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Coumarins Preparation by Pechmann Reaction Under Ultrasound Irradiation. Synthesis of Hymecromone as Insecticide Intermediate

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Abstract Hymecromone, an important insecticide intermediate, were synthesized under solvent-free conditions by Pechmann reaction upon ultrasound irradiation in the presence of acid zeolites possessing different structural features. This methodology offers significant improvements for the synthesis of coumarins with regards to yield of product, simplicity in operation, and avoiding toxic catalysts and solvents.

Keywords Acid zeolites · Coumarin derivatives · Pechmann reaction · Insecticide intermediates · Hymecromone · Ultrasound irradiation

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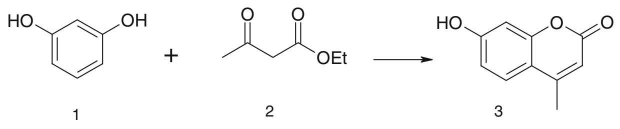
1 Introduction

Coumarins and their derivatives are important compounds in the synthetic organic and medicinal chemistry and are used for the preparation of coumarino-pyrones, furocumarins, chromenes, and 2-acylresorcinols [1]. These compounds find applications in synthesis of pharmaceuticals, fragrances, agrochemicals, and insecticides [2]. The Hymecromone (product 3 in Scheme 1), 7-hydroxy-4-methylcoumarin or 7-hydroxy-4-methyl-2*H*-benzo[b]-pyran-2-one, is used commercially as laser dye [3], as biliary antispasmodic [4], and it is also the starting material for the production of some insecticides [5]. The Pechmann reaction is one of the simplest methods to produce coumarins. In a classical way, the reaction consists of the condensation of phenols with β-ketoesters using sulphuric acid as a catalyst [6]. Other acid catalysts like $FeCl_3$, P_2O_5, $AlCl_3$, HCl, trifluoroacetic acid, have been used for Pechmann reaction as well [7]. The homogeneous catalysts afford generation of side-products and long reaction times are needed with the consequent corrosion problems. For these reasons, there have been some attempts to find alternative, environmentally benign synthetic routes using a simple, cheap and reusable catalyst for the synthesis of coumarins [8]. With regard to that, a large variety of heterogeneous solid acids such as zeolite Beta, Nafion-H, Amberlyst [9], functionalized mesoporous Zr-TMS [10], $Sm(NO_3)_3 \cdot 6H_2O$ [11], $Bi(NO_3)_3 \cdot 5H_2O$ [12], sulfated $Ce_xZr_{1-x}O_2$ [13] and heteropolyacids [14], [15] have been investigated. Ionic liquids [16] or microwave irradiation under solvent-less conditions have also been reported [17].

Application of environmentally benign zeolites is one of the ways of our interest. Zeolites offer the possibility to tailor the size and connectivity of their pores together with concentration and strength of their acid sites [18].



Scheme 1 Pechmann reaction between resorcinol an ethyl acetoacetate to produce Hymecromone

Ultrasound irradiation presents an interesting option how to increase the rate of catalytic reactions [19]. Sonication [20–24] has been employed as energy source for enhancing the rate of chemical reactions. The chemical effects of ultrasounds (acceleration of the reaction, reduction of the induction period and enhancement of the catalyst efficiency) are well-documented [25] and have been attributed to the phenomenon of the cavitation, the implosive collapse of the bubbles formed during the interaction between a suitable acoustic wave field and a potential chemical system. The ultrasonic irradiation has several additional enhancement effects when one of the phases is a solid, which is especially useful for catalytic applications.

Recently, we have shown the potential of combination of zeolites with ultrasound irradiation in imidazole N-alkylation [26]. The use of ultrasound irradiation as tool for organic synthesis is rather under-explored. Nevertheless, several reactions have been described by using sonication. In this way, very recently it has been also reported on the use of ultrasound to enhance the efficiency of carbohydrate synthesis [27]. Moreover, our group investigated the effect of ultrasound on the catalytic activity of a series of basic solid materials such as activated carbons and zeolites, during the preparation of antiviral, antihypertensives, and antibacterial compounds through the Knoevenagel reaction, Claisen-Schmidt condensation or alkylation of heterocycles [28–33].

In the present study, we report on the combination of acid zeolites and ultrasound irradiation as simple but effective alternative method for the synthesis of coumarins, especially of 7-hydroxy-4-methylcoumarin (Hymecromone) via Pechmann condensation between resorcinol and ethyl acetoacetate (Scheme 1). The reaction proceeds under mild conditions with the possibility to reuse and recycle the catalysts, which is an important contribution from the point of view of the green chemistry concept [34].

2 Experimental

2.1 Catalysts Preparation and Characterization

Zeolites Beta, ZSM-5, Mordenite, and Y were purchased from different companies, see Table 1. All four zeolites were activated before the reaction by heating in a stream of air at 773 K for 2 h with a temperature rate of 10 K/min. Type and concentration of Brønsted and Lewis acid sites were determined by adsorption of d_3-acetonitrile followed by FTIR spectroscopy (Nicolet Protégé 460) using self-supported wafer technique. Prior to the adsorption experiment zeolite samples were pressed into the self-supporting wafers with the density of 6–12 mg/cm^2. The activation of zeolite wafers was carried out in a high vacuum at the temperature of 723 K overnight. The concentrations of Lewis and Brønsted acid sites in the samples were calculated with the extinction coefficients 3.6 ± 0.2 and 2.05 ± 0.1 cm μmol^{-1}, respectively [35]. The results are given in Table 1.

Surface areas of zeolites were determined with a Micromeritics ASAP 2020 volumetric instrument (Table 1). Sorption isotherms of nitrogen at 77.35 K were determined using a conventional static technique. This instrument is equipped with pressure transducers covering the 133 Pa, 1.33 kPa and 133 kPa ranges. Before each sorption measurement the zeolite sample was outgassed using a special heating program allowing for a slow removal of pre-adsorbed water at low temperatures. This was done to avoid potential structural damage of the sample due to surface tension effects and hydrothermal alternation. Starting at ambient temperature the sample was out-gassed

Table 1 Characterization of the zeolite catalysts under study

Catalyst	Origin	Channel structure	Si/Al ratio	Surface area (m^2/g)	Channel diameter (nm)	c_{LC} (mmol/g)	C_{BC} (mmol/g)
Beta	Zeolyst	3D	12.5	674	0.64 × 0.70 0.55 × 0.55	0.40	0.32
ZSM-5	Conteka	3D	75	396	0.53 × 0.56 0.51 × 0.55	0.05	0.02
NH_4Y	VÚRUP, Bratislava	3D	2.7	768	0.74	n.d.	n.d.
Mordenite	Zeolyst	2D	10	493	0.65 × 0.70 0.26 × 0.57	0.25	0.27

C_{LC} = concentration of Lewis acid sites

C_{BC} = concentration of Brönsted acid sites at 383 K (temperature rate of 0.5 K/min) until the residual pressure of 0.5 Pa was obtained. After further heating at 383 K for 1 h the temperature was increased (temperature rate of 1 K/min) until the temperature of 523 K was achieved. This temperature was maintained for 8 h.

2.2 Reaction Procedures

Prior to the reactions (both in thermal as well as in ultrasound mode) each zeolite was activated at 823 K for 2 h to ensure the formation of H-form of the zeolite.

2.3 Thermal Induced Reactions

Typically, 10 mmol of each reactant (resorcinol and ethyl acetoacetate) and the corresponding amount the catalyst (0.1, 0.2, or 0.3 g) were stirred at 303 and 333 K for 7 h. Subsequently, 10 mL of acetone were added to dissolve all products.

In order to follow the evolution of the reactions, liquid reaction products were sampled from the reaction mixture at regular intervals of 1 h and analyzed by GC and MS (Agilent 6890 GC and mass spectrometry—Hewlett-Packard HP 5971 A).

For recycle experiments, the catalysts were filtered off, washed with acetone, dried at 423 K for 4 h, and then reused without further treatment.

2.4 Ultrasound Induced Reactions

Resorcinol (10 mmol) and ethyl acetoacetate (10 mmol) were mixed in a flask without any solvent. The flask was suspended into the ultrasonic bath at the reaction temperature (303 and 333 K). Then, the catalyst was added and the reaction times started. The reactions were performed in an ultrasonic bath (Selecta Ultrasound-H) with a heating system, 40 KHz of frequency, and 550 W of power. (Caution: sonication of the reaction mixture for longer times more than 20 min rises the temperature of the reaction system, and reaction flask should be cooled after sonication every 20 min). After the reaction, the coumarin **3** was isolated by standard procedures and characterized by ^{1}H NMR and GC-MS. Previously to any experiment blank runs were carried out, which showed that the reaction, in absence of catalyst, was negligible.

3 Results and Discussion

3.1 Catalyst Characterization

The Si/Al ratio, pore dimensionality and channel aperture are presented in Table 1. As it is seen from Table 1, zeolites differing substantially in their channel sizes and dimensionality were used to clarify the role of the zeolite channel system on their activities and selectivities in the condensation of resorcinol and ethyl acetoacetate.

After the reaction, individual zeolite catalysts were separated from the reaction mixture, dried at 333 K overnight and re-activated by heating in a stream of air at 773 K for 2 h with a temperature rate of 10 K/min. No change/dealumination of zeolite samples was found during the reaction, which was evidenced not only on the basis of chemical analysis of the catalysts after the reaction but also on the FTIR investigation of regenerated zeolites with regard to the type and concentration of Brønsted and Lewis acid sites. Thus, it can be concluded that neither the effect of ultrasound nor the effect of the reaction conditions on the dealumination of zeolites under our reaction conditions was observed. The zeolites were regenerated and recycled at least four times without loss of activity.

3.2 Synthesis of Hymecromone (7-Hydroxy-4-Methylcoumarin) Via Pechmann Reaction

In this investigation, the influence of external parameters on the ultrasound and thermal activated reaction was studied for Pechmann reaction. The influence of the type and amount of the zeolite catalyst, the ratio resorcinol: ethyl acetoacetate, and the influence of the ultrasound were analyzed in a systematic way. Table 2 shows the effect of the type of zeolite on the production of coumarin **3** (Hymecromone) during the thermally and ultrasonically activated reactions at 303 K. From these results it can be concluded that the order to yield Hymecromone is: Mordenite $\approx$ Y > H-Beta > ZSM-5. The same trend is observed under thermal activation at the same reaction temperature. Table 3 displays the conversion of coumarin **3** at 333 K. Conversions of coumarin **3** around 74% with 100% selectivity were obtained for mordenite after 7 h under ultrasound activation. In contrast, under thermal conditions, conversions around 40% were achieved. It is important to remark that selectivity is around 99% in all cases under our experimental conditions.

Table 2 Conversions using thermal activation and US irradiation

Catalysts	Conversion to coumarin **3** (%)	
	Thermal	US
Mordenite	26	49
Y	18	40
Beta	12	33
ZSM-5	9	26

Condensation of resorcinol (10 mmol) with ethyl acetoacetate (10 mmol) at 303 K during 7 h. Catalysts amount: 0.3 g

Table 3 Conversions using thermal activation and US irradiation

Catalysts	Conversion to coumarin **3** (%)	
	Thermal	US
Mordenite	39	74
Y	35	70
Beta	30	65
ZSM-5	25	58

Condensation of resorcinol (10 mmol) with ethyl acetoacetate (10 mmol) at 333 K during 7 h. Catalysts amount: 0.3 g

It is expected that the acidic properties of zeolites have a particular influence on the activity and selectivity of the coumarins synthesis. The characterization data provided in Table 1 indicate that the ratio Si/Al (12.5) of Beta zeolite is slightly higher than Mordenite zeolite (10.0) and the concentration of acid centers found for Beta zeolite was higher than the rest of zeolites. Mordenite exhibited the highest conversion to product **3** among all other zeolite catalysts indicating that the higher acid strength of the acid centers the higher the conversions. It indicates that the acid strength is of a high importance for the synthesis of coumarins. In addition, the size of zeolite channels is also important when comparing medium (10-MR) and large pore zeolites (12-MR), e.g. ZSM-5 vs. mordenite or zeolite Beta. The best catalytic behavior in Pechmann reaction was obtained with H-mordenite, possessing 12-MR channels but also the highest acid strength of Si-OH-Al groups compared with H-Y and H-Beta zeolites. In the case of ZSM-5 zeolite smaller 10-MR channel system limits the diffusion of the products. This is clearly valid when the reaction is operated under both thermal as well as ultrasound reaction conditions.

The comparison between ultrasound and thermal activation here reported evidences that the sono-activation enhances the Pechmann reaction much better than thermal activation. In this way, sonochemistry through the cavitation effect, provides a unique interaction mode between energy and matter [19–21]. Interestingly, mordenite resulted as the best catalyst operating at both temperatures, 303 and 333 K. It is important to note that the reaction rate was almost negligible for the same reaction in the absence of the zeolite catalyst.

Experiments with different amounts of catalyst were conducted under US and thermal activation using Mordenite as solid with the best catalytic performance. Table 4 shows the conversion values achieved after 7 h at 333 K. From Table 4, it can be observed that when using 0.1 g of the Modernite catalyst conversion of 64% is obtained under US. Nevertheless, when using 0.2 or 0.3 g, conversions of 72 and 74% are obtained in both cases, respectively.

In order to investigate the effect of the ratio resorcinol: ethyl acetoacetate, different amounts of ethyl acetoacetate were condensed with resorcinol. Table 5 shows the conversion obtained when using Mordenite as catalysts under US and thermal activation. From the results in Table 5 it can be deduced that the higher the amount of ethyl acetoacetate is, the higher the conversion is, achieving values around 90% when the ratio resorcinol-ethyl acetoacetate is 1.0:2.0. It is important to remark that no traces of the corresponding pyranocoumarin were detected.

Table 6 shows the yields of isolated pure products (Hymecromone) obtained for different zeolite catalysts under thermal and ultrasonic activation after 7 h of reaction. Yields of coumarin **3** over ZSM-5 and modernite under thermal activation achieved 9 and 31%, respectively, with zeolite Y (26%) and Beta (19%) in between. Over all catalysts a substantial increase in the yield of coumarin **3** was observed using ultrasound activation (33–39% range). Differences in conversions and yield over different structural types of zeolites were explained by differences in the

Table 4 Influence of the catalysts amount

Catalyst amount (g)	Conversion to coumarin **3** (%)	
	Thermal	US
0.1	28	64
0.2	38	72
0.3	39	74

Condensation of resorcinol (10 mmol) with ethyl acetoacetate (10 mmol) at 333 K during 7 h. Catalyst: Mordenite

Table 5 Influence of the ratio resorcinol: ethyl acetoacetate

Resorcinol:ethyl acetoacetate ratio	Conversion to coumarin **3** (%)	
	Thermal	US
1.0:1.0	39	74
1.0:1.2	45	77
1.0:1.5	54	81
1.0:2.0	62	88

Condensation of resorcinol (10 mmol) with ethyl acetoacetate at 333 K during 7 h. Catalyst: Mordenite (0.3 g)

Table 6 Yields of isolated pure coumarin **3** obtained on zeolites upon thermal and US activation

Catalysts	Yield of pure coumarin **3** (%)	
	Thermal	US
Mordenite	31	70
Y	26	59
Beta	19	53
ZSM-5	9	48

Condensation of resorcinol (10 mmol) with ethyl acetoacetate (10 mmol) at 333 K during 7 h. Catalysts amount: 0.3 g size of the channels inducing shape selective effects and also in acidity, we can hardly expect that ultrasound will cause some changes in acidity. With regard to that we may speculate that ultrasound activation could have a positive influence on the rate of diffusion in zeolite channels.

4 Conclusions

The Pechmann condensation under ultrasound and thermal activation, in the absence of any solvent, has been investigated during the condensation between resorcinol and ethyl acetoacetate at moderate reaction temperatures to produce Hymecromene. An important enhancing effect in the conversion of the desired product was found when ultrasound was used. The results demonstrate that the Pechmann reaction with suitable acid zeolites results in an efficient, mild and effective synthesis of coumarins with nearly 100% selectivity. A yield of the pure isolated product around 70% was obtained under sonication when Mordenite was used as catalysts. The ultrasound irradiation combined with the acidity and structural characteristics shown by the selected zeolites, in particular by Mordenite, is presented as an alternative method for the clean production of Hymecromene and others coumarin derivatives, which are key intermediates in the production of insecticides. The zeolites could be regenerated and recycled at least four times without loss of activity

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