One-Pot Three-Component Synthesis of 2-Amino Pyrimidines in Aqueous PEG-400 at Ambient Temperature

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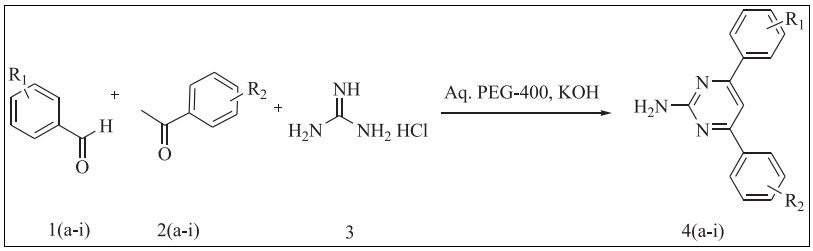

Amino pyrimidines have been synthesized by a one-pot procedure under environmentally friendly reaction conditions at room temperature. The use of aqueous PEG-400 circumvents the problems associated with the toxic, hazardous organic solvents and oxidizing agents.

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INTRODUCTION

Pyrimidines display a broad spectrum of biological activities in the field of medicinal chemistry [1]. Lobeglitazone [2], sulfadimidine [3], and bacimethrin [4] (Fig. 1) have pyrimidines moieties and antidiabetic, antibacterial, and antibiotic activities, respectively. Naturally occurring L-lathrine elicits wide range of biological activities such as hypoglycemic and antitumor activities [5]. Some pyrimidines are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children, and adult granulocytic leukemia [6]. Several biological activities are associated with polysubstituted pyrimidines [7]. Pyrimidines act as the inhibitors [8] of c-Jun N-terminal kinase, estrogen receptor–coactivator binding, vascular endothelial growth factor receptor, and Hsp90 molecular chaperone, and they also act as antagonists of calcium-sensing receptor [9]. The polysubstituted pyrimidines are also used for the treatment of hypoxemia [10], neurosis [11], and neuropathy [12]. They also act as potential antitumor agents [13].

Considering the pharmaceutical activities associated with pyrimidines, chemists have paid more attention to develop efficient/convenient synthetic routes for obtaining them in high yields. The various routes presently in use for obtaining 2,4,6-trisubstituted pyrimidines are well reviewed by Heravi *et al*. [14]. The cyclocondensation of chalcones with amidines at refluxed conditions in presence of triethylamine in ethanol [15], KOH in ethanol [16] or in methanol [17], in presence of peroxide [18], sodium isopropoxide in isopropanol [6], and dimethylformamide [19] is the most widely way for the synthesis of pyrimidines. These synthetic routes have drawbacks, as they need amidines, unsaturated ketones, aryl-β-vinyl imines, sulfonium salts, and imidazolium derivatives, which make the routes time-consuming. Also, they need toxic, hazardous, flammable solvents and oxidizing agents. Recently, Zhuang *et al*. [20] have reported a one-pot improved method for the synthesis of 2-amino pyrimidines, but it does not solve the problem potentially.

Literature reveals that poly(ethylene glycols) (PEGs) have become popular reaction media in the synthetic organic chemistry since the last decade. PEGs are known as non-toxic, inexpensive, non-flammable, and non-ionic liquid reaction media of low volatility [21]. This kind of solvent system fully meets the demands of green chemistry [22] and is found to be useful for various organic transformations [23]. PEG-400 has been found as an accelerator in various synthetic reactions [24].

Multicomponent reactions have gained much importance in organic chemistry as they reduce the steps and reaction time and also improve the yields of the products [25].

Considering the drawbacks of existing synthetic routes of pyrimidines, need of incorporation of green tools like nonvolatile organic solvents, namely, PEGs, CO_2(SC), water, and ionic liquids, and the importance of multicomponent one-pot synthetic approach for expediting organic transformation by safer way, here, it was thought worthwhile to develop a convenient route for the synthesis of amino pyrimidines.

In continuation of our earlier work carried out to develop the convenient synthetic protocols for the synthesis of bioactive heterocycles by applying green tools [26] and considering the aforementioned urgent need, here, we report on eco-sustainable one-pot synthetic protocol for the bioactive amino pyrimidines using aq. PEG-400 as medium and accelerator.

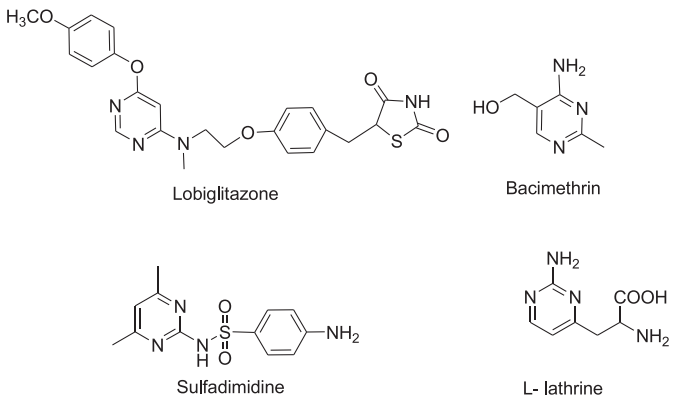

Figure 1. Biologically active amino pyrimidines.

RESULTS AND DISCUSSION

We have developed an environmentally benign one-pot synthetic protocol for the synthesis of polysubstituted amino pyrimidines **4** by allowing the interactions of aromatic aldehydes **1**, aromatic acetophenones **2**, and guanidine hydrochloride **3** in aq. PEG-400 at room temperature (Scheme 1, Table 1).

Before developing the aforementioned one-pot route, we performed the condensation of freshly prepared 3-(4-chlorophenyl)-1-(4-methoxyphenyl) prop-2-en-1-one and guanidine hydrochloride in alkaline ethanolic medium at reflux for 6–7 h and obtained the amino pyrimidine (**4e**) with 65% yield. Further, the attempt was made to carry out the aforementioned model reaction, replacing ethanol with 90% aq. PEG-400. It was found that the reaction was accomplished within 4 h at room temperature, giving better yield, of 78% of the amino pyrimidines (**4e**).

Keeping these results in mind, an attempt was made to cyclocondense the three components—aromatic aldehyde (**1e**), acetophenone (**2e**), and guanidine hydrochloride (**3**)—using KOH in different solvents, namely, dimethylformamide, methanol, ethanol, and isopropanol at room temperature and obtained the titled 2-amino pyrimidine (**4e**) with moderate yields, and results are shown in Table 1. Most of the solvents employed have been volatile, toxic, flammable, and corrosive. Therefore, to provide green medium, the aforementioned referred model multicomponent condensation was performed by stirring the compounds in PEG-400 as green, safer medium. It was found that the cyclocondensation was completed within 24 h, giving 80% yield of the 2-amino pyrimidine (**4e**).

Table 1

Selection of the medium for the synthesis of **4e**.

Solvent	Time[a] (h)	Yield[b] (%)
DMF	30	47
Methanol	24	55
Ethanol	24	60
Isopropanol	24	68
PEG-400	24	80
90% aq. PEG-400	10	89

DMF, dimethylformamide.
[a]Reaction carried at room temperature.
[b]Isolated yields.

In another attempt, the multicomponent one-pot condensation was run using 90% aq. PEG-400, and we noticed that the condensation was completed within 10 h at room temperature and gave 89% yield of 2-amino pyrimidines (Table 1).

To optimize the medium composition, we performed the condensation using various aq. solutions of PEG-400, and results are summarized in Table 2. From this, it was noticed that for the reference reaction, the best composition of the medium for obtaining excellent yield in reduced time was 90% aq. PEG-400, and results are summarized in Table 2.

Using this composition of aq. PEG-400, the other reactions were performed at room temperature, and we obtained

Scheme 1. One-pot synthesis of amino pyrimidines in aq. PEG-400 at room temperature.

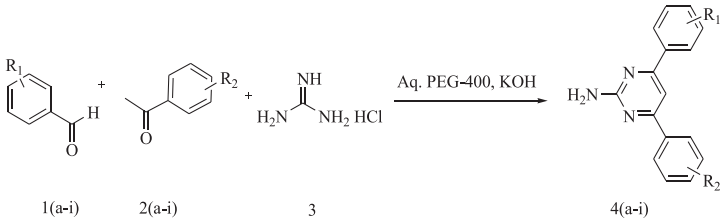

Table 2

Aqueous solutions of PEG-400.

% of aq. PEG-400 (v/v)	Time[a] (h)	Yield[b] (%)
100	24	80
95	12	85
90	10	89
85	13	80
80	15	78

[a]Reaction carried at room temperature.
[b]Isolated yields.

excellent yields of the 2-amino pyrimidines by using multicomponents; acetophenones, aryl aldehydes, guanidine hydrochloride, and KOH data are shown in Table 3.

The developed synthetic strategy for amino pyrimidines has been economical by recovering and recycling PEG-400 for the same reaction sequences. After completion of the cyclocondensation, the reaction mass was poured into ice water, and the obtained solid was filtered. Recovery of PEG-400 was made by removing water from the aqueous filtrate using vacuum distillation [27]. The recovered PEG-400 has been reused for the same reaction sequence and gave moderate to excellent yield of amino pyrimidine (**4e**) (Table 4).

The following is a possible explanation for the rate acceleration of the condensation by aq. PEG-400 leading in the formation of amino pyrimidines. PEG-400 might have a dual role: (i) PEG-400 is a nonvolatile unique solvent for many of the organic substrates as it has the ability to dissolve hydrophilic and hydrophobic solutes. The multicomponents, therefore, would have been dissolved at room temperature in 90% aq. PEG-400, forming concentrate homogenous mass, which would have helped to accelerate the rate of the condensation. (ii) Here, PEG-400 might ameliorate the electrophilic character of carbonyl carbon of aromatic aldehydes and also enhances the nucleophilic character of α carbon of the acetophenones by forming

Table 3

One-pot synthesis of amino pyrimidines in aq. PEG-400.

R_1	R_2	Products[a]	Melting points (°C)	Yield[b] (%)
4-CH_3	H	**4a**	119–120	85
4-F	H	**4b**	118–120	82
4-Cl	H	**4c**	146–147	87
2-Cl	H	**4d**	120–122	86
4-Cl	4-OCH_3	**4e**	148–149	89
4-CH_3	4-OCH_3	**4f**	128–129	87
4-Br	H	**4g**	153–155	82
4-OCH_3	4-OH	**4h**	180–182	87

[a]All products are characterized by ^{1}H-NMR and mass spectral analyses and are in good agreement with those reported in the literature [18].
[b]Isolated yields.

Table 4

Recovering and reusability of aq. PEG-400.

Batch	Yield[a] (%)
Fresh	89
1st	80
2nd	75
3rd	70

[a]Isolated yield.

the intermolecular H-bondings between the terminal H of hydroxyl group of PEG and carbonyl oxygen of aldehydes and the H-bonding between ethereal oxygen of PEG-400 and enolic hydroxyl group of acetophenones, respectively. This, therefore, accelerates the Claisen–Schmidt condensation at room temperature, leading to the intermediates 2-propen-1-ones (chalcones). The *in situ* generated chalcones might be then undergone 1,4 successive Michael addition with guanidine. The rate of this Michael addition has been accelerated because of H-bonding between amino hydrogen of guanidine and ethereal oxygen of PEG-400, enhancing the nucleophilic character of nitrogen of the guanidine and the electrophilic character of carbonyl carbon of the chalcones.

CONCLUSION

Thus, we have developed an economical, ecosustainable, scalable, and safer one-pot synthetic protocol for the synthesis of polysubstituted amino pyrimidines using aq. PEG-400 as medium and accelerator. The fascinating scope of this synthetic strategy to afford the amino pyrimidines alleviates the use of toxic, hazardous organic solvents and oxidizing agents.

EXPERIMENTAL

Aromatic acetophenones, aromatic aldehydes, guanidine hydrochloride, KOH, and PEG-400 were obtained from SD Fine-Chem Limited, Spectrochem, and Merck. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 MHz on Geol. The mass spectra were recorded on Shimadzu GCMS. The melting points were taken in open capillary and are uncorrected.

General experimental procedure for 2-amino-4,6 diarylpyrimidines 4 (a–g). Potassium hydroxide (20 mmol) was dissolved in 90% aq. PEG-400 solution (10 mL). To the aforementioned solution, acetophenones (10 mmol) were added, and the reaction content was stirred for 0.5 h. After that, aromatic aldehydes (10 mmol) were introduced to the stirred mass, and stirring was then continued at room temperature for 5.3 h. The completion of the reaction was

monitored by thin-layer chromatography. After confirming *in situ* formation of the intermediates chalcones, guanidine hydrochloride (12 mmol) was added to the reaction mass in portions. Then, the reaction content was further stirred at room temperature for 4 h until completion of the condensation. The progress of the reaction was monitored by thin-layer chromatography (TLC). It was then poured into ice-cold water. Thus, obtained solid was filtered, washed with water, and crystallized by using proper solvents. PEG-400 was recovered from the filtrate by vacuum distillation of the aqueous filtrate and recycled for the same reaction sequences.

Experimental procedure for 2-amino-4-(4-hydroxyphenyl)-6-(4-methoxyphenyl) pyrimidine 4i. Potassium hydroxide (20 mmol) was dissolved in 90% aq. PEG-400 solution (10 mL). To the aforementioned solution, 4-hydroxy acetophenone was added, and the reaction content was stirred for 0.5 h. After that, 4-methoxy benzaldehyde (10 mmol) was introduced to the stirred mass, and stirring was then continued at room temperature for 5.3 h. The completion of the reaction was monitored by thin-layer chromatography. After confirming *in situ* formation of the intermediate chalcone, guanidine hydrochloride (12 mmol) and KOH (10 mmol) were added to the reaction mass in portions. The reaction content was further stirred at room temperature for 4 h until the completion of the condensation. The completion was confirmed by thin-layer chromatography. It was then poured into ice-cold water and neutralized by HCl. Thus, obtained solid was filtered, washed with water, and crystallized by using proper solvents. PEG-400 was not recovered from the filtrate.

Spectroscopic data of representative compound. 4-(4-Chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-amine **(4e)**: ^{1}H-NMR (δ ppm, 400 MHz, DMSO-d_6): 3.8 (s, 3H, –OCH_3), 6.71 (s, 2H, –NH_2), 7.05 (d, 2H, J = 8 Hz, Ar–H), 7.57 (d, 2H, J = 8 Hz, pyrimidine-H), 7.68 (s, 1H, Ar–H), 8.21 (q, 4H, J = 8 Hz, Ar–H); ^{13}C-NMR (δ ppm, 100 MHz, DMSO-d_6): 55.8 (–OCH_3), 101.5, 114.4 (2 × Ar–C), 129.1 (2 × Ar–C), 129.2, 130.0 (2 × Ar–C), 135.6 (2 × Ar–C), 136.8 (2 × Ar–C), 161.8, 163.8, 164.4, 165.2: gas chromatography mass spectrometry (m/z): 312 [M + 1], 314 [M + 3].

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