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# L-Proline catalyzed synthesis of heterocyclic compounds: A review

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**Abstract**
Catalysis plays an important role in organic synthesis. L-proline as a natural amino acid has emerged as an efficient and environmentally benign organocatalyst for the synthesis of biologically important heterocyclic compounds.This review present an overview of the applications of L-proline as an organocatalyst for the synthesis of structurally diverse and biologically important heterocyclic compound. This review summarized some recent literature report of L-proline catalyzed synthesis of some heterocyclic compounds published during the period 2014 to 2025.

**Keywords:** L-proline, Heterocyclic compound, Organocatalyst

## Introduction

Heterocyclic compounds represent one of the most important classes of organic compounds due to their widespread occurrence in natural product and their extensive application in pharmaceuticals, agrochemicals, dyes, materials and other biologically active compounds [1-2]. Several heterocyclic compounds exhibits significant pharmacological properties such as antimicrobial, antiviral, anticancer, anti-inflammatory, analgesic, and antioxidant activities [3]. Therefore, the development of efficient and environmentally benign methods for the synthesis of heterocyclic compound has received considerable attention in synthetic organic and medicinal chemistry.

Conventional approaches for the synthesis of heterocyclic compound often involve hazardous or toxic organic solvent, transition-metal catalyst and relatively harsh reaction condition. Although these methods can provide efficient access to heterocyclic compound, the use of hazardous and environmentally unfavorable solvent and metal based catalyst can create concern related to toxicity, waste generation and sustainability. In addition, conventional synthetic procedure may require multistep workup and purification process, which can increase solvent consumption and overall environmental impact. Therefore, the green chemistry principal encouraged researchers to develop catalytic methodologies that minimize waste, reduce toxicity and operate under mild and sustainable condition [4-7].

Organocatalysis has become an important alternative to metal based catalysis. Organocatalysts are metal-free organic molecule capable of accelerate chemical transformation through different modes of substrate activation, including transient covalent and non-covalent interaction such as hydrogen bonding, ion pairing and electrostatic interaction [8, 9]. L-proline is a secondary amino acid containing both a carboxylic acid group and secondary amine (Fig. 1). Its bifunctional nature enables it to participate in different catalytic pathways, particularly through enamine and iminium-ion formation [10]. Among various organocatalysts L-proline has attracted considerable attention because it is a naturally occurring amino acid, readily available, inexpensive and relatively non-toxic. Moreover, L-proline has demonstrated as an organocatalyst, catalyze a broad range of carbon-carbon and carbon-heteroatom bond forming reactions [11-13]. Importantly the chiral environment provides by L-proline can also promote asymmetric transformation with high level of stereo selectivity [14]. The structure of L-proline is given below.

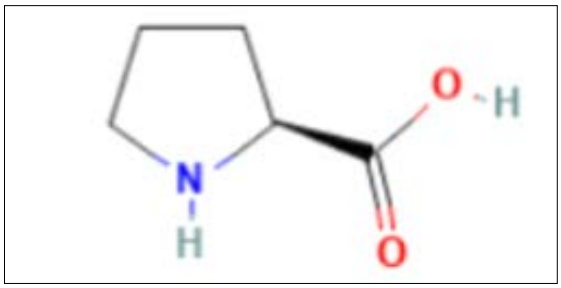



**Fig 1:** The structure of L-Proline

The application of L-proline in heterocyclic synthesis is particularly significant because it enable the synthesis of structurally diverse heterocyclic compound under relatively mild reaction condition. These reactions often provide good to excellent yield while reducing the need for expensive metal catalyst and hazardous reagents [15, 16]. Another important advantage of L-proline catalysis is its compatibility with green synthetic principal. Several L-proline catalyzed reaction have been performed using water, ethanol, aqueous media, solvent free condition, recyclable catalytic system and one pot multicomponent strategies can further improve the efficiency and sustainability of these synthetic process [17].

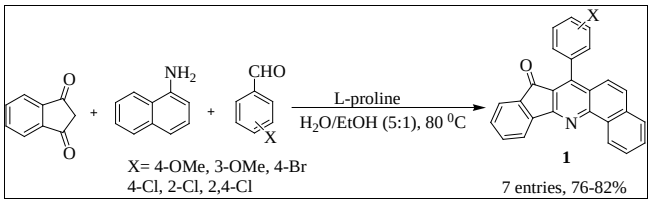
In this review we discuss L-proline catalyzed synthesis of some important bioactive heterocyclic compounds reported in the literature that may provide reliable literature for further research in this field.

**L-Proline Catalyzed Synthesis of Some Heterocyclic Compounds.**

L-proline has been found to be an efficient catalyst for the synthesis of various biologically active heterocyclic compounds. Some of them are discussed below.

### 1. Synthesis of Quinoline derivatives

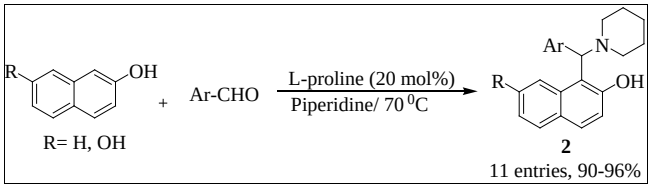
E. Davoodi and coworker [18] reported the synthesis of benzo [b]-indeno [1, 2-b] quinoline derivatives [1] via one pot three component reaction of 2H-indene-1, 3-dione, naphthalene-1-amine and aldehyde stirred at 80 ºC in aqueous media using L-proline as catalyst (Scheme-1).



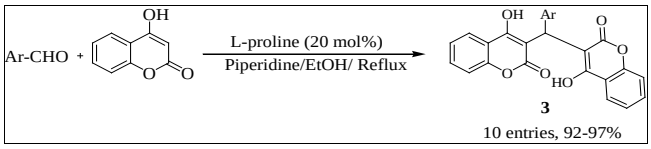

**Scheme 1:** Synthesis of Quinoline derivatives

### 2. Synthesis of Betti Base and Biscoumarin derivatives

S. Zahiri, *et al.* [19] used L-proline as catalyst for the synthesis of Betti base [2] via modified Mannich reaction by the condensation reaction of aldehyde, 2-naphthol, or 2, 7-naphthalendiol and piperidine stirred at 70 ºC (Scheme-2). Also the L-proline was used for the synthesis of Biscoumarin derivatives [3] from aromatic aldehyde and 4-hydroxy coumarin in ethanol under reflux condition (Scheme-3).



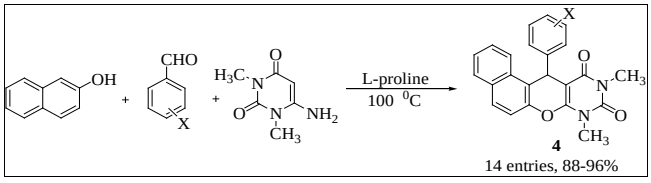

**Scheme 2:** Synthesis of Betti Base




**Scheme 3:** Synthesis of Biscoumarin derivatives

### 3. Synthesis of Naphthopyranopyrimidines derivatives

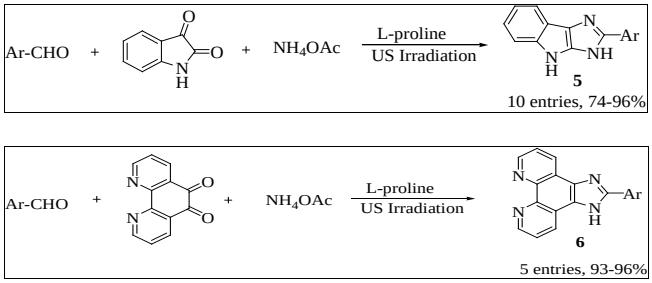
S. C. Azimi [20] employed L-proline as catalyst for the synthesis of naphthopyranopyrimidine derivatives [4] by the reaction of β-naphthol, aldehyde and 6-amino-1, 3-dimethyluracil under solvent free condition at 100 ºC. Author reported that several aldehyde having electron withdrawing or donating group gives corresponding naphthopyranopyrimidine derivative with good to excellent yield. Short reaction time, easyworkup, excellent yield, use of non-toxic catalyst and solvent free condition are the main advantages of this method (Scheme-4).




**Scheme 4:** Synthesis of Naphthopyranopyrimidines derivatives

### 4. Synthesis of Substituted Imidazole derivatives

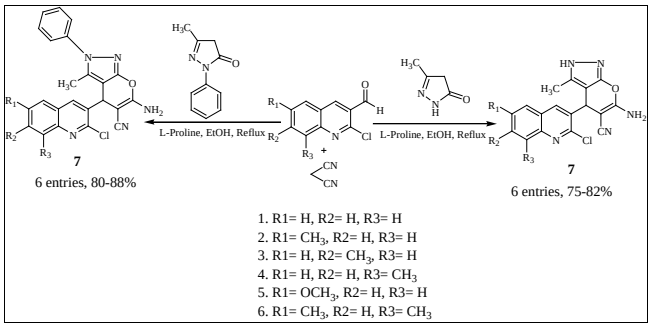
S. Damavandi and R. Sandaroos [21]described the efficient synthesis of 3, 4-dihydro-aryl-imidazo [4,5-b] indole derivatives [5] via multicomponent reaction of aromatic aldehyde, indoline-2, 3 dione and ammonium acetate and 2-aryl-1H-imidazo[4,5f] phenanthroline derivatives [6] via multicomponent reaction of aromatic aldehyde, 1, 10-phenanthroline-5, 6-dione and ammonium acetate catalyzed by L-proline under ultrasound irradiation (Scheme-5).




**Scheme 5:** Synthesis of substituted Imidazole derivatives

### 5. Synthesis of pyrano [2, 3-C] pyrazole-5-carbonitrile derivatives

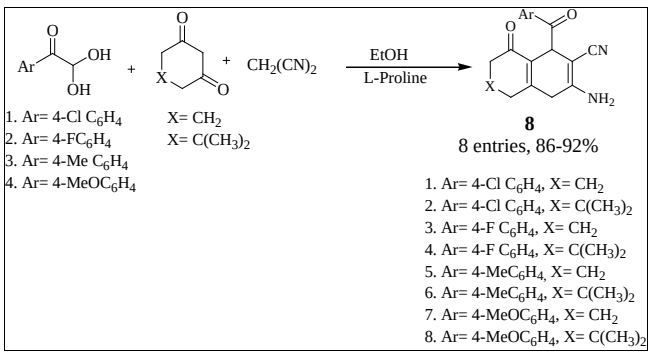
The synthesis of pyrano[2, 3-C] pyrazole-5-carbonitrile derivatives [7] from the reaction of 2-chloro quinoline-3-carbaldehyde derivative, malononitrile and 3-methyl pyrazoline-5-one derivatives refluxed in ethanol using L-proline as catalyst was reported by K. S. Mani and S. P. Rajendran [22] (Scheme-6).




**Scheme 6:** Synthesis of pyrano [2, 3-C] pyrazole-5-carbonitrile derivatives

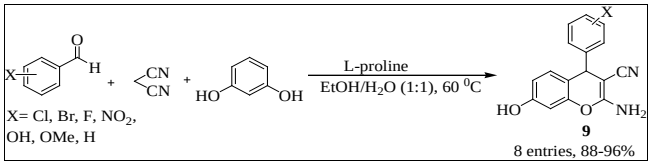
### 6. Synthesis of Chromene derivatives

P. M. Ahmad and coworker [23] described the synthesis of 4H-Chromene derivatives [8] from substituted aryl glyoxal monohydrate with 1, 3 diketone and malononitrile in ethanol catalyzed by L-proline catalyst (Scheme-7).




**Scheme 7:** Synthesis of 4H-Chromene derivative

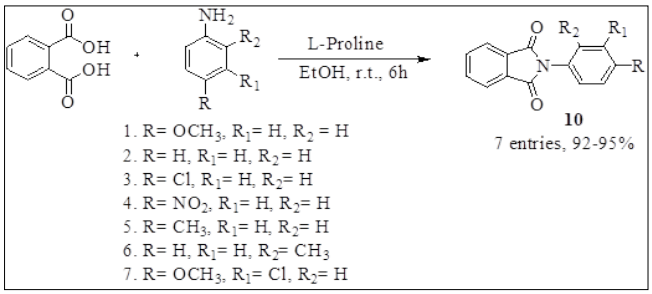
Z. Moghadasi [24] also reported the synthesis of 2-amino-4H-chromene derivatives [9] using L-proline as catalyst from the reaction of aldehyde, Malononitrile and resorcinol in EtOH/$H_2O$ (1:1) stirred at 60 ºC (Scheme-8). The uses of bioorganic and reusable catalyst, high yield of product, use of green solvent and short reaction time are some main advantages of this method.




**Scheme 8:** Synthesis of 2-amino 4H-chromene derivatives

## 7. Synthesis of phthalimide derivatives

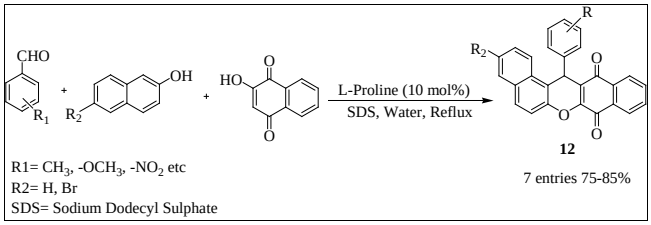
S. Perveen and R. Orfali [25] described the synthesis of pthalimide derivatives [10] catalyzed by L-proline from the reaction of phthalic acid and aryl amine stirred at 30 °C room temperature (Scheme-9).




**Scheme 9:** Synthesis of phthalimide derivatives

## 8. Synthesis of Xanthene derivatives

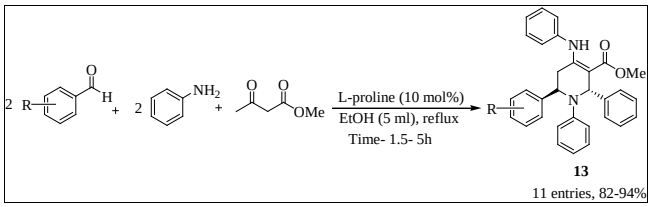
K. Ahmed *et al.* [26] reported the synthesis of 12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-one derivatives [11] and 14-aryl-14H-dibenzo [a, i] xanthene-8, 13-dione derivatives [12] via condensation reaction of β-naphthol, aromatic aldehyde, dimedone or 2-hydroxy, 1, 4-naphthoquinone refluxed at 100 ºC in aqueous medium catalyzed by L-proline as catalyst (Scheme-10). In This reaction the sodium dodecyl sulphate (SDS) was added to speed up this reaction.




**Scheme 10:** Synthesis of Xanthene derivatives

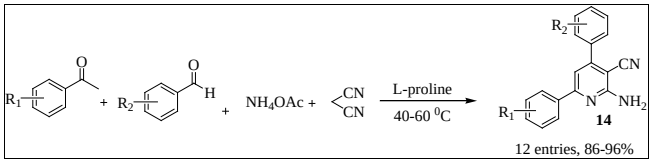
## 9. Synthesis of Tetrahydropyridinederivatives

M. Muhiebes *et al.* [27] described the synthesis tetrahydropyridine derivatives [13] by the reaction of aniline, methyl acetoacetate and aromatic aldehyde in ethanol under reflux condition using L-proline as catalyst (Scheme-11). The key advantages of this method are transition metal free catalyst, good yield, mild reaction condition and use of ecofriendly catalyst.




**Scheme 11:** Synthesis of Tetrahydropyridine derivatives

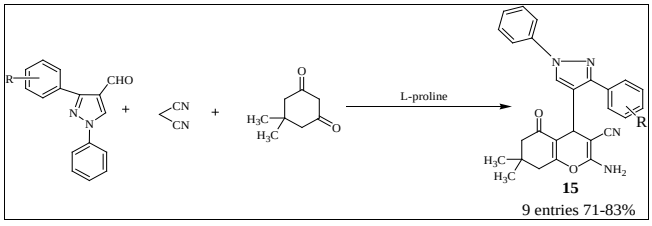
P. K. Bhadke and coworker [28] also reported the L-proline catalyzed synthesis of 2-amino, 3-cynopyridine derivatives [14] by the reaction of malononitrile aromatic aldehyde, acetophenone and ammonium acetate at 60 °C (Scheme-12).




**Scheme 12:** Synthesis of 2-amino, 3-cynopyridine derivatives

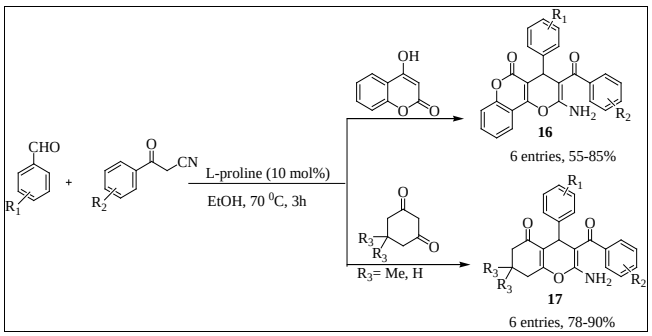
## 10. Synthesis of pyran derivatives

P. Kate *et al.* [29] used L-proline as catalyst for the synthesis of tetrahydrobenzo [b] pyran derivatives [15] from substituted pyrazole carbaldehyde, malononitrile and dimedone in aqueous ethanol (50 %) stirred at reflux temperature (Scheme-13).




**Scheme 13:** Synthesis of tetrahydrobenzo [b] pyran derivatives

M. S. Rao and coworker [30] used L-proline as catalyst the synthesis of 2-amino-3-aroyl-4-aryl-4H,5H-pyrano-[3,2-c] [1] benzopyran-5-one derivatives [16] and 2-amino-3-aroyl-4-aryl-4,6,7,8-tetrahydro—5H-1-benzopyran-5-one derivatives [17] by the reaction of benzaldehyde, 4-hydroxy coumarin (dimedone/1, 3 cyclohexanedione) and benzoyl acetonitrile in ethanol at 70 ºC (Scheme-14). This process involves domino condensation and Michael addition reaction.




**Scheme 14:** Synthesis of polysubstituted pyran derivatives

## Conclusions

This review article provides an overview of recent L-proline catalyzed synthesis of some bioactive heterocyclic compounds reported during the period of 2014 to 2025.

Literature report revealed that L-proline is an inexpensive, readily available, relatively non-toxic organocatalyst providing alternative to many conventional metal based catalyst. In this review article we have compile the literature report of synthesis of some nitrogen and oxygen containing heterocyclic compounds includes Quinoline, Coumarin, Pyranopyrimidine, Imidazole, Pyranopyrazole, Chromene, Pthtalimide, Xanthenes, Pyridine and Pyran derivatives catalyzed by L-proline. This review will be helpful to the students, researchers and synthetic chemists in the research areas of organic synthesis and medicinal chemistry for the utilization of L-proline as catalyst for the synthesis of heterocyclic compounds.

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