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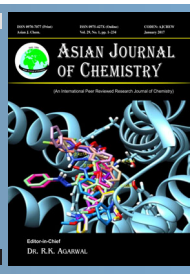

Green Synthesis and Characterization of 3-Carboxycoumarin and Ethylcoumarin-3-carboxylate *via* Knoevenagel Condensation

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Environmentally benign, simple, efficient and clean syntheses of 3-carboxycoumarins and ethyl coumarin-3-carboxylate have been synthesized *via* Knoevenagel condensation using green catalysts such as aqueous extract of *Acacia concinna* pods and amino acids. These syntheses were carried out in solvents as well as solvent-less media. The yields obtained (between 86 % to 96 %) for the reactions were equal or better than those previously reported. The products were isolated, purified and characterized through melting points, TLC, IR, GC Mass and ^{1}H NMR spectroscopy. The characterized molecules showed structural and compositional conformity with the predicted reactions. The green route used for these reactions has shown to be efficient in reducing the time of reaction and in avoiding the toxic nature of the catalysts employed in classical reaction.

Keywords: Green protocol, *Acacia concinna*, Amino acids, 3-Carboxycoumarins, Knoevenagel condensation.

INTRODUCTION

Knoevenagel condensation is a classic C-C bond formation condensation reaction between aldehydes or ketones and active methylene compounds [1]. Usually ammonia and other amines like pyridine and piperidine are used as a catalyst in Knoevenagel reactions [2]. Pyridine and piperidine are health hazards. Pyridine easily dissolves in water and harms both animals and plants in aquatic systems. Piperidine can seriously affect eyes, skin and respiratory system [3]. In recent times, various modern homogeneous and heterogeneous catalysts have also been introduced for this purpose, such as microwave-promoted, ultrasound, clays, solid phase, ionic liquids and biotechnology catalyzed as well as solvent-free Knoevenagel reactions have been studied and reported [4]. But the use of expensive reagents, drastic reaction conditions, undesired side products, tedious workups, prolonged reaction times and poor yields are still existed limitations of these methodologies. To deal with these tangible obstacles, Knoevenagel reaction has been studied within the green chemistry perspective.

Literature shows that there are few references for the use of amino acids and their derivatives for catalyzing of almost all types of chemical reactions [5-7] including Knoevenagel condensation [8]. During the last two years, amino acids have also been found as efficient catalyst in Biginelli synthesis [9], triarylimidazoles [10] and pyrazoleacryloyl syntheses [11].

An aqueous extract of *Acacia concinna* pods has been investigated as an environmentally benign catalyst for the Knoevenagel condensation as well as acylation of amines [12]. The aqueous extract of these pods is acidic in nature (pH, about 2.1) due to the presence of an acaciac acid which is a trihydroxy-monocarboxylic acid (Fig. 1) [13].

These new approaches have been very useful in the development of more environmentally supportable products and chemical processes [14].We had earlier explored the utility amino acids for coumarin-3-carboxylic acid in only one reaction [8]. With the benefit of foresight, we aimed to extend this work for efficacy of amino acids and aqueous extract of *Acacia concinna* pods as catalysts in other Knoevenagel reactions by using variety of active methylene molecules.

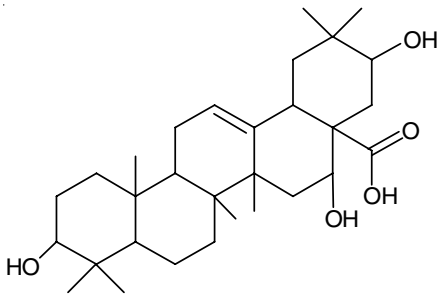
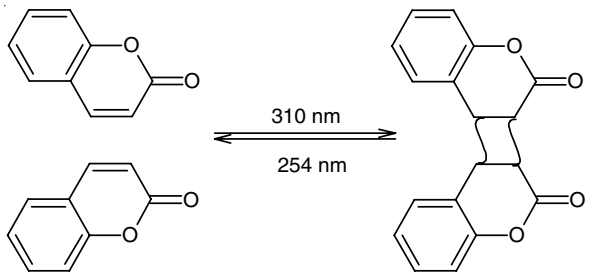


Fig. 1. Chemical structure of acaciac acid

Knoevenagel condensation is one of the important protocols for the synthesis of coumarins. Coumarin and its derivatives have long been recognized to possess biological activities including anticancer [15,16], antibacterial [17], antifungal [18], anticoagulant [19], anti-inflammatory [20], antitumor [21], anticonvulsant [22], anti-HIV activity [23] and cholinesterases inhibitors [24,25]. In addition, these compounds are used as additives in food and cosmetics, dispersed fluorescent brightening agents and as dyes for tuning lasers [26]. Photoresponsive coumarins when grafted to silica surface have been found as drug carrier agents [27]. The coumarin part is dimerized by the irradiation with UV light longer than 310 nm, the molecular "hinged double doors" of the pore in MCM-41 are closed and guest molecules are stored inside. On the other hand, when these particles are exposed to a UV light of wavelength around 250 nm, cleaves the coumarin dimer to regenerate its monomer and opens the "double doors" of the pore in MCM-41, resulting in the release of guest molecules as shown in **Scheme-I**. Photo controlled reversible release of phenanthrene as a guest molecule from coumarin modified mesoporous silica is a typical example of this process [27].



Scheme-I: Reversible photodimerization and photocleavage of coumarin derivatives

Due to extensive applications of coumarin and its derivatives numerous synthetic routes to coumarins syntheses have been the subject of extensive study over many decades [19,28-30].

In the present work, another green approach with efficient yield is being utilized for the syntheses of coumarins. These syntheses have been carried out by using five different amino acids *viz.* glycine, L-proline, L-cysteine, tryptophan, β-alanine as well as aqueous extract of *Acacia concinna* pods.

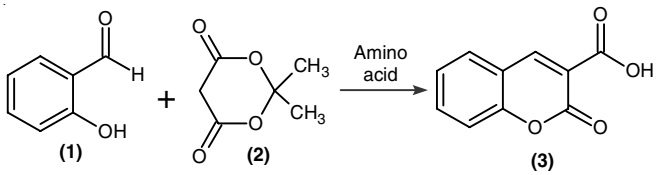
EXPERIMENTAL

Most of the chemicals used during this research work were of laboratory grade and used without further purification. Commercial TLC plates and UV light were used as a spot locating agent. Infrared spectra (IR) spectra were recorded on Perkins Elmer FTIR (spectrum RXI) spectrometer. Mass spectra were recorded on mass (MAT 312 Model) and GC-MS Shimadzu QP2010. ^{1}H NMR spectra were recorded on (NMR; Jeol JNM-ECA500).

General procedure for the preparation of catalyst: Powdered pods of *Acacia concinna* fruit (20 g) and water (100 mL) in a 250 mL conical flask were boiled for 15 min. The material was allowed to stand overnight then filtered off and the aqueous extract was employed as a catalyst for the following syntheses. The major content of this extract was acacia acid (pH = 3-4).

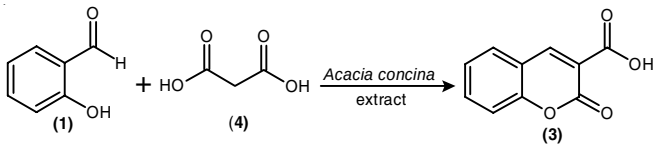
Synthesis of 3-carboxycoumarins

Method I: A mixture of salicylaldehyde (2 mmol) (**1**), Meldrum's acid (2 mmol) (**2**) and 0.05 g of amino acid and 5 mL ethanol were taken in a round-bottomed flask and heated under reflux on water bath for 1 h. After completion of the reaction, the reaction mixture was cooled to room temperature, poured off in ice cold water and a solid product was filtered off, washed well with water and recrystallized to obtain pure product (**Scheme-II**).



Scheme-II: Condensation of salicyldehyde and Meldrum's acid in presence of amino acid

Method II: A mixture of salicylaldehyde (**1**), malonic acid (**4**) and 5 mL of 20 % aqueous extract of *Acacia concinna* were heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature then it was poured off in ice cold water. Solid product was filtered off and the crude product was recrystallized by water to obtain pure coumarin-3-carboxylic acid (**3**) (**Scheme-III**).

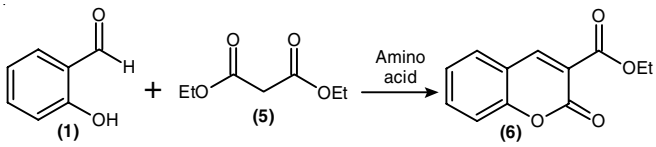


Scheme-III: Condensation of salicyldehyde and malonic acid in presence of *Acacia concina* extract

Synthesis of ethyl coumarin-3-carboxylate

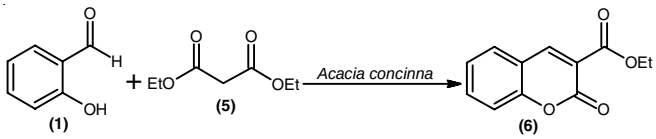
Method-I: A mixture of salicylaldehyde (**1**), (2 mmol), malonic ester (2 mmol) (**5**) and 0.05 g amino acid were taken in a round-bottomed flask and heated along with stirring at boiling water bath for 2 h. After completion of the reaction, the reaction mixture was cooled to room temperature, poured in ice cold water and a solid product was filtered off, washed well with water and recrystallized to obtain pure product (**Scheme-IV**).

Method II: A mixture of salicylaldehyde (**1**), (2 mmol), malonic ester (2 mmol) (**5**) and aqueous extract of *Acacia concinna* were taken in a round-bottomed flask and heated along with stirring at boiling water bath for 2 h. After completion of the reaction, the reaction mixture was cooled to room



Scheme-IV: Condensation of salicyldehyde and malonic ester in presence of amino acid

temperature, poured in ice cold water and a solid product was filtered off, washed well with water and recrystallized to obtain pure product (**Scheme-V**).



Scheme-V: Condensation of salicyldehyde and malonic ester in presence of aqueous extract of *Acacia concina*

RESULTS AND DISCUSSION

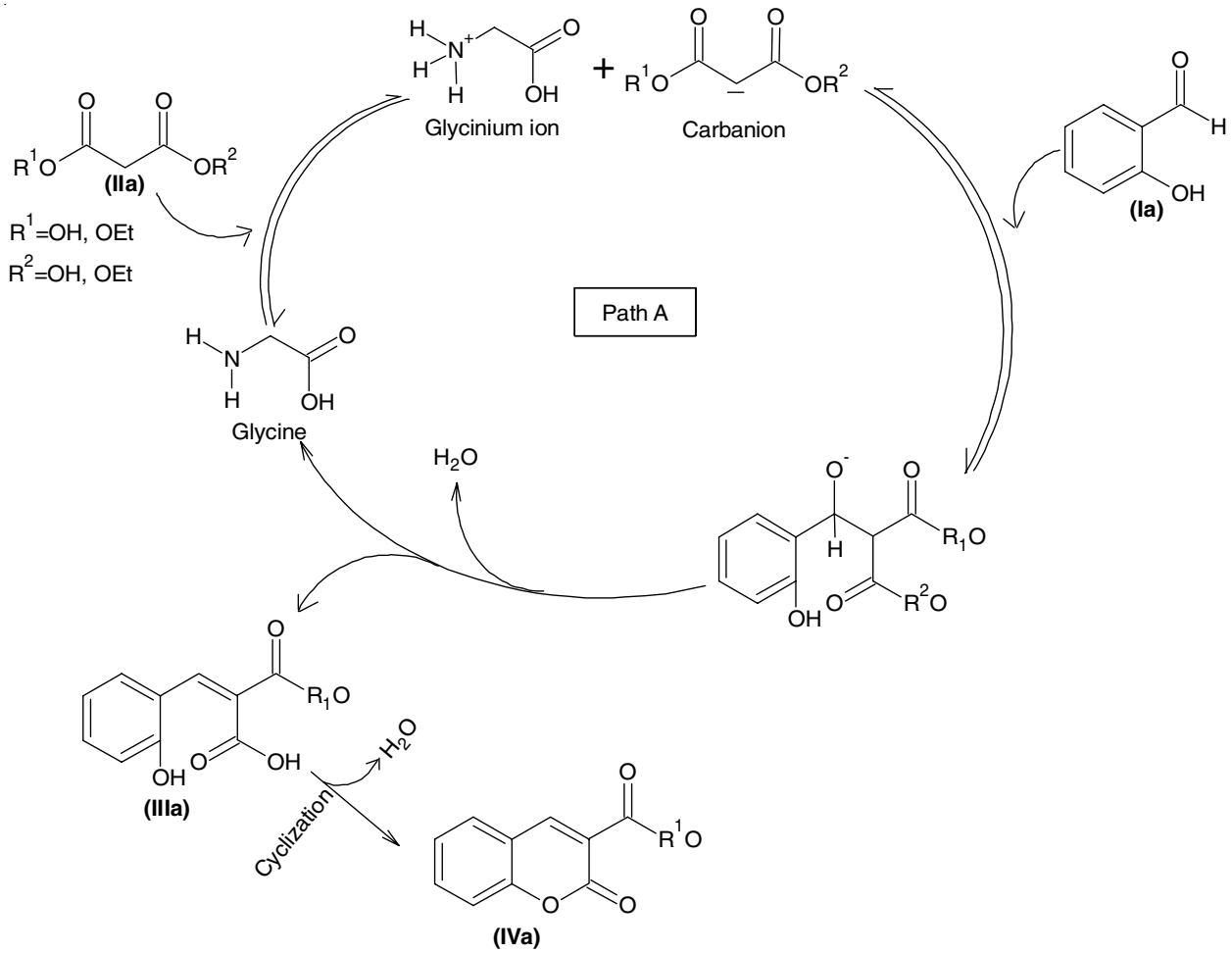
In continuation of our research interest concerning the investigation of new natural catalyst and development of new methodologies, a highly efficient method for Knoevenagel synthesis of coumarin-3-carboxylic acid and ethyl coumarin-3-carboxylate under mild conditions with excellent yields using amino acid as well as aqueous extract of *Acacia concinna* pods is reported in this paper.

Coumarin-3-carboxylic acid: In recent years, amino acids have drawn much interest in different organic reactions due to their experimental simplicity, ease of handling and high reactivity.

Condensation of salicyldehyde (**1**) with Meldrum's acid (**2**) was carried out in the presence of glycine as catalyst as a test reaction. This reaction gave a good yield of coumarin-3-carboxylic acid (**3**). With a successful reaction it was then carried out in the presence of some other amino acids (Table-1). Amino acid catalyzed reactions also gave good (85 %) to excellent (96 %) yields.

Amino acids have been recognized as catalysts due to their existence in dipolar form known as zwitterions (ampholyte ions) in aqueous media. Plausible mechanism for the glycine-catalyzed (or any other amino acid-catalyzed) synthesis of coumarin been proposed (**Schemes VI** and **VII**). The reaction may proceed through two different pathways. Path A provides carbanion formation that is produced by abstraction of active proton from active methylene molecule. The carbanion intermediate then condenses with the carbonyl carbons of salicyldehyde (**Ia**) followed by dehydration to afford the intermediate (**IIIa**), which then rearranges to the required coumarin.

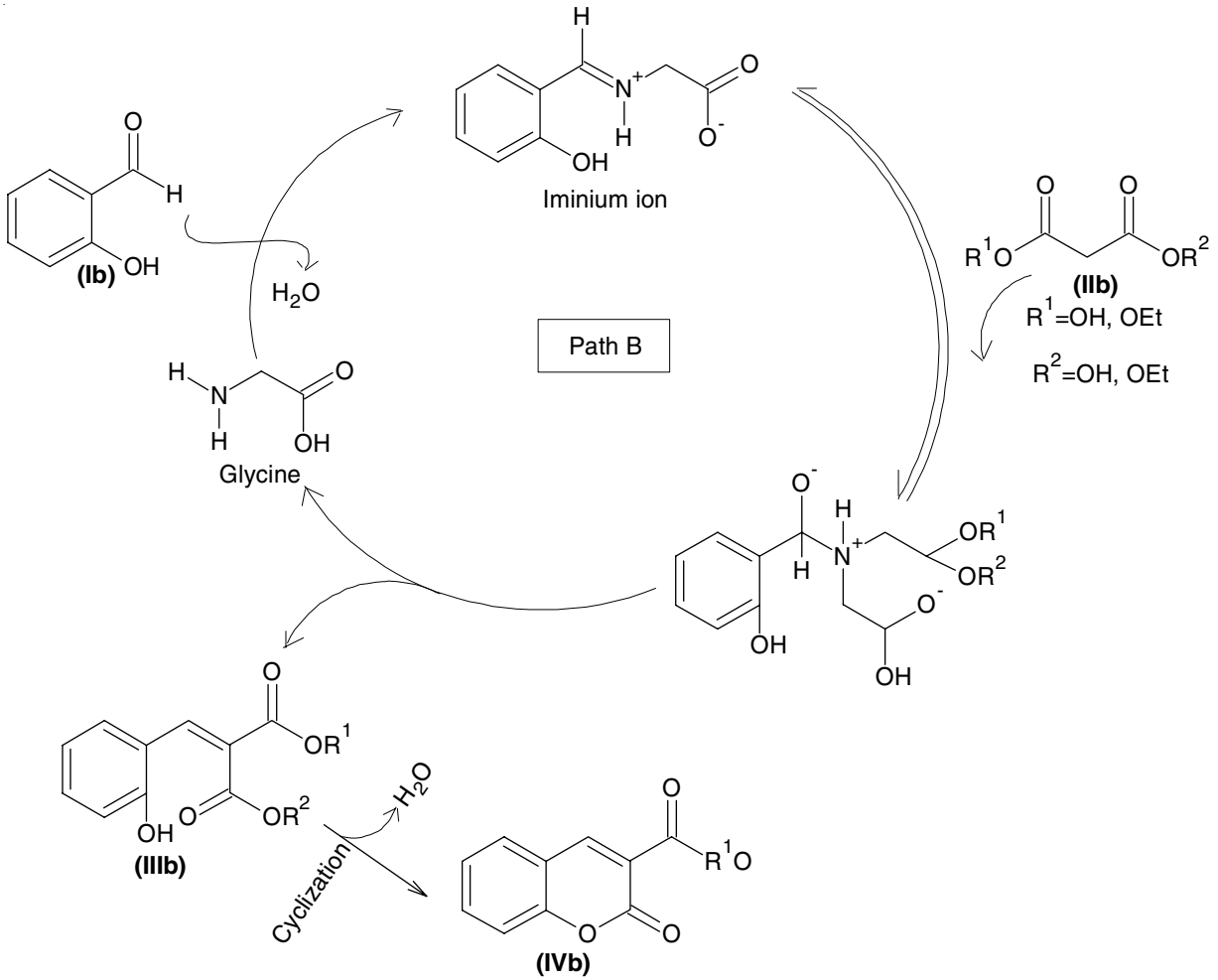
Path B involves the activation of aldehydic oxygen by acid part of glycine *via* intermolecular hydrogen bonding and subsequent condensation with active methylene molecule intermediate. The intermediate undergoes dehydration to



Scheme-VI: Plausible path A for synthesis of coumarin

TABLE-1
PHYSICO-CHEMICAL PROPERTIES OF THE PRODUCTS OBTAINED BY THE CONDENSATION OF SALICYLDEHYDE WITH MELDRUM'S ACID

Catalyst	Colour	Yield (%)	m.p. (°C)	m.p. (°C) [Ref. 31]	IR (ν_{max}, cm^{-1})	Mass (*m/z*)	^1H NMR
Glycine	White	90	187	189-192	3317 (O-H), 2985 (arom C-H), 1725 (C=O)	190 (31 %) M^+; 146 (100 %); 118 (67 %); 89 (60 %); 63 (64 %).	DMSO, 500 MHz OH: 12.21 (broad peak), 1H: 8.37 (s), 1H: 7.38 (d) overlapping Hz 7.64, 1H 7.72 (t), 1H: 7.41 (t) overlapped, 1H 7.89 (d) 7.64
L-Proline	Pale yellow	85	188				
L-Cysteine	Yellow	88	187				
Tryptophan	White	93	189				
β-Alanine	Yellow	86	190				
Acacia concinna	Light brown	95	190				



Scheme-VII: Plausible path B for synthesis of coumarin

produce intermediate (**IIIa**). Cyclization and dehydration of intermediate (**IIIa**) results in respective coumarin.

One of the major advantages of this protocol is the isolation and purification of the desired product which have been achieved by simple washing and crystallization of the crude product.

Aqueous extract of *Acacia concinna*, another biodegradable catalyst has been reported in this study. Aqueous extract of *Acacia concinna* has been found as a catalyst in the acylation of amines [13] and in Knoevenagel condensation [12] of salicyldehyde (**1**) with malonic acid (**4**). Chavan and Bandgar [12] optimized the concentration of aqueous extract of *Acacia concinna*. They reported that 20 % solution gives the maximum yield. They [12] also reported a comparison of yields of synthesis of coumarin derivatives using various surfactants as catalysts such as DBSA (68 %), SDS (60 %), Triton X-100 (52 %), CPB (40 %), CTAB (45 %) and aqueous extract of *Acacia concinna* (98 %). Keeping in view the previous studies, in this research work the reactions were carried out on different concentrations and verified that the optimum concentration is 20 %. So herein, all the reported reactions were conducted in the presence of 20 % aqueous extract of *Acacia concinna*.

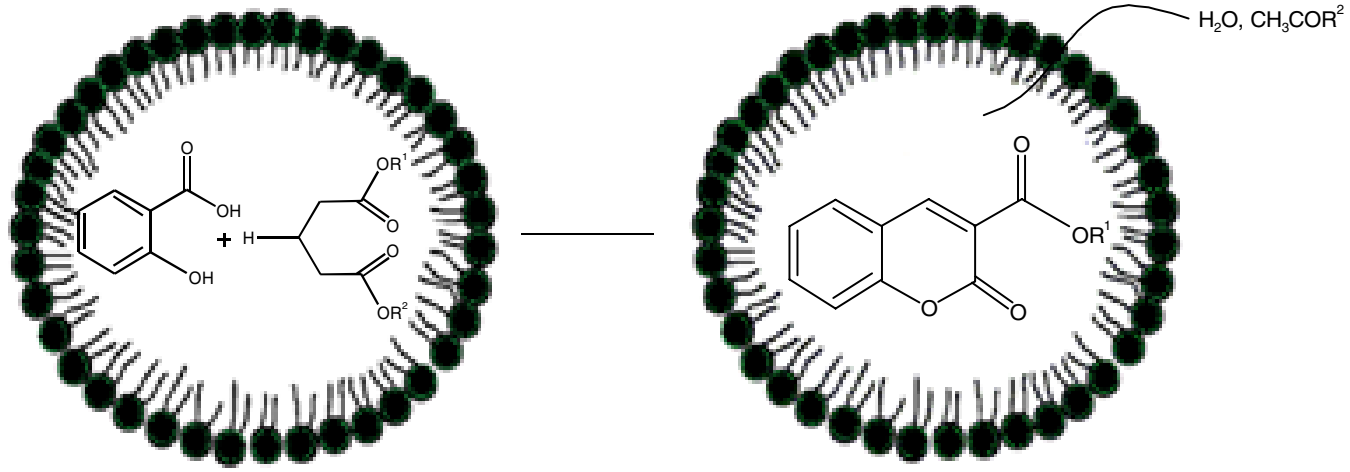
The rate enhancement in the aqueous extract of *Acacia concinna* pods is mainly due to its surfactant property and acidic pH. The extract can solubilize the reactant species strongly by hydrogen bonding and helps to increase the number of effective collisions between the reactant species. Further encapsulation of the reactants in micellar cages may drive the equilibrium toward the product side by expelling the water molecule out of its hydrophobic interior that increases the speed

TABLE-2
PHYSICO-CHEMICAL PROPERTIES OF THE PRODUCTS OBTAINED BY THE CONDENSATION OF SALICYLDEHYDE WITH MALONIC ACID

Catalyst	Colour	Yield (%)	m.p. (°C)	m.p. (°C) [Ref. 31]	IR (ν_{max}, cm^{-1})	Mass (*m/z*)	^{1}H NMR
Glycine	White	92	191	189-192	3317 (O-H), 2985 (arom C-H), 1725 (C=O)	190 (31 %) M^+; 146 (100 %); 118 (67 %); 89 (60 %); 63 (64 %).	DMSO, 500 MHz OH: 12.21 (broad peak), 1H: 8.37 (s), 1H: 7.38 (d) overlapping Hz 7.64, 1H 7.72 (t), 1H: 7.41 (t) overlapped, 1H 7.89 (d) 7.64
L-Proline	Pale yellow	87	192				
L-Cysteine	Yellow	85	189				
Tryptophan	White	90	188				
β-Alanine	Yellow	92	190				
Acacia concinna	Light brown	90	190				

TABLE-3
PHYSICO-CHEMICAL PROPERTIES OF THE PRODUCTS OBTAINED BY THE CONDENSATION OF SALICYLDEHYDE WITH MALONIC ESTER

Catalyst	Colour	Yield (%)	m.p. (°C)	m.p. (°C) [Ref. 31]	IR (ν_{max}, cm^{-1})	Mass (*m/z*)	^{1}H NMR
Glycine	White	96	92	92-95	3185 (arom C-H), 2986 (alkyl C-H) 1752 (C=O)	218 (31 %) M^+; 173 (90 %); 146 (100 %)	DMSO, 500 MHz 1H 8.52 (s); 1H 7.63; 1H 7.35; 2H 4.41 (m); 4,6 1H; 3H`. 41 (t) overlapped; 5,7 1H
L-Proline	Pale yellow	90	90				
L-Cysteine	Yellow	86	92				
Tryptophan	White	92	93				
β-Alanine	Yellow	90	93				
Acacia concinna	Light brown	95	92				



Scheme-VIII: Micelle-promoted syntheses of coumarin

as well as the yields of products. This remarkable enhancement in reaction rate prompted us to explore the potential of this protocol for the synthesis of 3-carboxycoumarins and ethyl-coumarin-3-carboxylate.The efficiency of this aqueous approach was studied for the synthesis of 3-carboxycoumarin and ethylcoumarin-3-carboxylate using mild reaction conditions and the results are summarized in Tables 2 and 3.

A model reaction was performed by using salicyldehyde, Meldrum's acid and aqueous extract of *Acacia concinna*. The product was isolated, purified and characterized. The results verified the formation of coumarin-3-carboxylic acid. Afterwards the syntheses were carried out by employing malonic acid. The products (**3**) was characterized with the product obtained with glycine (m.p., mixed m.p., TLC, IR). This remarkable enhancement in reaction rate and efficiency of this approach prompted us to explore the potential of this protocol for the synthesis of ethyl coumarin-3-carboxylate.

Ethyl coumarin-3-carboxylate: In continuation of our interest in the green catalysts condensation of salicyldehyde (**1**) with ethyl acetoacetate (**6**) was carried out in the presence of glycine. This reaction gave a yield of 92 %. The results confirmed the presence the formation of ethyl coumarin-3-carboxylate. So the catalytic activity of few other amino acids and aqueous extract of *Acacia concinna* was attempted. All these reactions gave excellent yields.

Conclusion

For the present work, only salicyldehyde and a few representative active methylene compounds were used to check the feasibility of amino acid as well as *Acacia concinna* catalysts in these reactions. The yields in all these cases were comparable and these catalysts can be extended using other salicyldehyde derivatives and active methylene compounds. In conclusion, an efficient and another eco-friendly method for the syntheses

of 3-carboxycoumarin and ethylcoumarin-3-carboxylate have been explored. The high yield of products in a short reaction time with high purity, mild reaction conditions and a simple workup procedure makes this procedure attractive for large scale preparation of coumarins.

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