MOLECULAR DIVERSITY FROM THE L-PROLINE-CATALYZED, THREE-COMPONENT REACTIONS OF 4-HYDROXYCOUMARIN, ALDEHYDE, AND 3-AMINOPYRAZOLE OR 1,3-DIMETHYL-6-AMINOURACIL

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GRAPHICAL ABSTRACT

Abstract The three-component reaction of 4-hydroxycoumarin, aldehyde, and aminopyrazole in the presence of a catalytic amount of L-proline in ethanol under reflux conditions provided the cyclized product (dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridine-6(7H)-one), whereas under similar reaction conditions, replacing aminopyrazole by 1,3-dimethyl-6-aminouracil provided the acyclic three-component product (6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione). This method is metal free and atom economical, and avoids column chromatographic purification as all the products can be purified by recrystallization.

Keywords Coumarin-fused polycyclic heterocycles; 1,3-dimethyl-6-aminouracil; L-proline; multicomponent reaction

INTRODUCTION

Multicomponent reactions (MCRs) have proved to be one of the efficient bond-forming tools in organic and medicinal chemistry. MCRs are economically
and environmentally profitable as they allow compounds to be synthesized with a minimum of synthetic time and effort.\cite{1,2} Also diverse chemical libraries of drug-like molecules could be generated from MCRs and may appear attractive from a drug discovery perspective. Synthesis of coumarin-fused polycyclic heterocycles attracts intensive attention in recent years due to the potential pharmaceutical applications of coumarin derivatives such as anticoagulant,\cite{3-5} antifungal,\cite{6} antimicrobial,\cite{7} antiasthmatic,\cite{8} antitumor,\cite{9} and anti-HIV\cite{10} agents and in drug discovery.\cite{11,12} Further, 3-aryl-substituted coumarins have wide application as additive in foods, perfumes, and cosmetics.\cite{13} Similarly, aminopyrazole and aminouracil are also important synthetic building blocks in modern heterocyclic chemistry because of their wide biological activities.\cite{14,15} Recently two methods have been reported in the literature for the synthesis of coumarin-fused polycyclic heterocycles using molecular iodine\cite{16} and tetrabutylammonium bromide (TBATB)\cite{17} as catalyst. Some of the biologically active coumarin-fused polycyclic heterocycles and 3-substituted coumarin derivatives are shown in Fig. 1.

Organocatalysts have gained immense interest in organic synthesis as they are typically nontoxic and environmentally friendly and thus make the process green.\cite{18} We have chosen L-proline as organocatalyst for this reaction as it is one of the cheap, readily available, and most explored organocatalysts.\cite{19,20} Considering the importance of coumarins, aminopyrazole, and pyrimidine moieties and also as a part of our continuing efforts\cite{21} to develop a new route for the access of functionalized heterocyclic molecules, herein we have demonstrated a direct route to access both polycyclic coumarin-fused heterocycles and 6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-diones via a sequential three-component reaction of aldehydes, 4-hydroxycoumarin, and 3-aminopyrazole derivatives or 1,3-dimethyl-6-aminouracil in the presence of L-proline as an organocatalyst in ethanol (Scheme 1).

**Figure 1.** Biologically active coumarin-fused polycyclic heterocycles and 3-substituted coumarin derivatives.
RESULTS AND DISCUSSION

In our initial studies, the reaction of 4-hydroxycoumarin, 4-chlorobenzaldehyde, and 3-amino-5-methylpyrazole was taken as a model reaction (Table 1). First we tried this model reaction in the absence of catalyst but we did not observe the desired product 1d at room temperature even after 24 h of stirring (Table 1, entry 1). Then the same reaction was performed under reflux conditions in ethanol in the absence of catalyst and gave the desired product 1d in only 44% yield even after 10 h (Table 1, entry 2). The product was fully characterized by infrared (IR) and 1H and 13C NMR spectroscopy. Then we chose L-proline as organocatalyst for this reaction, and interestingly, when the same reaction was performed in the presence of L-proline as catalyst, the yield was improved. The reaction was performed in

![Scheme 1. Synthesis of dihydrochromeno[4,3-b]pyrazolo[4,3-c]piperidin-6(H)-ones and 6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-diones.](image)

| Entry | Catalyst            | Solvent | Time (h) | Yieldb (%) |
|-------|---------------------|---------|----------|------------|
| 1.    | No catalyst         | EtOH    | 24       | NRc        |
| 2.    | No Catalyst         | EtOH    | 10       | 44         |
| 3.    | L-proline (5 mol%)  | EtOH    | 12       | 46         |
| 4.    | L-proline (10 mol%) | EtOH    | 10       | 58         |
| 5.    | L-proline (15 mol%) | EtOH    | 10       | 70         |
| 6.    | L-proline (20 mol%) | EtOH    | 8        | 84         |
| 7.    | L-proline (20 mol%) | CH3CN   | 16       | 51         |
| 8.    | L-proline (20 mol%) | CH2Cl2  | 14       | Traces     |
| 9.    | L-proline (20 mol%) | Water   | 16       | 40         |
| 10.   | L-proline (20 mol%) | THF     | 20       | Traces     |

*Table 1. Optimization of reaction conditions*

*All the reactions were carried out using 4-hydroxycoumarin, 4-chlorobenzaldehyde, and 3-amino-5-methylpyrazole in 1:1:1 ratio.

**Isolated yield.

cYield at room temperature.

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the presence of 5, 10, 15, and 20 mol% of catalyst (Table 1, entries 3–6). The best result was obtained in terms of yield (84%) and reaction time (8 h) when the reaction was performed using 20 mol% of L-proline (Table 1, entry 6). To find the best solvent for this reaction, various other solvents such as CH3CN, dichloromethane (DCM), water, and tetrahydrofuran (THF) were screened under reflux conditions on the same model reaction. Among all these solvents, EtOH was proved to be the best solvent for this reaction in terms of yield and reaction time (Table 1, entry 6).

After optimizing the reaction conditions, the generality and scope of this three-component reaction was studied by varying aromatic aldehydes and aminopyrazoles, and the results are summarized in Table 2. A wide range of aromatic aldehydes having substituents such as -CH3, -OCH3, -Cl, -F, -NO2, and -CH(CH3)2 were found suitable for this L-proline-catalyzed three-component reaction to provide the corresponding cyclized products in 60–84% yields (Table 2, entries 1–10).

Next, we tried to explore 1,3-dimethyl-6-aminouracil as one of the substrate by replacing aminopyrazole derivatives under the similar reaction conditions. Interestingly, when 1,3-dimethyl-6-aminouracil was treated with 4-hydroxycoumarin and 4-chlorobenzaldehyde under the similar optimized reaction conditions, the corresponding three-component acyclic product 2c was obtained instead of the desired cyclic product as shown in Scheme 2. Compound 2c was fully characterized by spectroscopic techniques. Considering the presence of two biologically important molecules connected through an alkyl/aryl group in this acyclic three-component product, we turned our attention to study the scope of this reaction by varying

| Entry | R1        | R     | Product | Time (h) | Yield (%) |
|-------|-----------|-------|---------|----------|-----------|
| 1.    | C6H5      | -CH3  | 1a      | 8        | 79        |
| 2.    | 4-CH1C6H4 | -CH3  | 1b      | 6        | 67        |
| 3.    | 4-OCH1C6H4| -CH3  | 1c      | 6        | 72        |
| 4.    | 4-ClC6H4  | -CH3  | 1d      | 8        | 84        |
| 5.    | 3-NO2C6H4 | -CH3  | 1e      | 10       | 60        |
| 6.    | 4-FC6H4   | -CH3  | 1f      | 6        | 71        |
| 7.    | 4-CH(CH3)2C6H4 | -CH3 | 1g | 7 | 70 |
| 8.    | 4-OCH1C6H4| -H    | 1h      | 5        | 74        |
| 9.    | 4-ClC6H4  | -H    | 1i      | 8        | 77        |
| 10.   | 4-FC6H4   | -H    | 1j      | 6        | 75        |

aAll the reactions were carried out using 4-hydroxycoumarin (1 mmol), aromatic aldehydes (1 mmol), and 3-amin-5-methylpyrazole (1 mmol) in ethanol by using L-proline (20 mol%) under reflux condition.

bYields refer to isolated products.
aldehydes and keeping 4-hydroxy coumarin and 1,3-dimethyl-6-aminouracil as fixed substrates. The results of this study are summarized in Table 3. All these products were fully characterized by the usual spectroscopic techniques and further confirmed by recording single-crystal x-ray structure of 2g (Fig. 2).

A plausible mechanism has been described in Fig. 3. Aldol condensation–Michael addition sequence is common in both the protocols but the intramolecular condensation–tautomerization sequence gives the synthesis of polycyclic coumarin-fused heterocyclic molecules while only the tautomerization leads to the synthesis

Table 3. Synthesis of 6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-diones

| Entry | R_1             | Product | Time (h) | Yield b (%) |
|-------|-----------------|---------|----------|-------------|
| 1.    | 4-CH_3C_6H_4    | 2a      | 5        | 80          |
| 2.    | 3-BrC_6H_4      | 2b      | 3        | 78          |
| 3.    | 4-ClC_6H_4      | 2c      | 6        | 83          |
| 4.    | C_6H_5          | 2d      | 4        | 78          |
| 5.    | Cyclohexyl      | 2e      | 10       | 67          |
| 6.    | 4-NO_2C_6H_4    | 2f      | 7        | 76          |
| 7.    | 4-CH(CH_3)_2C_6H_4 | 2g    | 5        | 81          |

All the reactions were carried out using 4-hydroxycoumarin, aldehyde derivatives, and 1,3-dimethyl-6-aminouracil in 1:1:1 ratio by using L-proline (20 mol%) in ethanol under reflux condition.

Yield refers to isolated products.
of 6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-diones. When aminouracil cyclization did not occur, this may be due to the presence of a carbonyl group (amide) conjugated to the enamine moiety of compound 2, which reduces the nucleophilicity of the amino group.

Figure 2. Single-crystal x-ray crystallographic structure of 2g (CCDC 1024914).

Figure 3. Proposed mechanism for the three-component reaction.
CONCLUSION

We have described an efficient diversity-oriented multicomponent reaction for the synthesis of dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridine-6(7H)-ones and 6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-diones in ethanol under reflux conditions using L-proline (20 mol%) as an organocatalyst. This methodology offered several advantages including simple experimental procedure, no column chromatography, good yields, and no toxic by-product. Further functionalization of these molecules and their biological activity studies are under investigation and will be reported in due time.

EXPERIMENTAL

All the reagents were commercially available and used without additional purification. Reactions were monitored by thin-layer chromatography (TLC). Melting points were determined in a digital melting-point apparatus. IR spectra were recorded on a Shimadzu FTIR spectrophotometer in KBr pellets. 1H NMR and 13C NMR spectra were recorded in dimethylsulfoxide (DMSO-d6) and CDCl3 using Me4Si as internal standard on a Bruker 500-MHz or Avance II 400-MHz spectrometer. Elemental analyses were carried out in a Perkin-Elmer 2400 automatic carbon, hydrogen, and nitrogen analyzer. All unknown compounds were characterized by usual spectroscopic techniques and known compounds’ data were compared with the literature data and melting points.

General Synthetic Procedure of Compounds Dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridine-6(7H)-ones (1a–1j)

A mixture of aromatic aldehyde (1 mmol) and 4-hydroxycoumarin (1 mmol) in ethanol (3 ml) was stirred at the boiling temperature of ethanol for 30 min in the presence of L-proline (20 mol%). Then 3-amino-5-methylpyrazole (1 mmol) was added to the mixture and stirred under the reflux conditions until completion of the reaction according to thin-layer chromatography (TLC). The resulting precipitate was filtered, washed, and recrystallized with ethanol and ethylacetate (2:1) mixture to get the pure product.

8-Methyl-7-phenyl-9,11-dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridine-6(7H)-one (1a)

Yield, 79%; white solid; mp = 301–303 °C (lit.[16] 303–304 °C); IR (KBr): 3171, 3072, 1670, 1612 cm⁻¹; 1H NMR (500 MHz, DMSO-d6): δ 12.00 (s, 1H), 10.51 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.20-7.26 (m, 3H), 5.12 (s, 1H), 1.93 (s, 3H) ppm; 13C NMR (125 MHz, DMSO-d6): δ 161.9, 152.3, 147.8, 146.1, 145.7, 135.3, 132.2, 131.8, 129.5, 128.3, 128.0, 127.7, 126.6, 123.4, 116.3, 114.1, 103.5, 97.5, 37.2, 9.5 ppm. Anal. calcd. for C20H15N3O2 (329.35): C, 72.94; H, 4.59; N, 12.76. Found: C, 73.01; H, 4.56; N, 12.68.
Typical Experimental Procedure for the Synthesis of 6-Amino-5-
((4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-
2,4(1H, 3H)-diones (2a–2g)

A mixture of 4-hydroxycoumarin (1 mmol), 4-chlorobenzaldehydes (1 mmol),
and L-proline (20 mol%) were dissolved in EtOH (1 ml) and stirred under reflux con-
dition for 15 min. Afterward, 1,3-dimethyl-6-aminouracils (1 mmol) was added to the
solution, and stirring was continued until the completion of the reaction as shown by
TLC. Then the reaction mixture was allowed to cool at room temperature and the
resulting precipitate was filtered, washed, and recrystallized with ethanol and ethyl
acetate (2:1) mixture to afford the pure product.

6-Amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)(p-tolyl)methyl)1,3-dimethyl Pyrimidine-2,4(1H,3H)-dione (2a)

Yield, 80%; white granular solid; mp = 218–220 °C; IR (KBr): 3411, 3361, 3215, 3051, 2951, 1699, 1673, 1659, 1571, 1452, 1066, 1038, 855, 766 cm⁻¹; ¹H
NMR (400 MHz, CDCl₃): δ 13.59 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0
Hz, 1H), 7.31–7.25 (m, 2H), 7.11–7.07 (m, 4H), 6.69 (s, 2H), 5.70 (s, 1H), 3.57 (s,
3H), 3.33 (s, 3H), 2.31 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 165.4,
164.7, 154.9, 152.3, 150.7, 135.8, 134.4, 132.3, 129.2, 126.2, 124.9, 124.6, 117.4,
116.2, 104.3, 89.3, 36.3, 30.0, 28.7, 21.0 ppm. Anal. calcd. for C₂₃H₂₁N₃O₅
(419.43): C, 65.86; H, 5.05; N, 10.02. Found C, C, 65.93; H, 5.09; N, 10.14.

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SUPPLEMENTAL INFORMATION

Supplemental materials for this article can be accessed on the publisher’s
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