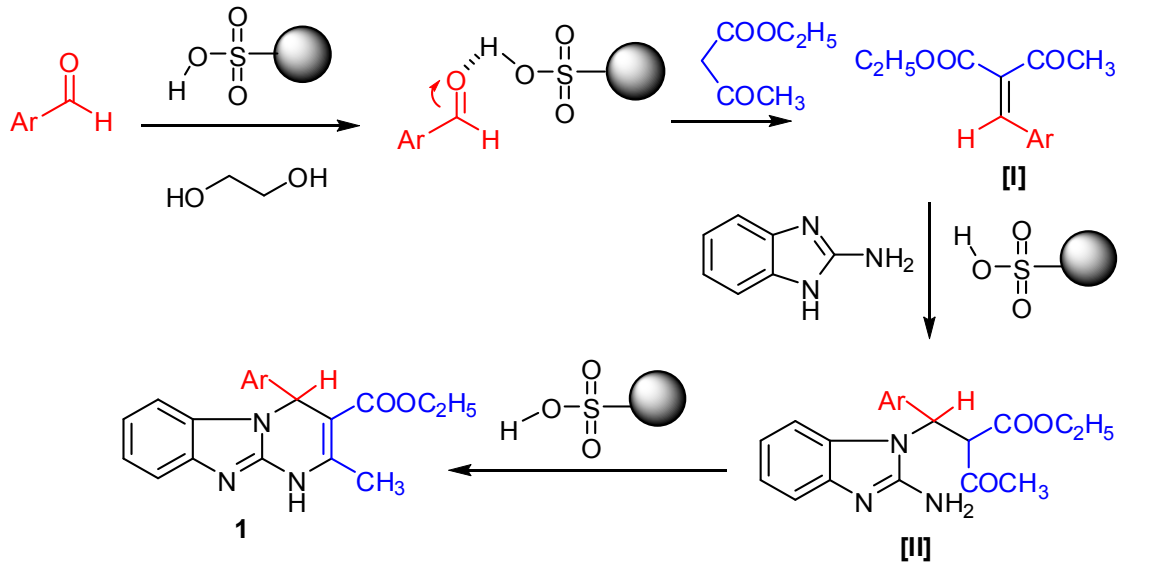
Only two papers [19, 36] have reported the preparation of benzo[4,5]imidazo[1,2-*a*]-pyrimido[4,5-d]pyrimidin-4(1H)-one derivatives. However, this methodology still has some disadvantages such as long reaction time. So, continuing this work on the multi-component synthesis of heterocyclic compounds with environmentally begin EG as a reaction medium was achieved. Different catalysts and solvents were investigated with regard to the best yield and low reaction time to synthesize 2,5-bis(4-fluorophenyl)-2,3,5,12-tetrahydrobenzo- [4,5] imidazo[1,2-*a*]pyrimido[4,5-d]pyrimidin-4(1*H*)-one **3a** where, the reaction was carried out using various catalysts (namely PPA/SiO_2, $HClO_4SiO_2$ or SSA) alone to set up standard reaction conditions in order to obtain the best catalyst as shown in Table **3**. From the obtained results, it was found that, the best catalyst in terms of yield and reaction time was silica sulfuric acid (Table **3**, entry 4). The attention was then focused toward the effect of solvent on the yield of the one-pot assembly of the model. Upon replacing ethylene glycol by water, methanol, ethanol or $CHCl_3$



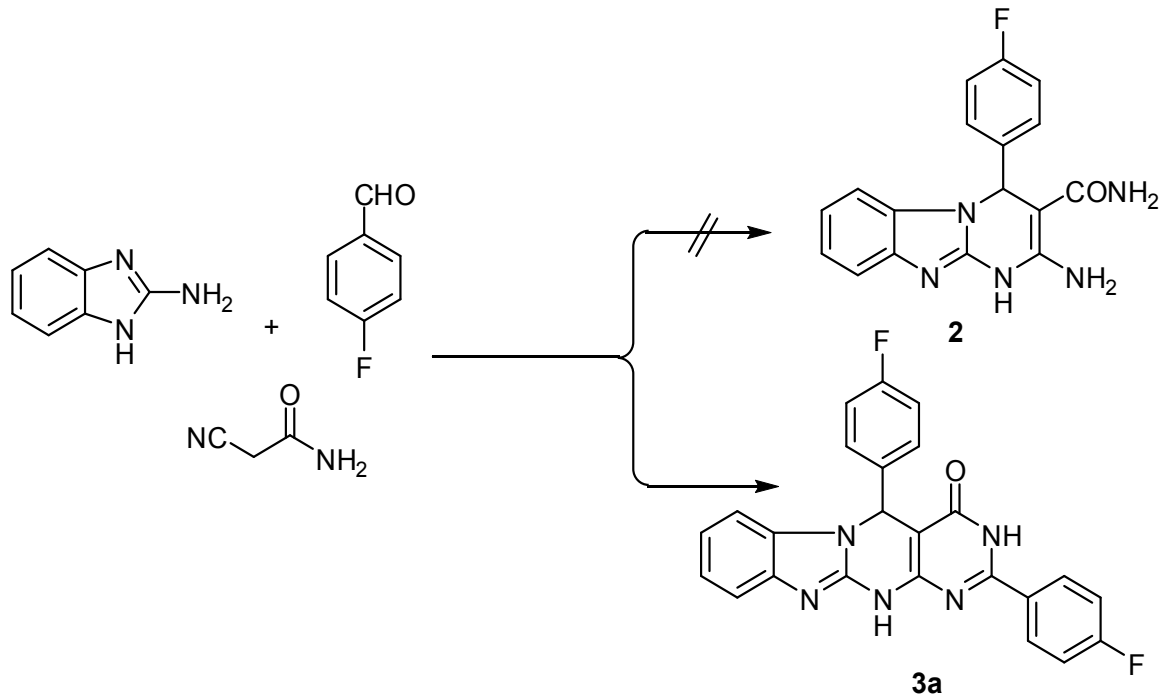
Scheme 2. One-pot synthesis of ethyl 4-aryl-2-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole-3-carboxylates 1a-g

TABLE 2. Reaction times and yields of ethyl 4-aryl-2-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole-3-carboxylates 1a-g

Entry	Compd. No.	Ar	Found		Reported	
			Time (min.)	Yield	Time (min.)	Yield
1	**1a**	Ph	10	76	45 40 8h 5h 6h	92 [24] 90 [36] 88 [35] 90 [28] 83 [16]
2	**1b**	4-FC_6H_4	30	71	7 5h 7h 6h	87 [35] 91 [28] 83 [16] 68 [25]
3	**1c**	3-$OMeC_6H_4$	35	94	40 35	95 [24] 87 [36]
4	**1d**	2,5-$(OMe)_2C_6H_3$	30	86		
5	**1e**	4-OHC_6H_4	25	88	6h 6h	71 [25] 64 [29]
6	**1f**	5-methylfuran-2-yl	30	76		
7	**1g**	2-thienyl	30	70	6h	71 [29]



Scheme 3. A plausible mechanism for the one-pot synthesis of ethyl 4-aryl-2-methyl-1,2,3,4-tetrahydropyrimido[1,2-a] benzimidazole-3-carboxylates



Scheme 4. the reaction of 2-aminobenzimidazole, 4-fluorobenzaldehyde, and cyanoacetamide

TABLE 3. Results of preparing 2,5-bis(4-fluorophenyl)-2,3,5,12-tetrahydrobenzo[4,5]- imidazo[1,2-a] pyrimido[4,5-d]pyrimidin-4(1H)-one 3a 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	87
3	$HClO_4$/SiO_2 (0.11)	$(CH_2OH)_2$/ 120	10	93
4	**SSA (0.11)**	**$(CH_2OH)_2$/ 120**	**1**	**99**
5	SSA (0.11)	H_2O/ reflux	30	75
6	SSA (0.11)	MeOH/ reflux	60	80
7	SSA (0.11)	EtOH/ reflux	10	87
8	SSA (0.11)	$CHCl_3$/ reflux	10	77
9	SSA (0.11)	DMF	90	80
10	SSA (0.15)	$(CH_2OH)_2$/ 120	1	93
11	SSA (0.05)	$(CH_2OH)_2$/ 120	1	87
12	SSA (0.025)	$(CH_2OH)_2$/ 120	1	90

(Table 3, entries 5, 6, 7, 8, respectively) produced the product **3a** in yield lower than that produced by the entry 4. Replacing ethylene glycol by DMF (entry 9) produced the model in a yield slightly lower than that of the product obtained by the (entry 4).

Moreover, studying the efficacy of the ratio of the catalyst (0.11, 0.15, 0.05, 0.025 mol) revealed that 0.11 mol of the catalyst was the optimum ratio (Table **3**, entry 4). From the obtained results, it was found that, the best catalyst was silica sulfuric acid (0.11 mol). Optimized condition was established in ethylene glycol as a solvent; it gave the best result with 99% yield of the required 2,5-bis(4-fluorophenyl)-2,3,5,12-tetrahydrobenzo[4,5]- imidazo[1,2-a] pyrimido[4,5-d]pyrimidin-4(1*H*)-one **3a** (Table **3**, entry 4). Due to this remarkable activation in reaction rate, the potential of this protocol for the synthesis of other tetrahydrobenzo[4,5] imidazo[1,2-*a*]pyrimido[4,5-d]pyrimidin-4(1*H*)-one derivatives, was explored.

The scope and limitations of this three-component reaction under optimized conditions were explored using a variety of aromatic and heterocyclic aldehydes (Scheme 5). Thus, 2-aminobenzimidazole and cyanoacetamide were reacted with varying aldehydes in the presence of SSA. The reactions were finished at specified time and afforded the corresponding tetrahydrobenzo[4,5]imidazo[1,2-a] pyrimido[4,5-d]pyrimidin-4(1*H*)-one derivatives **3a-e** in good yields (80-99%) as shown in Scheme **4** and Table **4**. Regarding the effect of the aromatic and heterocyclic aldehydes: 4-fluorophenyl moiety and 3-methoxyphenyl moiety afforded the higher yield of the product (**3a** and **3e**; 99%) when compared to other aryl moieties. 3-Bromophenyl moiety (**3d**, entry 4), and phenyl moiety (**3a**, entry 2) showed yield results 89 % and 84 % respectively. 3-Chlorophenyl moiety (**3c**, entry 3) showed the lowest yield (80 %). Under identical conditions, heterocyclic aldehydes such as 5-methylfuranal and 2-thienyl aldehyde gave none of the corresponding benzo[4,5]imidazo[1,2-a] pyrimido[4,5-d]pyrimidin-4(1*H*)-one derivatives.

The ^{1}H NMR spectrum of benzo[4,5] imidazo[1,2-a]pyrimido[4,5-d]-pyrimidin-4(1H)-one derivative 3e, as representative example, was characterized by the presence of two singlet signals at δ = 3.79 and 3.82 ppm corresponding to protons of the two methoxy groups. The characterizing singlet signals at 5.26 and 6.06 ppm were assigned to H-2 and H-5 protons, respectively. The protons of aromatics were assigned as douplet (H-7), triplet (H-8), triplet (H-9) and douplet (H-10) signals at 5.81, 6.67, 6.94 and 7.01 ppm, respectively, with one proton integral value. The protons of the two 3-methoxyphenyl moieties were assigned as three multiplets signals in 7.05 - 7.65 ppm region with eight protons integral value. The three broad exchangeable signals at 8.20, 9.40, 12.73 (D_2O-

exchangeable) ppm were assigned for the imine protons.

A plausible mechanism for the formation of benzo[4,5]imidazo-[1,2-*a*]pyrimido[4,5-*d*]-pyrimidin-4(1*H*)-ones **3** is depicted in Scheme 6. At first Knoevenagel condensation occurred between 2-cyanoacetamide and the aldehydes to form the intermediate I. Then, Michael addition of 2-aminobenzimidazole to the C=C bond of I forms the iminomethylene derivative intermediate **(II)** followed by intramolecular cyclization to forms the intermediate (**III)** which is subjected to condensation with aldehyde to forms the intermediate (**IV)** that could undergo further intramolecular cyclization to give the benzo[4,5] imidazo-[1,2-a]pyrimido[4,5-*d*]pyrimidin-4(1*H*)-ones **3**

Experimental Section

All melting points are recorded on digital Gallen Kamp MFB-595 instrument are uncorrected. The IR spectra (KBr) (cm^{-1}) were measured on a JASCO spectrophotometer. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 400 & 300 MHz) and are reported relative to deuterated solvent signals in deuterated dimethylsulfoxide (DMSO-d_6). ^{13}C NMR spectra were recorded on Bruker Spectrometers in deuterated dimethylsulfoxide (DMSO-d_6).

General procedure for the synthesis of the ethyl 4-aryl-2-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole-3-carboxylates 1a-g

To the mixture of 2-aminobenzimidazole (1 mmol), ethyl acetoacetate (1 mmol) and the desired aldehyde (1 mmol) in ethylene glycol (5 mL), SSA (42.6 mg, 0.11 mol %) was added. The mixture was heated at 120 °C for the 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 filteration. The organic layer was dried over Na_2SO_4; the solvent was evaporated. The product was purified by column chromatography on silica-gel using *n*-hexane/ethyl acetate as an eluent.

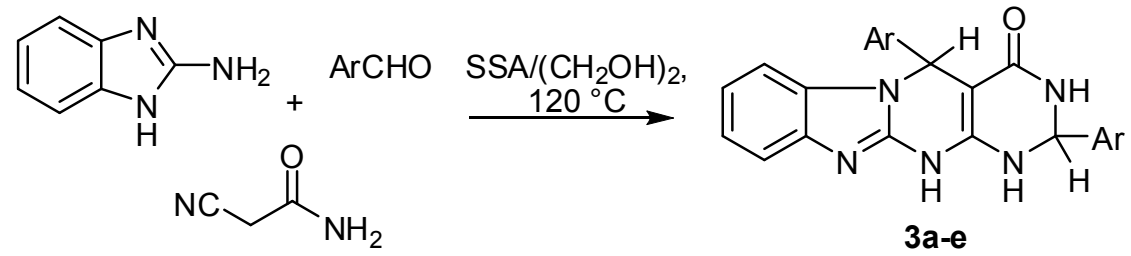
Ethyl 2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (1a): Yield 76%; m.p. 284 °C (Lit. 281-283 [24, 28, 36], 294-296 [16, 35]); IR: ν/cm^{-1}: 3445 (NH), 2974, 2927, 2865 (CH-$_{aliph}$), 1698 (C=O), 1654 (C=N); Anal. Calcd for $C_{20}H_{19}N_3O_2$ (333.38): C, 72.05; H, 5.74; N, 12.60; Found: C, 72.10; H, 5.54; N, 12.11 %.

Ethyl 4-(4-fluorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (1b): Yield 71%; m.p. 272 °C (Lit. > 300 [16, 28, 35]); IR: ν/cm^{-1}: 3478 (NH), 2978, 2927, 2863 (CH-$_{aliph}$), 1696 (C=O), 1655 (C=N); Anal. Calcd for $C_{20}H_{18}N_3O_2$ (351.37): C, 68.36; H, 5.16; N, 11.96; Found: C, 68.32; H, 5.01; N, 11.78 %.

Ethyl 4-(3-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (1c): Yield 94%; m.p. 230 °C (Lit. 210-213 [24, 36]); IR: ν/cm^{-1}: 3437 (NH), 2920, 2841 (CH-$_{aliph}$),1700 (C=O), 1656 (C=N); ^{1}H NMR (400 MHz, DMSO): δ/ppm = 1.17 (t, 3H, *J* = 7.2 Hz, CH_3), 2.46 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.11(q, 2H, *J* = 17.6 Hz, CH_2), 6.41 (s, 1H, CH), 6.75 (d, 1H, *J* = 6.76 Hz, Ar-H), 6.88 (m, 1H, Ar-H), 6.94 (m, 1H, Ar-H), 7.00 (m, 2H, Ar-H), 7.17 (t, 1H, *J* = 7.16 Hz, Ar-H), 7.29 (d, 1H, *J* = 7.30 Hz, Ar-H), 7.35 (d, 1H, *J* = 7.35 Hz, Ar-H), 10.8 (br, 1H, NH); Anal. Calcd for $C_{21}H_{21}N_3O_3$ (363.41): C, 69.41; H, 5.82; N, 11.56; Found: C, 69.32; H 5.18; N, 11.57 %.

Ethyl 4-(2,5-dimethoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]- pyrimidine-3-carboxylate (1d): Yield 86%; m.p. 252 °C; IR: ν/cm^{-1}: 3438 (NH), 2930, 2836 (CH-$_{aliph}$),1698 (C=O), 1657 (C=N); ^{1}H NMR (400 MHz, DMSO): δ/ppm = 1.10 (t, 3H, *J* = 7.2 Hz, CH_3), 2.46 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3) 3.99 (q, 2H, *J* = 12.75 Hz, CH_2), 6.60 (s, 1H, CH), 6.76 - 6.93 (m, 5H, Ar-H), 7.22 (d, 1H, *J* = 4.9 Hz, Ar-H), 7.30 (d, 1H, *J* = 7.5 Hz, Ar-H), 10.72 (br, 1H, NH); ^{13}C NMR (101 MHz, DMSO): 14.4, 19.0, 19.2, 51.8, 55.7, 56.4, 59.6, 96.9, 109.8, 112.9, 113.5, 116.0, 117.1, 120.5, 122.0, 130.9, 132.3, 142.6, 146.4, 147.5, 151.2, 153.4, 165.7; Anal. Calcd for $C_{22}H_{23}N_3O_4$ (393.44): C, 67.16; H, 5.89; N, 10.68; Found: C, 67.01; H 5.14; N, 10.44 %.

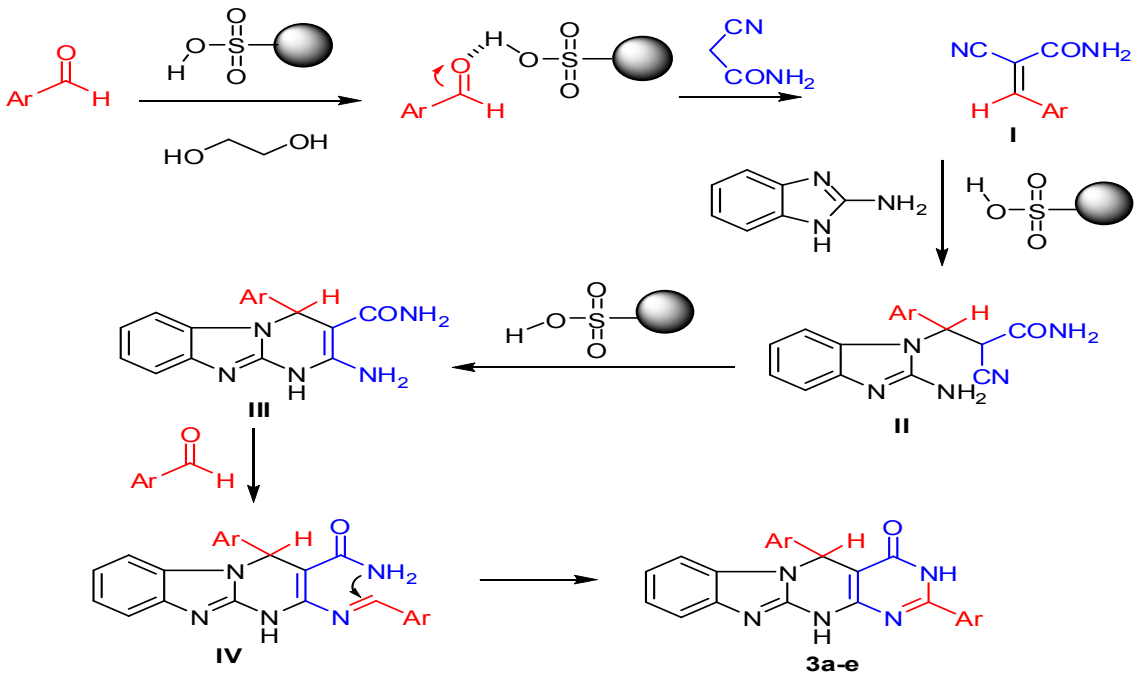
Ethyl 4-(4-hydroxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (1e): Yield 88%; m.p. 250 °C (Lit. >300 [25]); IR: ν/cm^{-1}: 3225 (NH), 2704 (CH-$_{aliph}$), 1694 (C=O), 1644 (C=N); Anal. Calcd for $C_{20}H_{19}N_3O_3$ (349.38): C, 68.75; H, 5.48; N, 12.03; Found: C, 68.34; H, 5.54; N, 11.98 %.



Scheme 5. Reaction of 2-aminobenzimidazole and aldehydes with cyanoacetamide

TABLE 4. Reaction times and yields of tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimido[4,5-d]-pyrimidin-4(1H)-one derivatives 3a-e

Entry	Compd. No.	Ar	Found		Reported	
			Time (min.)	Yield %	Time (min.)	Yield %
1	**3a**	4-FC_6H_4	1	99	2h 60	89 [20] 90 [37]
2	**3b**	Ph	1	84	3h 62	90 [20] 90 [37]
3	**3c**	3-ClC_6H_4	1	80	2h 69	89 [20] 89 [37]
4	**3d**	3-BrC_6H_4	1	89	70	91 [37]
5	**3e**	3-$OCH_3C_6H_4$	1	99		



Scheme 6. Mechanistic formation of the benzo[4,5]imidazo-[1,2-a]pyrimido[4,5-d]pyrimidin-4(1H)-ones 3

Ethyl 4-(2-methyl-4-(5-methylfuran-2-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]- pyrimidine-3-carboxylate (1f): Yield 76%; m.p.240 °C; IR: ν/cm^{-1}: 3387 (NH), 2917, 2847 (CH-$_{aliph}$),1702 (C=O), 1658 (C=N); ^{1}H NMR (400 MHz, DMSO): δ/ppm = 1.28 (t, 3H, *J* = 7.05 Hz, CH_3), 2.18 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 4.24 (q, 2H, *J* = 7.05 Hz, CH_2), 5.82 (d.1H, *J* = 2.4 Hz, Ar-H), 6.16 (d, 1H, *J* = 2.7 Hz, Ar-H), 6.52 (s, 1H, CH), 7.16 - 7.27 (m, 2H, Ar-H), 7.47 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.56 (d, 1H, *J* = 7.5 Hz, Ar-H); ^{13}C NMR (101 MHz, DMSO): 13.8, 14.6, 19.2, 59.8, 63.3, 94.9, 107.0, 109.0, 110.2, 117.3, 120.7, 122.3, 132.0, 142.7, 146.1, 148.0, 151.5, 151.6, 165.6; Anal. Calcd for $C_{19}H_{19}N_3O_3$ (337.37): C, 67.64; H 5.68; N, 12.46; Found: C, 67.55; H 5.10; N, 12.12 %.

Ethyl 2-methyl-4-(thiophen-2-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (1g): Yield 70 %; m.p.260 °C; IR: ν/cm^{-1}: 3437 (NH), 2843 (CH-$_{aliph}$),1699 (C=O), 1656 (C=N); ^{1}H NMR (400 MHz, DMSO): δ/ppm = 1.18 (t, 3H, *J* = 7.05 Hz, CH_3), 2.45 (s, 3H, CH_3), 4.09 (q, 2H, *J* = 5.4 Hz, CH_2), 6.81 (s, 1H, CH), 6.86 (t, 2H, *J* = 3.8 Hz, Ar-H), 6.88 - 7.09 (m, 2H, Ar-H), 7.30 - 7.46 (m, 2H, Ar-H), 7.47 (d, 1H, *J* = 3.7 Hz, Ar-H), 10.5 (br, 1H, NH); Anal. Calcd for $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H 5.05; N, 12.38; Found: C, 63.55; H 5.10; N, 12.32 %.

General procedure for the synthesis of 2,3,5,12-tetrahydrobenzo[4,5]imidazo[1,2-a]-pyrimido[4,5-d]pyrimidin-4(1H)-one derivatives 3a-f.

To the mixture of 2-aminobenzimidazole (1 mmol), 2-cyanoacetamide (1 mmol) and the desired aldehyde (2 mmol) in ethylene glycol (5 mL), SSA (42.6 mg, 0.11 mol %) was added. The mixture was heated at 120 °C for the appropriate time (Table 4). After completion of the reaction (TLC), 10 mL EtOAc was added to the reaction mixture and the catalyst was recovered by filteration. The organic layer was dried over Na_2SO_4; the solvent was evaporated and the residue was purified by recrystallization from ethanol.

2,5-Diphenyl-2,3,5,12-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimido[4,5-d]pyrimidin-4(1H)-one (3a): Yield 84%; m.p. 237 °C; (Lit. 223-225 [20, 37]); IR: ν/cm^{-1}: 3481, 3348, 3302 (NH), 2854 (CH-$_{aliph}$), 1718 (C=O), 1637 (C=N); Anal. Calcd. for $C_{24}H_{19}N_5O$ (393.44): C, 73.27; H, 4.87; N, 17.8; Found: C, 73.33; H, 4.91; N, 17.64 %.

2,5-Bis(4-fluorophenyl)-2,3,5,12-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimido[4,5-d]pyrimidin-4(1H)-one (3b): Yield 99%; m.p. 230 °C; (Lit. 230 [20], 231-233 [37]); IR: ν/cm^{-1}: 3486, 3460, 3351 (NH), 2853 (CH-$_{aliph}$), 1717 (C=O), 1634 (C=N); Anal. Calcd. for $C_{24}H_{17}F_2N_5O$ (429.42): C, 67.13; H, 3.99; N, 17.8; Found: C, 67.23; H, 4.02; N, 17.66 %.

2,5-Bis(3-chlorophenyl)-2,3,5,12-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimido[4,5-d]pyrimidin-4(1H)-one (3c): Yield 80%; m.p. 243 °C; (Lit. 235-236 [20]; 237-239 [37]); IR: ν/cm^{-1}: 3486, 3355, 3348 (NH), 2852 (CH-$_{aliph}$), 1720 (C=O), 1634 (C=N); Anal. Calcd. for $C_{24}H_{17}Cl_2N_5O$ (462.33): C, 62.35; H, 3.71; N, 15.15; Found: C, 62.42; H, 3.76; N, 15.23 %.

2,5-Bis(3-bromophenyl)-2,3,5,12-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimido[4,5-d]pyrimidin-4(1H)-one (3d): Yield 89%; m.p. 255 °C (Lit. 236-238 [37]); IR: ν/cm^{-1}: 3488, 3356, 3305 (NH), 2851 (CH-$_{aliph}$), 1720 (C=O), 1634 (C=N); ^{1}H NMR (400 MHz, DMSO): δ/ppm = 5.30 (s, 1H, CH), 5.81 (d, 1H, *J* = 6.4 Hz, Ar-H), 6.11 (s, 1H, CH), 7.19 (t, 1H, *J* = 9.2 Hz, Ar-H), 7.21 - 7.26 (m, 2H, Ar-H), 7.39 (s, 1H, Ar-H), 7.72 - 7.81 (m, 3H, Ar-H), 7.87 (s, 1H, Ar-H), 7.92 - 7.96 (m, 2H, Ar-H), 8.06 (d, 1H, *J* = 10.4 Hz, Ar-H), 8.12 (s,1H, Ar-H), 8.18 (s, 1H, Ar-H), 8.26 (br, 1H, NH), 9.45 (br, 1H, NH), 12.8 (br, 1H, NH); ^{13}C NMR (101 MHz, DMSO): 63.3, 108.8, 116.5, 122.5, 122.7, 122.8, 129.0, 129.2, 131.4, 131.7, 132.0, 132.7, 134.7, 135.1, 135.6, 137.9, 149.4, 155.6, 162.8, 163.9, 164.2; Anal. Calcd for $C_{24}H_{17}Br_2N_5O$ (551.23): C, 52.29; H, 3.11; N, 12.70; Found: C, 52.34; H, 3.09; N, 12.63 %.

2,5-Bis(3-methoxyphenyl)-2,3,5,12-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimido[4,5-d]pyrimidin-4(1H)-one (3e): Yield 99%; m.p. 224 °C; IR: ν/cm^{-1}: 3466, 3357, 3302 (NH), 2839 (CH-$_{aliph}$), 1716 (C=O), 1632 (C=N); ^{1}H NMR (400 MHz, DMSO): δ/ppm = 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.26 (s, 1H, CH), 5.81 (d, 1H, *J* = 7.67 Hz, Ar-H), 6.06 (s, 1H, CH), 6.67 (t, 1H, *J* = 8.0 Hz, Ar-H), 6.94 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.01 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.05 - 7.25 (m, 5H, Ar-H), 7.35-7.55 (m, 2H, Ar-H), 7.65 (m, 1H, Ar-H), 8.20 (br, 1H, NH), 9.40 (br, 1H, NH), 12.73 (br, 1H, NH); ^{13}C NMR (101 MHz, DMSO) δ: 55.5, 55.6, 59.6, 62.4, 107.4,

111.1, 111.6, 113.6, 115.3, 116.2, 118.7, 119.6, 121.1, 123.0, 129.8, 130.8, 134.6, 137.1, 142.8, 150.9, 153.5, 156.1, 159.5, 163.2, 164.1, 165.8; Anal. Calcd. for $C_{26}H_{23}N_5O_3$ (353.18): C, 68.86; H, 5.11; N, 15.44; Found: C, 68.74; H, 5.04; N, 15.53 %.

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