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An Efficient and Novel Method Catalyst for Synthesis of Warfarin Derivative Through One-Pot Pseudo Three-Component Reactions Using Alum as a Green Catalyst

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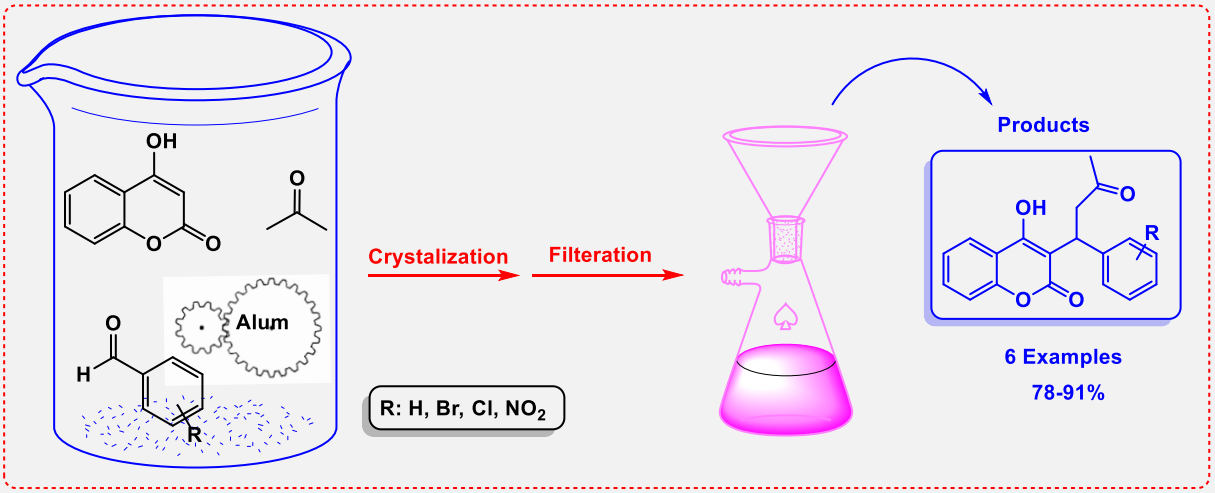
ABSTRACT: Coumarins display a remarkable array of biochemical and pharmacological activities such as anticoagulant, anticancer, antioxidant, antiviral, anti-diabetic, anti-inflammatory, antibacterial, antifungal and anti-neurodegenerative. Warfarin derivatives are a valuable example of bioactive molecules containing coumarin structure that have many applications in medicinal chemistry. In this paper, the molecules of 4-hydroxycumarin, acetone, and aldehydes are combined in a single pot to form a pseudo three-component condensation that produces new warfarin derivatives in high yields with a fast reaction time. Alum, a non-toxic, reusable, affordable, and widely accessible reagent, served as the catalyst for this environmentally friendly protocol.



KEYWORDS: Coumarins, Warfarin, Medicinal Chemistry, Alum as catalyst, Recoverable catalyst.

■ Introduction

Many pharmaceuticals, biological substances, and natural products contain the coumarin ring skeletons, including the cytostatic alkaloids warfarin [1], acenocoumarol [2], tecarfarin [3], dicoumarol [4], novobiocin [5], clorobiocin, trioxsalen, calanolide, and phenprocoumon (**Figure 1**) [6–8]. The fundamental building blocks of many synthetic medications, coumarins are significant heterocyclic compounds with a wide range of biological activities, including anticoagulant [9,10], antibiotic [11], antiviral [12], antifungal [13], anticancer [14], and anti-HIV. [15] In terms of lead generation and lead optimization, multicomponent reactions (MCRs) have been crucial in the contemporary drug discovery process [16–18]. MCRs have piqued the interest of organic chemists in the one-pot, quick, and atom-efficient production of highly functionalized organic molecules and pharmaceutically significant heterocycles.

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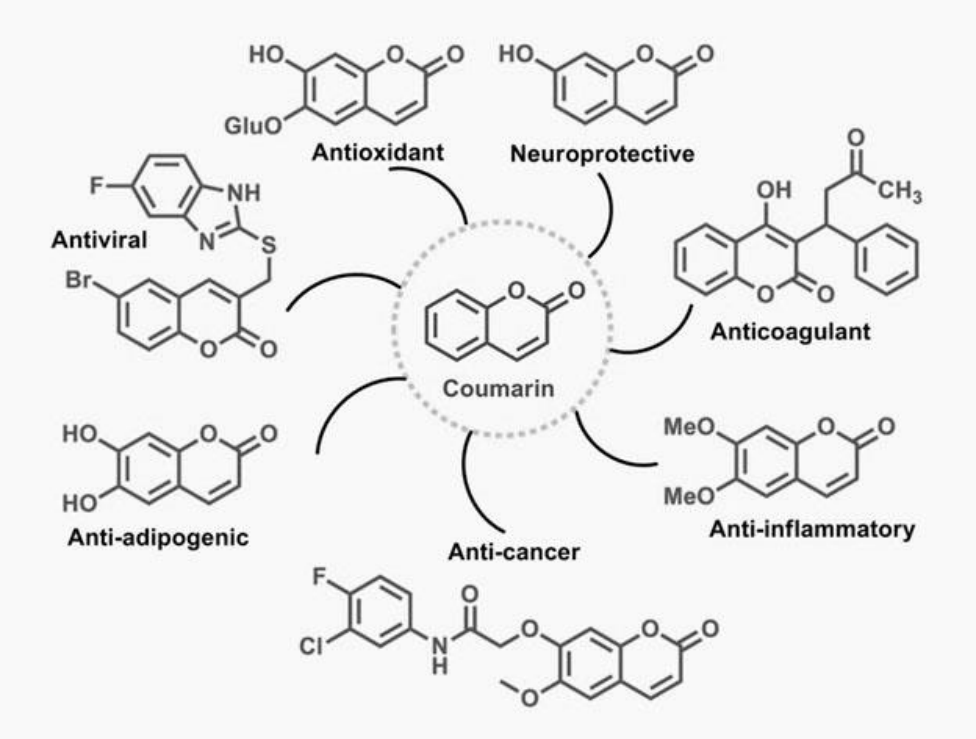
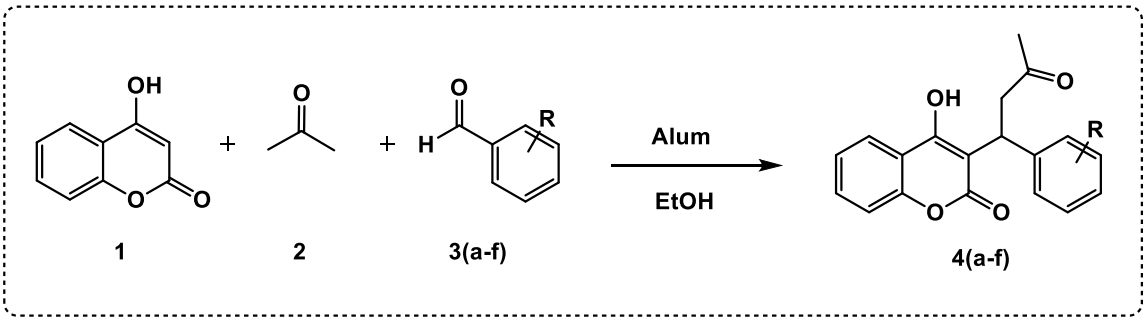


Figure 1. Several examples of bioactive molecules containing coumarin ring skeletons.

■ Result and discussion

Several methods have been reported for the synthesis of chromene-2-one derivatives. The Perkin reaction, Vilsmeier-Haack and Suzuki cross-coupling reactions, Pechmann condensation, Wittig reaction, Knoevenagel condensation, Reformatsky reaction, and Claisen rearrangement are only a few examples of traditional methods that can be used to make coumarins. [19] Here, we present a first-ever heterogeneous alum catalysis reaction between three molecules of 4-hydroxycumarin (**1**), acetone (**2**), and aldehydes **(3a-f)** in a single pot to create 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one **(4a-f).** The advantages of utilizing this catalyst are its non-toxicity, non-hazardous nature, accessibility, ease of work-up for separation, and reusability without significant activity loss (**Scheme 1**).



Scheme 1. Three-component reaction of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-ones (**4a-f**).

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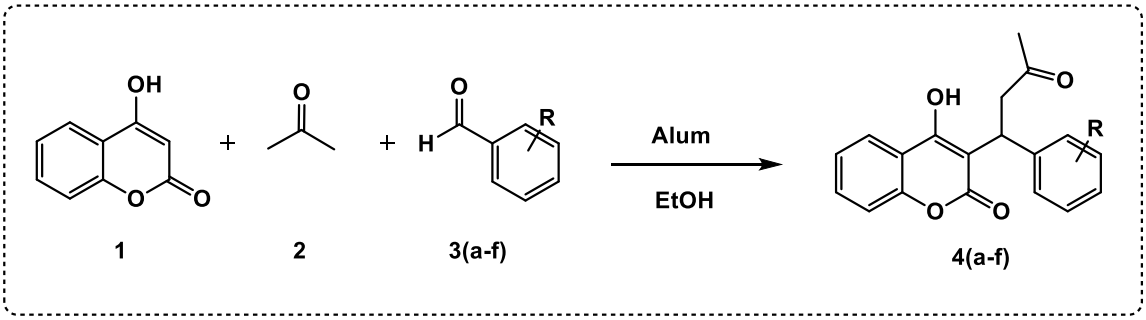
4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (**4a)** was obtained in 87% yield from a combination of 4-hydroxycumarin (1 mmol), acetone (1 mmol), aldehyde (1 mmol), and alum (0.3 g). The reaction was run under refluxed conditions for 120 minutes (until the thin-layer chromatography analysis revealed that the 4-hydroxycumarin had vanished).

Table 1. Synthesis of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-ones **4(a-f)** catalyzed by alum [a,b]



Product	R	Time (h)	Yield%	Mp (C)	Lit. Mp (C)
4a	H	2	87	160-162	160[20]
4b	4-Br	2.5	91	184-186	-
4c	4-Cl	3	90	172-175	-
4d	4-NO_2	2	83	194-197	196-199[21]
4e	2-Cl	3	80	153-156	-
4f	2-Br	3.5	78	177-179	-

[a] Reaction conditions: all the reaction were carried out using 4-hydroxycumarin (1 mmol), acetone **(**1 mmol), and aldehyde (1 mmol), reflux conditions for 2 h. [b] Isolated yield

The effects of different solvents (ethanol, methanol, dichloromethane, Water, and others), catalyst concentrations (0.01, 0.2, 0.3 and 0.4 g), and temperatures (RT, 50°C, 70°C, and reflux) were examined. These conditions produced the best yield and quickest reaction time. Several aldehyde derivatives were treated with 4-hydroxycumarin and acetone in order to demonstrate the generality of this catalytic reaction. The outcomes are shown in **Table 1**.

Although a plausible approach is shown in Scheme 3, we have not yet definitively developed a precise mechanism for the synthesis of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one **(4a-f)**. First, thermal dehydration (monitored by TLC) produces 4-phenylbut-3-en-2-one **(a)** from the condensation of acetone and aldehyde. Then in the presence of alum, the 4-phenylbut-3-en-2-one **(a)** would undergo condensation with the 4-hydroxycumarin *via* nucleophilic attack to produce the final product, 4-hydroxy-

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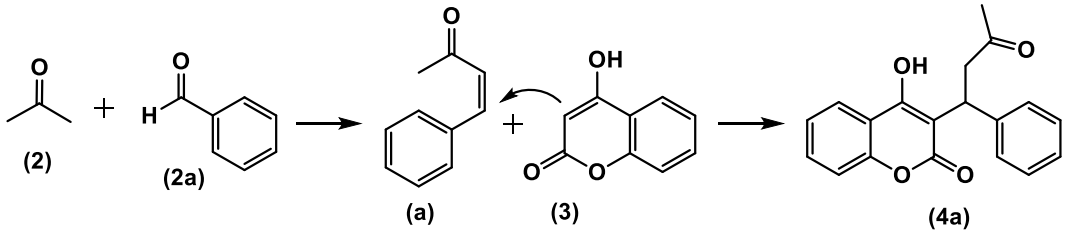
3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (**4a)**. Product (**4a)** was established by the 1H-NMR spectroscopy and Heraus CHN rapid analyzer. We tried hardly, unfortunately, none of the compounds were crystalized properly for the X-ray crystallography. The structures of other products were characterized by melting point analysis.



Scheme 2. A plausible mechanism for synthesis of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-ones **4(a-f)** catalyzed by alum.

■ Summary and outlook

In summary, the pseudo three-component reaction described herein provides a simple and direct entry into a number of interesting novel warfarin analogies The method offers several advantages including high yield of products, easy experimental work-up procedure, using the inexpensive, non-toxic, and easily available alum as catalyst. Surprisingly, this reaction selectively gives 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one derivatives.

■ Experimental

General methods. Melting points were obtained in open capillary tubes and were measured on an electro-thermal 9200 apparatus. 1H-NMR spectra were determined on a Bruker 400 DRX Avance instrument at 400 MHz. Elemental analysis for C, H, and N were performed using a Heraus CHN rapid analyzer.

General experimental procedure for synthesis of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-ones (4a-f).

The following ingredients were introduced to a 20 mL round bottom flask with a magnetic stirring bar: 5 mL of ethanol and 0.2 g (0.3 mmol) of alum. The mixture was then given a 1 mmol addition of 4-hydroxycumarin (**1)**, 1 mmol of acetone (**2)**, and 1 mmol of aldehyde (**3)**, and allowed to aggressively agitate at reflux for the duration shown in Table 1. The solvent was evaporated under reduced pressure, water (10 ml) was added to the reaction mixture, and the resultant solid was separated by filtration when the reaction (as monitored by TLC, ethyl acetate / n-hexane, 2:1) had finished. The crude product was washed with hot ethanol to afford the pure product.

4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (4a): White solid, Yield : 87%; m.p: 160-162 (°C); (m.p.=160°C) [22]; 1H NMR (400 MHz, $CDCl_3$) ppm: 2.1(s, 3H, CH_3), 3.00(q, J= 6 Hz, J= 7Hz, 1H, CH_2), 3.2(q, J=5 Hz, J= 7Hz, 1H, CH_2), 4.01(t, J=7 Hz, 1H, CH), 6.17(s, 1H, OH), 7.24(m, 3H, ArH), 7.37-

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7.38(m, 2H, ArH), 7.41-7.43(m, 1H, ArH), 7.45-7.48(m, 2H, ArH), 7.49-7.50 (m, 1H, ArH). Anal Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23; O, 20.76%, Found: C, 73.93; H, 5.34%.

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