Microwave-Assisted One-Pot Synthesis of Dihydrocoumarins from Phenols and Cinnamoyl Chloride

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Abstract: A facile approach has been developed for the synthesis of dihydrocoumarin derivatives through the reaction of phenols and cinnamoyl chloride in the presence of ecofriendly solid-acid catalyst montmorillonite K-10 via a tandem esterification–Friedel–Crafts alkylation process under microwave irradiation. The catalyst could be easily recovered and recycled.

Key words: microwave-assisted synthesis, dihydrocoumarins, phenols, cinnamoyl chloride, montmorillonite K-10

Dihydrocoumarins, which exist extensively in a number of natural molecules and show a wide range of biological activities,[1] are important synthetic intermediates for pharmaceutical industry, useful pesticides, and bioactive compounds. Many synthetic methods for dihydrocoumarin derivatives have been reported till now: (i) reduction of coumarins;[2] (ii) hydroarylation of substituted cinnamates or cinnamic acid with phenols in strong acidic conditions or under Lewis acid catalysis;[3] (iii) Lewis acid catalyzed reaction of acrylonitrile with phenols;[4] (iv) rhodium-mediated reaction of 3-(2-hydroxyphenyl)-cyclobutanones;[5] (v) reaction of chromium Fisher carbene complexes with ketene acetals.[6] However, there are quite a few disadvantages in these accomplished protocols mostly involving long reaction time,[2b,3b,d,e,5] complicated starting materials,[3e] employment of expensive, non-regenerable and pollutive catalysts[3b–e,5] and also lack of substrate generality. Consequently, there is a great need for efficient and practical approaches for the synthesis using inexpensive, easily handled and environmentally friendly catalysts and starting materials.

Microwave irradiation has been widely applied in organic synthesis recently and achieved great success for many reactions with high efficiency and good yields.[7] In our previous studies, we have reported the microwave-assisted one-pot synthesis of 1-indanones from substituted benzenes and α,β-unsaturated acyl chlorides under the catalysis of aluminum chloride.[8] As continuation of our previous work and development of a general and facile method to offer various useful dihydrocoumarin derivatives, the microwave-assisted one-pot synthesis of dihydrocoumarins has been examined, starting from phenols and α,β-unsaturated acyl chlorides via a tandem esterification–Friedel–Crafts-alkylation sequence. Initially, the same catalyst aluminum chloride was attempted. However, the esterification products of α,β-unsaturated acyl chlorides with phenols favored to undergo a Fries rearrangement as those under traditional heating conditions. Therefore, an appropriate catalyst for the aimed synthesis was necessary.

Mild solid acids have been used to catalyze the synthesis of coumarin derivatives in recent years.[9–12] Use of these heterogeneous catalysts, such as zeolites, clays, and ion-exchange resins, results in simplified product recovery and a reduction in undesirable waste stream associated with conventional Lewis acid catalysts. Shukla et al.[9] synthesized substituted 3,4-dihydrocoumarins from substituted cinnamic acids and phenol in the H–Y zeolite-catalyzed procedure. Lee et al.[10] prepared dihydrocoumarins derivatives via the montmorillonite K-10 catalyzed esterification–cyclization reactions of phloroglucinol and cinnamoyl chloride under conventional heating for 12 hours. By condensation of 1,3-dihydroxybenzene and 1,3,5-trihydroxybenzene with propenoic acids using montmorillonite KSF as catalyst under microwave irradiation, de la Hoz et al.[11] prepared 4-nonsubstituted dihydrocoumarins in good yields. With phenols and cinnamic acids impregnated on solid support, preactivated montmorillonite K-10 clay, and along with one drop of concentrated H_2SO_4, Singh et al.[12] have also described the microwave-assisted solvent-free synthesis of 3,4-dihydro-4-phenylcoumarins and 4-phenylcoumarins in good yields.

Although the synthesis of some dihydrocoumarins has been successfully approached by employing montmorillonite K-10 catalyst, these reactions usually need long reaction times under the classical heating conditions, or occurred in solvent-free pattern in a domestic microwave oven, and only for the electron-rich phenols. In this letter, we wish to present a facile synthesis of 3,4-dihydrocoumarins from various phenols and cinnamoyl chloride in the presence of montmorillonite K-10 under temperature-controlled microwave irradiation.

First, we used conventional heating to preliminarily estimate the reactivity of the selected reaction. Esterification furnished in almost quantitative yield when a mixture of 2-naphthol and cinnamoyl chloride in chlorobenzene was stirred at room temperature for 1 hour. After refluxing for 6 hours, the ester converted completely (determined by

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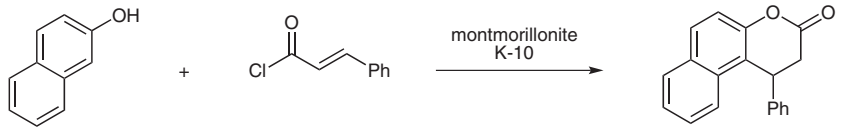
Table 1 Synthesis of 1,2-Dihydro-1-phenyl-3*H*-naphtho[2,1-*b*]pyran-3-one (**3a**)[a]



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

Entry	Solvent	Reaction conditions	Reaction time	Catalyst amount (g/mL)	Yield (%)[b]
1	PhCl	r.t. + 130 °C[c]	1 h + 6 h	0.3	57
2	PhCl	MW,[d] 140 °C	1 min	0.3	Trace
3	PhCl	MW, 160 °C	1 min	0.3	13
4	PhCl	MW, 160 °C	3 min	0.3	56
5	PhCl	MW, 160 °C	5 min	0.3	78
6	PhCl	MW, 160 °C	10 min	0.3	73
7	PhCl	MW, 160 °C	15 min	0.3	62
8	PhCl	MW, 160 °C	5 min	0.25	81
9	PhCl	MW, 160 °C	5 min	0.2	72
10	PhCl	MW, 160 °C	5 min	0.15	62
11	PhMe	MW, 160 °C	5 min	0.25	30
12[e]	PhCl	MW, 160 °C	5 min	0.25	Trace

[a] Reaction scales: **1a** (2 mmol), **2** (2 mmol), solvent (4 mL).
[b] Isolated yields.
[c] Stirred at r.t. for 1 h and then conventional heating at 130 °C for 6 h.
[d] Microwave irradiation using a CEM Discover reactor.
[e] Cinnamic acid was used instead of **2**.

TLC) to afford the desired dihydrocoumarin in the yield of 57% (entry 1, Table 1). However, the product yielded from phenol and cinnamoyl chloride was relatively low. Thus, the reaction of 2-naphthol and cinnamoyl chloride was selected as a model reaction to optimize the reaction conditions. Experimental conditions under microwave irradiation have been carefully investigated via regulating temperature, solvents, irradiation time, and the amount of catalyst to get the maximum yield. The results are summarized in Table 1. The ester formed, but did not convert completely under microwave irradiation at 140 °C for 1 minute (entry 2, Table 1); while complete conversion was achieved with irradiation at 160 °C for the same time (entry 3, Table 1). Therefore, reaction temperature was set at 160 °C. As solvent, toluene was more electron rich than chlorobenzene and can take part in reaction process and caused comparatively low yield of desired product (entry 11, Table 1), and nitrobenzene was difficult to remove after reaction due to its higher boiling point. Thus, chlorobenzene was chosen as the solvent. It was found that entry 7 (Table 1) provided the best preparation of the desired product in 81% yield at 160 °C with 0.25 g/mL of montmorillonite K-10 under microwave irradiation (closed-vessel mode) for 5 minutes. The reactivity of cinnamic acid, which is a much cheaper substrate, was also investigated. It was a pity that only trace of desired product was obtained under the same optimized microwave conditions of acyl chloride (entry 12, Table 1).

With optimal conditions in hand, we expanded the scope of the reaction to various substituted phenols (Table 2). The reaction of cinnamoyl chloride (**2**) with the electron-rich 2-naphthol (**1a**) gave 1,2-dihydro-1-phenyl-3*H*-naphtho[2,1-*b*]pyran-3-one (**3a**) in 81% yield (entry 1, Table 2). Similar reactions with 3,5-dimethylphenol (**1b**) and 3,4-dimethylphenol (**1c**) as multialkyl-substituted phenols gave the corresponding dihydrocoumarins **3b** and **3c** plus **3c′** in high yields, respectively (entries 2 and 3, Table 2). In the reactions of **2** with cresols, 4-methylphenol (**1d**), 3-methylphenol (**1e**), and 2-methylphenol (**1f**), the corresponding dihydrocoumarins **3d**, **3e** plus **3e′**, and **3f** were obtained in 66, 54, and 45% yields, respectively (entries 4–6, Table 2). The reaction with phenol (**1g**) gave 3,4-dihydro-4-phenylcoumarin (**3g**) in 47% yield (entry 7, Table 2). However, the reactions with alkoxyl-substituted phenols, such as 4-methoxyphenol (**1h**) and 3,5-dimethoxyphenol (**1i**), afforded 3,4-dihydro-6-methoxy-4-phenylcoumarin (**3h**) and 3,4-dihydro-5,7-dimethoxy-4-phenylcoumarin (**3i**) in comparatively low yields of 42 and 30%, respectively (entries 8 and 9, Table 2). An electron-deficient phenol, 4-chlorophenol (**1j**), afforded only 25% yield of dihydrocoumarin (**3j**, entry 10, Table 2).

Generally, electron-rich phenols gave rise to products in higher yield than electron-deficient ones. In addition to inductive effect, steric hindrance of substituents affected the reactivity obviously (entries 4–6, Table 2).

Both of 3,4-dimethylphenol and 3-methylphenol unexpectedly provided structural isomers **3c** plus **3c′** and **3e** plus **3e′**. These two pairs of structural isomers could be chromatographically separated and characterized via ^{1}H NMR. The isomers of 5,6-dimethyl dihydrocoumarin **3c′** and 7-methyl dihydrocoumarin **3e** were isolated as the major products with different regioselectivity.

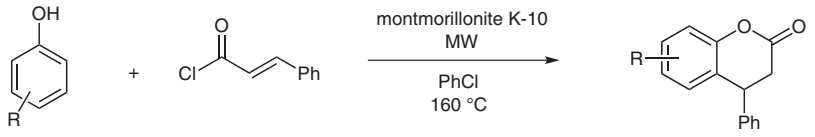
As electron-rich substrates, 4-methoxyphenol (**1h**) and 3,5-dimethoxyphenol (**1i**) should give dihydrocoumarins (**3h** and **3i**) in high yields, while only 42% and 30% yields of products were obtained, respectively. We presumed that the methoxy group might have an oxy-atom coordination with the catalyst montmorillonite K-10, resulting in decrease of efficient catalyst as the effect in the asymmetric borane reduction of ketones.[13] So we increased the amount of catalyst and kept other reaction conditions unchanged. The yields of desired products were indeed improved. Since the reactant mixture became slurry and hard to be stirred, the maximum catalyst amount used was limited to 0.6 g/mL. The results are presented in Table 3.

We have also examined the reuse and recovery of the catalyst on the tandem esterification–Friedel–Crafts alkylation of 2-naphthol to get dihydrocoumarin **3a**. The results shown in Table 4 indicated that another attractive behavior of montmorillonite K-10 lies in the fact that it can be reused after simple washing with ethyl acetate, together with non-toxicity, cheapness, and commercial availability of this catalyst, rendering the synthetic process more economic.

We also extended the reaction to crotonyl chloride. However, no desired products were obtained except for 3,5-dimethoxylphenol, which gave rise to the desired product, 3,4-dihydro-5,7-dimethoxy-4-methylcoumarin in 32% yield.

In summary, we have established a general and facile heterogeneous catalytic approach for the preparation of dihydrocoumarin derivatives from simple starting materials using a microwave-assisted one-pot protocol. Straightforward operation, nontoxic, low-cost, and recyclable catalyst, very short reaction time, and simple purification of products are the key features of this general method, which might make it an attractive alternative to the existing literature procedures.

Table 2 Synthesis of Dihydrocoumarins from Phenols and Cinnamoyl Chlorides[a,14,15]



1 **2** **3**

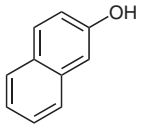
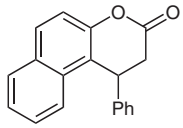
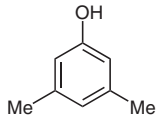
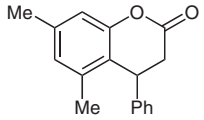
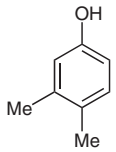
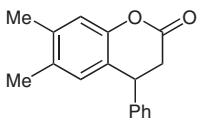
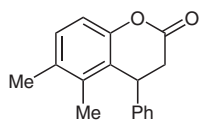
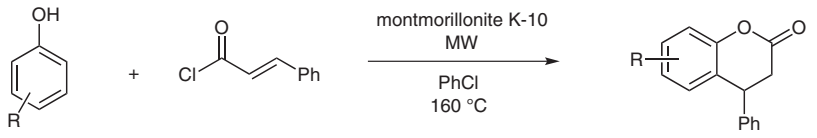
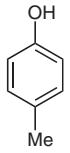
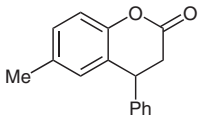
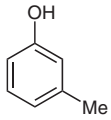
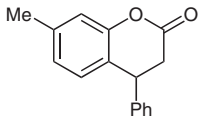
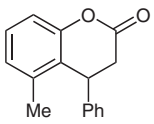
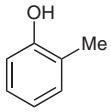
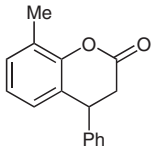
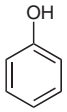
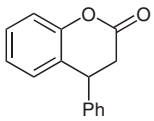
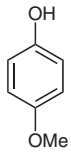
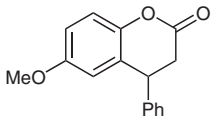
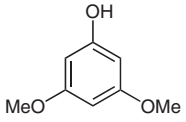
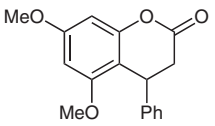
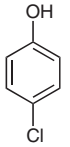
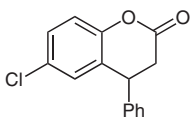
Entry	Phenol	Product	Yield (%)[b]
1	 **1a**	 **3a**	81
2	 **1b**	 **3b**	92
3	 **1c**	 **3c** +  **3c′**	33 42

Table 2 Synthesis of Dihydrocoumarins from Phenols and Cinnamoyl Chlorides[a,14,15] (continued)



1 **2** **3**

Entry	Phenol	Product	Yield (%)[b]
4	 **1d**	 **3d**	66
5	 **1e**	 **3e** +  **3e′**	35 19
6	 **1f**	 **3f**	45
7	 **1g**	 **3g**	47
8	 **1h**	 **3h**	42
9	 **1i**	 **3i**	30
10	 **1j**	 **3j**	25

[a] Reagents and conditions: phenol (2 mmol), cinnamoyl chloride (2 mmol), chlorobenzene (4 mL), catalyst (1 g); all of reactions were irradiated for 5 min.
[b] Isolated yields.

Table 3 Synthesis of Dihydrocoumarins **3h** and **3i** with Increased Amounts of Catalysis[a]

Entry	Product	Catalysis amount (g/mL)	Yield (%)[b]
1	**3h**	0.25	42
2	**3h**	0.5	66
3	**3i**	0.25	30
4	**3i**	0.5	55
5	**3i**	0.6	62

[a] Reagents and conditions: phenol (2 mmol), cinnamoyl chloride (2 mmol), chlorobenzene (4 mL); all of reactions were irradiated for 5 min.
[b] Isolated yields.

Table 4 Repeated Use of Montmorillonite K-10 for Synthesis of 1,2-Dihydro-1-phenyl-3*H*-naphtho[2,1-*b*]pyran-3-one (**3a**) under Microwave Irradiation[a]

Entry	Number of uses	Reaction time (min)	Yield (%)[b]	Recovery of catalyst (%)
1	1	5	75	98
2	2	5	66	86
3	3	10	61	80

[a] Reagents and conditions: **1a** (0.5 mmol/mL), **2** (0.5 mmol/mL), chlorobenzene as solvent, recycled catalyst (0.3 g/mL).
[b] Isolated yields.

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(14) **General Procedure for the Synthesis of Dihydrocoumarins**
A solution of phenol (2 mmol), cinnamoyl chloride (2 mmol, 0.33 g), and montmorillonite K-10 (1.0 g) in dried chlorobenzene (4 mL) was added to a sealed microwave tube. The reaction mixture was irradiated at a set temperature of 160 °C for 5 min with stirring using a CEM Discover microwave reactor in the closed-vessel mode. The reaction mixture was filtered and the catalyst montmorillonite K-10 was washed with EtOAc. The organic filtrates were combined. After removal of solvent, the residue was separated on a silica gel column with a mixture of hexane and CH_2Cl_2 (3:1 to 2:1, v/v) as eluent to afford the desired pure dihydrocoumarin as product. For dihydrocoumarins **3c** and **3c′** (also for **3e** and **3e′**), another silica gel column chromatography (hexane–EtOAc, 20:1) was conducted to separate the isomeric products.

(15) **Analytic Data for Unknown Products 3c′ and 3e′**
3,4-Dihydro-5,6-dimethyl-4-phenylcoumarin (**3c′**): yellowish crystals, mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3 H), 2.25 (s, 3 H), 3.01 (dd, *J* = 15.8, 3.5 Hz, 1 H), 3.03 (dd, *J* = 15.8, 5.5 Hz, 1 H), 4.47 (dd, *J* = 5.3, 3.4 Hz, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 7.04 (d, *J* = 6.2 Hz, 2 H), 7.13 (d, *J* = 8.2 Hz, 1 H), 7.20–7.29 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 20.0, 37.7, 38.7, 114.4, 123.1, 127.1, 127.4, 129.1, 130.0, 133.2, 135.1, 140.3, 150.5, 167.4. ESI-MS: *m*/*z* = 274.9 $[M + Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}O_2$: 252.1150; found: 252.1153.
3,4-Dihydro-5-methyl-4-phenylcoumarin (**3e′**): yellowish crystals, mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 3.04 (dd, *J* = 15.8, 3.1 Hz, 1 H), 3.06 (dd, *J* = 15.8, 5.9 Hz, 1 H), 4.41 (dd, *J* = 5.9, 3.1 Hz, 1 H), 7.00 (d, *J* = 7.6 Hz, 1 H), 7.03–7.06 (m, 3 H), 7.19–7.30 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 37.6, 38.2, 115.1, 123.2, 126.4, 126.9, 127.5, 128.6, 129.1, 137.0, 140.0, 152.2, 167.2; ESI-MS: *m*/*z* = 260.8 $[M + Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}O_2$: 238.0994; found: 238.0997.