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L-PROLINE: AN EFFICIENT CATALYST FOR THE SYNTHESIS OF COUMARINS VIA PECHMANN REACTION

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ABSTRACT

An efficient and facile route for the synthesis of coumarins via the Pechmann reaction catalyzed by *L*-proline has been described. The reaction proceeded in dichloromethane at room temperature with good to excellent yields.

Keywords: Coumarins, Ethyl acetoacetate, *L*-Proline, Pechmann reaction, Phenols.

INTRODUCTION

Coumarins form very important group of organic compounds not only in organic synthesis but also in biology and food, as well as in materials science. The synthesis of coumarins and their derivatives has attracted considerable attention of organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. Coumarin ring consists of a benzene ring fused with a ά-pyrone ring. The first coumarin compound, which was isolated from sweet clover plant was bishydroxy coumarin or dicoumarol. Thus, the synthesis of this heterocyclic nucleus is of much interest. The prominence of coumarin in natural products and biologically active molecules has encouraged considerable efforts to synthesize coumarin derivatives. Coumarin and its derivatives are associated with various biological activities viz. antiinflammatory[1], anti-convulsant[2], anti-viral[3], anticoagulant[4], antioxidant[5], antibacterial[6], antifungal[7], anti-HIV[8], anti-carcinogenic material[9], and antihistamine[10]. Apart from this, they are attracting considerable attention of chemists as a large number of natural products contain this

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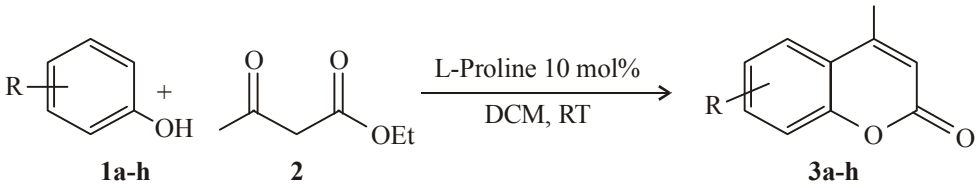
heterocyclic nucleus and are widely used as additives in food, perfumes, cosmetics, pharmaceutical[11], optical brighterners[12], dispersed fluorescent and laser dyes[13].

In literature, coumarin synthesis has been achieved by employing various methods like Von-Pechmann[14-16], Knoevenagel[17-21], Perkin[21], Reformatsy[22] and Wittig reaction[23]. In general, a valuable method for the synthesis of coumarin is the Von-Pechmann reaction. It is simple and straight reaction employing ethyl acetoacetate and substituted phenol together with an acid catalyst. Literature prevalence suggested that acids like H_2SO_4[23], TFA[24], etc. have been widely utilized for this conversion into coumarin synthesis. In addition, some other catalysts were also reported viz. P_2O_5[25], $AlCl_3$[26], ionic liquid[27], sulfated zircona[28], indium halides[29], palladium[30] and dipyridine copper chloride[31]. However, many of these procedures suffered from harsh reaction conditions, difficulties in workup, and the use of stoichiometric and / or toxic, relatively expensive reagents. Coumarin derivatives are increasingly useful and important in pharmaceutical industries, the development of simple, environmentally benign, low cost protocols is still desirable.



1a-h **2** **3a-h**

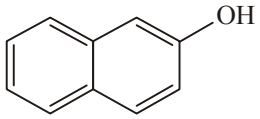
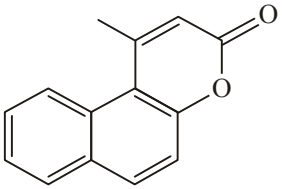
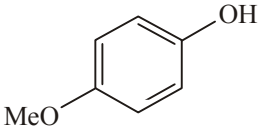
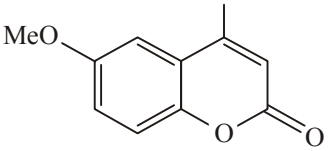
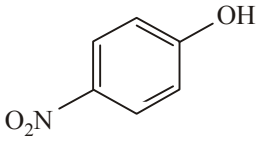
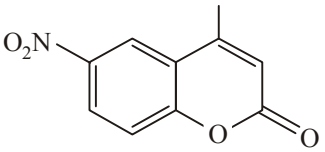
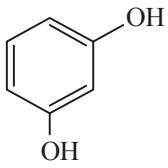
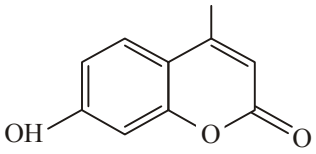
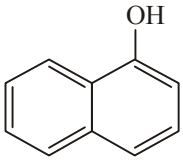
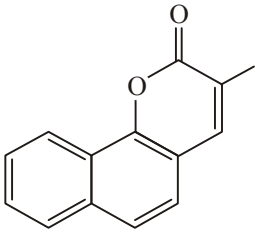
Scheme 1

L-proline is an efficient bi-functional abundant chiral organo-catalyst, which is inexpensive and available in both enantiomeric forms[32]. These two functional groups can act both; as acid or base and can also facilitate chemical transformations in concert, similar to enzymatic catalysis. It has been extensively used in the synthesis of various heterocycles[33] as well as in aldol, Mannich and Michael reactions[34]. As the mechanism of multi-component Hantzsch reaction originally involves aldol related reactions such as Knoevenagel condensation and Michael addition, the use of *L*-proline for the same reaction will be a useful and attractive modification for the same.

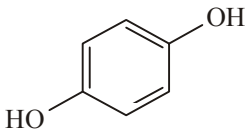
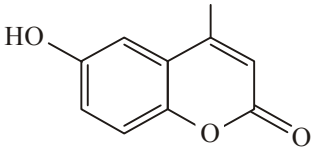
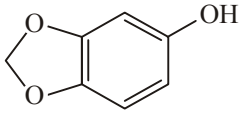
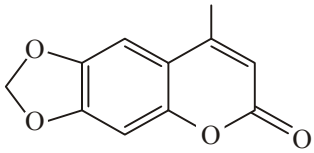
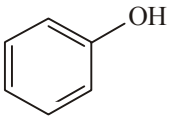
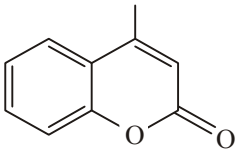
Herein, we report first time the use of *L*-proline as an organo-catalyst for the synthesis of novel 4-methyl coumarin derivatives starting from various substituted phenols and ethyl acetoacetate. Our results demonstrate that *L*-proline is a very effective, environmentally friendly catalyst for the synthesis of coumarins in dichloromethane as solvent at room temperature in excellent yields (Table 1). The method offers several advantages such as mild reaction conditions, shorter reaction time, high yields, and a simple

experimental operation leading to a useful and attractive process for the preparation of coumarins. Its further application in organic synthesis is currently being explored in our laboratory. In conclusion, the efficient protocol for the synthesis of coumarin and its derivatives via Von-Pechmann condensation of various substituted phenols with β- keto ester i. e. ethyl acetoacetate using *L*-proline as a catalyst in dichloromethane at room temperature was found to be much suitable.

Table 1: *L*-Proline catalyzed Pechmann reaction

Entry	Substrate	Product	Reaction time (h)	Yield[a] (%)	M. p. (^{o}C)
3a			6	88	155
3b			5	93	162
3c			8	84	157
3d			5	86	182
3e			6	89	152

Cont…

Entry	Substrate	Product	Reaction time (h)	Yield[a] (%)	M. p. (^{o}C)
3f			5	90	240
3g			8	92	192
3h			6	90	80

[a]Isolated yield based on phenols. The products were characterized by IR, and ^{1}H NMR spectral analysis and comparison of their mp with the available reports

General procedure for the synthesis of coumarins (3a-h)

In a mixture of phenol **1** (10 mmol), ethyl acetoacetate **2** (10 mmol) and dichloromethane (25 mL) as a solvent, *L*-proline (10 mmol %) was added as catalyst. The reaction mixture was stirred at room temperature for appropriate time (Table 1). The completion of reaction was monitored by TLC by using petroleum ether and ethyl acetate (8 : 2) as an eluent. The reaction mixture was poured into crushed ice, extracted with ethyl acetate (3 x 25 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and purified by crystallization from ethyl alcohol to give the corresponding products **3**.

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