



L-Proline Derived Secondary Aminothiurea Organocatalyst for Synthesis of Coumarin Derived Trisubstituted Methanes: Rate Enhancement by Bifunctional Catalyst over Cooperative Catalysis

Grace Basumatary¹ · Rahul Mohanta¹ · Ghanashyam Bez¹

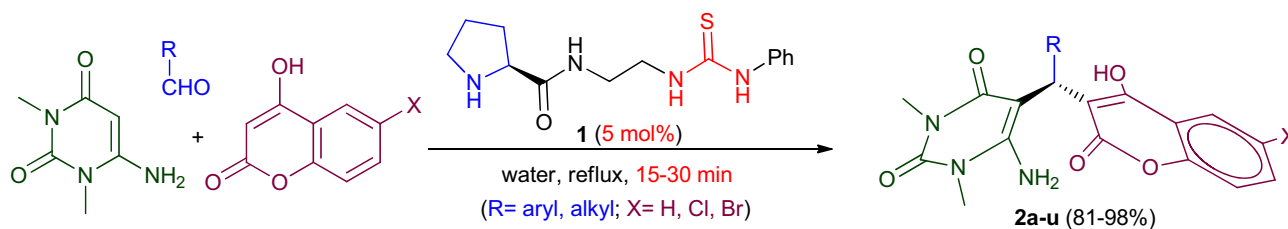
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Abstract

Although L-proline derived aminothiureas are being used as catalyst in asymmetric synthesis, their applications in multi-component reactions are not yet reported in the literature. We report herein a L-proline derived secondary aminothiurea as a multifunctional catalyst in multicomponent reaction for synthesis of coumarin-based unsymmetrical trisubstituted methanes whose prototype has been found to be acetylcholinesterase inhibitor. The method requires low catalyst loading (5 mol%), very short reaction time (15–30 min) to give excellent yields. For the first time, it is observed that our bifunctional catalyst significantly increases the rate of conversion in comparison to that of two cooperative organocatalysts having similar catalytic sites.

Graphical Abstract

L-Proline derived secondary aminothiurea organocatalyst in multicomponent reaction: synthesis of coumarin derived trisubstituted methanes



- First L-proline derived aminothiurea organocatalyst in MCRs
- Rate enhancement by bifunctional catalyst over cooperative catalysis
- Excellent yields of unsymmetrical trisubstituted methanes
- Low catalyst loading (5 mol%) and Very short reaction time (15-30 min)
- No chromatographic purification
- No use of organic solvent

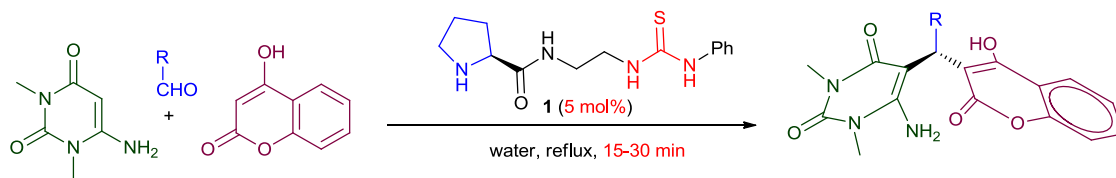
Keywords L-Proline · Secondary aminothiurea · MCRs · 4-Hydroxycoumarin · 6-Aminouracil · Unsymmetrical trisubstituted methanes

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Extended author information available on the last page of the article

1 Introduction

Since the discovery of L-proline as a bifunctional organocatalyst for organic synthesis [1], many catalysts with similar functional features have come to the fore. Despite its huge



Scheme 1 Synthesis of coumarin based trisubstituted methanes

catalytic applications, numerous efforts are being made to derivatize L-proline to address its solubility issues by keeping its stereochemical features, the bifunctional character and overall catalytic efficiency intact [2–11]. In recent years, aminothiureas have found immense applications as bifunctional catalysts for carbon-carbon bond forming reactions after the success of chincona alkaloid derived organothiureas [12, 13]. Although some L-proline derived thiurea organocatalysts are reported in the literature for stereoselective synthesis [14–17], there are hardly any report on use of L-proline derived aminothiureas to catalyze multicomponent reactions (MCRs). Since L-proline is used extensively for MCRs [18], we proposed to study simple, easily accessible and cost-effective L-proline derived aminothiureas to improve upon its catalytic efficiency in MCRs. Given the recent emphasis on using green solvents [19], we aimed to carry out the reaction preferably in water so that the purification can be done by simple filtration and recrystallization.

Coumarin is a privileged structural motif that exist in numerous pharmacophore derived from natural and synthetic sources [20]. In recent years, coumarins have been found to slow down the progression of alzheimer disease (AD) by inhibiting acetylcholinesterase (AChE). The AChE terminates the impulse transmission through rapid hydrolysis of the neurotransmitter acetylcholine (ACh), the progressive decline of which leads to pathogenesis of AD [21–23]. While various coumarin derivatives are reported for acetylcholinesterase inhibition, we have very recently observed that coumarin-based unsymmetrical trisubstituted methane (uTRSM), 3-(6-amino-1,3-dimethyluracilyl)benzyl-4-hydroxycoumarins (**2a**, Table 2) acts as a potent AChE inhibitor with IC_{50} value at 48.49 ± 5.6 nM which is much better than the reference drug donepezil ($IC_{50} = 74.13 \pm 8.3$ nM) [24]. In contrast, the corresponding biscoumarin, 3,3'-methylene-bis(4-hydroxy coumarin), MHC showed relatively inferior inhibition (80.16 ± 7.1 nM). Encouraged by the findings, we planned to synthesize a series of coumarin based uTRSMs by MCR which could be screened for inhibition of AChE.

There are two reports for synthesis of 3-(6-amino-1,3-dimethyluracilyl)benzyl-4-hydroxycoumarins derived from multicomponent reaction of 4-hydroxy coumarin, aryl aldehydes and 6-aminouracil employing L-proline [25] and

a tertiary aminothiurea [26]. In both the cases, the reaction took high catalyst loading (20 mol%) and long reaction time (3–12 h) at reflux temperature. Since most of the tertiary aminothiurea catalyzed reactions involve activation of unactivated ketones [13], we hardly saw any reason to employ the tertiary amine group for activation of highly acidic 4-hydroxy coumarin (pK_a 5.3) in the said reaction. We were curious to know if simpler organothiurea would be enough to accomplish the reaction without needing the amine altogether. Our study led to development of a new secondary aminothiurea catalysed method for synthesis of coumarin-based uTRSMs (Scheme 1).

2 Experimental Section

2.1 Materials and Instruments

The chemicals and reagents were available commercially and that were used without further purification. (S)-2-[[3,5-Bis(trifluoromethyl)phenyl]thioureido]-N-benzyl-N,3,3-trimethyl-butanamide was purchased from Sigma Aldrich. The products were characterized by IR, 1H NMR, ^{13}C NMR, Mass spectroscopy and elemental analysis. The IR spectra were recorded on a Perkin Elmer spectrophotometer. 1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker AC-400 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. The mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, and the elemental analyses of the complexes were performed on a Perkin-Elmer-2400 CHN/S analyzer. HPLC analysis was carried out on an Waters M515 equipped with Chiracel OD-H and Chiralcel AD-H columns using n-hexane and 2-propanol as mobile phase at room temperature.

2.2 Synthesis of 2-(3-Phenylthioureido)ethyl prolinamide, 1

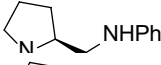
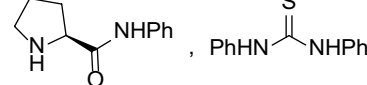
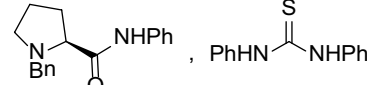
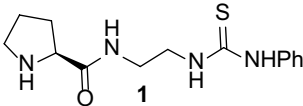
To a stirred solution of Boc-L-proline (3 g, 13.95 mmol) in anhydrous CH_2Cl_2 at -5 °C, triethyl amine (1.94 mL, 13.95 mmol) and ethyl chloroformate (1.46 mL, 15.34 mmol) were added dropwise. After 20 min of stirring, the reaction

mixture was washed successively with a cold solution of citric acid (5% aqueous, 20 mL), a solution of sodium bicarbonate (10%, 20 mL) and water (20 mL). The organic layer was dried over Na₂SO₄, filtered, and diluted with CH₂Cl₂ to a volume of 200 mL. This solution was added dropwise (30–60 min) to a vigorously stirred solution of ethylenediamine (4.66 mL, 69.77 mmol, 5 equiv.) in CH₂Cl₂ (200 mL) previously cooled to –78 °C. When the addition was completed, the mixture was stirred for 10 min at that temperature and then warmed to room temperature and stirred overnight. The reaction mixture was concentrated in vacuo to a volume of about 50 mL, and extracted with 1 M aqueous HCl solution (2 × 20 mL). The aqueous layer was basified with concentrated ammonia and it was thoroughly extracted with CHCl₃ (10 × 25 mL). The organic phases were combined, dried over Na₂SO₄, filtered, and the solvent was evaporated in vacuo to give the product **1a** as colourless oil (3.15 g, 87%). Part of the crude product (**1a**) (2.056 g, 8 mmol) was dissolved in anhydrous CH₂Cl₂ (20 mL) and phenyl isothiocyanate (0.96 mL, 8 mmol) was added dropwise at 0 °C with continuous stirring. The reaction was allowed to stir for 1 h at room temperature for complete conversion (part of the crude product was purified by column chromatography to get the 2-(3-phenylthioureido)ethyl-*N*-Boc-prolinamide as white solid). The remaining solution was cooled to 0 °C and TFA (2 mL) was added with stirring. After the consumption of the starting material, as indicated by TLC analysis, the reaction mixture was diluted with H₂O (10 mL) and the resulting solution was neutralized with aqueous NaHCO₃ solution. The reaction mixture was extracted with CH₂Cl₂ (2 × 20 mL) and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The solid crude product was recrystallized from methanol to get the pure product **1** as white solid in 77% overall yield (2.079 g, 7.12 mmol). M.p. 110–112 °C; IR (KBr): ν 3435, 2923, 1650, 1525, 1104 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, δ ppm): 1.65–2.09 (m, 6H, 2-CH₂, 2NH), 2.90–3.00 (m, 2H, –CH₂), 3.47–3.77 (m, 5H, 2-CH₂, –CH), 6.81 (m, 1H, ArH), 7.22–7.43 (m, 4H, ArH), 7.87 (s, 1H, –NH), 7.99 (s, 1H, –NH); ¹³C NMR (100 MHz, CDCl₃, δ ppm): 25.67, 31.99, 38.58, 45.18, 46.90, 60.20, 122.71, 125.03, 126.72, 128.32, 129.63 136.70, 173.25, 181.16; ESI-MS (*m/z*): 292.12 (M⁺).

2.3 General Procedure for the Synthesis of uTRSMs

To an equimolar solution of 6-amino-1,3-dimethyluracil (0.155 g, 1 mmol), aldehyde (1 mmol) and 4-hydroxycoumarin (0.162 g, 1 mmol) in 1 mL of water, 5 mol% of thiourea catalyst was added and the solution was stirred under reflux condition. In about 5 min, the product started forming (as evident from TLC). The stirring was continued until completion of the reaction (monitored by TLC). The resulting mixture was cooled to room temperature and the solid

Table 1 Screening of the catalyst for the model reaction

Entry	Catalyst	t (h:min)	% Yield ^a
1	<i>N,N'</i> -Diphenyl thiourea	2:00	80
2	<i>N</i> -Benzyl- <i>N'</i> -phenyl thiourea	2:00	82
3	<i>N,N'</i> -Diphenyl thiourea, pyrrolidine	1:30	89
4	<i>N,N'</i> -Diphenyl thiourea, piperidine	2:30	86
5	<i>N,N'</i> -Diphenyl thiourea, L-proline	1:30	90
6	L-Proline	1:30	90
7		1:00	89
8		0:40	88
9		1:30	76
10		0:20	93

Reaction conditions: 3-Nitrobenzaldehyde (1 mmol), 4-hydroxy coumarin (1 mmol), 6-amino-1,3-dimethyluracil (1 mmol) was heated to reflux in water (1 mL) with the specified catalyst (0.05 mmol)

^aYield of the purified product

that precipitated out of the solution was filtered off, washed with water and then with ethanol twice to remove any unreacted starting materials and trace of catalyst present. The solid crude product was then dissolved in ethanol and kept overnight to get the pure recrystallized product.

3 Results and Discussion

Initially, we optimized the reaction conditions for a model reaction of an equimolar mixture of 6-amino-1,3-dimethyluracil, *m*-nitrobenzaldehyde and 4-hydroxycoumarin (1 mmol each). When the model reaction was carried out in 1 mL of water in the presence of 10 mol% of *N,N'*-diphenylthiourea at reflux temperature (Table 1, entry 1), it was completed in 2 h to give 80% isolated yield. Catalysis of the model reaction by *N*-Benzyl-*N'*-phenyl thiourea also took similar reaction time with no appreciable difference in yield. The observations revealed that organothiourea alone can catalyze the reaction in the absence of an amine source and the role of the tertiary amine group is very nominal in the reaction reported by Parvin et al. [26]. This might be due to the fact that the tertiary amine groups in organothioureas basically acts a base to catalyze the reaction via enolization

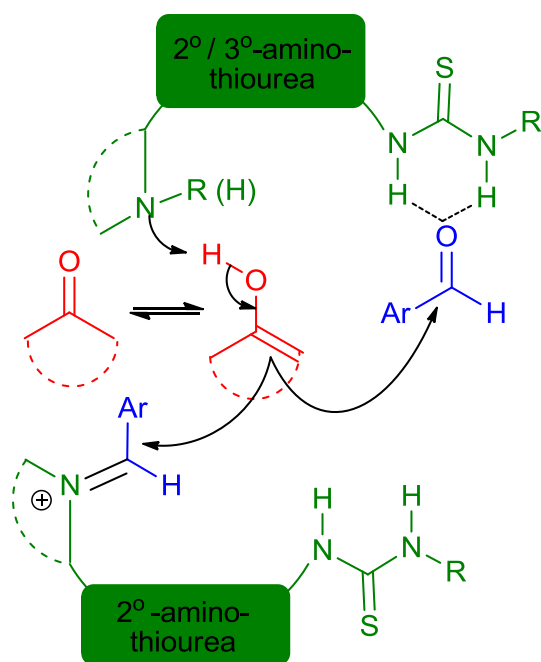
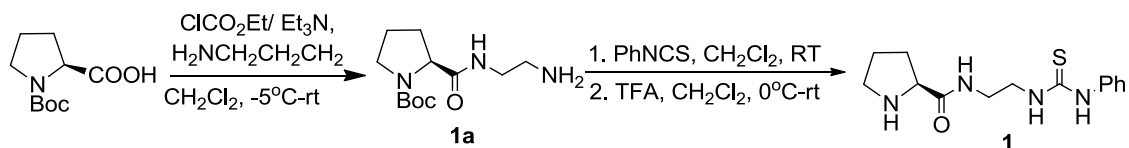


Fig. 1 2°/3°-aminothiurea catalyzed C–C bond forming reaction



Scheme 2 Synthesis of the catalyst

of unactivated ketone (Fig. 1). In this case, the 4-hydroxy coumarin is naturally an enol and hardly requires any base catalyst for activation to undergo addition reaction at reflux temperature. The fact that a secondary amine can work both as base and nucleophile, we proposed to add a pyrrolidine source along with organothiurea as catalysts to accelerate the rate of the reaction between 4-hydroxy coumarin and the aldehyde (via iminium salt formation) further.

We planned to study whether an equimolar mixture of secondary amine and thiourea can positively affect the model reaction. To that effect, we treated the reaction mixture with *N,N'*-diphenylthiourea (10 mol%) and pyrrolidine (10 mol%) in water (Table 1, entry 3). The reaction time was reduced (1.5 h) slightly to generate the desired product in 87% yield. The fact that nucleophilicity of L-proline in water is slightly higher than pyrrolidine [27], the reaction mixture was refluxed in water with L-proline (10 mol%) as well. The reaction took similar time (1.5 h) to obviate 90% isolated yield of the desired product, but it was comparable to L-proline (Table 1, entry 6) with no visible contribution

from *N,N'*-diphenylthiourea. We reasoned that the thiourea group in *N,N'*-diphenylthiourea and the carboxylate group in L-proline might have engaged in H-bonding interaction leading to partial functional deactivation of the thiourea group [28]. Similar observation was made when the model reaction was carried out with phenyl prolinamide as catalyst, but significant reduction of reaction time (1 h) was noted. The same catalyst completed the reaction within 40 min in the presence of 10 mol% *N,N'*-diphenylthiourea as co-catalyst. These observations confirmed that the presence of both functionalities may be critical to achieve faster completion of the reaction. But when the reaction was carried out with *N*-benzyl-*N'*-phenyl prolinamide with *N,N'*-diphenylthiourea as co-catalyst (entry 8), the reaction took almost the same time as that of *N,N'*-diphenylthiourea as the sole catalyst (entry 1). It shows that the presence of the secondary amine in pyrrolidine accelerated the reaction much faster than that of the tertiary amine (entry 9) in the presence of thiourea unit. In order to see if a bifunctional catalyst having the same catalytic sites could be a better catalyst than cooperative catalysis by separate pyrrolidine moiety and thiourea, we decided to synthesize a secondary aminothiurea **1** from L-proline (Scheme 2). The catalyst (**1**) was synthesized by

converting Boc-protected L-proline to the amide derivative (A) followed by treatment with phenyl isothiocyanide in methylene chloride and then TFA in three simple steps [29].

With the secondary aminothiurea in hand, we carried out the model reaction with 10 mol% of the catalyst **1** in 1 mL of water by heating at reflux temperature. Gratifyingly, we observed complete conversion of the starting aldehyde within 20 min to obviate the desired product with an excellent isolated yield of 93%. It was interesting to observe that the reaction with the catalyst **1** took much lesser time than those where equimolar mixture of pyrrolidine and thiourea were used. This proves for the first time that catalytic efficiency of bifunctional catalyst is better than cooperative catalysis by two monofunctional catalysts.

In order to see the effect of solvents on efficacy of the reaction, we first screened the solvents like ethanol, methanol, water, ethanol-water (1:1), CH₃CN, THF, CHCl₃, and DCM at various reaction temperatures (Table 1S in supplementary materials). The best result was obtained in water where the

Table 2 Synthesis of coumarin based Trisubstituted methanes via Scheme 1

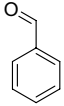
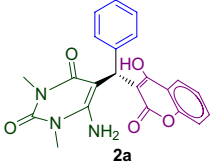
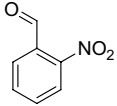
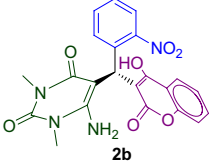
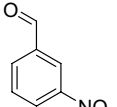
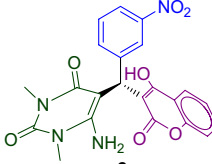
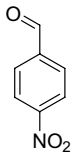
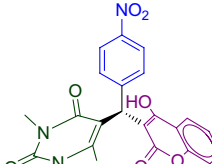
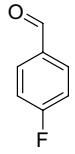
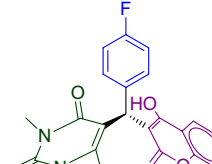
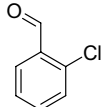
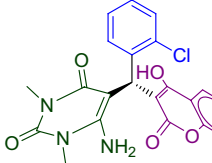
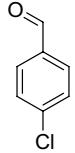
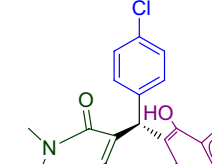
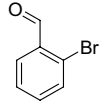
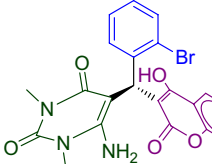
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					Found	Reported
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2		 2b	15	98	220–221	NA
3		 2c	15	93	230–232	NA
4		 2d	15	95	205–207	NA
5		 2e	15	95	246–248	248–250 [3]
6		 2f	15	97	227–229	227–228 [3]
7		 2g	15	95	219–220	218–220 [2]
8		 2h	15	96	210–212	NA

Table 2 (continued)

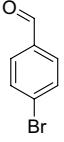
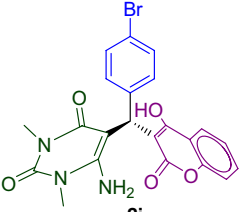
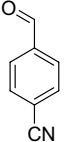
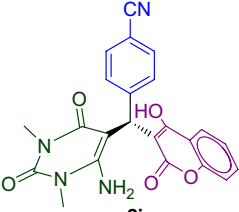
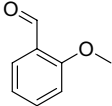
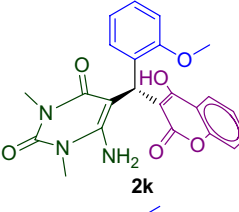
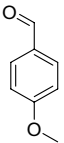
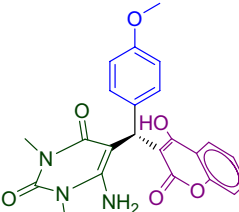
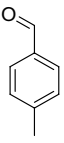
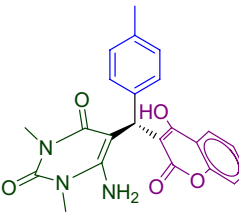
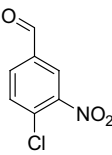
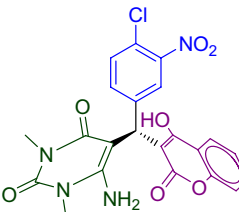
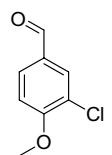
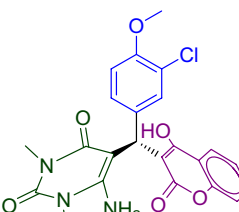
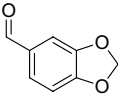
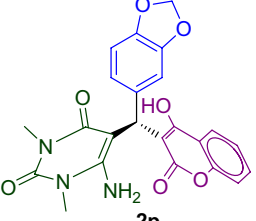

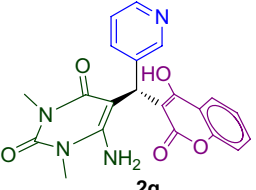
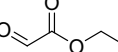
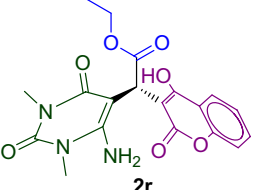
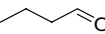
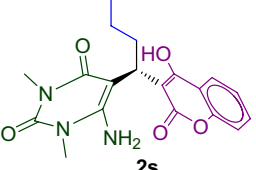
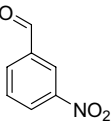
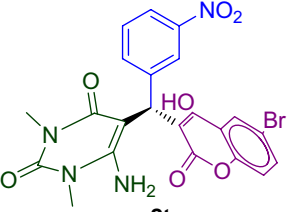
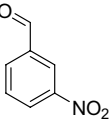
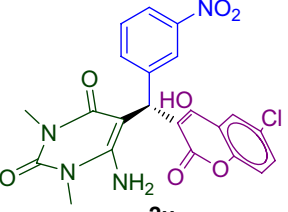
Entry	Aldehyde	Product	Time (min)	%Yield ^a	mp (°C)	
					Found	Reported
9		 2i	15	95	236–238	237–238 [3]
10		 2j	15	95	221–222	221–223 [3]
11		 2k	20	90	200–202	NA
12		 2l	20	90	180–181	178–180 [2]
13		 2m	20	92	202–204	NA
14		 2n	20	98	230–231	NA
15		 2o	20	91	228–230	NA

Table 2 (continued)

Entry	Aldehyde	Product	Time (min)	%Yield ^a	mp (°C)	
					Found	Reported
16		 2p	15	91	239–240	NA
17		 2q	20	92	223–225	NA
18		 2r	30	88	195–197	NA
19		 2s	30	81	110–111	NA
20 ^b		 2t	15	93	265–267	NA
21 ^c		 2u	15	95	243–245	NA

Reaction conditions: Stoichiometric mixture of 6-amino-1,3-dimethyluracil, aldehyde and 4-hydroxycoumarin in 1 mL water (solvent) with 5 mol% of the catalyst **1** at reflux temperature

^aIsolated yield

^b6-Bromo-4-hydroxycoumarin was employed

^c6-Chloro-4-hydroxycoumarin was employed

NA not available

Table 3 Effect of catalyst and reaction conditions on stereoselectivity of the model reaction

Entry	Catalyst	Temp.	t (h:min)	% Yield ^a	%ee ^b
1	1 (5 mol%)	RT	12:00	70	nil
		10 °C	48:00	–	–
2	(5 mol%)	RT	12:00	67	nil
3	(5 mol%) and (5 mol%)	RT	12:00	77	nil
4	(5 mol%)	RT	12:00	28	nil

Reaction conditions: 3-nitrobenzaldehyde (0.1 mmol), 4-hydroxy coumarin (0.1 mmol), 6-amino-1,3-dimethyluracil (0.1 mmol) was in water (0.2 mL) with the specified catalysts

^aYield of the purified product

^b%ee was determined by HPLC using Chiralcel AD-H column

reaction was completed within 20 min of heating at reflux temperature to obviate the desired product in 93% isolated yield.

Then we went on to optimize the catalyst loading (Table 2S in the supplementary materials) for the reaction. Under catalyst-free condition, only a trace amount of product was obtained upon stirring for 12 h. The same reaction when carried out employing 1 mol% of the catalyst resulted in 70% yield of the desired product within 1 h of stirring under reflux. But, a significant increase in reaction rate was observed upon increasing the catalyst loading to 5 mol% to obtain the desired product with 93% yield within 20 min. However, further enhancement of catalyst loading to 10–15 mol% did not reduce the reaction time appreciably and gave almost similar yields.

3.1 Substrate Scope

Having achieved the optimum reaction conditions, we expanded the scope of our protocol by varying the aldehyde in the model reaction. The results are summarized in Table 2. The reaction worked extremely well with almost all the aldehydes. Aromatic aldehydes having electron-withdrawing substituents (entries 2–10) as well as the ones containing electron-donating substituents (entries 11–13) gave very good to excellent yields. Thus the nature and position of the substituents did not have much of an effect on the reaction rate. The reaction also worked well with a heteroaromatic aldehyde (entry 17), ethyl glyoxalate (entry 18) and an

aliphatic aldehyde (entry 19) producing the desired products in good to excellent yields. When the reaction was expanded to the substituted 4-hydroxy coumarins, we noted excellent conversion under the optimised conditions (Entries 20–21).

3.2 Study of Asymmetric Induction

Although this L-proline derived bifunctional amidothiurea catalyst is asymmetric in nature, it did not give any stereoselectivity probably due to the high reaction temperature. In our bid to achieve enantiomeric induction by conducting the reaction at room temperature, we observed the reaction for 12 h to get 70% yield and no enantioselectivity (Table 3, entry 1). The reaction at 10 °C did not give the desired product at all within 48 h. Interestingly, the reaction failed to show any enantioselective induction when the reaction was catalysed by *N*-phenyl L-prolinamide in the presence of a chiral thiourea catalyst, (*S*)-2-[[3,5-bis(trifluoromethyl)phenyl]thioureido]-*N*-benzyl-*N*,3,3-trimethylbutanamide at room temperature (Table 3, entry 3–4).

3.3 Mechanistic Perspective

While trying to unfold the mechanism of the reaction, we carried out two control experiments by reacting *m*-nitrobenzaldehyde with 4-hydroxycoumarin and 6-amino-1,3-dimethyluracil separately under the optimized reaction

Scheme 3 Control experiments

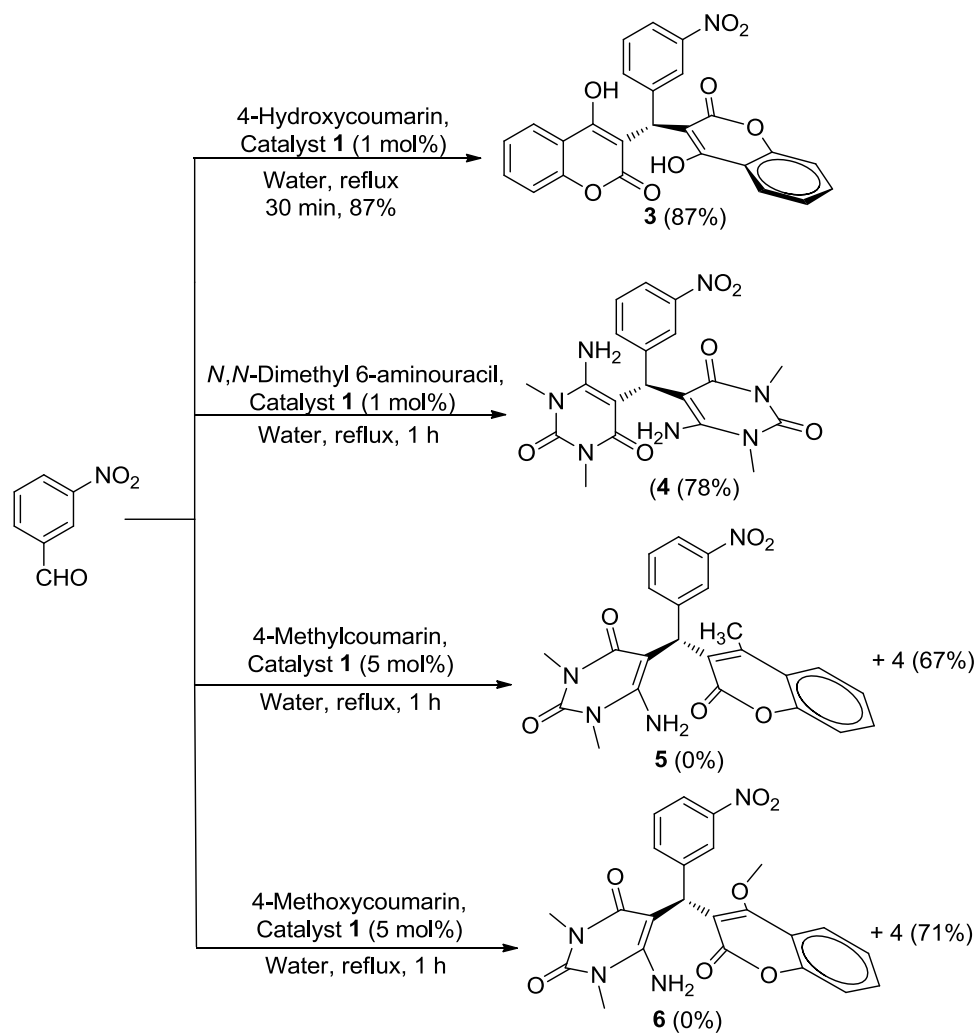
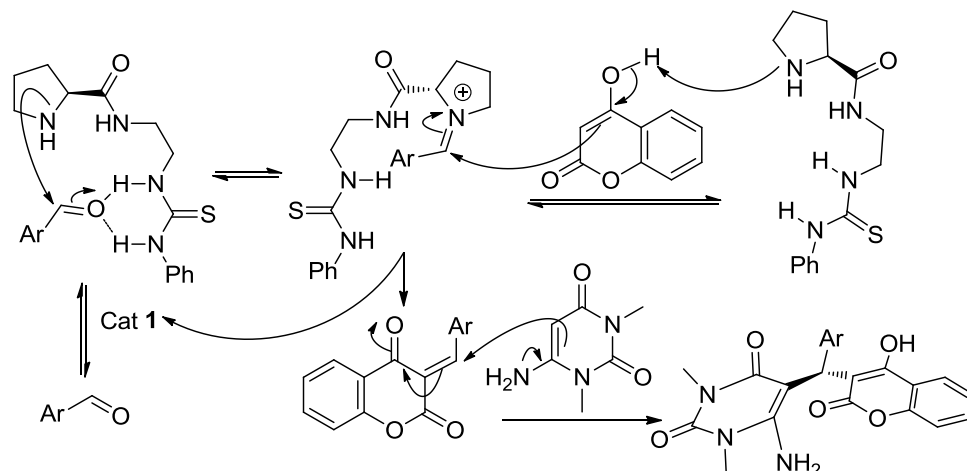


Fig. 2 Plausible reaction mechanism



conditions. The formation of symmetrical trisubstituted methanes (**3**) from the reaction of 4-hydroxycoumarin took only 30 min for complete conversion, while the reaction of 6-amino-1,3-dimethyluracil with the same aldehyde

under similar reaction conditions took almost double the reaction time (1 h) for complete conversion to the corresponding symmetrical TRSM, **4** (Scheme 3). On the other hand, the reaction with other coumarin derivatives such as

4-methylcoumarin, and 4-methoxycoumarin did not generate unsymmetrical TRSMs **5** and **6**, but the symmetrical TRSM, **4** only.

Above observations suggest that (i) the hydroxy group at 4-position of the coumarin is vital for the reaction, (ii) the pyrrolidine moiety has acted as a base to activate 4-hydroxy coumarin to form the Knoevenagel product, and (iii) the activation of the aldehyde by the thiourea for addition of the pyrrolidine nucleophile is true in all the cases. The base catalyzed activation of 6-amino-1,3-dimethyluracil does not arise at all, rather it is driven by the amino group in it. The thiourea scaffold might have also catalyzed the formation of the iminium salt through H-bond activation of aldehyde for nucleophilic attack by pyrrolidine moiety of the catalyst **1**. Due to greater electrophilicity of H-bond activated aldehyde, the formation of iminium ion with proline derived pyrrolidine is much faster which ultimately affects overall reaction time. It may be noted that the transformation of the carbonyl compound into an iminium species increases the electrophilicity of the carbonyl compound for the subsequent attack of nucleophiles [30]. The higher electrophilicity of the resultant iminium ion might have facilitated easier C–C bond forming reaction with C-3 carbon of 4-hydroxy coumarin to yield the Knoevenagel product. Since 6-amino-1,3-dimethyluracil is a softer nucleophile than 4-hydroxy coumarin, the former will undergo 1,4-addition reaction preferentially with the Knoevenagel product to give the desired product. With all probabilities, the Michael addition of 6-aminouracil to the Knoevenagel product may be very fast and requires no catalyst. As a result, the reaction did not show any stereoselective induction in the presence of the chiral catalysts (Table 3). The plausible mechanism is schematically presented in the Fig. 2.

4 Conclusion

For the first time, we have reported the catalytic application of L-proline derived aminothiourea **1** in a multicomponent reaction. The bifunctional catalyst **1** demonstrated multiple catalytic role in the multicomponent synthesis of coumarin-based unsymmetrical trisubstituted methanes whose prototype has been found to be acetylcholinesterase inhibitor. The secondary aminothiourea core of the L-proline derived catalyst has shown excellent catalytic activity in the synthesis of coumarin based trisubstituted methanes. The better activity of the catalyst **1** is explained to be the result of dual catalytic role of the secondary amine group as base and nucleophile to accelerate the reaction rate. The method requires low catalyst loading (5 mol%) and very short reaction time (15–30 min) to give excellent yields. The use of water as a reaction medium facilitated isolation of the product by simple filtration and therefore chromatographic separation employing hazardous organic solvents could be avoided. Nevertheless, we report for the first time that catalytic

efficiency of bifunctional catalyst is better than cooperative catalysis by two monofunctional catalysts.

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