

# Microwave-Assisted Synthesis of Ethyl 4-Hydroxy-3-ethoxycinnamate Through A Catalytic Pathway Utilizing Cationic Exchange Resin

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**Abstract:** Ethyl 4-hydroxy-3-methoxycinnamate was synthesized by reaction of ethanol and 4-hydroxy-3-methoxycinnamic acid using an efficient cation-exchange resin as catalyst under microwave irradiation. The catalyst activity was investigated by single factor experiments. The reaction conditions - amount of catalyst, microwave irradiation time, microwave power and alcohol/acid ratio - were investigated by single factor experiments and orthogonal experiments. The optimal reaction conditions are as follows: 4-hydroxy-3-methoxycinnamic acid 0.1 mol; molar ratio of ethanol to 4-hydroxy-3-methoxycinnamic acid 5:1; percentage weight of resin 30%; microwave power 300W; irradiation time 30 min. Yield of the reaction was 84.2% under the optimal conditions. The catalyst is recyclable and the yield remained over 78% after recycling the catalyst for 5 times.

## Introduction

4-Hydroxy-3-methoxycinnamic acid is a ubiquitous phenolic compound in plants. It has several applications in the medicine industry, the food industry and the cosmetics industry as well [1,2]. It has been approved as an additive antioxidant to form a resonance-stabilized phenoxy radical which accounts for its free radical-scavenging effect. It could also be used for cardiovascular and cerebrovascular diseases treatment. However, because of its low liposolubility, it can hardly cross the lipid bilayer of biological membrane and its pharmacological action is hardly observed[3]. To overcome these barriers, its modification has recently been studied in order to increase the liposolubility and biological activity in lipophilic conditions[4,5].

The traditional synthesis of ethyl 4-hydroxy-3-methoxycinnamate was catalyzed by sulfuric acid under direct heating method. The esterification, dehydration and oxidation effects of sulfuric acid lead to a series of side reactions, which make the product purification and raw materials recovery almost impossible. Furthermore, sulfuric acid catalysis may also cause environmental pollution and equipment corrosion. Comparing with sulfuric acid, ion exchange resin is a low-cost, recyclable and environmentally friendly catalyst that requires lower reaction temperature[6,7]. In our previous work, cation exchange resin catalyst was found to be easily recovered and reused many times without obvious decrease in catalytic activity [8].

Microwave-assisted catalytic synthesis is a clean and efficient synthetic technology. It has been successfully used for the synthesis of a variety of esters [9]. Hu Siqian *et al.* [10] catalyzed synthesis of 1-methyl naphthalene using a cation exchange resin catalyst under microwave irradiation. The results showed that the microwave can strengthen the catalytic activity of cation exchange resin. In this paper, ethyl 4-hydroxy-3-methoxycinnamate is synthesized with the synergy of microwave irradiation and cation exchange resin catalyst. The influence of microwave on the catalytic activity of ion exchange resin was investigated, and the conditions of the synthesis were optimized.

## Materials and Methods

**Chemicals and Instruments.** 4-Hydroxy-3-methoxycinnamic acid was purchased from Wuhan Yuancheng Chemical Technology Company. The 723 resin was purchased from Sinopharm Chemical Reagent Company, Shanghai. Sodium bicarbonate, methyl ether, ethanol and n-hexane

were purchased from Guangzhou Chemical Reagent Factory. Hydrochloric acid was purchased from Xiantao Chemical Technology Company.

Microwave-ultrasonic reactor(QW-HU), Guangzhou Keweimicrowave energy company. 1100 HPLC-MS Trap XCT, Agilent Technologies; Nicolet NEXUS470 Fr-IR spectroscopy, Thermo Fisher Scientific; VARIAN UNITY INOVA 500 NMR Spectrometer, VARIAN; AVANCE-300 NMR Spectrometer, Bruker Corporation.

**Activating methods of catalyst.** Previous studie [8] shows that the cation exchange resin 732 is the best catalyst for the synthesis of ethyl 4-hydroxy-3-methoxycinnamate. Therefore, cation exchange resin 732 was selected as catalyst.

Conventional drying method: Cation exchange resin 732(100g) was added to a saturated sodium chloride solution (300mL) and soaked overnight. The resin was then rinsed with deionized water several times and soaked in hydrochloric acid ( 5wt%, 300mL) overnight. The resin was filtered, rinsed with deionized water, dried at 80 °C and stored.

Microwave drying method: After having been soaked in sodium chloride solution and hydrochloric acid , the cation exchange resin was dried with microwave oven for about 20 min.

**Synthesis.** 4-Hydroxy-3-methoxycinnamic acid (19.4g) and a thorough mixture of ethanol ( $n_{\text{ethanol}}$ ) and cation exchange resin 732 ( $w_{\text{catalyst}}$ ) were added to a round bottom flask. The flask was fixed in the microwave oven, and the radiation back reaction took place for a certain time ( $t_{\text{microwave}}$ ) in a settled power (W). The reaction mixture turned yellow.

Refinement: The pH value of the yellow mixture was adjusted to 7.5 with sodium bicarbonate solution (10% wt). The mixture was then washed with saturated NaCl solution several times until the organic phase became clarified and well-seperated with the aqueous phase. The ester layer was extracted by 100mL ether for three times. The extracts were combined and washed with distilled water. After vacuum evaporation of the extract, the resulting off-white crystals were collected and recrystallized in hexane.

## Results and Discussion

**Activating methods of catalyst.** Reaction conditions: dosage of 4-Hydroxy-3-methoxycinnamic acid is 0.1mol, the molar ratio of alcohol to acid is 5:1, the amount of cation exchange resin is 30% wt to the total weight of reactants, the microwave power is 300W and the reacting time is 30min. The yields using different methods are showed in Table 1.

Table 1 Effect of activating methods of catalyst on the yield

activating methods of catalyst	Conventional drying method	Microwave drying method
Yield [%]	78.3	83.7

The yield of microwave drying method is higher than that of conventional drying method as shown in Table 1. This indicates that microwave irradiation is a more effective drying method that enhances the catalytic activity of resin 732. Therefore, microwave drying method is preferred.

**Experiment of single factor.** The results of parallel single factor experiments were shown in Table 2-5.

Table 2 Effect of amount of catalyst on the yield

w(catalyst) [%]	10	20	30	40	50
Yield [%]	46.3	62.9	83.7	84.5	84.3

Note: molar radio of ethanol to acid is 5:1, microwave power is 300W, reaction time is 30 min.

Table 2 shows that with increasing mass fraction of catalyst, the yield increased significantly. The results indicated that the yield has a positive correlation with the amount of catalyst in a certain range, and the yield stabilized when the catalyst concentration was up to 30%.

Table 3 Effect of microwave power on the yield

Power of microwave [W]	100	200	300	450	600
Yield [%]	65.4	76.2	83.7	81.5	74.3

Note: molar ratio of ethanol to acid is 5 : 1, mass percent of resin is 30% of the reagent, reaction time is 30 min.

Table 3 shows that in the range of 100W to 300W, the yield increases with the increase of microwave power, indicating that the microwave power is a positively related factor, and the highest yield was reached when the microwave power was 300W. When tested in 450 W microwave, the mixture began to boil about 5 min after the irradiation started. And the increase of ethanol loss due to evaporation resulted in a lower reaction yield.

Table 4 Effect of microwave time on the yield

t(microwave) [min]	10	20	30	40	50
Yield [%]	58.6	75.1	83.7	82.9	80.5

Note: molar ratio of ethanol to acid is 5:1, mass percent of resin is 30% of the reagent, microwave power is 300W.

As shown in Table 4, the yield increased with the increase of reaction time, due to the fact that esterification reaction needs some time to complete. Completion of the reaction was reached after 30 minutes of irradiation.

Table 5 Effect of molar ratio of ethanol to 4-hydroxy-3-methoxycinnamic acid on the yield

n(alcohol) : n(acid)	3 : 1	4 : 1	5 : 1	6 : 1	7 : 1
Yield [%]	75.4	80.3	83.7	82.5	77.4

Note: mass percent of resin is 30% of the reagent, microwave power is 300W, reaction time is 30 min.

It was found that when the molar ratio of alcohol to acid is less than 3:1, 4-hydroxy-3-methoxycinnamic acid can not be dissolved by ethanol, so 3:1 was set as a minimum alcohol:acid molar ratio to start with. Table 5 shows that with an increasing amount of ethanol, the yield increased at first and then decreased when the amount of ethanol was over a certain percentage. It is explained that an excessive volume of the reaction mixture makes the esterification less effective.

**Orthogonal Experimental Design.** According to the result of the single-factor experiments, orthogonal experimental design were performed using an  $L_9(4^3)$  array on the factors of alcohol-acid molar ratio, catalyst dosage, duration of microwave radiation, and power of microwave radiation. The result is listed in Table 6.

Table 6 Results and Analysis of Orthogonal Experiments

No.	n(alcohol) : n(acid)	w(catalyst) [%]	t [min]	Power [w]	Yield [%]
1	4:1	25	25	200	68.9
2	4:1	30	30	300	80.3
3	4:1	35	35	450	81.4
4	5:1	25	30	450	80.1
5	5:1	30	35	200	74.3
6	5:1	35	25	300	81.6
7	6:1	25	35	300	79.3
8	6:1	30	25	450	78.7
9	6:1	35	30	200	74.3
k1	76.9	76.1	76.4	72.5	
k2	78.7	77.8	78.2	80.4	
k3	77.4	79.1	78.3	80.1	
R	1.8	3.0	2.9	7.9	

As shown in Table 6, under conditions and level of variations applied in the experimental design, a ranking of impact of each factor on the reaction yield is drawn as below: power of microwave radiation > catalyst dosage > duration of microwave radiation > alcohol-acid molar ratio. Considering energy consumption as an additional factor, an optimized set of experiment conditions is finally concluded - n(alcohol):n(acid) = 5:1, w(catalyst) = 35%, t(microwave) = 30min, microwave power = 300w.

**Contrast experiments between microwave-irradiating method and directly heating method.**

The result of contrast experiments between microwave-irradiating method and directly heating method were shown in table 7.

Table 7 Contrast experiment result between microwave-irradiating method and directly heating method

Heating method	n(alcohol) : n(acid)	w(catalyst) [%]	t [min]	Power [w]	Yield [%]
Microwave irradiating	5 : 1	30	30	300	84.2
Direct heating	5 : 1	30	30	/	32.3

Table 7 shows that in the same reaction conditions the yield of microwave radiation heating method is much higher than that of conventional heating method. It indicates that the microwave irradiation has a good synergy effect with the cation exchange resin in the synthesis of ethyl 4-hydroxy-3-methoxycinnamate.

**Catalyst recyclability.** Under the optimized reaction conditions, the resin catalyst was separated and regenerated after the reaction. Using the recycled catalyst, a consecutive set of reactions were carried out and their yields were shown in Table 8.

Table 8 Recycle times of catalyst and the reaction yield

Recycle times	1	2	3	4	5
Yield [%]	84.2	83.5	82.3	80.9	78.6

It can be seen from Table 8 that the recycled catalyst shows good performance - when reusing for 5 times, the yield is still over 78%. It indicates that the catalyst has good stability and recyclability, although the yield decline slightly with the increase of catalyst recycle times.

**Characterization.** The product was characterized by mass spectrometry, infrared spectroscopy, nuclear magnetic resonance analysis.

MS spectrum of the product showed the mass to charge ratio of M-1 peak is 220.9. The relative molecular weight of the product is 221.9, the same as the molecular weight of 4- hydroxy -3- methoxy ethyl cinnamate(C<sub>12</sub>H<sub>14</sub>O<sub>4</sub>).

The FTIR spectra showed the absorbing peak of the product: 3393.3, 3071.3, 3005.3, 2971.4, 1701.0, 1680.9, 1604.4, 1589.5, 1514.1, 1436.4, 1263.0, 1186.7, 1159.8, 1122.1, 1031.2, 980.7, 958.7, 928.4, 862.2, 815.7 cm<sup>-1</sup>. The broad peak around 3526.9 cm<sup>-1</sup> is associated with hydroxyl stretching vibration., There is an absorption peaks at 3176.6cm<sup>-1</sup>. which could be ascribed to the stretching vibration of the group of C-H in the benzene ring. The absorption peak at 2971.1cm<sup>-1</sup> is attributed to the stretching vibration of group of saturated C-H. The absorption peak at 1678.3cm<sup>-1</sup> is due to the stretching vibration of group of C=O. The absorption peak at 1629.9cm<sup>-1</sup> is caused by the stretching vibration of group of C=C. The peaks at 1593.0cm<sup>-1</sup> and 1518.0cm<sup>-1</sup> are due to the stretching vibration of the skeleton of the benzene ring. The absorption peak at 1474.4cm<sup>-1</sup> and 1371.5cm<sup>-1</sup> are attributed to the bending vibration of the group of -CH<sub>2</sub> and -CH<sub>3</sub>. The strong peaks at 1285.0cm<sup>-1</sup> and 1253.8cm<sup>-1</sup> are the stretching vibration of the group of =C-O-C group. The multiple absorption peaks around 900-1200cm<sup>-1</sup> are attributed to the of C-O-C. The absorption peak at 842.4cm<sup>-1</sup> and 816.0cm<sup>-1</sup> are the characteristic peaks of meta-substituted and para-substituted benzene ring correspondly.

δ(ppm) of <sup>13</sup>CNMR (75MHz, CDCl<sub>3</sub>): 56.2(s, C<sub>12</sub>), 60.8(s, C<sub>2</sub>), 77.5(t, C<sub>1</sub>), 109.9(s, C<sub>11</sub>), 115.3(s, C<sub>8</sub>), 115.7(s, C<sub>4</sub>), 127.2(s, C<sub>6</sub>), 145.3(s, C<sub>5</sub>), 147.4(s, C<sub>10</sub>), 148.5(s, C<sub>9</sub>), 167.9(s, C<sub>3</sub>), are the same as the carbon atoms of a 4- hydroxy -3- methoxy ethyl cinnamate molecule (Fig.1).

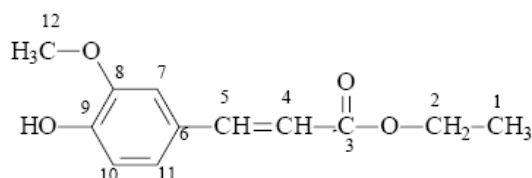


Fig.1 Chemistry Structure of ethyl 4-hydroxy-3-methoxycinnamate

$\delta$ (ppm) of  $^1\text{H}$ NMR (300MHz,  $\text{CDCl}_3$ ): 1.3(3H, m,  $\text{CH}_3$ ), 3.8(3H, s,  $\text{OCH}_3$ ), 4.2(2H, t,  $j=6.4$ ,  $\text{CH}_2$ ), 6.2(1H, s, =CH), 6.5(1H, s, =CH-Ar), 6.9~7.0(3H, m, Ar-H), 7.6(1H, s, O-H), are the same as the hydrogen atoms of a 4-hydroxy-3-methoxy ethyl cinnamate molecule

Composite of the MS spectrum, FTIR spectrum and NMR spectra analysis, it can be determined that the product is 4-hydroxy-3-methoxy ethyl cinnamate.

## Conclusion

(1) It takes much shorter time to activate the cation exchange resin 732 using microwave treatment than using conventional method. The conventional method requires at least 40h before the catalyst is completely activated and dry, while using the microwave activation only need about 20min. On the other hand, the activity of cation exchange resin 732 treated by microwave is higher than that treated by conventional method.

(2) Under the same reaction conditions, the yield of reactions utilizing microwave irradiation is much higher those using conventional heating method. It can be explained that microwave radiation can enhance the catalytic activity of cation exchange resin 732 with a synergistic effect.

(3) The optimal reaction conditions were dosage of 4-hydroxy-3-methoxycinnamic acid being 0.1mol, molar ratio of ethanol to 4-hydroxy-3-methoxycinnamic acid being 5:1, mass percent of resin being 30 of the reagent, microwave power being 300W, reaction time being 30 min. The yield was 84.2% under the above conditions.

(4) Cation exchange resin 732 is an excellent catalyst for the synthesis of ethyl 4-hydroxy-3-methoxycinnamate with a good recyclability. And upon its 5th time recycling, the reaction yield is still over 78%.

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## References

- [1] T. Masuda, K. Yamada, T. Maekawa. *Journal of Agricultural and Food Chemistry*, 54 (2006)6069-6074.
- [2] F. Xu, K. Sho and S. Motohiro. *European Journal of Lipid Science and Technology*, 108 (2006)97-102.
- [3] R. T. Wang, S. Y. Zhou and L. N. Liu. *China New Medicine*, 9(2004)41. (In Chinese)
- [4] J. Y. Xin, Y. Zheng and X. M. Wu. *Fine Chemicals*, 924(2007)172-177. (In Chinese)
- [5] D. M. Li, T. Lv and J. Chen. *Contemporary Chemical Industry*, 34(2005)318-320. (In Chinese)
- [6] S. Q. Wang and C. Gao. *Applied Chemical Industry*, 33(2004) 41. (In Chinese)
- [7] S. Z. Gong. *Advanced Materials Research*, 554-556(2012)772-777.
- [8] S. Z. Gong, Z. J. Li and G. J. Liao. *China Surfactant Detergent & Cosmetics*, 40(2010)186-188. (In Chinese)
- [9] Y. Li, L. Huang and S. J. Li. *Ion Exchange and Adsorption*, 24(2008)467-472. (In Chinese)
- [10] S. Q. Hu, L. L. Chen and H. L. Chen. *Ion Exchange and Adsorption*, 23(2007) 564-568. (In Chinese)