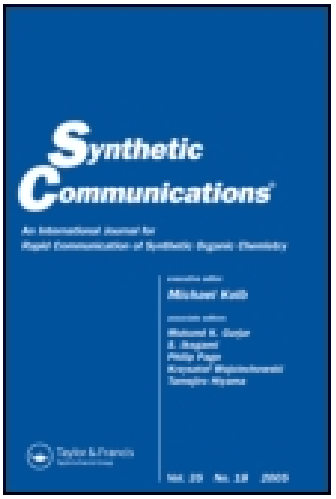

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$FeCl_3$-Catalyzed Cascade Reaction: An Efficient Approach to Functionalized Coumarin Derivatives

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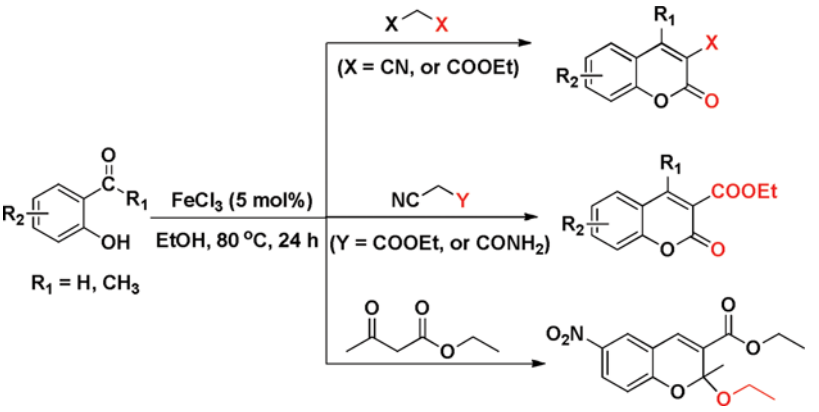
GRAPHICAL ABSTRACT



Abstract *An efficient and environmentally benign synthesis of 3-substituted or 3,4-disubstituted coumarins was accomplished via iron(III) chloride–catalyzed cascade reactions of salicylaldehydes and activated methylene compounds. The reaction preceded cleanly under mild reaction conditions to provide the desired coumarin derivatives in good to excellent yields.*

Keywords Activated methylene compounds; cascade reaction; catalysis; coumarins; iron(III) chloride

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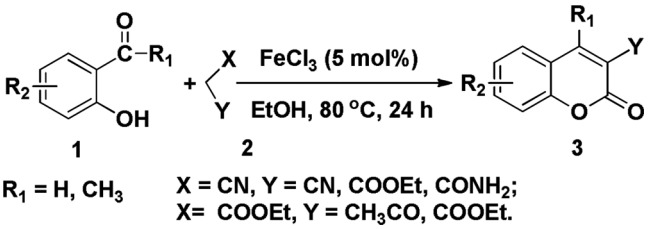
INTRODUCTION

Coumarins, which are chemical derivatives of benzo-2-pyrones or chromen-2-ones, are widely distributed in various species of plants.[1] Coumarins have been reported to exhibit antibacterial, anticarcinogenic, and analgesic activity.[2] In addition, they also serve as antioxidant and anti-inflammatory agents and HIV protease inhibitors.[3] The major synthetic methods for the preparation of coumarins include the Pechmann reaction and its modifications,[4] the Knoevenagel condensation,[5] the Wittig reaction,[6] the Claisen rearrangement,[7] the Vilsmeier–Haack and Suzuki cross-coupling reactions,[8] Pd-catalyzed site-selective cross-coupling reactions,[9] nickel-catalyzed cycloaddition reaction,[10] as well as other reactions.[11] However, there are usually some drawbacks including demanding reaction conditions, tedious manipulation, long reaction time, and poor overall yield in these reported methods. Thus, the development of novel, concise, and efficient synthetic methods for 3-substituted/3,4-disubstituted coumarins is desirable and significant from both chemical and biological viewpoints.

In recent years, environmental concerns have directly influenced the development of new methodologies, which requires higher standards for synthetic efficiency, atom economy, and reaction costs. Because iron is one of the most abundant metals on the earth, many iron complexes could be obtained for relatively low costs and are usually environmentally benign: therefore, they have been regarded as promising alternatives to many other widely used traditional metal complexes in the catalysis of various reactions.[12] Despite these advantages and recent impressive progress in related fields, iron was still relatively underrepresented in the field of catalysis compared to other transition metals.[13] Very recently, iron trichloride has received much attention in the catalytic synthesis of heterocyclic compounds,[14] multicomponent reactions,[15] cross-coupling reactions,[16] and cyclization reactions.[17] Herein, we report a new method for the synthesis of 3-substituted/3,4-disubstituted coumarins via a $FeCl_3$-catalyzed cascade reaction of commercially available salicylaldehydes and activated methylene compounds. This methodology represents a simple route to 3-substituted/3,4-disubstituted coumarins in good to excellent yields under mild reaction conditions (Scheme 1).

RESULTS AND DISCUSSION

At first the reaction conditions were explored using the commercially available substrates salicylaldehyde (**1a**) and malononitrile (**2a**) by varying the loading amount



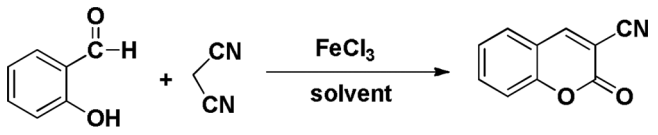
Scheme 1. Synthesis of coumarins via $FeCl_3$-catalyzed cascade reactions.

of the catalyst $FeCl_3$ in ethanol (Table 1). It is found that 5 mol% of the catalyst is optimal for the reaction (Table 1, entry 1). While the use of several other solvents such as methanol, acetonitrile, tetrahydrofuran (THF), dimethylformamide (DMF), H_2O, toluene, and dimethylsulfoxide (DMSO) did not improve the yield (Table 1, entries 8–14), prolonging the reaction time to 24 h led to improved yield. Thus the reaction was best performed with 5 mol% of $FeCl_3$ in ethanol, producing the coumarin (**3a**) in 72% yield after 24 h at 80 °C (Table 1, entry 7).

Following the optimal reaction conditions, we next examined the scope of this reaction by reacting various salicylaldehydes with malononitrile (**2a**) or ethyl 2-cyanoacetate (**2b**), and the results are summarized in Table 2. Generally, the yields obtained with malononitrile (Table 2, entries 1–3) were less than those obtained with ethyl 2-cyanoacetate (Table 2, entries 10–12). As to malononitrile (**2a**), when salicyladehydes bearing a strong electron-donating group at the *para* position of the aldehydes or a strong electron-withdrawing group at the *para* position of the phenol hydroxyl group were used, the reaction hardly took place (Table 2, entries 6–9). Interestingly, for ethyl 2-cyanoacetate (**2b**), the reaction was not affected by such substituent effects, while the reaction in this case was extremely sensitive to the sterical factors of the salicylaldehyde (Table 2, entry 13). The structure of the product **3b** was confirmed by x-ray crystallographic analysis as shown in Fig. 1.

To test the versatility of this reaction, the optimized reaction condition was further applied to the reaction of other activated methylene compounds such as 2-cyanoacetamide and diethyl malonate with 2-hydroxy acetophenone (**1h**) or

Table 1. Optimization of the reaction conditions[a]

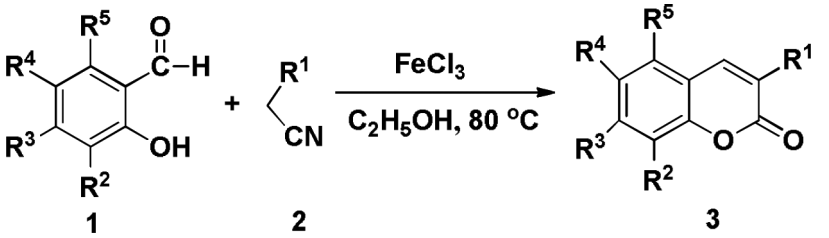


1a **2a** **3a**

Entry	$FeCl_3$ (mol %)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	5	C_2H_5OH	80	8	60
2	10	C_2H_5OH	80	10	58
3	25	C_2H_5OH	80	10	45
4	50	C_2H_5OH	80	10	52
5	100	C_2H_5OH	80	10	50
6	5	C_2H_5OH	80	16	65
7	5	C_2H_5OH	80	24	72
8	5	CH_3OH	60	24	60
9	5	CH_3CN	80	24	48
10	5	THF	60	24	18
11	5	DMF	80	24	Trace
12	5	H_2O	80	24	Trace
13	5	Toluene	80	24	25
14	5	DMSO	80	24	15

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), solvent (5 mL), 80 °C.
[b]Yield of the isolated product.

Table 2. Synthesis of a series of 3-substituted coumarin derivatives



Entry	**2** (R^1)	**1** (R^2, R^3, R^4, R^5)	Product	Yield (%)[a]
1	**2a** (CN)	**1a** (H, H, H, H)	**3a**	72
2	**2a**	**1b** (H, H, Cl, H)	**3b**	75
3	**2a**	**1c** (H, H, Br, H)	**3c**	75
4	**2a**	**1d** ($C(CH_3)_3$, H, $C(CH_3)_3$, H)	**3d**	93
5	**2a**	**1e** (H, OCH_3, H, H)	**3e**	80
6	**2a**	**1f** (H, H, NO_2, H)	—	Trace
7	**2a**	**1h** (H, H, F, H)	—	Trace
8	**2a**	**1g** (H, NEt_2, H, H)	—	Trace
9	**2a**	**1i** (H, NMe_2, H, H)	—	Trace
10	**2b** (CO_2Et)	**1a**	**3f**	95
11	**2b**	**1b**	**3g**	89
12	**2b**	**1c**	**3h**	85
13	**2b**	**1d**	—	Trace
14	**2b**	**1e**	**3i**	80
15	**2b**	**1f**	**3j**	70
16	**2b**	**1g**	**3k**	80

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $FeCl_3$ (0.05 mmol), EtOH (5 mL), 80 °C, 24 h.

salicyladehydes such as 2-hydroxy-1-naphthaldehyde (Table 3). Except for when compared to salicylaldehyde **1a**, its ketone counterpart 2-hydroxy acetophenone (**1h**) showed significantly lower reactivity in that an additional base was usually required to give acceptable yields of the desired product (Table 3, entries 1–3). Likewise, diethyl malonate and 2-hydroxy-1-naphthaldehyde (Table 3, entries 12,

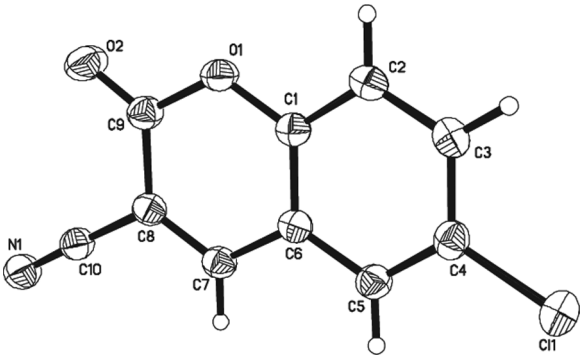
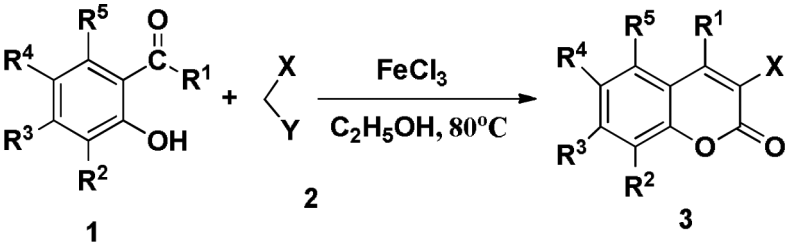


Figure 1. X-ray single-crystal structure of **3b**.

Table 3. Synthesis of 3/3,4-disubstituted coumarins with various substrates via $FeCl_3$-catalyzed cascade reaction

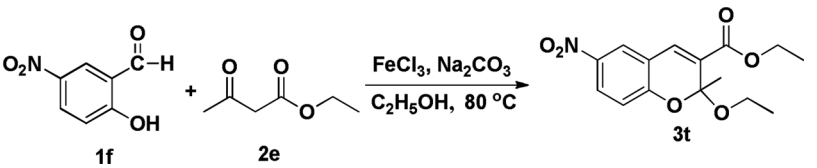


Entry	**2** (X, Y)	**1** (R^1, R^2, R^3, R^4, R^5)	Product	Yield (%)[a]
1	**2a** (CN, CN)	**1h** (CH_3, H, H, H, H)	**3l**	50[c]
2	**2b** (CO_2Et, CN)	**1h**	**3l**	63[c]
3	**2c** ($CONH_2$, CN)	**1h**	**3m**	41[c]
4	**2c**	**1b** (H, H, H, Cl, H)	**3g**	73
5	**2c**	**1c** (H, H, H, Br, H)	**3h**	71
6	**2c**	**1f** (H, H, H, NO_2, H)	**3i**	68
7	**2c**	**1e** (H, H, OCH_3, H, H)	**3j**	72
8	**2c**	**1g** (H, H, NEt_2, H, H)	**3n**	58
9	**2a**	**1i** (H, H, H, -CH=CH-CH=CH-)	**3o**	75
10	**2b**	**1i**	**3p**	92
11	**2c**	**1g**	**3q**	85[b]
12	**2d** (CO_2Et, CO_2Et)	**1a** (H, H, H, H, H)	**3f**	96
13	**2e** (CH_3CO, COOEt)	**1c**	**3r**	53[c]
14	**2e**	**1g**	**3s**	38[c]

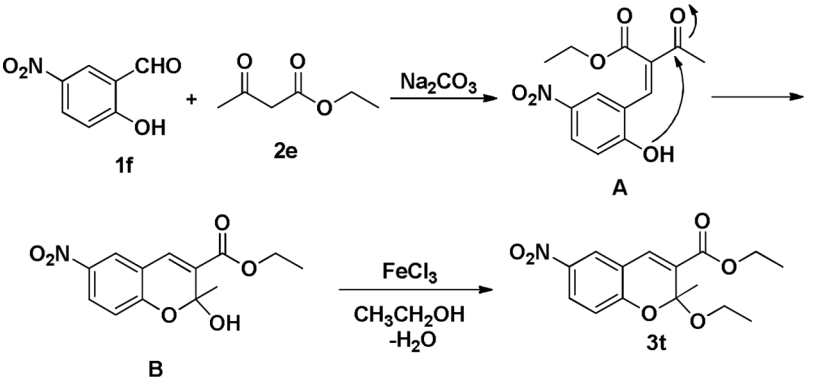
[a]Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $FeCl_3$ (0.05 mmol), EtOH (5 mL), 80 °C, 24 h.
[b]Methanol as solvent.
[c]Na_2CO_3 (1.0 mmol) was used as an additive.

9, and 10) also reacted efficiently to produce the expected coumarins **3f, 3o, and 3p** in 96%, 75%, and 92%, respectively. When ethyl acetoacetate was used as substrate, the reaction appeared to be quite general with respect to the activemethylene compounds. The activity of ethyl acetoacetate is much less than malononitrile or ethyl 2-cyanoacetate, for sodium carbonate is necessary in this reaction. Furthermore, salicyladehydes bearing Br and NEt_2 groups could undergo smooth conversion in the present reaction condition to yield the desired compounds in 53% and 38% (Table 3, entries 13 and 14).

Interestingly, when 2-cyanoacetamide was used, the major isolated product was not the expected 3-formamide coumarins, but instead the same products as those



Scheme 2. $FeCl_3$-catalyzed cascade reaction of salicyladehyde and ethyl acetoacetate to form ethyl 2-ethoxy-2-methyl-6-nitro-2*H*-chromene-3-carboxylate (**3t**).

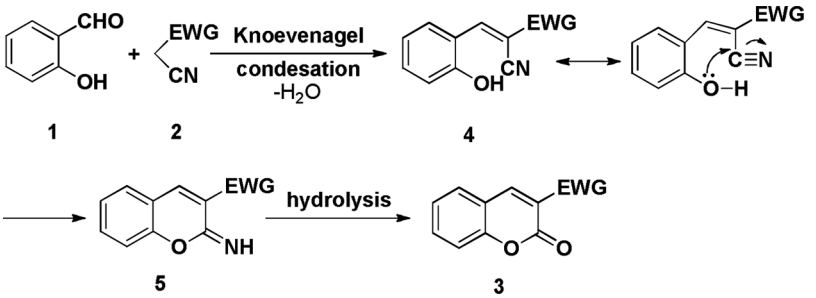


Scheme 3. Plausible reaction pathway for the formation of compound **3t**.

obtained using ethyl 2-cyanoacetate (Table 3, entries 4–7) in moderate yields. This result might be attributed to alcoholysis of the acetamide functionality under the reaction conditions (Table 3, entry 11). When 2-hydroxy-5-nitrobenzaldehyde was used (Scheme 2), the major isolated product was not coumarin or chromenol but only obtained ethyl 2-ethoxy-2-methyl-6-nitro-2*H*-chromene-3-carboxylate (**3t**) in 95% yield. This result might be attributed to the strong electron-withdrawing ability of the NO_2 group.

A plausible mechanism was proposed for the formation of the compound **3t**. First, 2-hydroxy-5-nitrobenzaldehyde (**1f**) reacted with ethyl acetoacetate (**2e**) in the presence of Na_2CO_3 to form the intermediate **A** (Knoevenagel condensation). Subsequently, the oxygen of hydroxyl attacked the carbanyl group of the intermediate **A** to form the intermediate **B** (intermolecular cyclization reaction). Then, alcohol reacted with the intermediate **B** in the presence of $FeCl_3$ to generate the desired compound **3t** through dehydration process.

On the basis of these experimental results, we proposed a plausible mechanism for this $FeCl_3$-catalyzed cascade reaction as shown in Scheme 4. First, salicyladehyde **1** reacted with the activated methylene compounds **2** in the presence of $FeCl_3$ to form benzylidene compounds **4** (Knoevenagel condensation). Subsequently, the oxygen of hydroxyl attacked the cyano- group of the intermediate **4** to form the intermediate **5**, which then underwent hydrolysis to give the corresponding coumarin products.



Scheme 4. Plausible mechanism leading to coumarins via $FeCl_3$-catalyzed cascade reaction.

EXPERIMENTAL

General Procedure for the Synthesis of Substituted Coumarin Derivatives 3

Anhydrous $FeCl_3$ (0.05 mmol) was added to a stirred solution of salicyladehyde **1a** (1 mmol) and malononitrile **2a** (1.2 mmol) in ethanol (3 mL). The mixture was heated in an oil bath at 80 °C for 24 h and cooled down to room temperature. The solvent was removed under vacuum, and the residue was directly purified by flash column chromatography on silica gel (200–300 mesh) with ethyl acetate and petroleum ether (1:6–1:8, v/v) as eluting solvent to afford the product **3a** (123 mg, 0.72 mmol) in 72% yield.

2-Oxo-2*H*-chromene-3-carbonitrile (3a)[18]

White solid; yield: 123 mg (72%); mp 175–176 °C. IR (KBr) *v*: 3107, 3072, 3045, 2924, 2229, 1774, 1728, 1604, 1560, 1446, 1369, 1288, 1257, 1188, 1149, 1051, 972, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.22 (s, 1H, CH), 7.67 (t, $J = 7.5$ Hz, 1H, ArH), 7.56 (d, $J = 7.4$ Hz, 1H, ArH), 7.35 (d, $J = 4.6$ Hz, 2H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.9, 135.6, 129.3, 125.8, 117.5, 113.5, 106.8, 101.0 ppm. HRMS (ESI) calcd for $C_{10}H_5NO_2$ ($M+H^+$) 172.0398, found 172.0393.

CONCLUSIONS

In summary, we have successfully developed a novel, operationally simple, $FeCl_3$-catalyzed cascade reaction for the synthesis of 3-substituted/3,4-disubstituted coumarins from salicyladehydes and cyanide methylene compounds under mild reaction conditions. This synthetic approach was also applicable to the corresponding reaction with ethyl acetoacetate to synthesize substituted chromenols.

FUNDING

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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