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Citric Acid Catalyzed Efficient and Convenient Synthesis of Coumarin Derivatives

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ABSTRACT

A coumarin derivatives has been synthesized via Pechmann condensation Substituted phenol with a β-ketoester using Citric acid as a green and efficient catalyst. The optimal conditions are: molar ration of reagents (1:1), Citric acid (15mol %) at 130℃ for hrs in solvent-free conditions. Advantages of this Catalyst short reaction time, eco-friendly, good to excellent yield, non toxic and easy to handle.

Keywords : Coumarins, Phenols, β-Ketoesters, Pechmann Reaction, Citric acid

I. INTRODUCTION

Coumarins are an essential class of benzopyrones wich consist of a benzene ring joind to a pyrone ring [1] . The synthesis of coumarins and their derivatives has usual attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in ,agrochemicals,cosmetics,food,pharmaceuticals [1] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable dye lasers [2]. They have varied bioactivities, such as, inhibitory of platelet aggregation[3], antibacterial [4], anticancer [5], inhibitory of steroid 5_-reductase [6] and inhibitory of HIV-1 protease [7]. Coumarins also act as intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols [8]. Their properties turn coumarins very interesting targets to organic chemists, and several strategies for their synthesis were already developed. Coumarins can be synthesized by various methods such as Pechmann [9], Perkin [10], Knoevenagel [11], Reformatsky [12] and Witting [13] reactions. Pechmann condensation is one of the most common procedures for the preparation of coumarin and its derivatives.This method involves the reactions between a substituted phenol and a β-keto ester in the presence of an acidic catalyst. Simple starting materials are required here to produce various substituted coumarins in good yields.

Different acid catalysts like H2SO4, P2O5, FeCl3, ZnCl2, POCl3, AlCl3,HCl, H3PO4 and CF3-COOH acid are known to affect this condensation [14]. However, in the current context of environmental impact, these methods are not attractive as they require catalyst in excess, for example, sulfuric acid in 10–12 equivalents [15],trifluoroacetic acid in three to four equivalents [14b] and phosphorus pentoxide in

five-fold excess [16]. Further, such reactions required long reaction time or heating the reaction mixtures above 150oC. In addition, aformation of undesired sideproducts alongside coumarins have been observed in these cases ,and in other cases gave lower yields[16b]. Recently, cation exchange resins [17] and solid acid catalysts [18] have been tried for this reaction. These reactions also have been attempted using microwave irradiation [19] for accelerated syntheses of different coumarins. In previous years a profound interest was shown in the use of ionic liquids [20] for organic synthesis and on green chemistry [21]so we report in this paper a solvent-free synthesis of coumarins using an inexpensive and non-polluting catalyst.

In recent years, acid catalysts are gaining more importance due to enviro-economic factor.The catalyst is generally is low cost and can be easily handled or removed. Thus there will be no undesirable wastes that cause environmental pollution. To the best of our knowledge, no report has been made about the use of acid catalyst for synthesis of coumarins via Pechmann condensation using citric acid catalyst.

II. Experimental Procedure

General procedure

A mixture of Resorcinol (3 mmol), ethyl acetoacetate (3 mmol) and acid catalyst (15mol %) were added into a 50-mL round-bottomed flask then the reaction mixture was stirred in oil bath heated at 130°C for the desired time.The reaction was monitored by thin layer chromatography (TLC). After completion of the reaction,mixture was filtered to remove the catalyst, then filtrate was cooled in ice water cooled filtrate to result a solid (crude product) that it was filtered and then was recrystallized with ethanol to obtain pure product. The physical data (mp, NMR, IR) of these known compounds were found to be identical with those reported in the literature.

Characterization of selected compounds

5,7-dihydroxy-4-methyl-2H-chromen-2-one

The product was obtained as off white solid in **82**% yield **^{1}H NMR** (500 MHz, DMSO) δ 10.56 (s, 1H), 10.34 (s, 1H), 6.26 (s, 1H), 6.17 (s, 1H), 5.85 (s, 1H), 2.48 (s, 3H). **^{13}C NMR** (126 MHz, DMSO) δ **3a** 161.52, 161.33, 160.60, 158.31, 156.94, 155.48, 109.31, 102.54, 99.48, 94.96, 23.90.

7, 8-dihydroxy-4-methyl-2H-chromen-2-one

The product was obtained as off white solid in 78% yield **^{1}H NMR** (500 MHz, DMSO) δ 10.12 (s, 1H), 9.34 (s, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.11 (s, 1H), 2.34 (s, 3H) **^{13}C NMR** (126 MHz, DMSO) δ 160.75, 154.48, 149.69, 143.70, 132.49, 115.99, 113.26, 112.52, 110.64, 18.70.

Scheme 1 synthesis of coumarin derivatives in presence of citric acid

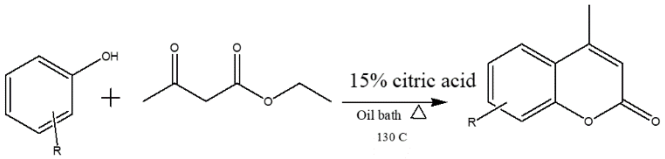
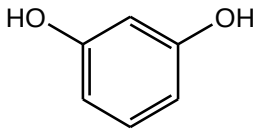
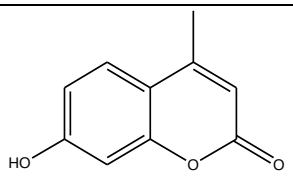
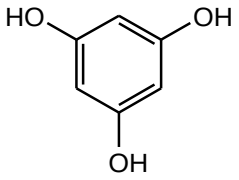
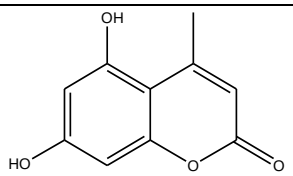
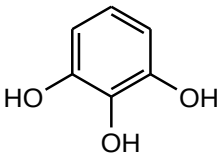
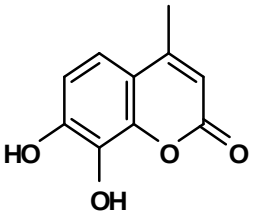
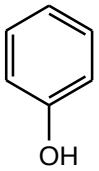
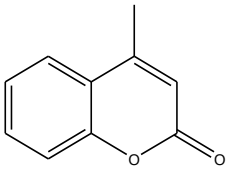
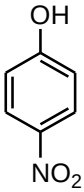
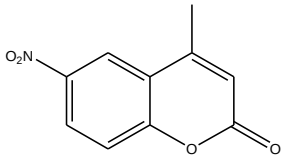


Table 1 Optimization of the catalysta

Entry	Catalyst (mol %)	Yieldb %
1	-----	No reaction
2	5	35
3	10	65
4	15	82
5	20	82

Table 1 Synthesis of coumarin derivatives in the presence of Citric acid

Entry	Reactant	Product	Time	Yield %	M.P
a			17 hr	80	184- 186
b			15hr	82	286- 288
c			18hr	78	242- 244
d			22hr	68	78-80
e			26hr	55	151- 157

III. RESULTS AND DISCUSSION

To explore the citric acid used as the catalyst for the synthesis of coumarin derivatives. At the initially of this study, resorcinol and ethyl acetoacetate (EAA) were employed as model reaction. The model reaction was tried out using different concentration of catalyst under the solvent-free system. The results are summarized in Table 1. During this study, we have observed that yield of the product decreases with decreasing the amount of catalyst. When 15 mol% catalyst was added, the reaction yield was 82% (Table 1, entry 4), and when 10 mol% catalyst was added, the reaction yield decreased to 65% (Table 1, entry 3). Interestingly, no reaction took place in the absence of catalyst after 45 min (Table 1, entry 1). After this study, we observed that, 15 mol% catalysts proved to be an efficient catalyst to carry out the reaction smoothly.The Pechmann condensation reaction of substituted phenols and ethyl acetoacetate in the presence of citric acid was accomplished under the optimized reaction conditions (Scheme 1).

Encouraged by these results, we build the generality of reaction the reaction worked well with phenols containing electron-donating and electron-withdrawing substituents on the aromatic ring.

IV. CONCLUSION

In conclusion, we have developed a simple and efficient synthesis of substituted coumarins via Pechmann Condensations using citric acid catalyst under solvent-free conditions. Moreover the low cost of the catalyst, solvent-free condition, low toxicity of the catalyst, fast reaction times, simple experimental procedure, recyclablity of the catalyst and high yields of the products are the advantages.

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