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# One-Pot Synthesis of 2-amino-4H-chromenes using L-Proline as a Reusable Catalyst

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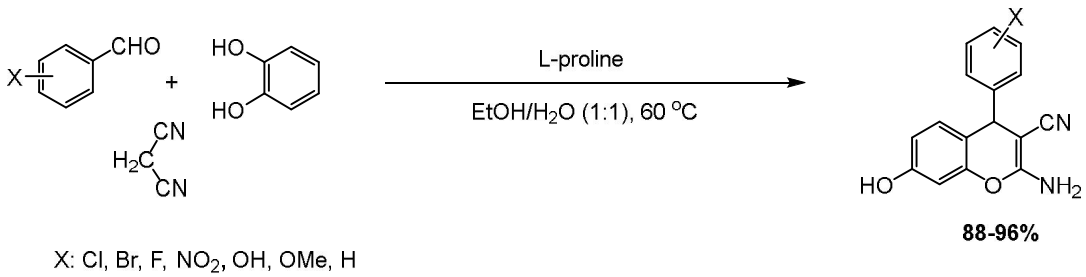
**ABSTRACT**

A new and efficient synthesis of2-amino-chromenes is achieved by one pot three-component reaction of aldehydes, malononitrile, and resorcinol using *L*-proline as a reusable catalyst. The key advantages of the present process are the use of a bioorganic and reusable catalyst, high yields of products, using green solvent and short reaction times from the principles of green chemistry point of view. *L*-proline can be reused five consecutive times without a noticeable loss in activity.

**GRAPHICAL ABSTRACT**




## 1. Introduction

Heterocycles are important molecules in medicinal and pharmaceutical chemistry, because are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor,mantibiotic, anti"inflammatory, antidepressant, antimalarial, anti"HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents.[1-6] They have also been frequently found as key structural units in synthetic pharmaceuticals and agrochemicals.[1] 4H-pyran derivatives are important heterocyclic compounds due to their excellent biological activities and have been widely applied in pharmaceutical and medicinal fields.[7]

The 4H-pyran were found to exhibit anti-proliferative, cancer chemopreventive, antimyopic, antirheumatic, antibacterial, hypotensive, and antiasthmatic activities.[8-11]Among the important 4H-pyran heterocyclic compounds, 2-amino-chromenes are widely used as pigments, potential agrochemicals, cosmetics, and represent an important class of chemical entities being the main constituents of many natural products.[12-14] The biological activity of 2-amino-chromene derivatives has encouraged chemists to develop numerous one-pot, green strategies for their preparation.Recently, a number of protocols for several modified procedures have been reported for the synthesis of 2-amino-4H-chromenes using different homogeneous or heterogeneous catalysts.[14]

In recent times, multicomponent reactions have become a very popular strategy in the discovery of biologically active novel molecules due to its simple experimentation, atom economy and high yields of the products.[15-16]

## 2. Result and discussion

In recent times, the catalytic activity of *L*-proline for organic reactions has been reported in a wide range of publications. Herein we wish to report a newt and environmentally friendly procedure for the synthesis of 2-amino-4H-chromenes using *L*-proline as an efficient catalyst. In order to optimize the reaction conditions and obtain best catalytic activity, the model reaction (4-chloro benzaldehyde (1 mmol), malononitrile (1 mmol) and resorcinol (1 mmol)) was conducted in different reaction parameters such as solvent and amount of catalyst (**Scheme1**). First, the effect of several solvent was tested on the model reaction. As shown in **Table 1**, the best yield was obtained when the reaction was performed in EtOH/H2O (1:1). Then, the influence of catalyst amount on

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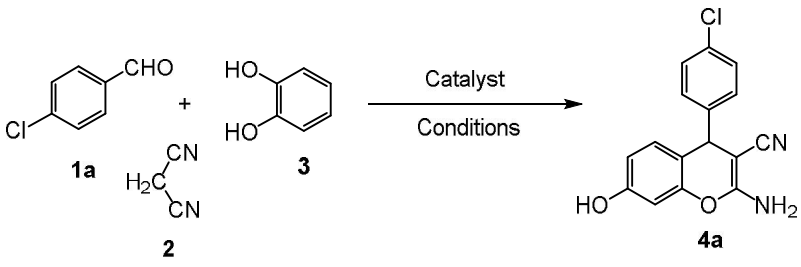
the reaction was tested by different amount of catalyst. It was observed that while the amount of catalyst increased from 0.01 to 0.03 g, the product yield raised signi from 56% to 96%, which is probably due to theavailability of more acid sites (**Table 1, Entry 8**). Therefore, the best results obtained when 0.03 g of catalyst in EtOH/H2O (1:1) at 60 °C. In the absence of catalyst, only 15% product was observed after 120 min. To determine the scope of the designed protocol, a number of commercially available aldehydes were examined in this transformation under optimized reaction condition (**Scheme 2**), and the results were summarized in **Table 2**. As shown in **Table 2**, aldehydes were found to afford the expected product. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields.

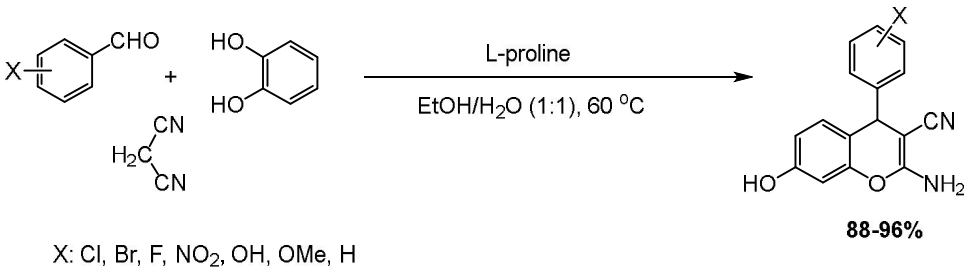



**Scheme 1.** L-proline catalyzed the model reaction.

**Table 1.** Optimization of reaction conditions [a]

| Entry | Solvent (Tem) | Catalyst amount (g) | Time (min) | Yield (%) [b] |
|---|---|---|---|---|
| 1 | $CH_3CN$ (Ref) | 0.01 | 60 | 68 |
| 2 | EtOH (Ref) | 0.01 | 60 | 80 |
| 3 | $H_2O$ (Ref) | 0.01 | 60 | 79 |
| 4 | EtOH/$H_2O$ (1:1) (60 °C) | 0.01 | 60 | 86 |
| 5 | 1,4-dioxane (Ref) | 0.01 | 60 | 72 |
| 6 | THF (Ref) | 0.01 | 60 | 61 |
| 7 | EtOH/$H_2O$ (1:1) | 0.02 | 40 | 91 |
| 8 | EtOH/$H_2O$ (1:1) | 0.03 | 30 | 96 |
| 9 | EtOH/$H_2O$ (1:1) | 0.04 | 30 | 96 |
| 10 | EtOH/$H_2O$ (1:1) | --- | 120 | 15 |

[a] Reaction conditions:aldehyde (1 mmol), malononitrile (1 mmol), resorcinol (1 mmol),solvent (10 mL). [b] Isolated yield.




**Scheme 2.** L-proline catalyzed Synthesis of 2-amino-chromene derivatives.

The reusability of catalyst was tested on the model reaction. As shown in **Fig. 1**, *L*-proline can be reused five consecutive times without a noticeable loss in activity.

## 3. Conclusion

In summary, we described *L*-proline as a reusable, readily available, inexpensive and efficient catalyst for the one-pot synthesis of 2-amino-chromenes. The methodology offers several advantages including increased variations of substituent in the product with high yields, operational simplicity, minimum environmental effects and above all, the ease in purification of products simply by crystallization.

## 4. Experimental

A mixture of aldehyde (1 mmol), malononitrile (1 mmol), resorcinol (1 mmol) and L-proline (0.03 g) in EtOH:$H_2O$ (1:1)

(10 mL) was stirred at 60 °C. After completion of the reaction (monitored on TLC), ethanol was removed, Ethyl acetate and water were added and the product was extracted. The crude product was obtained recrystallized from ethanol and water. Next, extracted aqueous layer containing catalyst was washed with 10 ml of dichloromethane twice and was used for four times (Fig. 1).

**Table 2.** Synthesis of 2-amino-chromene derivatives.

| Entry | X | Product | Time (min) | Yield (%) [b] | MP (°C) |
|---|---|---|---|---|---|
| 1 | 4-Cl | **4a** | 30 | 96 | 160-162[16] |
| 2 | 4-OMe | **4b** | 50 | 91 | 108-111[16] |
| 3 | 4-$NO_2$ | **4c** | 65 | 88 | 165-167[16] |
| 4 | 4-OH | **4d** | 80 | 92 | 250-252[16] |
| 5 | 4-Br | **4e** | 30 | 95 | 221-223[16] |
| 6 | 4-F | **4f** | 30 | 90 | 185-188[16] |
| 7 | 3-$NO_2$ | **4g** | 55 | 91 | 166-169[16] |
| 8 | H | **4h** | 35 | 96 | 234-237[16] |

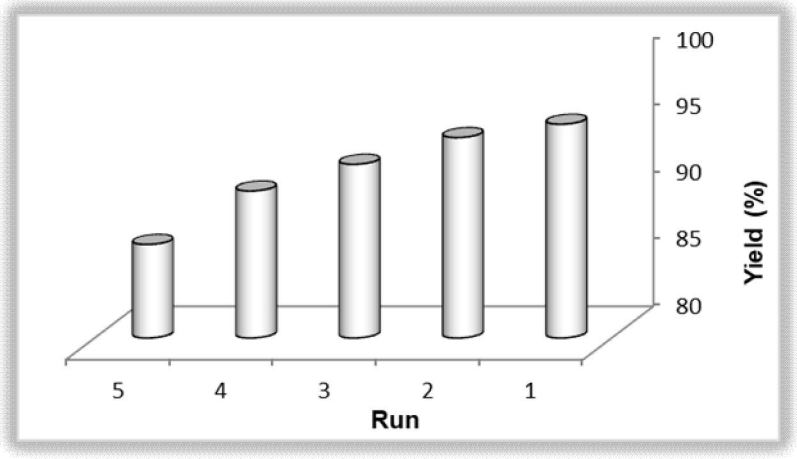



**Fig 1.** Reusability of L-proline in the model reaction.

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