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Metal-Free Construction of Fused Pyrimidines via Consecutive C−C and C−N Bond Formation in Water

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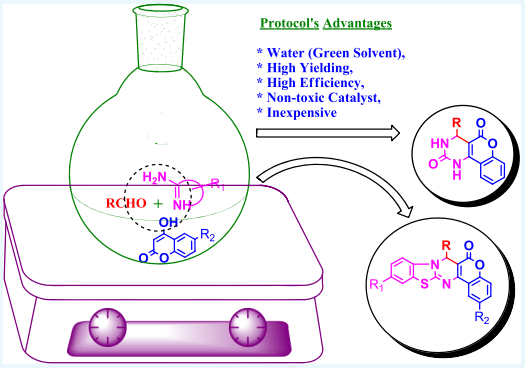
Supporting Information

ABSTRACT: A facile and efficient protocol has been developed for mild construction of fused pyrimidines via L-proline-catalyzed reaction of 4-hydroxy coumarins, aldehydes, and 2-aminobenzothiazoles/urea. The reaction has been carried out rapidly and efficiently in water under mild and metal-free conditions. Current etiquette has efficiently synthesized the heterocycles and avoids the use of hazardous solvents over conventional organic solvents. A plausible reaction mechanism has been established in this study. This study represents the first case in which L-proline as a homogeneous catalyst has been explored in the synthesis of fused pyrimidines in water in view of simple procedure and acceptable efficiency. This method gives the target product in excellent yield with ease of workup.



1. INTRODUCTION

Multicomponent reactions (MCRs) are emerging as a useful tool for the preparation of complex molecules with high efficiency via single step over the multistep synthesis. Worldwide, MCR has been explored as an efficient tool for the synthesis of many active drugs.[1,2] MCRs offer several advantages such as one-pot rather than multistep for target compound synthesis and avoid unnecessary expensive purification, high atom economy, toxic reagents, and solvents.[3]

Proline is a bifunctional chiral organocatalyst which has advantages over other catalysts such as inexpensive, efficient, and readily available.[4] L-Proline possesses acidic (−COOH) and basic (−NH) moieties and catalyzed chemical transformations similar to enzymatic catalysis.[5] L-Proline has effectively catalyzed various organic transformations,[6,7] direct catalytic asymmetric aldol,[8] Mannish,[9] Michael,[10] Diels−Alder,[11] α-amination reaction,[12] Knoevenagel-type condensation,[13] Biginelli reaction,[14] and asymmetric Hantzsch reaction.[15]

Thiazole moiety is a ubiquitous scaffold and has involved in many natural and synthetic molecules having interesting activities such as antiviral, anticancer, antimicrobial, anticonvulsant, antiparkinson, and anti-inflammatory activities.[16−23] Similarly, coumarin moieties have involved in plants[24] and have shown anticoagulation, antiviral,[25] anti-inflammatory,[26] antibacterial,[27] and anticancer[28] activities. Fused pyrimidines,[29] chromenopyrimidine,[30] and pyrimidines have also been reported as antiviral, antitumor, anti-inflammatory, antihypertensive activities,[31−33] calcium channel modulators,[34] and antimicrobial agents.[35−37] Coumarins and their derivatives (Figure 1A) such as warfarin, coumatetralyl, and difenacoum are used as an anticoagulant, whereas phenprocoumon and bromadiolone have antiviral and potent rodenticide, respectively.[38] Carbochromen[39] is an effective coronary vasodilator. In organic and medicinal chemistry, 3,4-dihydropyrimidin-2(1*H*)-ones have great importance among other promising categories.[40] Some drugs have a pyrimidine core in their structure such as monastrol (**A**),[41] trimethoprim (**B**),[42] and zidovudine (**C**)[43] (Figure 1B).

In our ongoing research interest to explore novel and convenient synthetic protocols for the construction of bioactive heterocyclic derivatives,[44] we report, herein, an alternative protocol for the three-component synthesis of fused pyrimidines in the presence of L-proline in water at 70 °C (Scheme 1).

2. RESULTS AND DISCUSSION

Initially, we studied the one-pot reaction of 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol), and 2-amino-benzothiazole (5 mmol) in water. The reaction was forwarded

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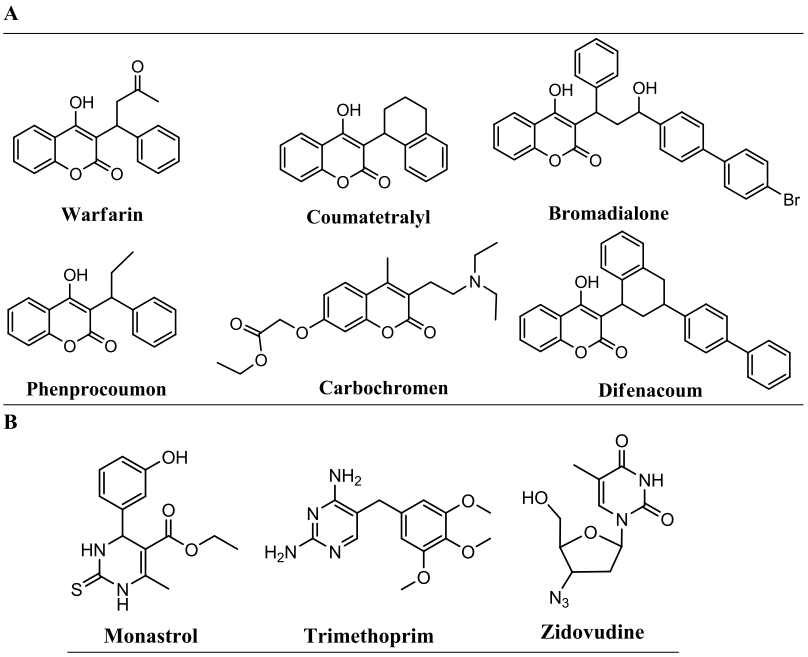
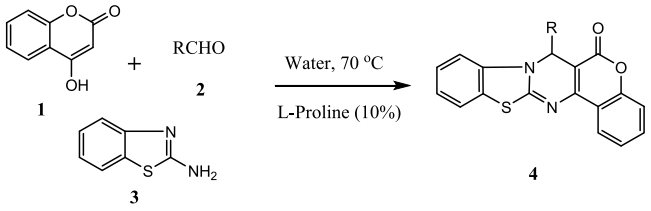


Figure 1. Some drugs with coumarin (A) and pyrimidine (B) core.

Scheme 1. Synthesis of Fused Pyrimidines



efficiently in water with good yield and time. However, water is a green, cheap, readily available, and efficient solvent for clean synthesis. That is why water has chosen as a green solvent for the first eco-friendly approach for the synthesis of pyrimidines. Further, we have studied the selection of catalyst and loading amount in water.

Different catalysts have been used in water as an eco-friendly solvent, and results are summarized in Table 1. It was observed that highest yield was found with L-proline after 3 h as compared to other catalysts (Table 1, entry 3). Catalysts such as (*p*-toluenesulfonic acid) *p*-TSA, KCl, TEA, $CaCl_2$, LiBr, H_2SO_4, and sulfamic acid have afforded moderate yield with higher time as compared to L-proline (Table 1, entries 5−11). Remaining catalysts have shown significant yield (Table 1, entries 12−16). Screening results have confirmed that L-proline was selected as the best catalyst for further study.

To investigate the catalyst loading, the reaction of 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol), and 2-amino-benzothiazole (5 mmol) has been performed with different amounts of L-proline (Table 1, entries 1−4) in water. Among the screening results, it was found that excellent yield was obtained with 10 mol % L-proline in water. There was no significant impact on yield and time when the amount of catalyst has been increased. That is why 10 mol % loading of L-proline as a catalyst was the optimized amount for promoting the reaction. To confirm the time for completion of reaction, reaction of 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol), and 2-aminobenzothiazole (5 mmol) has been

Table 1. Screening of Catalysts

entry	catalysts	time (h)	yield (%)[a]
1	L-proline (2 mol %)	8.0	78
2	L-proline (5 mol %)	4.0	87
3	L-proline (10 mol %)	3.0	91
4	L-proline (15 mol %)	3.0	91
5	*p*-TSA (10 mol %)	10.0	56
6	KCl (10 mol %)	6.5	35
7	TEA (10 mol %)	8.0	74
8	$CaCl_2$ (10 mol %)	10.0	71
9	LiBr (10 mol %)	150	79
10	H_2SO_4 (10 mol %)	160	72
11	sulfamic acid (10 mol %)	180	76
12	pyrrolidine	4.0	71
13	glycine	3.5	69
14	acetic acid	4.0	81
15	piperidine	5.0	77
16	methylamine	5.0	69

[a]Isolated Yield.

performed at different time intervals. After 3 h time interval, highest yield (91%) was found (Figure 2) which could not be increased further by increasing the time interval.

After screening the parameters, the scope of the present methodology has been investigated in the synthesis of various substituted fused pyrimidines using substituted aldehydes. Variety of electron-donating (methoxy, hydroxyl, methyl, and dimethylamino) and electron-withdrawing substituents (chloro and nitro) on aldehydes have been investigated, and results are incorporated in Table 2. From Table 2, it is clear that the reaction was performed smoothly with parasubstituents. Further, the synthesized pyrimidines have been characterized by spectroscopic analysis. The spectral data of synthesized fused pyrimidines (**4a−4k**) confirmed the probable structures, and characterization data have been placed in the Supporting Information. Copy of all ^1H and ^{13}C NMR spectra is incorporated in the Supporting Information.

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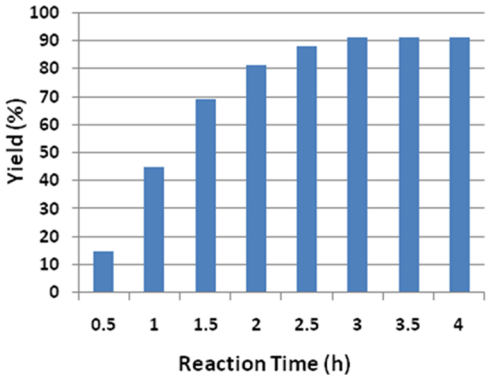


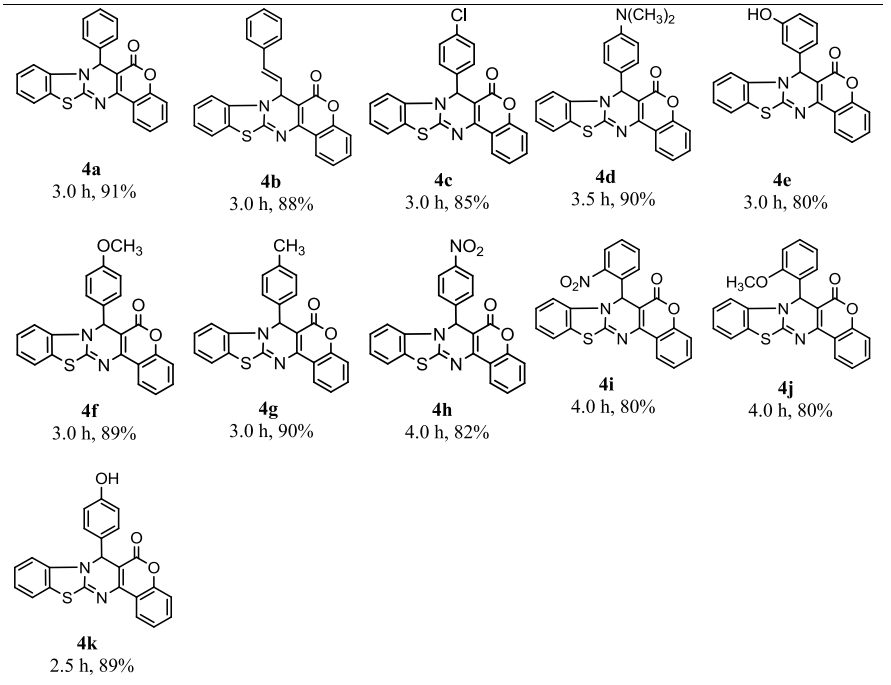
Figure 2. Comparison of reaction time with respect to yield.

Product formation was established using ^{1}H NMR wherein product **4a** depicted singlet at 6.39 δ which has been assigned for C−H and multiplet in the downfield region between 7.05−7.17 δ for three aromatic hydrogens and adjacent to it; another sharp triplet was observed at 7.17 δ which is assigned to two other protons of the aromatic ring, whereas the multiplet in downfield between 7.22−7.30 δ was observed for four protons of the coumarin ring. Furthermore, remaining aromatic protons of the benzothiazole ring were expected in the downfield region between 7.38 and 7.51 δ as a multiplet. ^{13}C NMR further confirmed the structure of **4a**, wherein the carbonyl resonates of the coumarin ring were found at δ 167. The adjacent carbon to coumarin oxygen resonates has been assigned at δ 152 and carbon of −C═N− resonates at δ 142. Carbon adjacent to the carbonyl group appeared at δ 102 and asymmetric carbon appeared at δ 68. Remaining aromatic carbon resonates were found at δ 114−131. Molecular ion peak in mass spectra was found at 383 [M + H] in the ESI which confirmed the probable structure of product **4a**. All of the remaining fused pyrimidine derivatives furnished satisfactory spectroscopic and analytical data.[44i] All of the data are in good agreement according to their assigned structures.

Reaction conditions in hand, we have explored the present methodology for the scope of substituents. To extend the scope, we used substituted benzothiazole and 4-hydroxy coumarin with urea and guanidine. As stated in Table 2, parasubstituted derivatives showed significant yield of fused pyrimidines. The reaction has undergone smoothly with the parasubstituent, leading to the formation of product with significant yield (Table 3, **5a**−**5d**). There was not any significant effect of substituents on 4-hydroxy coumarin and 2-aminobenzothiazole.

As stated earlier, coumarin derivatives are versatile molecules with good biological profile according to the slight changes in their structure. That is why, we have explored the current protocol using urea and guanidine instead of 2-aminobenzothiazole to develop new pyrimidines. Results are depicted in Table 4 which involve variety of electron-donating (methoxy, hydroxyl, and dimethylamino) and electron-withdrawing substituents (chloro and nitro) on aldehydes. Results from Table 4 clearly demonstrated that the reaction was performed smoothly with the substituent on aldehydes. Synthesized compounds have been characterized by spectroscopic analysis. The spectral data of the newly synthesized fused pyrimidines (**6a**−**6h**) confirmed the probable structures and concluded in the Supporting Information. Copy of all ^{1}H, mass, and ^{13}C NMR spectra is placed in the Supporting Information. To further explore the present methodology, we have examined heterocyclic aldehydes and found no impact on yield and time.

Table 2. Synthesis of Library of Fused Pyrimidines[a]



[a]Reaction conditions: 4-hydroxy coumarin (5 mmol), aldehydes (5 mmol), and 2-aminobenzothiazole (5 mmol) using L-proline (10 mol %) in water at 70 °C.

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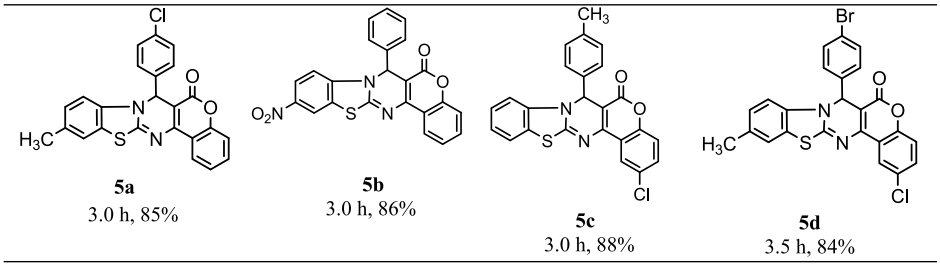
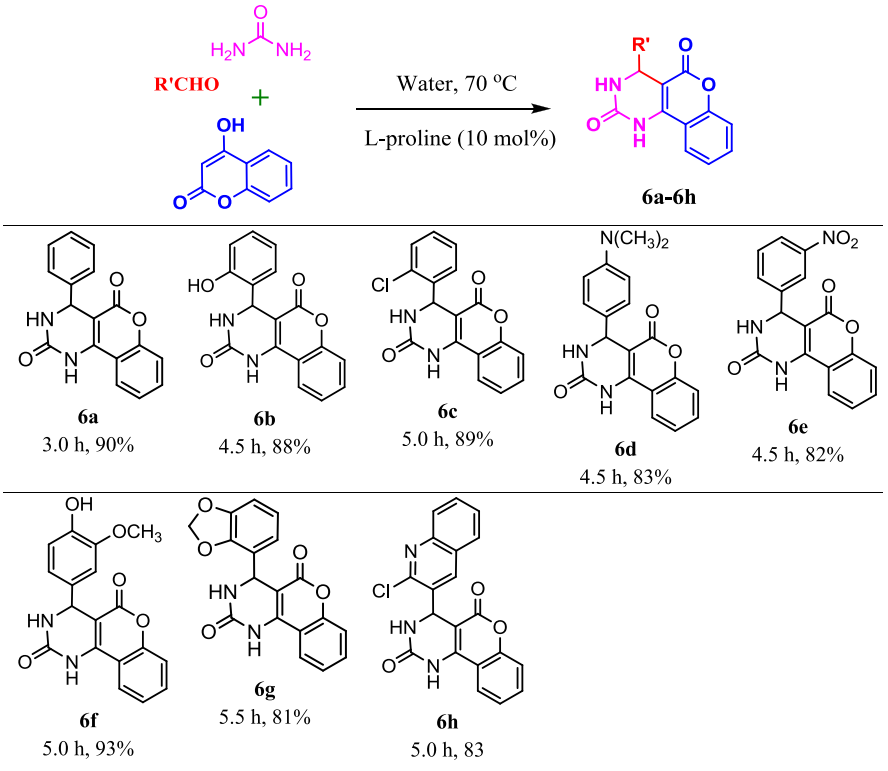
Table 3. Synthesis of Fused Pyrimidines Using Substituted Benzothioazole and 4-Hydroxy Coumarin[a]



[a]Reaction conditions: substituted 4-hydroxy coumarin (5 mmol), derived benzaldehyde (5 mmol), and substituted 2-aminobenzothiazole (5 mmol) using L-proline (10 mol %) in water at 70 °C.

Table 4. Synthesis of Library of Fused Pyrimidines Using Urea[a]



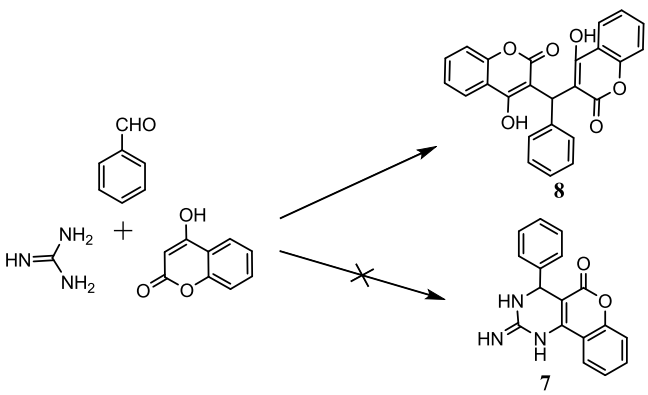
[a]Reaction conditions: 4-hydroxy coumarin (5 mmol), aldehydes (5 mmol), and urea (5 mmol) using L-proline (10 mol %) in water at 70 °C.

It was found that this three-component reaction has not been yet reported with guanidine. Hence, further reaction conditions have been explored with guanidine in place of urea or 2-aminobenzothiazole. Surprisingly, it has been found that the reaction could not be carried out with guanidine and biscoumarin; compound **8** was observed with poor yield instead compound **7** (Scheme 2). The structure of compound **8** was confirmed by ^{1}H and ^{13}C NMR spectra.

The proposed mechanism for the three-component reaction of 4-hydroxy coumarin (**1**), aldehydes (**2**), and 2-amino-benzothiazole (**3**) to synthesis fused pyrimidines (**4**) is shown in Scheme 3. Literature has been supported that L-proline having dual functionality and can catalyze aldol-related reactions such as Knoevenagel condensation and Michael addition.[45,46]

In this reaction, we could suggest that first of all iminium ions may be formed by using aldehyde catalyzed by L-proline which further facilitates the Knoevenagel condensation for the formation of intermediate **10**. Further, 2-aminobenzothiazole reacts with intermediate **10** through Michael addition to the

Scheme 2. Optimization with Guanidine



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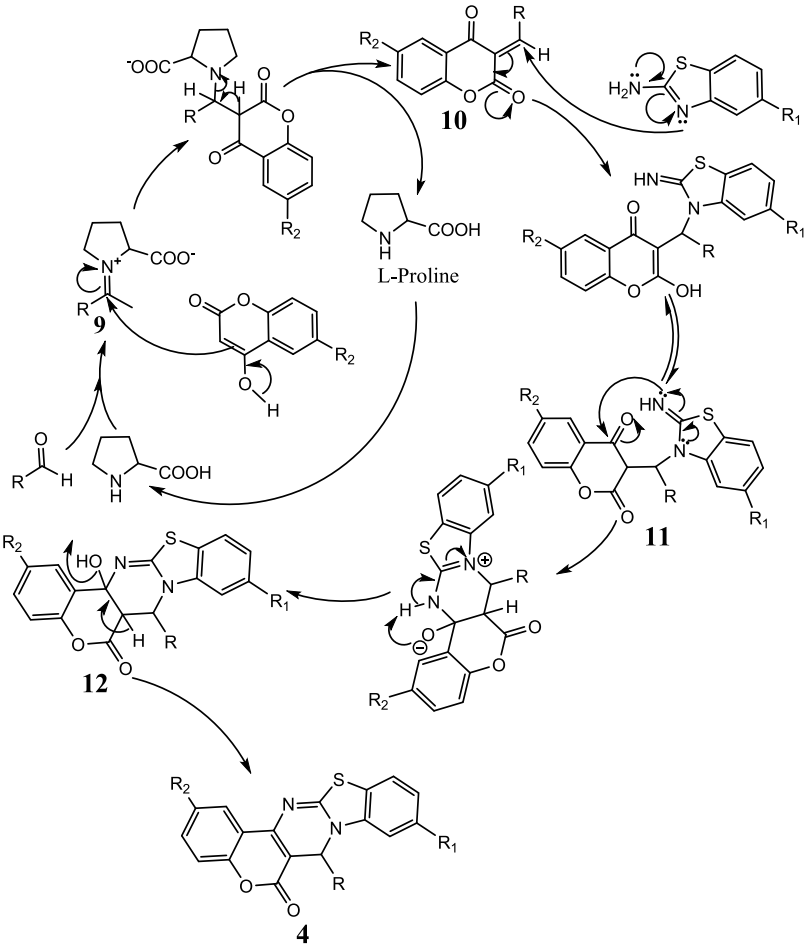
Scheme 3. Proposed Reaction Mechanism



C═C bond and forms intermediate **11**. Then, intermediate **11** reacts with amino group and forms intermediate **12** which finally forms target compound **4** through dehydration.

3. CONCLUSIONS

In conclusion, a clean, safe, mild, and metal-free protocol has been developed for the synthesis of fused pyrimidines with good yield in water as a green solvent using 2-aminobenzothiazole/urea, aldehydes, and 4-hydroxy coumarin. The results show that L-proline was successfully used in water as a homogeneous catalyst which generates a green platform in future for the synthesis of novel molecules. The protocol for the synthesis of fused pyrimidines was successfully implemented with excellent yield. Methodology has attempted the use of L-proline in the transformation of fused pyrimidines. In terms of green solvent, water was used as an environmental benign solvent, which is very inexpensive and having reactivity and selectivity toward reaction media. Over traditional methods, our method has many advantages such as simple set of workup, single shot purification, clean synthesis, and approachable yield.

4. MATERIALS AND METHODS

4.1. Experimental Section. All reagents such as L-proline, 4-hydroxy coumarin, aldehydes, and so forth were of analytical grade. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE II 500 NMR spectrometer using $CDCl_3$ and DMSO-d_6 as a solvent. Purity of the compound was checked by TLC. Melting points were determined in open capillary and are uncorrected.

4.2. Typical Procedure for Synthesis. To a round-bottomed flask equipped with a magnetic stirrer were added water (10 mL), L-proline (10 mol %), aldehydes (5 mmol), 4-hydroxy coumarins (5 mmol), and 2-aminobenzothiazole/urea (5 mmol). The resulting mixture was stirred and refluxed at 70 °C. Reaction completion has monitored by TLC analysis. After completion of reaction that was monitored by TLC, the mixture was cooled to room temperature. The solid was filtered and recrystallized in ethanol to provide the fused pyrimidines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01993.

General experimental procedures and details of characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

Preparation of compounds carried out in the laboratory of Department of Chemistry, Jiwaji University, Gwalior-474011, India, and Department of Industrial Chemistry, Jiwaji University, Gwalior-474011, India.

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