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CHITOSAN SULFONIC ACID AS AN EFFICIENT CATALYST FOR THE GREEN SYNTHESIS OF COUMARIN DERIVATIVES

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ABSTRACT:
An eco-friendly simple protocol has been devised for the preparation of coumarin derivatives using chitosan sulfonic acid (CS-SO_3H) as a catalyst. Solvent-free conditions were employed for the reaction of different substituted phenols with β-ketoester in CS-SO_3H to produce corresponding substituted coumarin derivatives in good to excellent yields at room temperature and with reduced reaction times. The reactions are characterized by high efficiency, short reaction time, high product yield, simple experimental procedure, availability of catalyst, and environmentally-friendly reaction conditions.

KEYWORDS: Chitosan sulfonic acid; β-ketoester; coumarin; multicomponent reaction; one-pot synthesis

1. INTRODUCTION

The "green chemistry" techniques continue to grow in importance, with the aim of conserving resources and reducing costs. In recent years, the focus on "green chemistry" using environmentally benign reagents and conditions has been one of the most fascinating developments in the synthesis of widely used organic compounds. Solvent free synthesis for organic reactions has received considerable attention in the arena of organic synthesis owing to its green credentials. Following the increasing demand for "green chemistry", the search for more environmentally benign forms of catalysis has received overwhelming attention, and one of the leading contestants for environmentally acceptable alternatives is the biodegradable materials [1].

Green chemistry efficiently utilizes renewable raw materials, eliminates waste, and avoids the use of toxic and/or hazardous solvents and reagents in the manufacture of chemical products. In this regard, inexpensive, biodegradable, renewable, and widely abundant biopolymers have attracted attention as catalytic reactions. During last decade, a variety of biopolymers have been used as catalyst for organic synthesis [2,3].

Coumarin is a heterocyclic compound, with a characteristic benzopyrone structure, where the benzene ring is condensed with a pyrone ring. It was first discovered when it was isolated from the plant *Coumarouna odorata Aube (Dipteryx odorata)* in 1820 [4]. Afterwards, coumarin and its derivatives were found in many other plants, in a free form or in a form of heterosides, like *Apiaceae*, *Asteraceae*, *Fabiaceae*, *Rosaceae*, *Rubiacae* and *Solanaceae* [5], predominantly in *Rutaceae* and *Umbelliferae* [6]. Plant coumarins are characterized as phytoalexins, compounds that are synthesized when the plant is subjected to adverse conditions, wilting, various diseases or pathogen attacks [7, 8]. They possess a wide variety of different pharmacological and biological effects and can be found in different extracts, like *Cortex Fraxini*, whose anti-inflammatory activity correlates to the presence of phenolic acids and coumarins, eculin, esculetin, fraxin and fraxetin. Many other examples of the bioactivity of different plant extracts due to the coumarin presence are described, emphasizing their great potential in pharmacology and medicine. Its structure allows a substitution at six different positions, thus providing numerous possibilities of synthetic modifications on the core structure, with a wide range of possible novel derivatives with novel biological activities.

Coumarins (2*H*-chromone-2-one) are considered a significant class of heterocyclic compounds due to their versatile biological and medicinal properties such as antihelmintic, antioxidant [9], anticonvulsant [10], antitumor and anti-inflammatory activities [11]. Broad range antimicrobial properties are also attributed to this core due to its distinct structural properties. Coumarins have important applications in cosmetics, fragrances, pharmaceuticals and food additives [12]. It is recognized to introduce resistance in plant tissues against microbial attack, which is evident by the presence of coumarin derivatives in commercially available pesticides [13]. One of the unique structural features of coumarin is the ease with which it could be assembled and modified using cheap and commercially available starting materials. During the past decades several methods used for the synthesis of coumarins include Pechmann [14], Wittig [15], Knoevenagel [16] and Refermatsky reactions [17]. Pechmann condensation is a widely used method in which phenols are reacted with β-ketoester to give 4-substituted coumarins in the presence of acid catalyst.

Chitin is ranked as the second most abundant resource after cellulose with an annual production estimated to be of several tons. It is routinely extracted from cell fungi; the exoskeletons of arthropods, such as crustaceans and insects; the radulas of mollusks; and the beaks of cephalopods. Chitosan, a derivative of chitin, contains repeat units of β-(1 → 4)-2-amino-2-deoxy-β-D-glucose and features a primary amine functionality (Figure 1). This functionality is typically afforded through deacetylation of chitin in basic media, resulting in hydrolysis of the acetamide group to form chitosan and acetic acid. A known unit of measurement to quantify this procedure is the degree of deacetylation (DDA), where pure chitin has a DDA of 0–15%, primarily containing acetamide groups at the C2 position, while chitosan has a DDA of 75–80%, with mostly amine functionalities on the C2 position. Due to this chemical modification *via* deacetylation, chitosan has a noted advantage in solubility in acidic, aqueous media compared to chitin, making chitosan highly applicable to current challenges [18]. .

Chitosan is one of the best biopolymeric substrates which is easily obtained from natural sources and can be used for a variety of applications in numerous industrial areas. It is easily derived by the random *N*-deacetylation of chitin, a by-product of the fishing industry, under alkaline conditions. Also, chitosan is a linear biopolymer with special features including hydrophilicity, crystallinity, ionic conductivity, high viscosity and nitrogen richness that make it to stand out from other biopolymeric materials [19]. Due to the presence of both amino and hydroxyl groups with proper geometry on the chitosan backbone, it has a great ability to form coordination interactions and covalent bonds with a variety of metals and organic compounds, respectively [20–23]. Hence, chitosan has been widely studied as an appropriate precursor or ingredient in various research areas. Interestingly, chitosan has been used as a heterogeneous catalyst alone in some organic transformations [24].

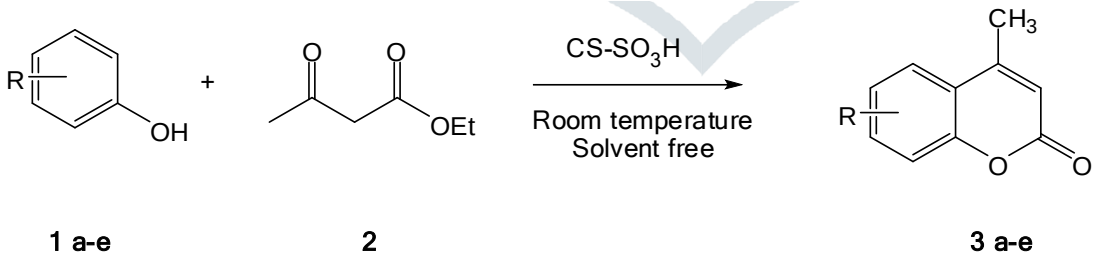
2. EXPERIMENTAL

2.1 Apparatus and analysis

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products unless otherwise stated. ^{1}H NMR (300 MHz) spectra was obtained using Bruker DRX-300 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer.

2.2 General procedure for the synthesis of coumarins (3a–e)

A round bottom flask was charged with phenol (**1a–e**) (1 mmol), β-ketoester (**2**) (1.2 mmol) and CS-SO_3H (5 mol %l) and stirred at room temperature. Reaction progress was monitored *via* thin layer chromatography using 1 : 1 ethyl acetate and *n*-hexane. After the appearance of single spotted product on TLC, the reaction mixture was allowed to cool, and work-up was done by addition of distilled water and stirring for 5 to 10 min. The produced crystalline product was filtered, and recrystallized using ethanol (Scheme-1).



Scheme – 1 Synthesis of coumarin derivatives from different substituted phenols using CS-O_3H as a catalyst.

2.3 Spectral data for the synthesized compounds (3a-e)

2.3.1 7-Hydroxy-4-methyl-2H-chromen-2-one (3a)

Colorless solid, yield (90%), MP (182–184 °C), FTIR (cm^{-1}): 1395, 1595, 1677, 3129, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.52 (s, 1H, OH), 7.55 (d, 1H, J = 8.7 Hz, HAr), 6.772–6.809 (dd, 1H, J = 2.4, 8.7 Hz, HAr), 6.69 (d, 1H, J = 2.4 Hz, HAr), 6.11 (s, 1H, CH), 2.34 (s, 3H, CH_3).

2.3.2 7-Hydroxy-4,5-dimethyl-2H-chromen-2-one (3b)

Colorless solid, yield (82%), MP (189–190 °C), FTIR (cm^{-1}): 1362, 1513, 1619, 3325, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.55 (s, 1H, OH), 6.56 (d, 2H, J = 10.5 Hz, HAr), 6.02 (s, 1H, CH), 3.44 (s, 3H, CH_3), 2.26 (s, 3H, CH_3).

2.3.3 5,7-Dihydroxy-4-methyl-2H-chromen-2-one (3c)

White solid, yield (85%), MP (280–282 °C), FTIR (cm^{-1}): 1365, 1558, 1670, 3129, 3412, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.53 (s, 1H, OH), 10.30 (s, 1H, OH), 6.25 (d, 1H, J = 2.4 Hz, HAr), 6.16 (d, 1H, J = 2.4 Hz, Ar-H), 5.84 (s, 1H, CH), 2.48 (s, 3H, CH_3).

2.3.4 7,8-Dihydroxy-4-methyl-2H-chromen-2-one (3d)

White solid, yield (87%), MP (243–244 °C), FTIR (cm^{-1}): 1313, 1588, 1655, 3218, 3404, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.0 (s, 1H, OH), 9.34 (s, 1H, OH), 7.05 (d, 1H, J = 8.7 Hz, HAr), 6.79 (d, 1H, J = 8.7 Hz, HAr), 6.10 (s, 1H, CH), 2.33 (s, 3H, CH_3).

2.3.5 4-(Methyl)-2H-benzo[h]chromen-2-one (3e)

Light yellow solid, yield (78%), MP (220–222 °C), FTIR (cm^{-1}): 1398, 1542, 1604, 3438, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.517 (m, 1H, HAr), 7.845 (m, 1H, HAr), 7.70 (m, 1H, HAr), 7.60 (m, 3H, HAr), 6.62 (s, 1H, CH), 4.72 (s, 2H, CH_2).

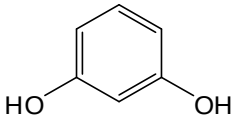
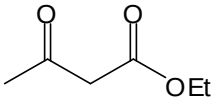
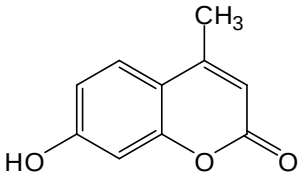
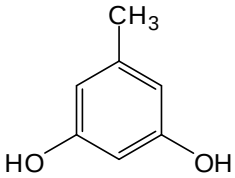
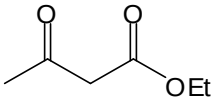
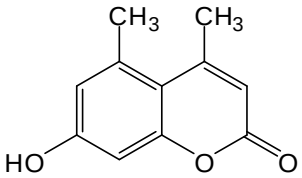
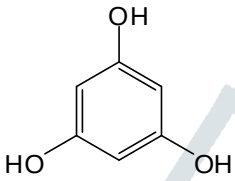
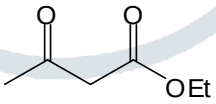
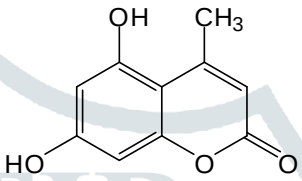
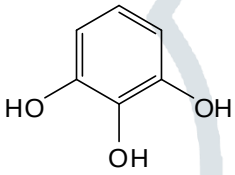
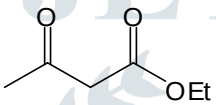
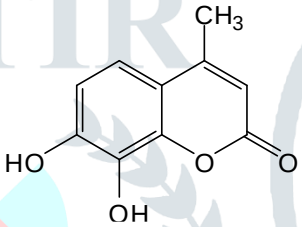
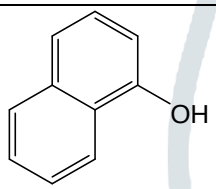
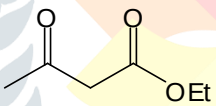
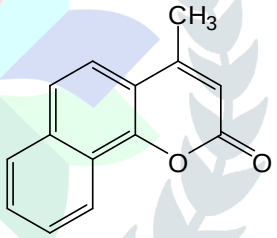
3. RESULTS AND DISCUSSION

3.1 Optimization of synthesis of coumarin derivatives

Reaction of resorcinol (**1a**) and ethyl acetoacetate (**2**) was carried out as a model reaction and the reaction conditions such as temperature, time and catalyst mol% were optimized for high yield of coumarin **3a** (Table 1). The condensation of resorcinol (**1a**) and ethyl acetoacetate (**2**) was more facile and proceeded to give highest yield using CS-SO_3H under solvent-free at room temperature. The reaction was completed within 80 min and the expected product was obtained in 90 % yield.

After optimization of conditions of **3a**, five other coumarin derivatives were prepared using different substituted phenols (**1a–e**) and β-ketoesters (**2**) under solvent-free, optimized conditions (Table 1). Yields of products and progress of reaction was affected by phenolic substitutions. Highest product selectivity was observed for reaction of resorcinol (**1a**) with ethylacetoacetate (**2**). Electron donating groups such as methyl and hydroxyl ones, substituted on *ortho*- or *para*- to both hydroxyls of resorcinol, also indicated best reaction rates and yields.

Table 1 Synthesis of coumarin derivatives from different substituted phenols using CS-O_3H as a catalyst[a]

Entry	Phenol	β-ketoester	Product	Time min	Yield (%)[b]
1				80	90
2				80	82
3				60	85
4				60	87
5				80	78

[a]Reaction conditions: Phenol (1 mmol) and β-ketoester (1.2 mmol) in the presence of CS-SO_3H (5 mol %) solvent free at room temperature.

[b]Isolated yield.

Recyclability of catalysts is an important aspect of a reaction from an economical and environmental point of view, and has attracted much attention in recent years. Thus the recovery and reusability of CS-SO_3H was investigated. After completion of the reaction, the reaction mixture was cooled to ambient temperature, CH_2Cl_2 was added, and the CS-SO_3H was filtered off. The recycled catalyst has been examined in the next run. The CS-SO_3H catalyst could be reused four times without any loss of its activity and yields ranged from 90 to 86 %.

4. CONCLUSION

In conclusion, a simple, efficient and green protocol was demonstrated for the synthesis of coumarin derivatives using chitosan sulfonic acid (CS-SO_3H) as a catalyst. Solvent-free conditions were employed for the reaction of different substituted phenols with β-ketoester in CS-SO_3H to produce corresponding

substituted coumarin derivatives in good to excellent yields at room temperature and with reduced reaction times. General applicability, operational simplicity, mild reaction conditions, non-toxic and inexpensive catalyst were the advantages of the present procedure.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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