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An Efficient Synthesis of Pyrido[2,3-*d*]pyrimidine Derivatives via One-Pot Three-Component Reaction in Aqueous Media

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ABSTRACT

A series of pyrido[2,3-*d*]pyrimidines derivatives have been prepared by one-pot three-component reaction of 4(6)-aminouracil, malononitrile and aromatic aldehydes. This efficient synthesis was done under microwave irradiation conditions (method A) and also using catalytic amount of diammonium hydrogen phosphate [$(NH_4)_2HPO_4$] (DAHP) in aqueous media (method B). This procedure has the advantages of good yields, easy work-up, and benign environmentally friendly character. Reaction could proceed *via* domino Knoevenagel-Michael-cyclization reactions.

Keywords: Diammonium Hydrogen Phosphate (DAHP); Microwave Irradiation (MWI); Water in Organic Synthesis; Pyrido[2,3-*d*]pyrimidine

1. Introduction

Pyridopyrimidine and its derivatives have been studied due to a variety of chemical and biological significance. The importance of pyridopyrimidines as biologically active compounds includes their use as antibacterial [1-3], antiallergic [4], antitumor [2,3] antifolate [5], tyrosine kinase [6], antimicroibial [7], calcium channel antagonists [8], antibacterial [9-12], anti-inflammatory, analgesic [13], antihypertensive [14], antileishmanial [15], tuber-culostatic [16], anticonvulsants [17], diuretic, potassiumsparing [18], and antiaggressive activities [19]. The need to reduce the amount of toxic waste and by-product arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as the reaction media [20-26].

Several approaches have been developed for the synthesis of pyridopyrimidines such as: 1) the reaction of benzylidene derivatives of malononitrile with 6-amino-3, 4-dihydropyrimidine in refluxing ethanol [27,28]; 2) the reaction of 6-amino-1-thio uracil with ethyl-3-phenyl-2-cyanoacrylate in absolute ethanol and in the presence of Et_3N by heating [29,30]; 3) the three-component reaction of aldehydes, alkyl nitriles and aminopyrimidines in water and in the presence of KF-Al_2O_3 as catalyst [31]; 4) the similar three-component reaction catalyzed by TEBAC [32] or reaction of amino-uracil with α,β-unsaturated compounds in ionic liquid at 90˚C [33]. Some of the reported methods have their merit such as: 1) multi-step synthesis with the use of expensive harmful reagents and 2) low yields. Thus, the development of efficient method for the synthesis of biologically active compounds such as pyrido[2,3-*d*]pyrimidines, in one-step would be highly valuable and desirable.

2. Methods

The utility of microwave energy in synthetic organic chemistry has been increasingly recognized in recent years. It was shown that MWI-irradiated multi-component reactions have constituted an especially attractive synthetic strategy for rapid and efficient library generation. It has some advantages such as environmentally friendly, improving the bond forming efficiency (BFE), time saving, experimental simplicity, and also in view of atom economy, multi-component reaction is preferred [34-36] and this approach was used for academic and industries research [37]. Meanwhile, there has been increasing interest in the development of new catalysts, which are cheap, and effective in aqueous media. Recently, diammonium hydrogen phosphate [$(NH_4)_2HPO_4$] (DAHP) in aqueous media has emerged as a very effective catalyst for various organic transformation, and our group has been developing organic synthesis in aqueous media. DAHP is

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very inexpensive, water soluble, non-toxic and commercially available so it can be used in the laboratory without special precautions [38]. This encouraged us to consider DAHP as an ideal catalyst for the one-pot synthesis of pyrido[2,3-*d*]pyrimidines.

Due to the potential interest in finding more new versatile procedures, a microwave-assisted synthesis and using DAHP as a mild catalyst in aqueous media was investigated.

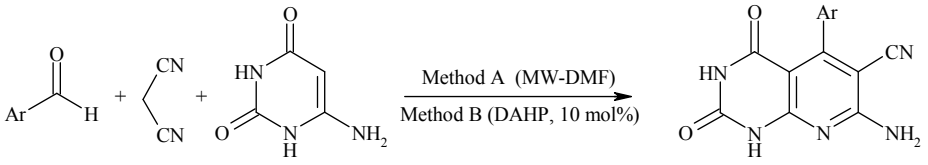
3. Results and Discussion

In this context, we introduce an efficient one-pot three-component reaction of aromatic aldehydes **1**, malononitrile **2**, and 4(6)-aminouracil **3** and MWI for the synthesis of pyrido[2,3-*d*]pyrimidines using microwave irradiation (**Scheme 1**, method A) and also in the presence of catalytic amounts of DAHP (10 mol%) in refluxing aqueous ethanol (**Scheme 1**, method B)

With the aim to develop more efficient processes, reduce the number of separate reaction steps, and minimize byproducts for the synthesis of pyrido[2,3-*d*]pyrimidines [39,40], and in continuation of our previous work on the development of new and efficient methods for the preparation of heterocyclic compounds [41-45], a convenient, practical, inexpensive, rapid procedure for the preparation of pyrido[2,3-*d*]pyrimidine derivatives **4**(**a-h**) was reported (**Scheme 1**, methods A, B).

To explore the scope and versatility of this method, various solvents were investigated. We used the reaction of 4-nitrobenzaldehyde (**1h**, 1 mmol), malononitrile (**2**, 1.2 mmol) and 4(6)-aminouracil (**3**, 1 mmol) for the preparation of compound **4h** as a model and various solvents such as glacial acetic acid (HOAc), ethanol, glycol, water and *N*,*N*-dimethylformamide (DMF) as solvent (1.0 mL) were used, also reaction was checked in solvent-free conditions at 120˚C respectively. All the reactions were carried out at the maximum power of 250 W. The results are summarized in **Table 1**. The heating characteristics of a solvent under microwave irradiation conditions are dependent on the dielectric properties of the solvent. This fact is shown in **Table 1**, where the best result was achieved using DMF as solvent. So DMF was chosen as the reaction solvent. More over in order to optimize the other reaction conditions the different powers and temperatures for the same reaction were examined, so microwave irradiation at 250 W gave the highest yield and the maximum temperature reached during the reaction was 120˚C. Therefore, microwave power of 250 W was chosen as the optimum power.

Table 2 shows the results obtained in the reaction of a series of representative aldehydes **1** with malononitrile (**2**, 1.2 mmol) and 4(6)-aminouracil (**3**, 1 mmol) under microwave irradiation. In method B we have used aqueous media catalyzed by DAHP at reflux conditions for the preparation of corresponding products **4**(**a-h**). In this manner and in order to optimize the reaction conditions the catalytic amount of DAHP was varied finding that 10 mol% of DAHP afforded the best yields. It is important to note that in the absence of DAHP the reaction times are increased, meanwhile the yields are decreased mainly. The results are summarized in **Table 2**. In order to optimize the reaction conditions the catalytic amount of DAHP was varied finding that 10 mol% of DAHP afforded the best yields. It is important to note that in the absence of DAHP the reaction did not take place at all. To show that DAHP is an efficient catalyst rather than a mild base, we adjusted the reaction conditions to pH 8, but we found that the reaction did not proceed.



1 **2** **3** **4**

Method A: MW-DMF (250 W, 120 ˚C).
Method B: 10 mol% diammonium hydrogen phosphate (DAHP), H_2O: EtOH, 2:1, reflux.

Scheme 1. Synthesis of 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile.

Table 1. Optimization of reaction conditions for the synthesis of compound 4h under microwave irradiation.

Solvent	Time (min)	T (˚C)	Yield (%)
HOAc	10	120	42
EtOH	7	120	61
Glycol	8	120	72
H_2O	12	120	71
DMF	5	120	93
Solvent-free	7	120	70

Table 2. Synthesis of 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile 4(a-h) under microwave irradiation (Method A); in aqueous media using DAHP at reflux conditions (Method B).

Product	Ar	Method A		Method B		Reported[17a]	
		Yield[a]	Time (min)	Yield[a]	Time (hr)	Yield[a]	Time (hr)
4a	C_6H_5	91	10	85	2	84.7	7
4b	2-Cl-C_6H_4	82	9	87	2	86.7	5
4c	2,4-Cl_2-C_6H_3	89	7	86	2	75.5	6
4d	3-OH-C_6H_4	93	10	93	2	-	-
4e	4-OCH_3-C_6H_4	89	11	82	2	75.9	7
4f	4-CH_3-C_6H_4	90	9	86	2	70.3	7
4g	3-NO_2-C_6H_4	94	6	92	2	73.7	7
4h	4-NO_2-C_6H_4	93	5	95	2	-	-

[a]Yields refer to those of pure isolated products characterized by IR, ^{1}H and ^{13}C NMR spectroscopic c data and mass spectrometry.

According to a plausible mechanism which is outline in **Scheme 2**, the formation of **4** is expected to proceed via initial condensation of aldehyde **1** with malononitrile **2** to afford olefin **5**, which further undergoes *in situ* Michael addition with 4(6)-aminouracil **3**, to yield intermediate **6**, which is then cyclized and subsequently dehydration to afford the aromatized product **4**.

Although we have not yet established the mechanism of the one-pot reaction of benzaldehyde derivatives, malononitrile and 4(6)-aminouracil in the presence of DAHP, a possible explanation is given in **Scheme 3**. We suggest that, DAHP can catalyze the formation of olefin **5** via conversion of aryl aldehyde **1** to a more reactive iminium ion **8**, which reacts easily with malononitrile **2** in a Knoevenagel condensation to produce olefin **5** after dehydration of intermediate **9**. DAHP can also act as a mild base for the deprotonation of 4(6)-aminouracil **3** to a proposed anion **10**, which adds to olefin **5** to generate **4**, after proton transfer, tautomerization and aromatization of intermediates **6** and **7** respectively (**Scheme 3**). This reaction could be categorized as domino Knoevenagel-Michael-cyclization reaction. The structure of compounds **4**(**a-h**) were deduced from their ^{1}H NMR, ^{13}C NMR and IR spectral data and their molecular weight confirmed by mass spectrometry. The mass spectra of these compounds showed the expected molecular ion signals, selected spectroscopic data have been given in general procedure section.

4. Conclusions

In conclusion, we have developed efficient methods for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives via three-component condensation of aromatic aldehydes, malononitrile and 4(6)-aminouracil in two different reaction conditions; 1) microwave-irradiation; 2) carrying out the reactions in aqueous media and in the presence of catalytic amount of a cheap catalyst (DAHP). The operational simplicity, simple purification procedure, high yields (82% - 95%), environmentally friendly character, and high-speed synthesis (Method A, 5 - 10 min) are advantages of this method compared to previous reported methods.

5. Experimental Section

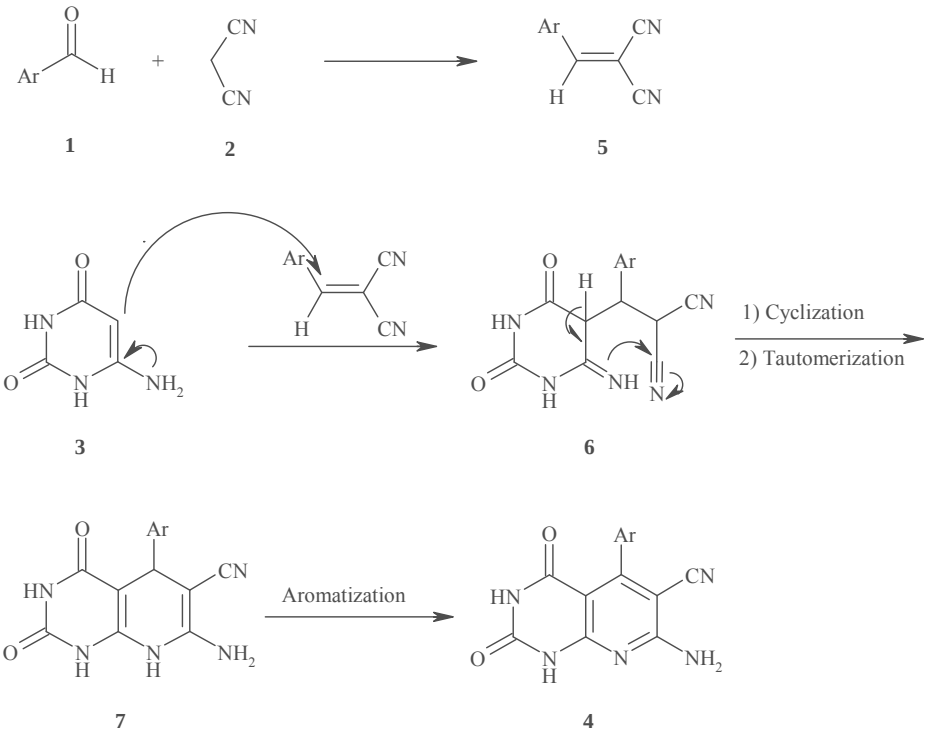
5.1. General

Melting points were determined with *Electrothermal* 9100 melting point apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR (FTLA 2000) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker DRX-500 AVANCE at 500 and 125 MHz respectively using TMS as internal standard and DMSO-d_6 as solvent. Mass spectra data were obtained by using GC-MS Hewlet Packard (EI, 70 eV) instrument.

5.2. General Procedure for the Synthesis of 7-Amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile 4(a-h)

Method A. A mixture of aromatic aldehyde **1** (1 mmol), malononitrile (**2**, 1.2 mmol), 4(6)-aminouracil (**3**, 1 mmol) and DMF (1.0 mL) were placed into teflon vessel, and subjected to microwave irradiation for a given time at power of 250 W and 120˚C. After completion of the reaction as followed by TLC examination at an interval of 30s, the reaction mixture was cooled to room temperature and then poured in to cold water. The solid product was filtered and washed with boiling water to give the pure product in excellent yield.

Method B. A solution of aromatic aldehyde **1** (1 mmol), malononitrile (**2**, 1.2 mmol), 4(6)-aminouracil (**3**, 1 mmol) and diammonium hydrogen phosphate (13.2 mg, 10 mol%) in H_2O (10 mL) and Ethanol (5 mL) was stirred at reflux for 2 h. The progress of the reaction was monitored with TLC in 1:1 ethanol-ethyl acetate as TLC solvent. Upon completion of the reaction, the reaction mixture was collected by filtration and purified by wash-



Scheme 2. Proposed mechanism for the one-pot synthesis of 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile under microwave irradiation.

ing with boiling water to afford the corresponding products in high yields.

7-amino-2,4-dioxo-5-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4a). White solid, Mp. > 300˚C, IR (KBr, cm^{-1}): 3403, 3331 (NH_2), 3174 (2NH br), 2224 (CN), 1707, 1643 (2CO). ^1H NMR (500 MHz, DMSO): δ 7.24 (m, 2H, H_{Ar}), 7.40 (m, 3H, H_{Ar}), 7.59 (br s, 2H, NH_2), 10.89 (s, 1H, NH), 11.44 (s, 1H, NH) ppm, ^{13}C NMR (DMSO) δ: 88.7, 98.3, 115.5, 127.5, 127.7, 128.3, 136.8, 150.3, 155.6, 159.0, 160.1, 160.9; MS: (M^+) m/z, 279, 278, 235, 208, 118, 77, 57, 43.

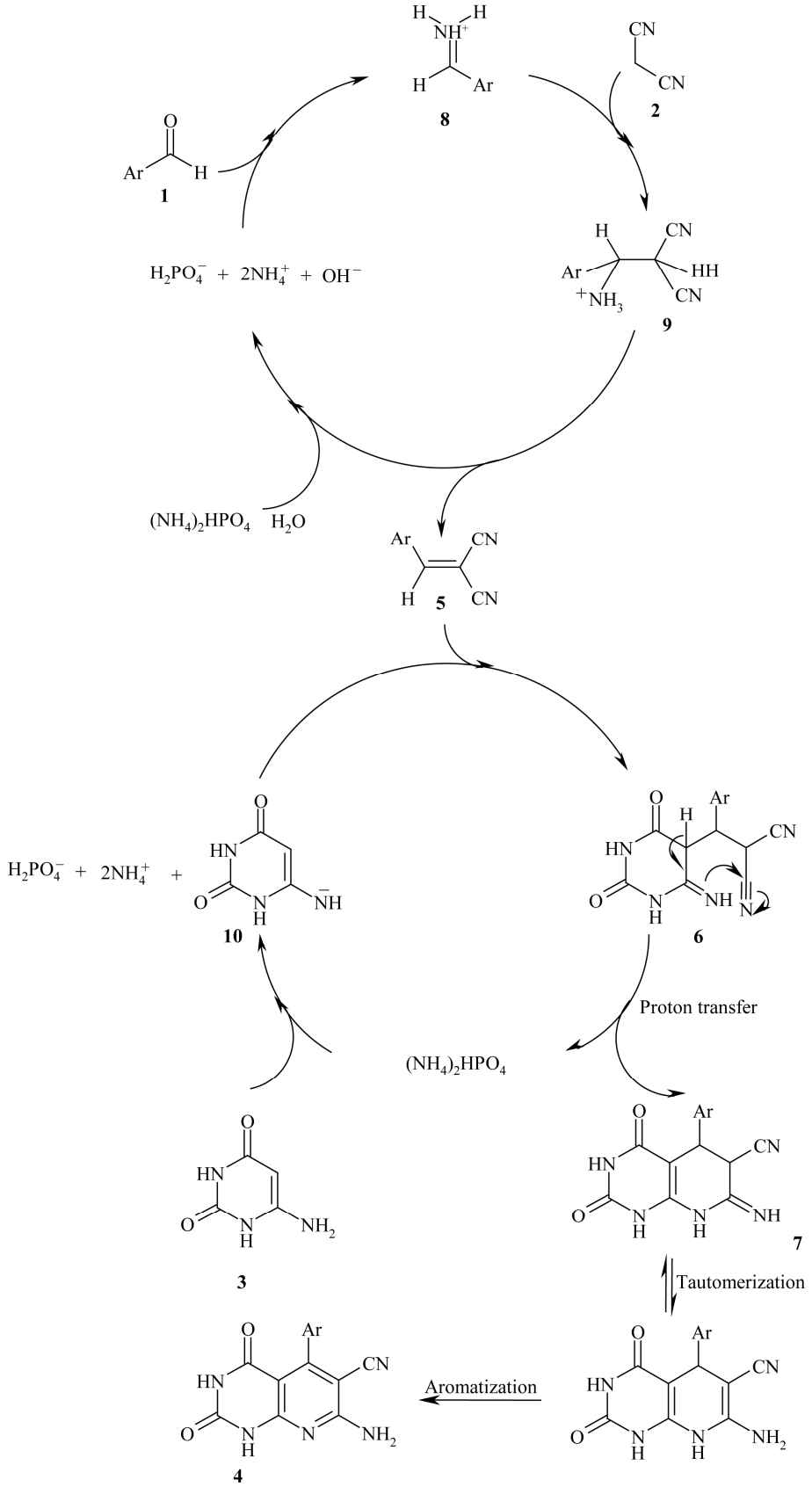
7-amino-2,4-dioxo-5-(2-chlorophenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4b). White solid, Mp. > 300˚C (Dec.), IR (KBr, cm^{-1}): 3390, 3311 (NH_2), 3188, 3091 (2NH), 2228 (CN), 1699, 1648 (2CO). ^1H NMR (500 MHz, DMSO): δ 7.28 (dd, 1H, H_{Ar}, J = 7.4, 1.5 Hz), 7.38 (t, 1H, H_{Ar}, J = 7.9 Hz), 7.43 (dt, 1H, H_{Ar}, J = 7.4, 1.5 Hz), 7.51 (d, 1H, H_{Ar}, J = 7.9 Hz,), 7.75 (br s, 2H, NH_2), 10.99 (s, 1H, NH), 11.55 (s, 1H, NH) ppm, ^{13}C NMR (DMSO) δ: 88.3, 98.5, 114.8, 126.9, 128.8, 129.0, 129.9, 130.5, 135.9, 150.1, 155.4, 155.8, 159.7, 160.9. MS: (M^+) m/z, 313, 278, 188, 153, 111, 77, 57, 43.

7-amino-2,4-dioxo-5-(2,4-dichlorophenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4c). White solid, Mp. > 300˚C (Dec.), IR (KBr, cm^{-1}): 3377, 3318 (NH_2), 3143, 3068 (2NH), 2206 (CN), 1699, 1648 (2CO). ^1H NMR (500 MHz, DMSO): δ 7.34 (d, 1H, H_{Ar}, J = 8.2 Hz), 7.50 (d, 1H, H_{Ar}, J = 8.2 Hz), 7.72 (br s, 1H, H_{Ar}), 7.81 (br s, 2H, NH_2), 11.06 (s, 1H, NH), 11.58 (s, 1H, NH) ppm, ^{13}C NMR (DMSO) δ: 88.1, 98.4, 114.7, 127.2, 128.4, 130.3, 131.7, 133.7, 135.0, 150.1, 154.6, 155.4, 159.8, 160.9. MS: (M^+) m/z, 348, 312, 277, 77, 57, 43.

7-amino-2,4-dioxo-5-(3-hydroxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4d). Brick-red solid, Mp. > 300˚C (Dec.), IR (KBr, cm^{-1}): 3391, 3322 (NH_2), 3164, 3071 (2NH), 2237 (CN), 1686, 1649 (2CO). ^1H NMR (500 MHz, DMSO): δ 6.59 (s, 1H, H_{Ar}), 6.62 (d, 1H, H_{Ar}, J = 7.4 Hz), 6.78 (dd, 1H, H_{Ar}, J = 8.0, 1.9 Hz), 7.18 (t, 1H, H_{Ar}, J = 8.0 Hz), 7.58 (br s, 2H, NH_2), 9.46 (s, 1H, OH), 11.06 (s, 2H, 2NH) ppm, ^{13}C NMR (DMSO) δ: 88.5, 98.3, 114.3, 115.2, 115.4, 118.1, 128.8, 137.9, 150.2, 155.4, 156.6, 159.0, 159.8, 160.8. MS: (M^+) m/z, 295, 294, 266, 251, 118, 77, 57, 43.

7-amino-2,4-dioxo-5-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4e). Brick-red solid, Mp. > 300˚C (Dec.), IR (KBr, cm^{-1}): 3404, 3328 (NH_2), 3188, 3150 (2NH), 2219 (CN), 1700, 1645 (2CO). ^1H NMR (500 MHz, DMSO): δ 3.80 (s, 3H, OCH_3), 6.94 (m, 2H, H_{Ar}), 7.19 (m, 2H, H_{Ar}), 7.57 (br s, 2H, NH_2), 10.59 (s, 1H, NH), 10.73 (s, 1H, NH) ppm, ^{13}C NMR (DMSO) δ: 55.0, 88.8, 98.3, 112.9, 115.7, 128.6, 129.23, 150.1, 155.5, 158.8, 159.3, 160.0, 160.8. MS: (M^+) m/z, 309, 265, 121, 77, 57, 43.

7-amino-2,4-dioxo-5-(4-methyphenyl)-1,2,3,4-tetrah



Scheme 3. Suggested mechanism for the synthesis of pyrido[2,3-*d*]pyrimidines in the presence of DAHP in aqueous media.

ydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4f). White solid, Mp. > 300˚C (Dec.), IR (KBr, cm^{-1}): 3394, 3281 (NH_2), 3167, 3031 (2NH), 2222 (CN), 1699, 1645 (2CO). ^{1}H NMR (500 MHz, DMSO): δ 2.36 (s, 3H, CH_3), 7.12 (d, 2H, H_{Ar}, J = 8.0 Hz), 7.20 (d, 2H, H_{Ar}, J = 8.0 Hz), 7.60 (br s, 2H, NH_2), 10.89 (s, 1H, NH), 11.43 (s, 1H, NH) ppm, ^{13}C NMR (DMSO) δ: 20.9, 88.7, 98.3, 115.5, 127.5, 128.1, 133.7, 137.4, 150.1, 155.5, 159.1, 159.9, 160.8. MS: (M^+) m/z, 293, 292, 249, 77, 57, 43.

7-amino-2,4-dioxo-5-(3-nitrophenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4g). Pale yellow solid, Mp. > 300˚C (Dec.), IR (KBr, cm^{-1}): 3384, 3321 (NH_2), 3172, 3081 (2NH), 2216 (CN), 1718, 1662 (2CO). ^{1}H NMR (500 MHz, DMSO): δ 7.75 (m, 2H, H_{Ar}), 7.77 (br s, 2H, NH_2), 8.19 (1H, H_{Ar}, J = 1.7 Hz), 8.29 (qd, 1H, H_{Ar}, J = 7.0, 1.1 Hz), 11.00 (s, 1H, NH), 11.54 (s, 1H, NH) ppm, ^{13}C NMR (DMSO) δ: 88.3, 98.3, 115.2, 122.8, 123.1, 129.4, 134.4, 138.4, 147.1, 150.1, 155.5, 156.1, 160.2, 160.8. MS: (M^+) m/z, 324, 277, 77, 57, 43.

7-amino-2,4-dioxo-5-(4-nitrophenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4h). Brick-red solid, Mp. > 300˚C (Dec.), IR (KBr, cm^{-1}): 3607, 3534 (NH_2), 3297, 3070 (2NH), 2222 (CN), 1703, 1590 (2CO). ^{1}H NMR (500 MHz, DMSO): δ 7.58 (d, 2H, H_{Ar}, J = 8.6 Hz), 7.75 (br s, 2H, NH_2), 8.27 (d, 2H, H_{Ar}, J = 8.6 Hz), 11.00 (s, 1H, NH), 11.55 (s, 1H, NH) ppm, ^{13}C NMR (DMSO) δ: 87.9, 98.2, 115.1, 122.9, 129.2, 144.0, 147.3, 150.2, 155.5, 156.6, 160.1, 160.8, 166.4. MS: (M^+) m/z, 324, 277, 77, 57, 43.

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