

Et₃N catalyzed cascade reaction of Meldrum's acid with *ortho*-hydroxyaryl aldehydes for the synthesis of coumarin-3-carboxylic acids under solvent-less condition

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Abstract The synthesis of coumarin-3-carboxylic acids in good yields is realized through a triethylamine catalyzed Knoevenagel-intramolecular cyclization tandem reaction of Meldrum's acid with various ortho-hydroxyaryl aldehydes. This method expands the catalyst library about the synthesis of coumarin-3-carboxylic acids and also has advantages of using much less water as solvent, a cheap and eco-friendly catalyst, clean reaction conditions, simple workup procedure and easy isolation.

Graphical Abstract



Keywords Coumarin-3-carboxylic acids · Triethylamine · Water · Environmentally friendly

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Introduction

Over the past few decades, the synthesis of coumarin and its derivatives has attracted considerable attention from organic and medicinal chemists due to coumarin (2-oxo-2H-1-benzopyran) heterocyclic moiety being a "privileged" structural motif both in numerous natural products and synthetic organic compounds of potential pharmacological activities [1-6]. They are also key components for flavoring of a diverse set of foods [7–11]. Coumarin-3-carboxylic acids are key precursors for the synthesis of coumarins and also act as vital building blocks of various natural and semisynthetic pharmacological agents [12]. Because of these advantages of coumarin-3-carboxylic acids, the search for new and more convenient methods to accomplish their synthesis is desirable and significant [13]. Several routes have been reported in the literature for the synthesis of coumarin-3carboxylic acid derivatives [14-16]. The Knoevenagel condensation of orthohydroxyarylaldehydes with Meldrum's acid is one of the simplest methiods because of several advantages in terms of yields, reaction times and purification of adducts [17, 18]. Many catalysts like sodium hydroxide [19], ammonium acetate [20, 21], heteropolyacids [8], potassium phosphate [22], SnCl₂·2H₂O [23], FeCl₃ [24], clays [25], lithium salts [26], Yb(OTf)₃ [13], silica sulfuric acid [16], K₂CO₃ or NaN₃ [18], and acacic acid [27], coupled with a variety of conditions such as solvent-free, heating, grinding, microwave irradiation and so on, have been utilized. 3-Carboxycoumarins can also be prepared from Meldrum's acid and salicylaldehyde by carrying out the reaction in water, avoiding the addition of any catalyst [28, 29]. Although a series of developments and modifications has been achieved, the limited number of substrates, long reaction time, low yields, tedious workup procedures, cooccurrence of several side reactions, use of large amount of organic solvents and need of chromatography for the purification of adducts are problematic [27, 29]. Consequently, there is ample room for further development of milder reaction conditions, better yields and increased variation in the substituent of both components [18].

Nowadays, environmental concerns have directly influenced the development of new methodologies [30]. The solvent-less reaction is an important synthetic procedure from the view point of green and sustainable chemistry [31]. Triethylamine (Et₃N) is a mild and cheap base, but plays an important role in accelerating the organic reactions [32, 33]. In connection with our efforts to develop mild and environmentally friendly methods as well as our interest in the application of Meldrum's acid to the synthesis of useful organic molecules [34, 35], we report here the results of our recent efforts devoted to the reaction of 2-hydroxybenzaldehydes



Scheme 1 The preparation of coumarin-3-carboxylic acid

with Meldrum's acid utilizing Et_3N as an efficient and cheap catalyst under solventless condition to afford coumarin-3-carboxylic acid (Scheme 1).

Experimental

General

Unless otherwise stated, all reagents were obtained from commercial sources and were used without further purification. Melting points were determined on a Beijing Tech X-5 Melting point detector and were uncorrected. The IR spectra were measured with a Bruker Shimadzu IR-460 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 400 MHz. The chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (*J*) in Hertz.

Typical experimental procedure for synthesis of 3

A mixture of Meldrum's acid (0.5 mmol) and salicylaldehydes (0.55 mmol) was placed in a 10-mL Schlenk tube, then Et_3N (0.015 mmol) and 50 μ L water were

Entry ^a	Catalyst (mol%)	Solvent	Reaction temperature (°C)	Time (h)	Yield ^b (%)
1	Et ₃ N (30 %)	_	60	6	80
2	DIPEA (30 %)	-	60	6	38
3	DBU (30 %)	-	60	6	69
4	DABCO (30 %)	-	60	6	78
5	Et ₃ N (50 %)	-	60	6	81
6	Et ₃ N (20 %)	-	60	6	62
7	Et ₃ N (30 %)	-	50	6	75
8	Et ₃ N (30 %)	_	70	6	68
9	Et ₃ N (30 %)	Water 50 µL	60	6	86
10	Et ₃ N (30 %)	Water 100 µL	60	6	81
11	Et ₃ N (30 %)	Water 25 µL	60	6	77
12	Neat	Water 50 µL	60	6	56
13 ^c	Et ₃ N (30 %)	Water 50 µL	60	6	90
14 ^d	Et ₃ N (30 %)	Water 50 µL	60	6	79
15	Et ₃ N (30 %)	Water 50 µL	60	4	90
16	Et ₃ N (30 %)	Water 50 µL	60	2	63

 Table 1
 The screening of reaction conditions

^a The reactions were carried out with salicylaldehyde and Meldrum's acid in equimolecular amounts of 0.5 mmol

^b Isolated yield

^c Salicylaldehyde 0.55 mmol

^d Meldrum's acid 0.55 mmol

added. The reaction mixture was stirred at the indicated temperature for 4 h. After completion of the reaction, 3 mL aqueous ethanol was added to the mixture and vigorously stirred for a moment. The pH was adjusted to 2–3 with dilute hydrochloric acid. Finally, the precipitate was separated by filtration and washed

Entry ^a	Product	Reaction temperature (°C)	Yield ^b (%)	m.p. (°C)
1	Соон	60	90	188–190 (188–190 [28])
2		85	23	230–232 (232–234 [18])
3	Br COOH	85	90	201–202 (194–196 [28])
4	CI COOH	85	85	158–160 (122–123 [18])
5	H ₃ C COOH	70	90	163–165 (167–168 [28])
6		60	93	199–201 (193–195 [28])
7		60	92	268–270 (260–262 [18])
8		60	Trace	
9	Br COOH Br 3i	60	36	201–203 (206–208 [18])
10		85	90	239–241 (216–218 [28])

 Table 2
 Substrate scope for the synthesis of 3-carboxycoumarins

 $^{\rm a}$ The reactions were carried out with salicylaldehyde/Meldrum's acid (0.55 mmol/0.5 mmol) under solvent-less condition

^b Isolated yield

with aqueous ethanol without further purification to afford the corresponding pure adducts.

Results and discussion

In view of the low melting points of the precursors 1 and 2, solvent-free conditions were attempted. We started our research by carrying out the condensation of salicylaldehyde with Meldrum's acid in equimolecular amounts of 0.5 mmol, and different organic bases were tested to evaluate their ability to promote the reaction at 60 °C for 6 h (Table 1). It was found that when triethylamine was used as the catalyst (Table 1, entry 1), the highest yield of the product (80 % yield) was obtained, and triethylenediamine (DABCO) (Table 1, entry 4) also had good catalytic ability (78 % yield), but N,N-diisopropylethylamine (DIPEA) gave a modest result (Table 1, entry 2). Then, we optimized the amount of Et₃N required for this reaction (Table 1, entries 5, 6), and the best load was found to be 30 mol% (Table 1, entry 1). The effect of the temperature on the reaction was also examined and the results show that reacted at 60 °C was a feasible option. Further raising or lowering the temperature is detrimental to the reaction (Table 1, entries 7, 8). As we know, water can promote the condensation of Meldrum's acid with aldehydes avoiding the addition of any catalyst [36] and exhibits unique reactivity in the reaction of 2-hydroxybenzaldehydes with Meldrum's acid for the synthesis of coumarin-3-carboxylic acids [28, 29]. Thus, the effect of adding a little water as solvent was surveyed (Table 1, entries 9-11). After some experimentation, we were pleased to find that adding 50 µL water could improve the yield (Table 1, entry 9). A control experiment without base was also examined in order to recognize the capability of the Et₃N (Table 1, entry 12). The model reaction gave an unsatisfactory result, which supported the accelerating activity of Et₃N. Further, we examined the fate of varying the ratio of substrates. A better conversion of reactants to afford the desired product in 90 % yield was observed when employing 1.1 equiv. of salicylaldehyde (Table 1, entry 13). The effect of the reaction time was also surveyed and the time decreased to 4 h (Table 1, entry 15). Continuously shortening the reaction time was unfavorable (Table 1, entry 16). So it is clear that the optimum conditions are salicylaldehyde and Meldrum's acid in a ratio of 1.1:1 and using 30 mol% Et₃N and 50 µL water (550 mol%) as accelerant at 60 °C for 4 h.

With the optimized reaction conditions in hand, we decided to explore the condensation reaction of Meldrum's acid with various structural diverse salicylaldehydes, and products were obtained in moderate to good yields. As shown in Table 2, the electronic density of the benzene ring would play an important role in the reaction. Introduction of a strongly electron-withdrawing group on the benzene ring reduced the yield of the reaction. Particularly, when employing 5-nitrosalicylaldehyde or 3,5-dichlorosalicylaldehyde as substrate, poor yield or little product was obtained (Table 2, entries 2, 8). On the other hand, the electron-rich aromatic aldehydes were transformed into the corresponding products in similar or a slightly higher yield than that of salicylaldehyde (Table 2, entries 5–7). Additionally, naphthyl-based salicylaldehyde also reacted successfully in this process to form the desired product in 90 % yield (Table 2, entry 10).

Conclusions

In summary, we have successfully elaborated a convenient and environmentally benign reaction to afford a series of coumarin-3-carboxylic acids with moderate to good yields. The combination of triethylamine (30 mol%) with 50 μ L water plays a unique role in this reaction. Solvent-less, mild and clean reaction conditions, simple workup procedure and using an inexpensive catalyst are the best features in this process.

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