A Review on Recent Advances in the Coumarin Derivatives Synthesis via Knoevenagel and Pechmann Condensation

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Abstract

Knoevenagel condensation and Pechmann condensation reactions are most important organic reactions for the synthesis of coumarin derivatives and has important applications in the field of pharmaceutical chemistry, synthetic organic chemistry. Thus, various methodologies have been reported for the synthesis of coumarin derivative compounds. Out of which, some methods are associated with longer reaction time toxic and catalysts, lower yield with less purity, less purity and formation of by-products along with the expected product and thus are not environmentally friendly. Therefore, many scientists recently developed mild, efficient, and environmentally friendly methods for the synthesis of coumarin derivatives via Knoevenagel condensation and Pechmann condensation with good to excellent yield and high purity. In this review article, we have mentioned various methods for the coumarin derivative synthesis via Knoevenagel condensation and also by Pechmann condensation.

Keywords: Knoevenagel condensation, Pechmann condensation, coumarin derivatives, environmentally friendly, efficient

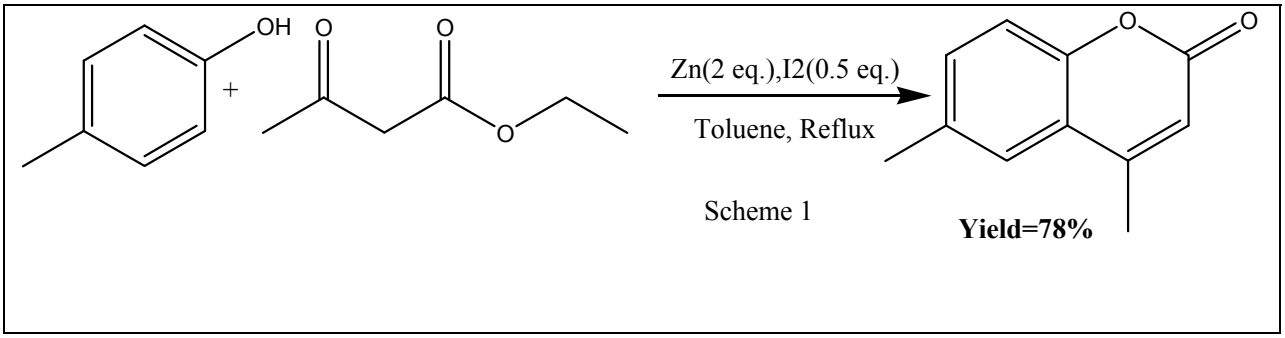
Introduction:

Coumarins compounds are an important class of oxygen-containing heterocyclic moiety originally found as secondary metabolites in some microorganisms and plants [1]. Large numbers of organic compounds containing coumarin as a basic unit have been found many important applications, such as anti-inflammatory [2-4], antibacterial [5-7], analgesic [8], antifungal [9], antioxidant [10-11], anticancer [12], antimicrobial [13] and anti-HIV [14-16]. Along with these applications, coumarin compounds have widely applied in other fields, such as food and dyes industries [17] fragrance and cosmetic [18].

The synthesis of coumarin and its derivatives has been attracted the attention of many scientist and industrialist because of wide range applications of coumarin compounds. Large number of methods has been established for the preparation of coumarin derivatives out of which Pechmann condensation and Knoevenagel condensation reactions are mostly useful for the coumarin derivative synthesis due to good to excellent yield of the products and simple reaction conditions. The present article represents a small review for the synthesis of coumarin derivatives by both Pechmann condensation and Knoevenagel condensation reactions.

Following are the various schemes developed for the synthesis of coumarin compounds.

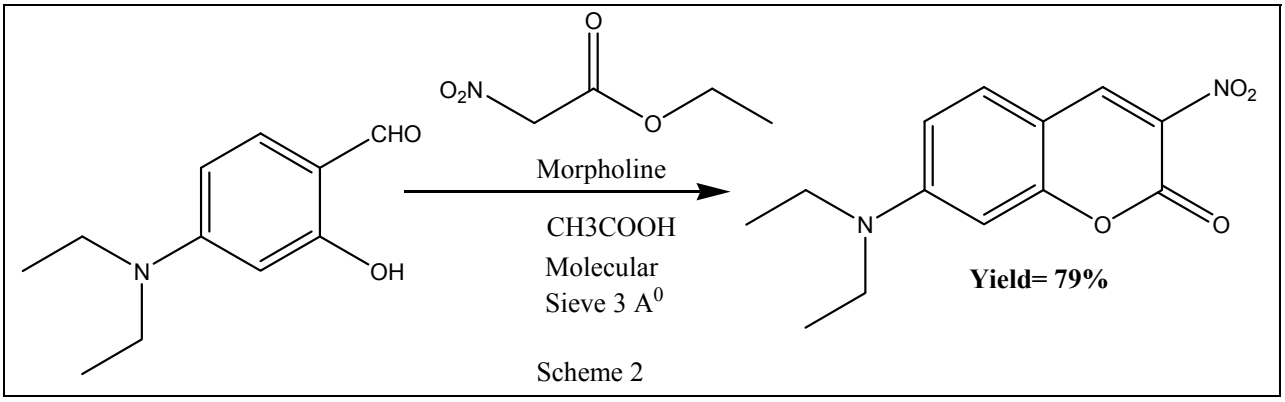
Scheme 1: S.P. Chavan et. al. [19] developed synthesis of coumarin derivatives by Pechmann condenation using Zn (2 eq.) and I2 (0.5 eq.) using toluene solvent under reflux condition.



Scheme 1

Yield=78%

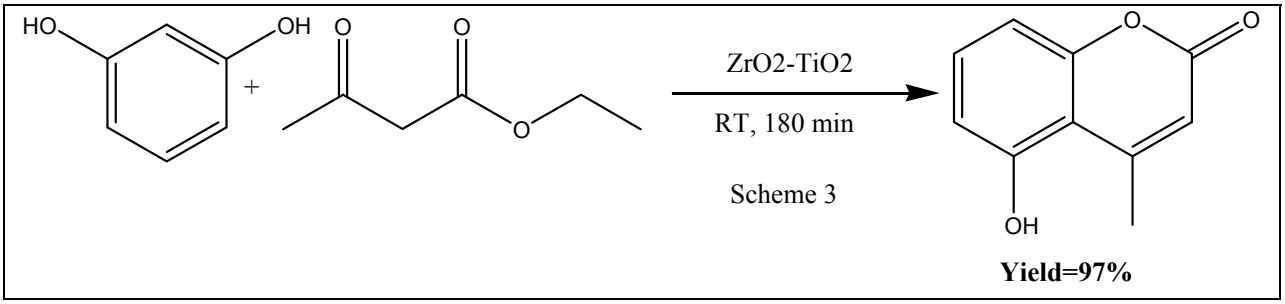
Scheme 2: Lee et. al.[20] have mentioned a synthesis of 7-diethylaminocoumarin compounds using 4-diethylaminosalisaldehyde and ethyl nitroacetate using morpholine and acetic acid as catalysts in the presence of molecular sieve via Knoevenagel condensation reaction in n-butanol solvent at 0^{o}C.



Yield= 79%

Scheme 2

Scheme 3: Khan et al.[21] reported the synthesis of coumarin compounds through Pechmann reaction in a solvent-free condition at room temperature using zirconia-based heterogeneous catalysts (ZrO2-TiO2).

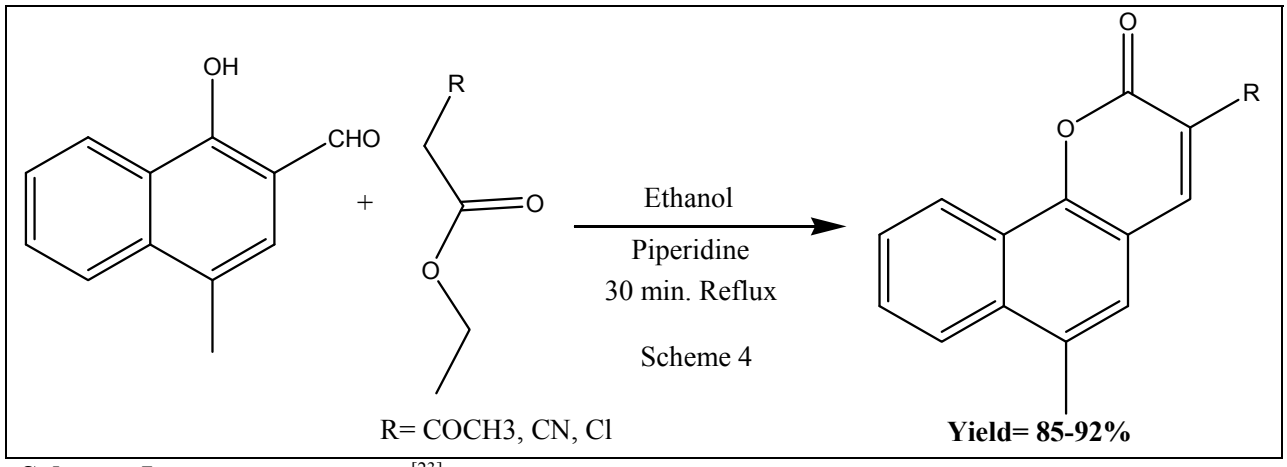


Scheme 3

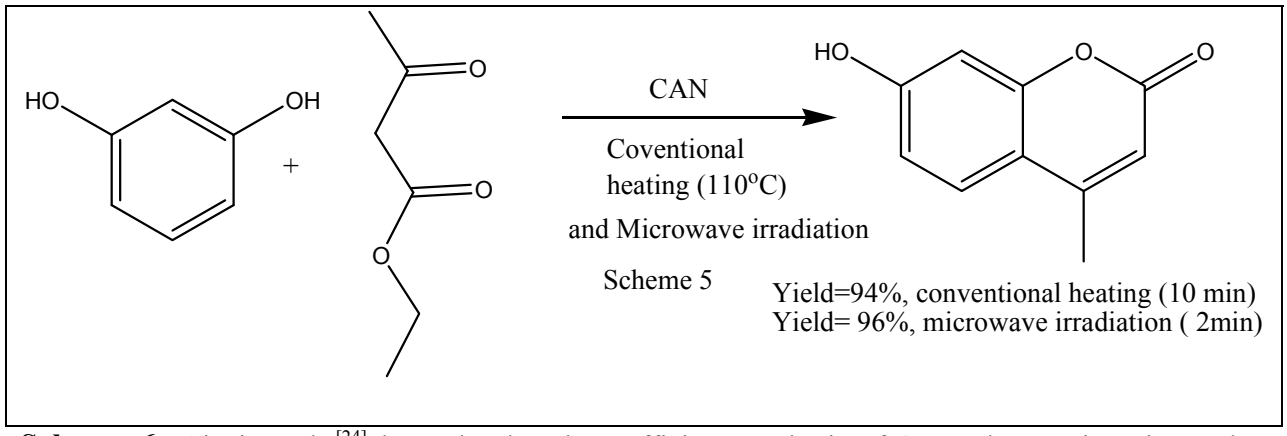
Yield=97%

Scheme 4: Sashidhara and coworkers [22] have developed synthesis of novel benzocoumarin derivatives via Knoevenagel condensation of 1-hydroxy-4-methylnaphthalene- 2-carbaldehyde with different active

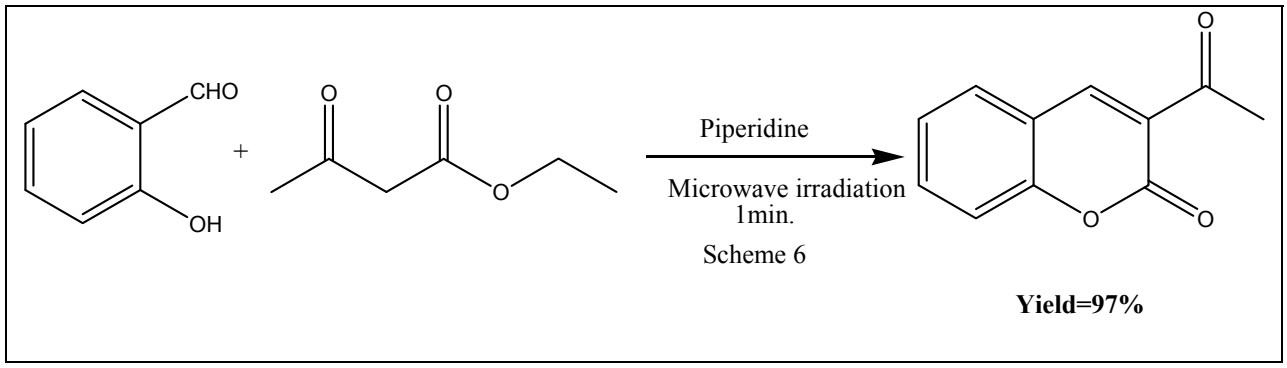
methylene compounds in ethanol solvent and in the presence of a piperidine. Products were obtained with high yields.



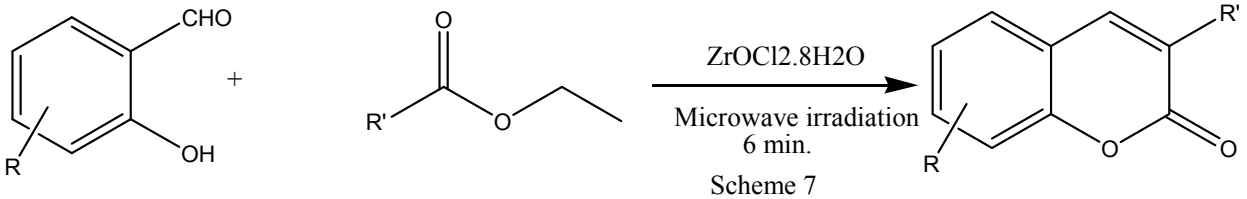
Scheme 5: Reddy Y. T. et. al.[23] developed an efficient and convenient method for the synthesis of substituted coumarins via Pechmann condensation of different phenols with ethylacetoacetate in a solvent free medium by using of ammonium cerium(IV) nitrate (CAN) as catalyst by both conventional heating and microwave irradiation.



Scheme 6: Ajani et al. [24] have developed an efficient synthesis of 3-acetylcoumarin using ortho-hydroxybenzaldehydes and ethyl acetoacetate under microwave irradiation and in the presence of piperidine.



Scheme 7: Use of microwave irradiation is the key for good yield of the product. Mirjafary et al. [25] have reported an efficient synthetic method for 3-substituted coumarins via Knoevenagel condensation using ortho-hydroxybenzaldehydes and various active methylene compounds under microwave irradiation in the presence of $ZrOCl_2.8H_2O$ as the catalyst which showed good yield of the products under solvent free conditions.



Scheme 7

Yield=60- 92%

With the rapid development in the field of synthetic organic chemistry and also medicinal chemistry, many researchers from both academia and industry have started giving serious thought to the unfavorable effect of non-green processes and chemicals on the environment. They have successfully developed several environmentally benign procedures to avoid, or to minimize, these effects. Syntheses of coumarin derivatives have been carried out successfully using solid acid catalysts and by combination of solid acid catalysts and microwave irradiation [26] as an alternative to conventional methods. Recently ionic liquids have achieved recognition as possible environmentally benign alternative solvent systems in various chemical methods. They have attracted the attention of chemists owing to their unique physical and chemical properties [27].

Tyagi B. et. al. [28] has reported synthesis of coumarin derivatives by using nano-crystalline sulfated-zirconia catalysts. The catalyst was prepared by one-step as well as two-step sol–gel technique, showed excellent catalytic activity for the synthesis of 7-substituted 4-methyl coumarins under solvent free condition via Pechmann reaction. The use of very small catalytic amount of sulfated-zirconia catalyst for the synthesis of coumarins with reusability of the catalyst after simple activation for several times.

Conclusion:

This review highlights some important biological applications of coumarin derivatives and shows few recent developments in the synthesis of coumarin derivatives through the Knoevenagel condensation and Pechmann condensation reactions using various catalytic systems and by conventional heating method and also by microwave irradiation method. This review will be useful to some extent to the researchers working in this field of coumarin derivative and related compounds and help them to develop new efficient nontoxic, inexpensive and environmentally friendly methods.

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