Research Article

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Study on effective synthesis of 7-hydroxy-4-substituted coumarins

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Abstract: Many coumarin derivatives have good biological activity and application value in fluorescent probes. Therefore, synthetic routes to coumarin derivatives have also attracted the attention of many research groups. In this work, based on the Pechmann coumarin synthesis method, the influence of various Lewis acids on the reaction was discussed, and the optimal synthesis conditions of 7-hydroxy-4-substituted coumarins were explored. Based on the experimental results, a possible mechanism was proposed, which provides a reference for future industrialized production of coumarins.

Keywords: coumarin, pechmann, mechanism explanation, industrialized production

1 Introduction

Coumarins, also known as *o*-hydroxycinnamic acid lactones, are a large class of compounds with the core structure of 1,2-benzopyranone. They are widely found in Umbelliferae, Rutaceae, Daphniaceae, Compositae, Leguminosae, Solanaceae, and other natural plants as well as microbial metabolites [1,2]. Because of the unique stability of the coumarin motif, more than 900 coumarin derivatives have been isolated from natural products since the discovery of coumarin in 1820 [3,4]. Many of these coumarin derivatives have anticoagulant, antiinflammatory, antibacterial, anticancer, and anti-HIV biological activities [5–8]. In addition, coumarin contains an α,β-unsaturated lipid structure, which leads to strong fluorescence of their derivatives, and it has important application value in fluorescent probes, dyes, and optical materials [9–13]. Among them, 7-hydroxycoumarin derivatives and 4-substituted coumarin derivatives are two large sub-families, and some compounds in these sub-families have been found to exhibit good biological activities. In fact, many of these compounds have become commonly used in clinical medicine or are being studied in proprietary medicinal research [14–16]. For example, 7-hydroxy-4-methylcoumarin is commonly clinically used as a choleretic drug. It can relax the sphincter of the bile duct and relieve sphincter pain [17]. As the representative of coumarin antibiotics, Novobiocin can inhibit the proliferation and metastasis of many kinds of cancer cells by inhibiting DNA gyrase, and it can reverse resistance to some anticancer drugs [18]. 4-Methyl-7-oxy-glucoside coumarin can effectively inhibit the proliferation of breast cancer cells. 7-Hydroxymethyl carbamate is being studied as a new antibacterial and antioxidant drug [19]. Dalbergin, a natural compound, has important biological activities such as antitumor, antibacterial, and antioxidant activities [20,21]. The natural compound Wedelolactone is commonly used in the treatment of septic shock, liver disease, and snakebites to protect the liver; in addition, its antipostmenopausal osteoporosis and anticancer effects are also being studied [22]. Sodium cromoglycate eye drops have become a common drug in the prevention and treatment of spring allergic conjunctivitis (Figure 1).

Coumarin compounds play an important role in improving human life and promoting societal well-being, so the synthesis and application of coumarin derivatives have attracted the attention of many research groups [23]. In the past two centuries, many typical coumarin syntheses have been reported, including the Knoevenagal synthesis, Pechmann synthesis, Perkin synthesis, and Vilsmeier–Haack synthesis [24,25]. However, research on the synthesis of new coumarins is still ongoing. Coumarin derivatives have been synthesized through coupling reactions with boric acid esters or boric acid by many research groups such as Serra's group, Blagg's group, Weissleder's group, and Yuan Jinwei's group [26–28]. The synthesis of coumarin derivatives has been reported by Baumgartner's group, Messagoudi's group, and McGlacken's group, using haloalkanes as a starting material via transition metals or

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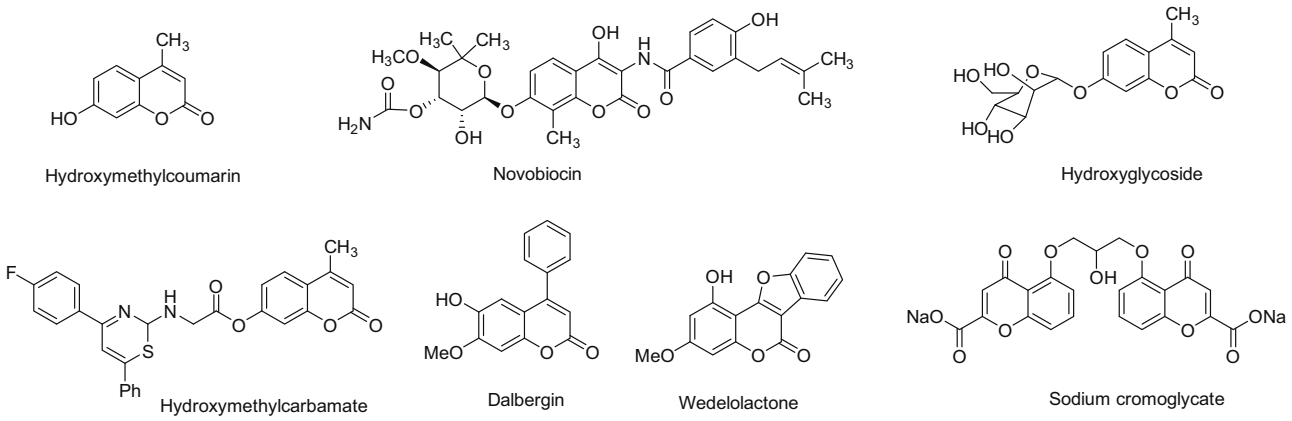


Figure 1: Representative compounds of 7-hydroxy-4-substituted coumarins.

photocatalysis [29–32]. 7-Hydroxy-4-substituted coumarins not only have their own biological activities and applications in optical materials but also can be used as key intermediates for the construction of many other derivatives [33]. Therefore, this research group focuses on exploring a more efficient way to synthesize 7-hydroxy-4-substituted coumarins, saving time and cost for industrial production. Based on the Pechmann coumarin synthesis method, we developed a more effective method to synthesize 7-hydroxy-4-substituted coumarin derivatives under different conditions.

First, 7-hydroxy-4-methylcoumarin (**1**) was synthesized by the condensation of ethyl 3-oxobutanoate with more nucleophilic resorcinol under the catalysis of different Lewis acids. In the original entries 1–4, AlCl3 was used as the catalyst to determine the optimal catalyst loading, amount of ethyl 3-oxobutanoate, and the appropriate solvent and reaction time. When AlCl3 was used with three equivalents and refluxed for 8 h, the yield reached 76% (entry 2). When the amount of ethyl 3-oxobutanoate was increased or toluene was used as solvent, the yield decreased to 63 and 58%, respectively (entries 3 and 4). When acetic acid was used as both solvent and acid catalyst, and the reaction was carried out at 100°C for 24 h, the yield was only 12%. Therefore, the weak acid, acetic acid, is not suitable for this reaction (entry 5). When trifluoroacetic acid was used as the solvent and catalyst, and the reaction was carried out under reflux for 2 h, the starting material disappeared and the yield was 80% (entry 6). We found that there were quite a few byproducts in entry 6, presumably from an excess of ethyl 3-oxobutanoate that continued to react with the product, so we reduced the ethyl 3-oxobutanoate to 0.95 equivalents, and obtained clean product with a yield of 95% (entry 7). When sulfuric acid was directly used as the solvent, the yield was 55% (entry 8). When benzene was used as solvent, the dispersion of sulfuric acid in the solvent was not good, but the yield could reach 77% (entry 9). The yields were 85 and 81% when the solvent and catalyst were methanesulfonic acid and triflic acid, respectively (entries 10 and 11). The solvent trifluoroacetic acid reacted at 80°C for an hour in a microwave oven and also gave a very good yield of 96%. However, due to no availability of a microwave reactor to scale up the reaction, no scale-up was done (entry 12). AlCl3 was used as the catalyst, and the amount of ethyl 3-oxobutanoate was similarly reduced to 0.95 equivalent, providing a yield of 78%, slightly higher than that at 1.5 equivalent. Using methyl sulfonic acid as the solvent, the reaction was carried out on the scale of tens of grams, and the yield was 88% (entry 14). Using trifluoroacetic acid as solvent, the tens of grams scale reaction provided the product with perfect yield (entry 15) (Table 1).

Description of basic conditions: All reactions protected by Argon at room temperature and then slowly heated to the set temperature. Entries 1–13 reaction substrate resorcinol 220 mg (2 mmol) and entries 14–15 reaction substrate resorcinol 22 g (0.2 mol). TLC monitoring performed every 30 min to stop the reaction, until the material disappeared or the shape of the plate no longer change significantly. The yields in entries 1–6 are calculated based on the resocinol, the others in entries 7–15 are calculated based on the ethyl acetoacetate.

On the basis of the previous work, we mainly optimized the conditions for the synthesis of 7-hydroxy-4-ethylcoumarin (**2**) catalyzed by aluminum trichloride, methanesulfonic acid, triflic acid or trifluoroacetic acid, respectively. Under the catalysis of $AlCl_3$, benzene was used as the solvent, and after refluxing for 10 h, the yield was 78% (entry 1). The yield reached 93% when methanesulfonic acid was used as the solvent and acid at 100°C reflux for 3.5 h (Entry 2). When triflic acid and

Table 1: Optimization of reaction condition for synthesizing 7-hydroxy-4-methylcoumarin (**1**)

Entry	Lewis acid (amount)	Ethyl acetoacetate (eq.)	Reaction conditions	Yield (%)
1	$AlCl_3$ (2.0 eq.)	1.5	Benzene 5 mL, reflux 15 h	45
2	$AlCl_3$ (3.0 eq.)	1.5	Benzene 5 mL, reflux 8 h	76
3	$AlCl_3$ (3.0 eq.)	2.0	Benzene 5 mL, reflux 8 h	63
4	$AlCl_3$ (3.0 eq.)	1.5	Toluene 5 mL, reflux 3 h	58
5	CH_3CO_2H (5 mL)	1.5	100°C, 24 h	12
6	CF_3CO_2H (5 mL)	1.5	Reflux 2 h	80
7	CF_3CO_2H (5 mL)	0.95	Reflux 2.5 h	95
8	H_2SO_4 (5 mL)	0.95	100°C, 1 h	51
9	H_2SO_4 (5.0 eq.)	0.95	Benzene 5 mL, reflux 16 h	77
10	CH_3SO_3H (5 mL)	0.95	100°C, 1.5 h	85
11	CF_3SO_3H (5 mL)	0.95	100°C, 1.5 h	81
12	CF_3CO_2H (5 mL)	0.95	Microwave 80°C, 1 h	96
13	$AlCl_3$ (3.0 eq.)	0.95	Benzene 5 mL, reflux 8 h	78
14	CH_3SO_3H (500 mL)	0.95	100°C, 3 h	88
15	CF_3CO_2H (500 mL)	0.95	Reflux, 3.5 h	97

trifluoroacetic acid were used as the solvents, the yields were 85 and 89% respectively (Entry 3, 4). In the pilot scale experiment, methanesulfonic acid and trifluoroacetic acid were used as the solvent, and the yields were 92 and 91% respectively (Entry 5, 6) (Table 2).

1.1 Description of basic conditions

All reactions are protected by Argon at room temperature and then slowly heated to the set temperature. All yields are calculated based on the amount of ethyl propionyl acetate, and the amount of ethyl propionyl acetate is 0.95 equivalent of resorcinol. From entry 1 to 4, the reactions are small scale, and the substrate of each reaction is 220 mg. TLC monitoring is performed every 30 min, and the reaction is stopped when the raw material disappears or the plate shape no longer changes significantly.

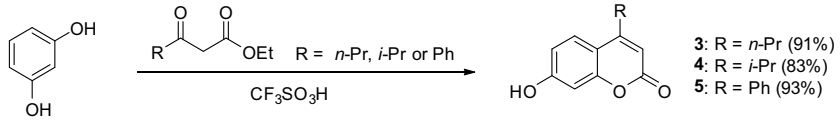
After similar experimental tests as described before, it was found that trifluoromethanesulfonic acid was the best solvent for the ring closure reaction with the larger group at the fourth position. Compounds 7-hydroxy-4-propylcoumarin (**3**), 7-hydroxy-4-isopropylcoumarin (**4**), and 7-hydroxy-4-phnylcoumarin (**5**) were synthesized respectively in the yields 91, 83, and 93%. (Scheme 1) A detailed experimental discussion is described in the supporting information.

Table 2: Optimization of reaction condition for synthesizing 7-hydroxy-4-ethylcoumarin (**2**)

Entry	Lewis acid (amount)	Reaction conditions	Yield (%)
1	$AlCl_3$ (3.0 eq.)	Benzene 5 mL , reflux 10 h	78
2	CH_3SO_3H (5 mL)	100°C, 3.5 h	93
3	CF_3SO_3H (5 mL)	100°C, 3 h	85
4	CF_3CO_2H (5 mL)	reflux 5 h	89
5	CH_3SO_3H (500 mL)	100°C, 8 h	92
6	CF_3SO_3H (500 mL)	100°C, 6 h	83
7	CF_3CO_2H (500 mL)	Reflux 10 h	91

2 Results and discussion

7-Hydroxy-4 substituted coumarins are a very useful class of compounds, which have excellent extended research value in medicine, pesticides, optical materials, etc. This experiment started by evaluating the effect of commonly used Lewis acid on the Pechmann ring condensation and



Scheme 1: Syntheses of compounds (**3**), (**4**), and (**5**) using CF_3SO_3H as solvent.

explored the optimal synthesis conditions of different 7-hydroxy-4-substituted coumarins to provide references for future industrial production. After analyzing the experimental results and the reaction mechanism, it was found that using the medium-strength acid trifluoroacetic acid as the catalyst is the best when the substituents at the fourth position are small (methyl or ethyl). The steric hindrance increases with the substituents increase on the fourth position of product, and strong acid catalysts, such as trifluoromethanesulfonic acid and aluminum trichloride, are more advantageous. After analyzing the reaction results, we give the possible reaction mechanism [34,35]. Activation of carbonyl groups under acidic conditions and then the Friedel–Crafts reaction were carried out. With the help of the hydroxyl lone pair electron, the benzene ring attacks the activated carbonyl group and condenses to get intermediate **a**. Proton is transferred from carbonyl oxygen to ethoxy, which changes the ethoxy group to a leaving group, and carbonyl aromatization into phenolic hydroxyl (intermediate **b**) takes place. The reaction of phenol hydroxyl with ester to remove ethanol is called transesterification. The final aromatization, at the same time remove a molecule of water, yields product (Figure 2).

3 Experimental part

3.1 Instruments and reagents

All instruments and chemical reagents are purchased from regular reagent companies (Aladdin, Macklin, BidePharm, Sinopharm). Bruker DRX-600 Nuclear Magnetic Resonance System was purchased from Bruker Company (Switzerland); Nicolet FTIR-870X infrared spectrometer was purchased from American Bole Company; Rotary Evaporator BC-R206 was purchased from Shanghai Hannuo Instrument Company; thermostatic magnetic stirrer 85–2A was purchased from Shanghai Sile Instrument Company; analytical balance AL204 was purchased from Shanghai Mettler Toledo Instrument Company; Liquid Mass Spectrometry Chromatograph LCMS-2020 was purchased from Japan Shimadzu Company; atmospheric pressure microwave chemical reactor MCR-3 was purchased from Gongyi Yuhua Instrument Company; and micro melting point instrument X-4B was purchased from Shanghai Inesa Optical Instrument Company. IR spectra were measured on a JNM FT/IR-460 Plus spectrometer. Melting points were recorded with a INESA-X-4B micro melting point apparatus.

3.2 General procedure for the 7-hydroxy-4-substiuted coumarins using CH_3CO_2H (or CF_3CO_2H, CH_3SO_3H, CF_3SO_3H, H_2SO_4) as acid catalyst

A mixture of resorcinol (220 mg, 0.2 mmol) and ethyl acetoacetate (24.7 mg, 0.19 mmol) [or ethyl propionylacetate (27.4 mg, 0.19 mmol), ethyl 3-oxohexanoate (30 mg, 0.19 mmol), ethyl isobutyryl acetate (30 mg, 0.19 mmol), and ethyl benzoylacetate (36.5 mg, 0.19 mmol)] in acetic acid (or trifluoroacetic acid, methanesulfonic acid, triflic acid, sulfuric acid) (5 mL) was stirred at 100°C (or reflux) under Ar protection for several hours. Until the starting material disappeared (or no more change) based on the thin-layer chromatography (TLC), the reaction mixture was treated with the addition of H_2O (20 mL) and AcOEt (10 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (10:1–3:1) to afford the desired products.

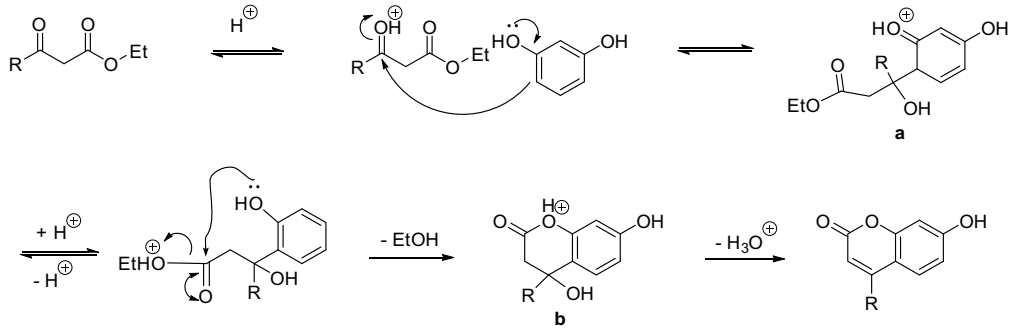
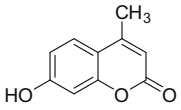


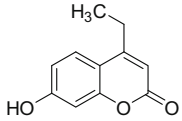
Figure 2: The mechanism of condensation and ring closure.

3.2.1 7-Hydroxy-4-methyl-2*H*-chromen-2-one (1)



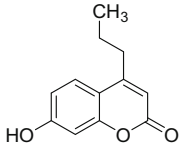
^{1}H NMR (600 MHz, chloroform-d, 25°C): δ 7.49 (d, J = 8.64 Hz, 1 H), 6.87 (s, 1 H), 6.82 (d, J = 8.64 Hz, 1 H), 6.15 (s, 1 H), 5.80 (s, 1 H), 2.40 (s, 3 H); ^{13}C (151 MHz, chloroform-d, 25°C): δ 161.18 (s), 159.12 (s), 155.16 (s), 152.76 (s), 126.00 (d), 113.82 (s), 112.78 (d), 111.96 (d), 103.39 (d), 18.76 (q). IR (KBr, cm^{-1}) 3500, 2426, 2368, 1676, 1600, 1392, 1068; HRMS (ESI): m/z calcd for $C_{10}H_9O_3$ [M+H]$^+$: 177.0548, found 177.0549. White solid, mp 182–184°C.

3.2.2 Ethyl-7-hydroxy-2*H*-chromen-2-one (2)



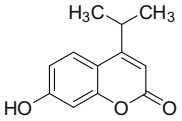
^{1}H NMR (600 MHz, chloroform-d, 25°C): δ 7.52 (d, J = 8.70 Hz, 1 H), 7.01 (d, J = 2.22 Hz, 1 H), 6.86 (dd, J = 8.70, 2.22 Hz, 1 H), 6.16 (s, 1 H), 2.79 (q, J = 7.44 Hz, 2 H), 1.33 (t, J = 7.44 Hz, 3H); ^{13}C (151 MHz, DMSO-d_6, 25°C): δ 161.48 (s), 161.04 (s), 158.82 (s), 155.43 (s), 126.58 (d), 113.39 (d), 111.60 (s), 108.78 (d), 102.81 (d), 24.47 (t), 12.77 (q). IR (KBr, cm^{-1}) 3481, 2426, 2138, 1723, 1611, 1000; HRMS (ESI): m/z calcd for $C_{11}H_{11}O_3$ [M+H]$^+$: 191.0703, found 191.0710. White solid, mp 168–170°C.

3.2.3 7-Hydroxy-4-propyl-2*H*-chromen-2-one (3)



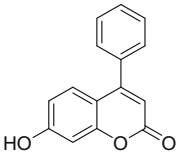
^{1}H NMR (600 MHz, chloroform-d, 25°C): δ 7.94 (br, 1 H), 7.53 (d, J = 8.64 Hz, 1 H), 7.08 (s, 1 H), 6.89 (d, J = 8.64 Hz, 1 H), 6.14 (s, 1 H), 2.72 (t, J = 7.38 Hz, 2 H), 1.73 (sext, J = 7.38 Hz, 1 H), 1.05 (t, J = 7.38 Hz, 3 H); ^{13}C (151 MHz, chloroform-d, 25°C): δ 162.92 (s), 160.16 (s), 157.79 (s), 155.26 (s), 125.78 (d), 113.56 (d), 112.69 (s), 110.04 (d), 103. 57 (d), 33.91 (t), 21.61 (t), 13.96 (q). IR (KBr, cm^{-1}) 3519, 3062, 2975, 1913, 1675, 1606, 1455,1348; HRMS (ESI): m/z calcd for $C_{12}H_{13}O_3$ [M+H]$^+$: 205.0859, found 205.0858. White solid, mp 129–131°C.

3.2.4 7-Hydroxy-4-isopropyl-2*H*-chromen-2-one (4)



^{1}H NMR (600 MHz, chloroform-d, 25°C): δ 7.57 (d, J = 8.76 Hz, 1 H), 6.99 (s 1 H), 6.85 (d, J = 8.76 Hz, 1 H), 6.75 (s, 1 H), 6.19 (s, 1 H), 3.26 (sept, J = 6.78 Hz, 1 H), 1.32 (d, J = 6.78 Hz, 6 H); ^{13}C (151 MHz, chloroform-d, 25°C): δ 162.86 (s), 162.67 (s), 159.36 (s), 155.43 (s), 125.50 (d), 113.10 (d), 112.37 (s), 107.75 (d), 103. 72 (d), 28.74 (d), 21.83 (q). IR (KBr, cm^{-1}) 3591, 3016, 1822, 1801, 1398; HRMS (ESI): m/z calcd for $C_{12}H_{13}O_3$ [M+H]$^+$: 205.0859, found 205.0856. White solid, mp 123–125°C.

3.2.5 7-Hydroxy-4-phenyl-2*H*-chromen-2-one (5)



^{1}H NMR (600 MHz, chloroform-d, 25°C): δ 10.63 (br, 1 H), 7.50–7.57 (m, 5 H), 7.28 (d, J = 8.76 Hz, 1 H), 6.77–6.81 (m, 2 H), 6.15 (s, 1 H); 13 C (151 MHz, chloroform-d, 25°C): δ 161.89 (s), 160.58 (s), 156.05 (s), 155.89 (s), 135.68 (s), 130.03 (d), 129.29 (d), 128.86 (d), 128.58 (d), 113.68 (d), 111.18 (s), 110.85 (d), 103.18 (d). IR (KBr, cm^{-1}) 3095, 1695, 1590, 1375, 1000; HRMS (ESI): m/z calcd for $C_{15}H_{11}O_3$ [M+H]$^+$: 239.0703, found 239.0705. White solid, mp 145–146°C.

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Author contributions: Dejun Zhou has done 60% of the work, including experiment content design, fund application, etc; Youchao Zhuang has done 25% of the work, organic experimental operation; Zuntian Sheng has done 15% of the work, sample inspection, etc.

Conflict of interest: Authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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