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An Efficient One-Pot Synthesis of 4-Methyl Coumarins Mediated by melamine formaldehyde resin Supported Sulfuric Acid

Yingjie Lei[1,✉], Mei Ding[1] and Qingjia Yao[2]

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ABSTRACT

An efficient one-pot synthesis of 4-methyl coumarins *via* Pechmann condensation from phenols with acetoacetic esters using melamine formaldehyde resin (MFR) supported sulfuric acid as recyclable catalyst under microwave-accelerated solvent-free condition has been developed, with a yielding of 85-95 % respectively. Structures of the corresponding products were elucidated by infrared and ^{1}H NMR spectra. This method is simple, requires short reaction times and environmentally benign compared with conventional acid catalyst.

KEYWORDS

4-Methyl coumarins, Melamine formaldehyde resin, Sulfuric acid, Microwave irradiation.

INTRODUCTION

As one of the important naturally occurring plant constituents, 4-methyl coumarins and their derivatives display a wide range of pharmacological and biological activities [1-3]. Therefore, the synthesis of 4-methyl coumarins has been an interesting target to organic chemists and several strategies were already deve-loped, in which Pechmann reaction involving activated phenols and acetoacetic esters or an unsaturated carboxylic acid in presence of an acid catalyst is gaining more prominence from the view of synthetic perspective [4]. However, the conventional homogeneous acids methods require drastic conditions and later different solid acid catalysts such as sulfuric acid, *p*-toluene sulfonic acid and ionic liquid have been studied [5-7]. Nevertheless, in the current context of environmental impact, these methods are not attractive because of excessive consumption of catalyst and longer reaction times for high yield. For these reasons, there have been some attempts to find alternative, environmentally benign synthesis routes. Nafion-H, zeolite H-BEA, Amberlyst 15 and other solid acids [8-10] have been employed for this purpose in the Pechmann condensation. In recent times, some solid acids have been employed for microwave-accelerated synthesis of coumarins, such as montmorillonite clay and graphite/K-10 [11,12]. However, it still suffers from the drawbacks such as limited substrate scope, use of appropriate solvent and sometimes the necessity of multi-step in synthesis.

Author affiliations:

[1]Department of Chemistry and Chemical Engineering, Tianjin University of Technology, Tianjin, 300384, P.R. China
[2]Sphinx Scientific Laboratory Corporation, Tianjin, 300457, P.R. China

✉To whom correspondence to be addressed:

Tel: +86 2260214259
E-mail: yingjlei@163.com

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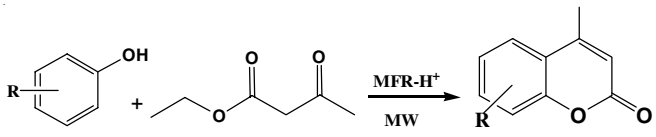
Recently, we have reported excellent activity of melamine-formaldehyde resin (MFR) supported sulfuric acid as a catalyst for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by microwave irradiation with a good yield [13]. In continuation of the efforts to extend the scope to this agent, herein we report the catalytic effect of melamine formaldehyde resin supported sulfuric acid on the synthesis of 4-methyl coumarin derivatives under solvent-free conditions in good yields (**Scheme-I**).



1a R=4-OH
1b R=2,3-OH
1c R= 3,5-OH
1d R=2-Me, 3-OH
1e R=3-OH, 5-Me
1f R=3-OMe
1g R=3-NH_2

3a R=7-OH
3b R=7,8-di-OH
3c R= 5,7-di-OH
3d R=7-OH-8-Me
3e R=5-OH-7-Me
3f R=7-OMe
3g R=7-NH_2

Scheme-I: Synthesis of 4-methyl coumarin derivatives catalyzed by MFR-H^+

EXPERIMENTAL

All the chemicals for synthesis were purchased from commercial suppliers and were used as received. Melting points were determined with an electrothermal micromelting point apparatus and uncorrected. IR spectra were recorded on FT-IR JASCO-680 using KBr disks and ^{1}H NMR spectra were recorded on a JEOL JNM-ECA 400 spectrometer using tetramethylsilane (TMS) as an internal standard. ESI mass spectra were obtained using an ESI-LTQ MS spectrometer. The microwave irradiations were performed in an unmodified Galanz WD 900M domestic microwave oven. All compounds were purified by thick layer chromatography using silica gel from Merck.

General procedure for the preparation of compound 3a-3g: Melamine formaldehyde resin-supported sulfuric acid was prepared according to reported method and dried in vacuum [13]. In a typical experimental procedure, acetoacetic esters (10 mmol) was added to a solution of (un)substituted phenols (**1a-1g**, 5 mmol) and melamine formaldehyde resin-supported sulfuric acid (2 g) in ethyl alcohol (10 mL). The slurry was mixed thoroughly and the solvent was removed by rotary evaporation. The solid obtained was irradiated inside a microwave oven at 900 W for 10-15 min. The reaction progress was monitored by TLC. After the completion of the reaction, the mixture was suspended in hot EtOH (20 mL) and filtered to separate the catalyst residue. The product was crystallized after cooling the reaction mixture and recrystallized to afford expected products **3a-3g** with good yields. The catalyst residue was washed with acetone to recover for subsequent use.

RESULTS AND DISCUSSION

As one of the most common procedures for the preparation of coumarin and its derivatives, Pechmann condensation involves the reaction between a phenol and a β-keto ester in the presence of an acidic catalyst. To overcome the disadvantage of drastic conditions in conventional methods, several solid acid catalysts have been utilized to catalyze the Pechmann reaction for substituted coumarins in good yields. However, the development of alternative environmentally friendly synthetic methods of coumarins is highly required.

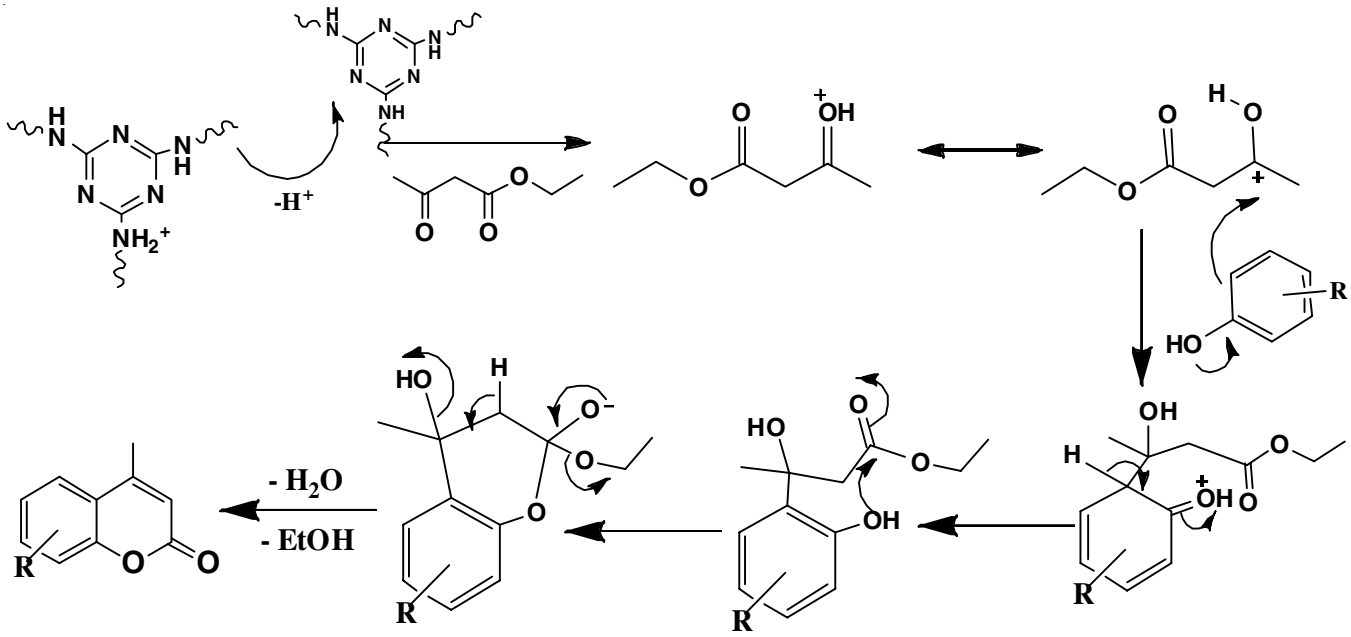
Melamine formaldehyde resin has a unique porous structural frame which makes it an attractive alternative to conventional organic or inorganic supports in catalytic applications. Recently, the approach has been used as supporting of sulfuric acid as a dehydrating agent. Meanwhile, this agent is generally of low cost and can be easily handled or removed. To the best of our knowledge, a versatile solvent-free protocol for the synthesis of 4-methyl coumarins by condensation of phenols with acetoacetic esters in the presence of melamine formaldehyde resin supported sulfuric acid has not been described before.

Thus we tried to use this reagent as an acidic catalyst to the reaction with resorcinol and ethyl acetoacetate and the corresponding product 7-hydroxy-4-methyl coumarin (**3a**) was successfully obtained. Similar reactions were carried out in a microwave oven and the results showed that transformation of the reactants under electromagnetic irradiation could be faster and more efficient. The optimum conditions employed are that a molar ratio of phenols and ethyl acetoacetate is 1:2 and irradiation time along with power level of microwave set-up are 10-12 min and 900 W.

However, phenolic substrates with and without having electron-donating groups showed different reactive properties with ethyl acetoacetate using MFR-H^+ catalyst for solvent free microwave accelerated synthesis of 4-methyl coumarins. For example, compared with the excellent yield of compound **3a** from resorcinol, the monohydroxy phenol was observed to be less active for the synthesis of 4-methyl coumarin under the same condition. Meanwhile, the reactivity of pyrogallol with ethyl acetoacetate was observed to be as efficient as that of resorcinol, even though its reactivity to β-ketoester is less than that of phloroglucinol in which two hydroxyl groups are at the *meta*-positions rather than *ortho*-positions. These results show that besides the strong absorbance of the microwave radiation of the polar molecules and the catalyst acidity, the electron-donating substituents of phenolic substrates could also play significant role in influencing the course of the cyclization which may be ascribed to the resonance effect of *m*-hydroxy group.

Furthermore, to check the stability of catalyst, the reaction of with resorcinol and ethyl acetoacetate in the presence of 30 mol % of melamine formaldehyde resin supported sulfuric acid was investigated. After workup of the reaction mixture, the catalyst was separated by filtration, washed with chloroform and dried at 75 °C in an oven. The recovered catalyst after each reaction was reused in other reaction. The results showed that MFR-H^+ catalyst can be recovered, activated and reused for four consecutive times with only slight variation in the yields of the products which were identified by comparison of analytical data of those reported for authentic samples.

7-Hydroxy-4-methyl-chromen-2-one (3a): Colourless solid; m.p.: 181-183 °C; Yield 95 %; IR (KBr, ν_{max}, cm^{-1}): 3340, 3050, 2900, 1690, 1615, 1590, 1500, 1080; ^{1}H NMR (DMSO-d_6) δ: 2.24 (s, 3H, CH_3), 5.98 (s, 1H, ArH), 6.57 (s, 1H, ArH), 6.72 (d, J = 8.8 Hz, 1H, ArH), 7.46 (d, J = 8.8 Hz, 1H, ArH), 10.50 (s, 1H, OH); MS (ESI): *m/z* 176 [M^+].



Scheme-II: Illustration of the plausible mechanism

7,8-Dihydroxy-4-methyl-chromen-2-one (3b): White solid; m.p.: 240-242 °C; Yield 89 %; IR (KBr, ν_{max}, cm^{-1}): 3231, 1668, 1613, 1576, 1080; ^{1}H NMR (DMSO-d_6) δ: 2.35 (s, 3 H, CH_3), 6.09 (s, 1H, ArH), 6.78 (1H, d, *J* = 8.4 Hz, ArH), 7.03 (d, *J* = 8.4 Hz, 1H, ArH), 9.35 (s, 1H, OH), 10.05 (s, 1H, OH); MS (ESI): *m/z* 192 [M^+].

5,7-Dihydroxy-4-methyl-chromen-2-one (3c): Colourless solid; m.p.: 280-282 °C; Yield 94 %; IR (KBr, ν_{max}, cm^{-1}): 3400, 3070, 2940, 1670, 1600, 1480, 1080; ^{1}H NMR (DMSO-d_6) δ: 2.38 (s, 3 H, CH_3), 5.83 (s, 1H, ArH), 6.78 (1H, d, *J* = 8.4 Hz, ArH), 7.06 (d, *J* = 8.4 Hz, 1H, ArH), 10.28 (s, 1H, OH), 10.51 (s, 1H, OH); ; MS (ESI): *m/z* 176 [M^+]

7-Hydroxy-4,8-dimethyl-chromen-2-one (3d): White solid; m.p.: 262-264 °C; Yield 85 %; IR (KBr, ν_{max}, cm^{-1}): 3400, 3070, 2940, 1670, 1600, 1480, 1080; ^{1}H NMR (DMSO-d_6) δ: 2.11 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.13 (s, 1H, ArH), 6.80 (d, *J* = 8.4 Hz, 1H, ArH), 7.42 (d, *J* = 8.4 Hz, 1H, ArH), 10.28 (s, 1H, OH); MS (ESI): *m/z* 190 [M^+]

5-Hydroxy-4,7-dimethyl-chromen-2-one (3e): White solid; m.p.: 250-252 °C; Yield 90 %; IR (KBr, ν_{max}, cm^{-1}): 3216, 3028, 2986, 1675, 1620, 1062; ^{1}H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.04 (s, 1H, ArH), 6.57 (d, *J* = 1.2 Hz, 1H, ArH), 6.64 (d, *J* = 1.2 Hz, 1H, ArH), 10.52 (s, 1H, OH) ; MS (ESI): *m/z* 190 [M^+].

7-Methoxy-4-methyl-chromen-2-one (3f): White solid; m.p.: 160-162 °C; Yield 94 %; IR (KBr, ν_{max}, cm^{-1}): 3050, 2890, 1698, 1613, 1580, 1502, 985; ^{1}H NMR (DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.22 (s, 1H, CCH), 6.73 (s, 1H, ArH), 6.88 (s, 1H, ArH), 7.50 (d, 1H, *J* = 8.8 Hz); MS (ESI): *m/z* 190 [M^+].

7-Amino-4-methyl-chromen-2-one (3g): Pale yellow solid; m.p.: 223-225 °C; Yield 92 %; IR (KBr, ν_{max}, cm^{-1}): 3437, 3250, 1688, 1610, 1580, 1080; ^{1}H NMR (DMSO-d_6) δ: 2.39 (s, 3 H, CH_3), 5.89 (s, 1H, ArH), 6.06 (brs, 2H, NH_2), 6.38 (s, 1H, CCH), 6.57 (d, *J* = 2.4 Hz, 1H, ArH), 7.42 (d, 1H, *J* = 8.8 Hz); MS (ESI): *m/z*175 [M^+].

Plausible mechanism: The suggested mechanism for the Pechmann condensation of phenols with β-ketoesters in the presence of MFR-H^+ catalyst was described in **Scheme-II**. The MFR-H^+ catalyst would cause dehydration and produce an olefinic bond, at the same time ethyl alcohol would be eliminated with the formation of coumarin ring.

Conclusion

A simple and efficient synthetic method of 4-methyl coumarins *via* Pechmann condensations using MFR-H^+ catalyst under solvent-free with microwave conditions is developed, despite of the observation that the less activated phenol substrates were inactive under the studied experimental conditions. Moreover, the catalyst is low cost and recyclable and the work-up is easy, which will be suitable to enlarge compound library of coumarins.

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