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## PAPER

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# An efficient, mild and metal free L-proline catalyzed construction of fused pyrimidines under microwave conditions in water<sup>†</sup>

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One-pot condensation of 4-hydroxy coumarins, aldehydes and urea/thiourea to build C–C and C–N bonds is described. Fused pyrimidines have been synthesized under mild reaction conditions using L-proline. The protocol has been performed rapidly and efficiently in water under metal free conditions. Heterocyclic derivatives have been synthesized using the present methodology and avoid the use of hazardous solvents over conventional organic solvents. A proposed mechanism could be established for three component reactions. The present study reveals the first case in which L-proline has been explored as a homogeneous catalyst in the synthesis of fused pyrimidines in water under microwave irradiation. This synthesis involves simple workup and acceptable efficiency. The most notable feature of this protocol is the ability of the catalyst to influence asymmetric induction in the reaction.

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## 1. Introduction

Multicomponent reactions (MCRs) have high efficiency and are a tool for development of different scaffolds for synthesis of many active drugs.<sup>1,2</sup> In modern organic chemistry, the development of environmentally benign procedures in chemical and pharmaceutical industries has become a crucial and demanding research area. MRCs offer several advantages such as one-pot rather than multi-step synthesis of target compounds, and avoiding unnecessary expensive purification, toxic reagents and solvents.<sup>3</sup> Proline is a chiral organo-catalyst having advantages over other catalyst such as being inexpensive, efficient and readily available.<sup>4</sup> Proline act as an acid or a base which catalyzes chemical transformations similar to enzymatic catalysis.<sup>5</sup> L-Proline has been effectively used in various organic transformations,<sup>6,7</sup> direct catalytic asymmetric

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra07517d aldol, Mannish and Michael.<sup>8-10</sup> Polysubstituted heterocyclic *ortho*-quinones,<sup>11</sup> pyridines,<sup>12</sup> acridine derivatives,<sup>13</sup> pyrans and thiopyrans,<sup>14</sup> and quinolines.<sup>15</sup>

Coumarin moieties are involved in plants<sup>16</sup> and showed anticoagulation, antiviral,<sup>17</sup> anti-inflammatory,<sup>18</sup> antibacterial<sup>19</sup> and anticancer<sup>20</sup> activities. Fused pyrimidines,<sup>21</sup> chomenopyrimidine,<sup>22</sup> and pyrimidines have also been reported as having anti-viral, anti-tumor, anti-inflammatory, and antihypertensive activities,<sup>23–25</sup> as well as being calcium channel modulators<sup>26</sup> and antimicrobial agents.<sup>27–29</sup> Coumarin derivatives (Fig. 1A) have become drugs such as the anticoagulants warfarin,<sup>30a</sup> acenocoumarin,<sup>30b</sup> and phenprocoumon,<sup>30c</sup> all acting as vitamin K antagonists, the choleretics armillarisin A,<sup>31a</sup> hymecromone (umbelliferone),<sup>31b</sup> and the antibiotic novobiocin<sup>32</sup> which is a potent inhibitor of bacterial DNA gyrase (GyrB). Some drugs such as Lamivudine,<sup>33a</sup> Raltegravir,<sup>33b</sup> Imatinib,<sup>34a,b</sup> Erlotinib<sup>34c,d</sup> and Lapatinib<sup>35</sup> are types of drugs with pyrimidine core (Fig. 1B).

Thus as part of our research aimed at development of synthetic methodologies using environmentally benign catalysts through MCRs,<sup>36</sup> we wish to report herein a metal free efficient and facile protocol for the three-component synthesis of fused pyrimidines in the presence of L-proline as an organo-catalyst in water at 70 °C, accompanied by moderate to good enantioselectivity (Scheme 1).

## 2. Materials and methods

### 2.1 Experimental

All reagents such as L-proline, 4-hydroxy coumarin, aldehydes *etc.* were analytical grade and have more than 98% purity. <sup>1</sup>H

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Fig. 1 Some drugs with coumarin and pyrimidine core.

and  ${}^{13}$ C NMR spectra were recorded on BRUKER AVANCE II 500 NMR spectrometer using CDCl<sub>3</sub> and DMSO-d<sub>6</sub> as solvent. Purity of the compound was checked by TLC. MS 1927 microwave starter kit was used for microwave reactions. Reaction was carried out under microwave conditions at 300 W



Scheme 1 Synthesis of fused pyrimidines.

in open to air conditions. E-Merck precoated TLC plates, RANKEM silica gel G for preparative thin-layer chromatography were used. Melting points were determined in open capillary and are uncorrected.

Table 1 Optimization of solver
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Entry	Solvents	Time (h)	Yield (%)		
1	Water	3.0	90		
2	Toluene	5.0	40		
3	DMF	7.5	41		
4	Ethanol	4.0	35		
5	Acetonitrile	5.5	40		
6	THF	5.0	53		

<sup>*a*</sup> Reaction conditions: 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol) and urea (5 mmol) using L-proline (10 mol%).

Entry	Catalysts	Time (h)	Yield (%)
1	-Proline (2 mol%)	8.0	61
2	L-Proline (5 mol%)	4.0	77
3	L-Proline (10 mol%)	3.0	90
4	L-Proline (15 mol%)	3.0	90
5	<i>p</i> -TSA (10 mol%)	10.0	49
6	TEA (10 mol%)	8.0	59
7	$CaCl_2$ (10 mol%)	10.0	60
8	$H_2SO_4$ (10 mol%)	160	70
9	Sulphamic acid (10 mol%)	180	42

<sup>*a*</sup> Reaction conditions: 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol) and urea (5 mmol) using water.



#### Typical procedure for synthesis 2.2

In a 50 mL, 3 necks round bottom flask, charged appropriate aldehydes (5 mmol), 4-hydroxy coumarin (5 mmol) and urea/ thiourea (5 mmol), water (10 mL) and L-proline (10 mol%). Stir the reaction mass and reflux at 70 °C. Reaction completion has monitored by TLC analysis. After reaction completion (monitoring by TLC), filtered the solid mass under vacuum then suck dried the solid and solid was recrystallized in ethanol.

#### 3. Results & discussion

Initially study has been started with screening of solvents in one-pot reaction 4-hydroxy coumarin (5 mmol), benzaldehyde (5 mmol) and urea (5 mmol). Reaction was efficiently promoted in water according to screening results as compared to other catalysts (Table 1, entry 1).

Above screening results revealed that the solvent plays a key role in this transformation. For instance, a best yield was obtained when water was utilized as medium (Table 1, entry 1). Nevertheless, when other solvents, such as toluene, DMF, ethanol, acetonitrile and THF were employed, we observed average yield of 4a even after 7.5 h at 70 °C (Table 1, entries 2–6). Additionally, water is an eco-friendly, cheaper, safe solvent and preferred as medium for clean synthesis. In respect of solvent selection, water has been selected as solvent or aqueous medium. Subsequently, same reaction has been done with different catalysts and results are shown in Table 2. As indicated in Table 2, good yield was obtained in the presence of L-proline (Table 2, entry 3). However, other catalysts (such as p-TSA, TEA, CaCl<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>, sulphamic acid) have been afforded moderate yield with higher reaction time (Table 2, entries 5-9). In the screening part, we have examined acids, amine and metal salt as catalysts. However, all catalysts showed some activity but were not efficient. L-Proline has dual functionality and both free NH and COOH groups of L-proline are essential for efficient transformation. L-Proline easily form iminium complex, this may be due the fact that protonation of amine moiety of catalyst which subsequent easily react with aldehyde. Protonation of amine may be easily achieved after dipolar structure of acid and amine resultant high yield was obtained due to combine effect of acid and amine moiety. Rest of catalysts have not this dual functionality or nature to catalyze the reaction efficiently results low yield was achieved.

After screening of solvents and catalysts, loading of catalyst has been evaluated in one pot condensation (Table 2, entries 1-4). Screening results have shown that catalyst amount play a crucial role in completion of reaction. Excellent yield was obtained with 10 mol% of L-proline which could not be raised by increasing the catalyst loading. Accordingly, 10 mol% of catalyst loading was acceptable for this transformation. The reaction was then conducted at different time interval, such as

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Table 3	Comparison of present methodology with reported catalysts											
Entry	Catalyst	Solvent	Conditions	Time (h/min)	Yield (%)	ee <sup>c</sup>	Reference					
1	HCl/chloro sulphonic acid	MeOH	60 °C	8.0 h	96	_	37					
2	HCl	EtOH	Reflux/MW <sup>a</sup>	12 h	94	_	38					
3	HCl	MeOH	Reflux	Overnight	59	_	39					
4	Chloro sulphonic acid	_	$60 ^{\circ}\mathrm{C/US}^{b}$	30 min	92	_	40					
5	HCl	EtOH	Reflux	12 h	74	_	41					
6	HCl/silica gel/acidic alumina/ montmorillonite-K10 clay	МеОН	110 $^{\circ}\text{C/MW}^{a}$	4–6 min	60/83/90/85	—	42					
7	K <sub>2</sub> CO <sub>3</sub>	EtOH/H <sub>2</sub> O	Reflux/MW <sup>a</sup>	7 h	53	_	43					
8	VCl <sub>3</sub>	Acetonitrile	Reflux	2 h	82	_	44					

MW<sup>a</sup>

10 min

Water

<sup>*a*</sup> Microwave conditions. <sup>*b*</sup> Ultrasonication. <sup>*c*</sup> ee = enantiomeric excess.

9

L-Proline

98

Present work

Table 4 Synthesis of library of fused pyrimidines under conventional Table 4 (Contd.)

		Time (h/min) Yield (%)					Time (h/min)		Yield (%)				
Entry	Product	CH <sup>a</sup>	MW <sup>b</sup>	СН	MW	ee%	Entry	Product	$CH^{a}$	$MW^b$	CH	MW	ee%
1	HN O HN O HN O H H H H H H H H H H H H H H H H H H H	3.0 h	10 min	90	92	98	7		5.0 h	10 min	89	88	90
2		4.5 h	8.0 min	88	86	89	8	HN O S N 4h	5.0 h	10 min	92	91	93
3		5.0 h	10 min	83	86	91	9		5.0	8.0 min	93	92	96
4	$\begin{array}{c} 4c \\ N(CH_3)_2 \\ \downarrow \\ 0 \\ HN \\ 0 \\ HN \\ H \\ $	4.5 h	10 min	83	85	86	10		5.0 h	10 min	92	90	92
5	4d NO <sub>2</sub> O HN O N HN O HN O HN O O HN O O O O O O O O O O O O O	4.5 h	8.0 min	82	81	83	11	$HN(CH_3)_2$	5.0 h	10 min	91	92	97
6	$4e$ $OH$ $OCH_3$ $OC$	5.0 h	5.0 min	89	87	89	12		5.0 h	8.0 min	87	85	85

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Table 4	Fable 4 (Contd.)						Table 4 (Contd.)						
		Time (	[h/min]	Yield	l (%)				Time	(h/min)	Yield	l (%)	
Entry	Product	$CH^{a}$	$MW^b$	CH	MW	ee%	Entry	Product	$\mathrm{CH}^{a}$	$MW^b$	CH	MW	ee%
13	OCH <sub>3</sub> HN S HN HN HN HN HN H HN H HN H H H H H	5.0 h	5.0 min	90	88	90	19	OCH3 HN N N H CH	4.5	10 min	81	82	89
14	$ \begin{array}{c}                                     $	5.0 h	5.0 min	90	91	91	20		5.0	10 min	77	81	85
15		5.0 h	8.0 min	79	83	84	<sup><i>a</i></sup> CH =	CH 4t	3 ing. <sup>b</sup> MW :	= microwav	e condi	tions.	
16		5.0 h	5.0 min	83	85	88	0.5 h, detern conclu obtain The dro-1 <i>H</i>	1.0 h, 1.5 h, 2. nine the optimum ided that after 3 ned (Fig. 2). ere are few report <i>H</i> -chromeno[4,3- <i>d</i> using 4-bydrow co	0 h, 2.5 h n time for h time int ts in litera ]pyrimidin	n, 3.0 h, 3 this transf erval, high ture for sy ne-2,5-dion	.5 h a format est yie nthesi e/thioi	nd 4.0 ion. It c ld (91% s of 3,4 ne c	h, to can be 6) was -dihy- leriva-
17	$ \begin{array}{c}                                     $	5.0 h	10 min	83	83	86	the provident of the pr	resence of homo ted methods show <sup>39,41,42</sup> and chloro as longer reaction as ultrasonication C and reflux), I 7 <sup>-39,41–44</sup> and ofte tion technology I	v that rese sulphonic n time, <sup>37-3</sup> used, <sup>38,40,4</sup> nazardous n lower y nas been sl	and heter archers has acid <sup>37,40</sup> w <sup>1</sup> <sup>9,41</sup> harsh r <sup>12,43</sup> higher solvent ( rield. <sup>39–43</sup> A nown feasil	ogeneo s used hich ha reactio temper MeOH llthoug ble on	a citls su acids su as draw n cond rature ( , EtOF ch the a small	alysts. uch as backs litions 60 °C, I and ultra- scale,
18		4.5	10 min	80	83	84	high chlorid solven reveale dysfur	energy requirem de has been used it (ACN) and high ed that exposure action, <sup>46</sup> hematolo	ent. <sup>45</sup> On as catalys er tempera e of vana ogical and	the othe the othe t <sup>44</sup> with low ature. Man dium may biochemi	r hand ver yiel y studi v cause cal alte	d, vana d, haza es have respi erations	adium rdous been ratory s, and

um ous een tory dysfunction,46 hematological and biochemical alterations, and renal toxicity47 reproductive and developmental toxicity immunotoxicity, mutagenicity<sup>48</sup> and neurotoxicity may also occur.<sup>49</sup> All above reported methods have at least one mentioned drawback resultant there is need to develop a methodology

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which remove all drawback in a single procedure. It is important to note that the previous above methods reported in the literature do not show any asymmetric induction, however target compound has a chiral centre. To solve this problem, Lproline was used as enantioselective organocatalyst in water as environmental benign solvent under microwave conditions and shown good enantioselectivity. Several advantages offered by this method such as its generality, simplicity, high yields and environmental friendly solvent used (Table 3).

To explore the catalytic activity of L-proline, the scope the present methodology has been applied in the synthesis of various substituted fused pyrimidines. Different electron donating and electron withdrawing substituents have been investigated and results are incorporated in Table 4. From Table 4, the reaction was performed smoothly with *para* substituents and synthesized compounds have been characterized by spectroscopic analysis. Copy of all <sup>1</sup>H and <sup>13</sup>C NMR spectra is placed in the ESI† and confirmed the proposed structure of heterocycles.

Energy transfer depends on the thermal conductivity which is relatively slow and insufficient upon conventional heating resultant higher reaction time is required for completion of reaction. In contrast, microwave conditions are required minimum time to complete the reaction. Apart from this, the advantages of numerous microwave (MW) induced reactions over conventional reactions, and their utility in organic synthesis, have been fully recognized in the last two decades.<sup>50</sup> To minimize the reaction time, reaction has performed under microwave conditions. The results showed that reaction has completed within 5–10 minutes with good yield under microwave conditions as compared to conventional heating. Therefore, microwave irradiation reducing the reaction time with good enantioselectivity (Table 4). The enantiomeric excess of the compounds synthesized was determined by employing chiral HPLC using OD-H column. Excellent enantioselectivity upto 98% ee was obtained (Table 4, entry 1). For the rest of the compounds enantiomeric excess was found to be in the range of to 83% ee to 97% ee. It is important to note that the previous methods reported in the literature do not show any asymmetric induction (Table 3).

Synthesized compounds **4a–4t** were confirmed by spectroscopic analysis. <sup>1</sup>H NMR of compound **4a** showed characteristic signal at 6.36 $\delta$  as singlet due to 4-H, multiplet for nine hydrogens of aromatic rings in the downfield region between 7.09– 7.39 $\delta$  and two singlet has been arised at 7.60 and 7.90 for –NH. Likewise derivatives **4d**, **4k** and **4f** demonstrated the singlet at 3.11 $\delta$  for six hydrogens of N(CH<sub>3</sub>)<sub>2</sub> and singlet at 3.73 $\delta$  for OCH<sub>3</sub> respectively. <sup>13</sup>C NMR of compound **4a** showed characteristic signal at 36 $\delta$  for C-1 carbon, signal at 104 has been assigned for C-2 carbon, other characteristic signal for ketonic carbon (C-4 and C-11) exhibited at 164 $\delta$  and 165 $\delta$ . Derivatives **4d**, **4k** and **4f** have been showed characteristic signal at 45 and 56 $\delta$  for  $-N(CH_3)_2$  and OCH<sub>3</sub> group. Mass spectra as well as elemental analysis also confirmed the structure of final product.

A plausible mechanism for reaction of 4-hydroxy coumarin (1), aldehydes (2), and urea/thiourea (3) to synthesis of fused pyrimidines (4) is depicted in Scheme 2. Based on literature, L-proline having dual functionality as acid and base can catalyze aldol related reactions such as Knoevenagel condensation as well as Michael addition.<sup>51</sup> Previous study has shown that



Scheme 2 Plausible reaction mechanism.

Knoevenagel condensation reaction efficiently catalyzed by amino acid catalyst and supports present mechanistic pathway.<sup>52</sup> The reaction presumably proceeds through initial activation of the aldehyde by L-proline to form an iminium complex<sup>53</sup> which further facilitates the Knoevenagel condensation to produce intermediate which pursue by Michael addition of urea/thiourea (**3**) on double bond of intermediate (**A**) to form intermediate (**B**). Furthermore, carbonyl and amino corner of the Michael adduct **B** was condensed through intramolecular cyclization to give desire target (**4**).

To support the plausible mechanism, proposed reaction intermediate (**A**) has been isolated and characterized. First of all reaction of 4-hydroxy coumarin and 2-hydroxy benzaldehyde has been carried out in optimized reaction conditions and formed the intermediate (**A**). Further intermediate (**A**) has been isolated and characterized by <sup>1</sup>H and <sup>13</sup>C NMR. Characterization data and literature have also been supported the structure of intermediate (**A**).<sup>54</sup> Then isolated intermediate (**A**) was react with third component (urea) and achieved the product (**4b**). Present investigation has confirmed proposed mechanistic pathway by which target compound was achieved.

## 4. Conclusions

In conclusion, an enantioselective and metal free L-proline catalyzed protocol for the synthesis of fused pyrimidines with good yield in water as a green solvent using urea/thiourea, aldehydes and 4-hydroxy coumarin. Environmental benign one pot strategy has been explored with L-proline successfully which generate a green platform in future for enantioselective synthesis of novel molecules in water. Operational simplicity, metal-free approach, compatibility with various aldehydes and 4-hydroxy coumarin, simple se of workup, neat and clean synthesis are notable advantages of this protocol. In term of green solvent, an environmental benign solvent *i.e.* water was used which is very inexpensive and having reactivity and selectivity toward reaction media. Most notable feature of this methodology is enantioselective synthesis with more than 98% ee.

## Conflicts of interest

There are no conflicts to declare.

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