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Zeolite catalysed synthesis of coumarin derivatives

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Abstract

The direct synthesis of coumarin derivatives from *m*-substituted phenols and α,β-unsaturated carboxylic acids catalysed by solid-acid catalysts, such as zeolite H-Beta or Amberlyst-15, in toluene as solvent was studied. The conversion involves esterification followed by alkylation (ring closure). Ring closure of the ester is promoted both by an appropriate substituent on the aromatic ring and by Michael activation of the β-carbon of the ester. These influences were studied by variation of the reactants. 7-Hydroxy-3,4-dihydrocoumarin is formed in high yield when resorcinol and propenoic acid are used as reactants.

Keywords: Coumarin synthesis; Zeolite H-Beta; 3-substituted phenol; α,β-unsaturated carboxylic acid

1. Introduction

Coumarin and its derivatives find the application as fragrances, pharmaceuticals and agrochemicals. Various procedures have been developed for the synthesis of coumarins from phenol (Pechmann reaction) [1,2], *o*-cresol (Raschig method) [3] and salicylaldehyde (Perkin reaction/Knoevenagel) [4,5]. In these methods non-reusable catalysts are applied, such as concentrated sulphuric acid (Pechmann) and metal oxides. For example, 7-hydroxy-4-methylcoumarin can be obtained in high yield upon reaction of ethyl acetoacetate with 1,3-dihydroxybenzene (resorcinol) with sulphuric acid as solvent and condensing agent [6]. Other condensing agents in this reaction are: phosphorus pentoxide [7], trifluoroacetic acid [8], aluminium chloride [9], zinc chloride [10] and alcoholic hydrogen chloride solution. In order to reduce the waste problem, heterogeneous catalysis of the Pechmann reaction by cation exchange resins [11] or by the perfluorinated sulphonic acid resin (Nafion-H) [12] has been reported.

In recent years considerable attention has been paid to the potential of zeolites to act as heterogeneous and regenerable catalysts in organic reactions [13]. The tunability of many properties such as hydrophobicity, acidity and the range of pore sizes make zeolites interesting alternatives for conventional non-regenerable catalysts. In 1987 it was reported that 3-hydro-4-methylcoumarin was formed as a side-product upon intramolecular reaction of phenyl acetate at 400°C on zeolite HY [14]. Subba Rao et al. described the formation of 4-methylcoumarin by cycloacylation of phenol with acetic anhydride over CeNaY zeolite at 380°C [15]. Recently we have reported on the solid-acid catalysed synthesis of 7-hydroxycoumarins from resorcinol with ethyl acetoacetate, propynoic acid and propenoic acid in the liquid

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phase [16]. In the latter case esterification takes place followed by alkylation of the aromatic nucleus. In this paper we examine the condensation of resorcinol with various α,β-unsaturated carboxylic acids catalysed by zeolite H-Beta in more detail. The reactivities of different reactants are investigated and a mechanism is proposed.

2. Experimental

2.1. Catalysts

Zeolite H-Beta (Si/Al = 12) was synthesised according to the Wadlinger procedure. After calcination of the as-synthesised Beta twice at 540°C, the zeolite was ion-exchanged three times with 1 M aqueous ammonium acetate at 70°C. Except where otherwise stated for a reaction 1.0 g of the resulting NH_4-Beta was converted to the active H-Beta by calcination at 450°C.

Amberlyst-15 was purchased from Aldrich.

2.2. Chemicals

Except for 3-methoxyphenol and *m*-cresol, which were distilled prior to use, chemicals were used without further purification as received from Aldrich and Janssen Chimica.

2.3. Reaction procedure

Reactions were carried out in a batch reactor equipped with a Dean-Stark condenser for water removal. A typical reaction procedure was as follows: 10 mmol resorcinol (1.10 g), 10 mmol propenoic acid (acrylic acid) (0.72 g) and 1.0 g nitrobenzene (internal standard) were stirred and heated to boiling in 40 ml toluene. At $t = 0$ the activated H-Beta was added to the reaction mixture. Samples were taken periodically and analysed by gas chromatography on a CP Sil 5 CB column.

^{1}H NMR spectra were obtained using a 60 MHz Varian NMR spectrometer. ^{1}H NMR spectra of 7-methoxy-3,4-dihydrocoumarin and 5-methoxy-3,4-dihydrocoumarin were recorded on a 400 MHz Varian NMR spectrometer. Mass spectra were performed on a VG 70SE mass spectrometer, using 70 eV as ionisation energy.

2.4. Thermogravimetric analysis (TGA) of used catalyst

After the reaction of acrylic acid with resorcinol, according to the above described procedure, the used zeolite H-Beta was recovered by centrifugation, washed with diethyl ether and dried in air. TGA was performed by heating 80 mg of the used zeolite under nitrogen (2.6 l/h) to 450°C at a heating rate of 5°C/min, until no loss of weight could be detected anymore. After cooling to room temperature, the measurement was repeated in air under the same conditions.

3. Results and discussion

3.1. Reaction of resorcinol and propenoic acid

Fig. 1 shows the course of the reaction when converting resorcinol and propenoic acid in presence of zeolite H-Beta and Amberlyst-15 as solid catalysts. The intermediate ester (Scheme 1) was not observed, indicating a relatively rapid intramolecular alkylation towards 7-hydroxy-3,4-dihydrocoumarin (**1**). Isolation of **1** was performed by filtrating the solid catalyst from the hot reaction mixture. The crude product precipitated from the filtrate and was recrystallised from a diethyl ether/toluene mixture. After work-up **1** was obtained in 66% yield. Fig. 1 also shows the formation of 3,4,6,7-tetrahydrobenzo[1,2-*b*:5,4-*b'*]dipyran-2,8-dione (**2**). By reacting 10 mmol of resorcinol with 20 mmol propenoic acid, **2** could be isolated after removal of the catalyst from the hot reaction mixture and cooling the filtrate. Compound **2** was characterised by ^{1}H NMR spectroscopy (δ (ppm): 7.03 (s), 6.73 (s), 2.80 (m)). For the conversion catalysed by zeolite H-Beta shown in Fig. 1 the TON (total turnover number of a catalytic site) was determined to be 5.8. The catalytic

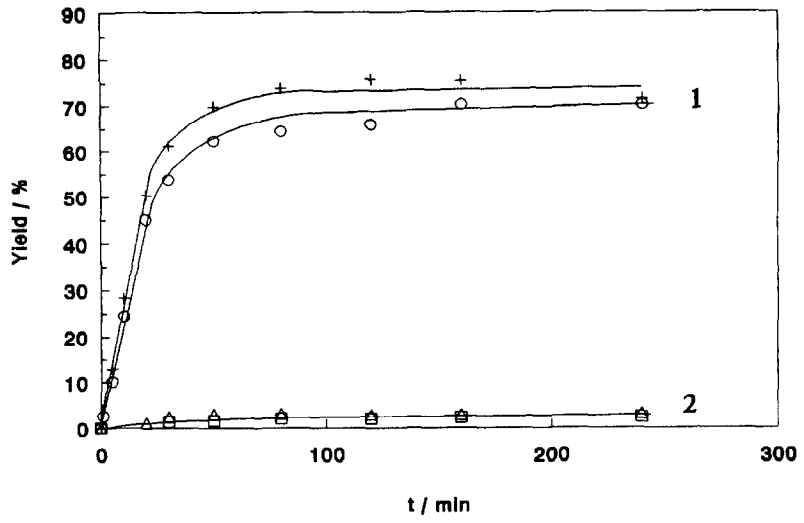
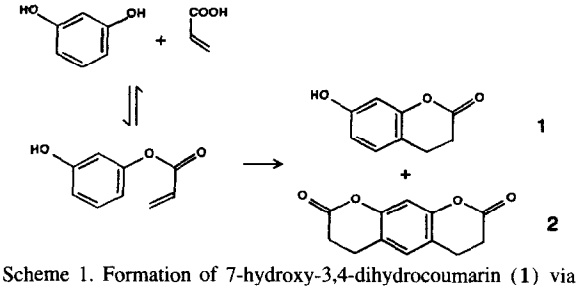


Fig. 1. Reaction of resorcinol (10 mmol) with propenoic acid (10 mmol) in 40 ml toluene under azeotropic removal of water catalysed by Amberlyst-15 (1.0 g) or zeolite H-Beta (1.0 g). (+) Amberlyst, (△) Amberlyst, (○) H- Beta, (□) H-Beta.

ability of zeolite H-Beta was more pronounced when 0.12 g zeolite was used under the same conditions. The TON was then found to be 21.2.

From the results presented further we assume that formation of **1** (Scheme 1) involves esterification followed by alkylation (ring closure). The β-carbon of the ester of resorcinol and propenoic acid is polarised by conjugation with the carbonyl group (Michael activation), making it activated to undergo electrophilic substitution at the aromatic nucleus, which is activated by the hydroxyl group substituted *para* to the position to be alkylated.

From Fig. 1 it can be seen that the final conversion is reached after 80 minutes. Catalyst deactivation takes place due to coke formation as was indicated by TGA. During heating in nitrogen, the loss of weight of the used catalyst is most likely to be caused by evaporation of weakly adsorbed reactants and solvent. As can be seen in Fig. 2, during heating in air almost 10% loss of weight could be detected, indicating a substantial amount of coke which was formed during the reaction. By GC-analysis it was found that no acrylic acid was present anymore in the reaction mixture, indicating that acrylic acid plays a role in the formation of coke.



Scheme 1. Formation of 7-hydroxy-3,4-dihydrocoumarin (1) via esterification followed by alkylation.

Table 1 illustrates the re-useability of zeolite H-Beta. After the reaction the zeolite was filtrated from the solution and washed with diethyl ether. Subsequently the zeolite was dried and reactivated at 450°C for the next catalytic cycle. After three cycles no loss of catalytic activity was detected. The increase of the TON was caused by a slight loss of the catalyst after a cycle during the recovery procedure.

3.2. *Variation of the aromatic substrate*

Scheme 2 presents the possible reaction products that are formed when phenol and 3-substituted phenols are used for the reaction with acrylic acid. In Table 2 the yields after 4 h reaction time are shown. Resorcinol and 3-methoxyphenol are suitable substrates for coumarin formation, whereas phenol and *m*-cresol are less suitable. In the case of the latter substrates the ester formation was not followed by a rapid ring closure. This makes the double bond available for further reac-

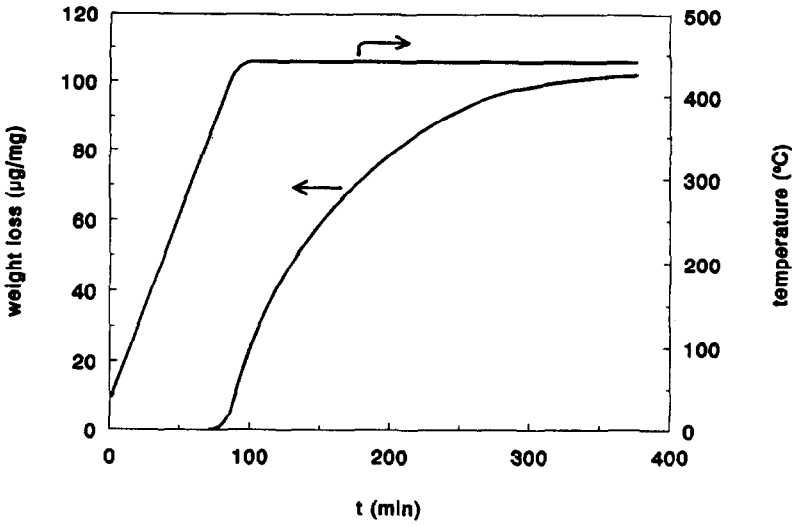
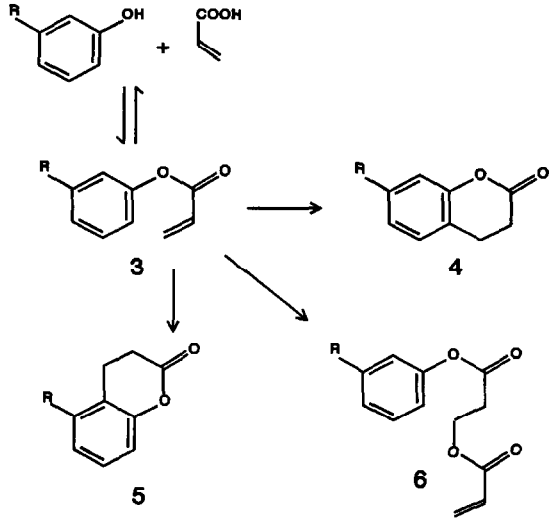


Fig. 2. TGA plot of zeolite H-Beta after use in the reaction of acrylic acid with resorcinol, heated in a stream of air. Prior to this measurement the zeolite was heated in nitrogen.

Table 1
Regenerability of zeolite H-Beta in the reaction of resorcinol with acrylic acid catalysed by zeolite H-Beta in toluene at 111°C

Cycle	Conversion to **1** (%)	TON
1	73	5.8
2	69	6.5
3	73	7.5



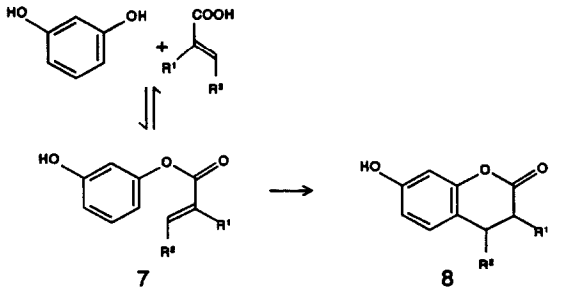
Scheme 2. Reaction products of the reaction of acrylic acid with various substrates.

tion with acrylic acid to **6**. In the case of resorcinol and 3-methoxyphenol the ester with acrylic acid was not detected in the reaction medium, which means that the ester formation was rapidly followed by ring closure. Interestingly, in the reaction of 3-methoxyphenol or *m*-cresol ring closure was also observed at the position *ortho* to the substituent R. Separation of 7-methoxy-3,4-dihydrocoumarin (**4**) and 5-methoxy-3,4-dihydrocoumarin (**5**) on a Silicagel 60 column with hexane/ethyl acetate (3:1) as eluent enabled us to identify these compounds. For **4** was found: δ (ppm): 2.75 (t), 2.93 (t), 3.78 (s), 6.59 (d), 6.65 (dd), 7.08 (d) and for **5**: δ (ppm): 2.74 (t), 2.97 (t), 3.85 (s), 6.66 (d), 6.69 (d), 7.20 (t). Similar orientation effects have been observed earlier for the Pechmann reaction [17]. The reaction with the less active substrates was slower than the reaction with resorcinol or 3-methoxyphenol. In the first cases the conversion to the coumarin **4**

Table 2
Variation of the substrate in the reaction with acrylic acid catalysed by zeolite H-Beta in toluene at 111°C after 4 h

		Conversion to (%)			
Substrate	R	**3**	**4**	**5**	**6**
Resorcinol	OH	–	73	–	–
3-Methoxyphenol	OCH_3	–	64	14	–
m-Cresol	CH_3	5	8	3	–[a]
Phenol	H	10	2	–	4

[a] Approximately 3% of the *m*-cresol was converted to an unidentified compound.

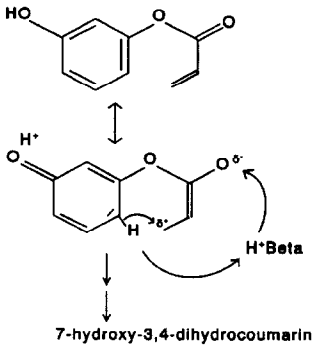


Scheme 3. Reaction products of resorcinol with various alkenoic acids.

Table 3
Variation of the alkenoic acid in the reaction with resorcinol catalysed by zeolite H-Beta in toluene at 111°C after 4 h

			Conversion to (%)	
Alkenoic acid	R^1	R^2	7	8
acrylic acid	H	H	–	73
methacrylic acid	CH_3	H	–	46
crotonic acid	H	CH_3	10	–[a]

[a] Approximately 4% of crotonic acid was converted to an unidentified compound.



Scheme 4. Mechanism of synthesis of 7-hydroxy-3,4-dihydrocoumarin catalysed by zeolite H-Beta.

after 24 h was 6% for phenol and 24% for *m*-cresol. From the above presented results it is clear that an electron donating substituent R (R = OH, OCH_3) activates the substrate for ring closure to the coumarin (**4**). When resorcinol is reacted with acrylic acid to **1**, the remaining hydroxyl group is still available to undergo esterification and so subsequently **2** is formed (2%). Our assumption that esterification takes place prior to alkylation is supported by the fact that treatment of 1,3-dimethoxybenzene with acrylic acid did not show any reaction. While the reaction of 3-methoxyphenol shows that the methoxy group strongly activates the aromatic nucleus to be alkylated, 1,3-dimethoxybenzene is not susceptible for alkylation by acrylic acid. These findings clearly illustrate the condition of esterification, bringing the alkylating group in the proximity of the aromatic nucleus.

3.3. Variation of the alkenoic acid

Scheme 3 and Table 3 show the results of the reaction of resorcinol with different alkenoic acids after 4 h reaction time. The reaction with methacrylic acid was slow; after 24 h the final conversion to **8** was 81%. When resorcinol is reacted with acrylic acid, the ring closure of **7** is promoted by the polarisation of the β-carbon of the ester (Michael activation). Due to methyl groups substituted at the double bond the Michael activation of the β-carbon is less pronounced, resulting in a low reaction rate in the reaction with methacrylic acid and an inhibition of ring closure in the reaction with crotonic acid. However, in the case of crotonic acid ring closure could also be inhibited because of sterical hindrance. Interestingly, when the reaction of resorcinol with crotonic acid was catalysed by Amberlyst-15 in chlorobenzene as solvent, low conversion to the corresponding coumarin **8** was observed. By raising the reaction temperature to 131°C, the conversion to **8** could be increased: however, the ester **7** still was the main product.

3.4. Mechanism

The results have led us to the following proposal for the mechanism, as shown in Scheme 4 for the reaction of resorcinol with acrylic acid. The first step is the esterification, which is followed by polarisation of the β-carbon of the ester by the carbonyl group. The electron donating substituent polarises the para position. Ring closure is facilitated by Brønsted acid sites in zeolite H-Beta, which protonates the carbonyl group and deprotonates the aromatic nucleus. The enol-form is subsequently converted to the 3,4-dihydroform.

4. Conclusions

A new approach to the synthesis of coumarin derivatives in the liquid phase, catalysed by regenerable solid acid catalysts, has been made possible by a suitable choice of *m*-substituted phenols and alkenoic acids. Zeolite H-Beta is the preferred catalyst above Amberlyst-15 because of its excellent regenerability. The reaction was found to involve esterification followed by ring closure. For rapid ring closure an electron donating substituent on the *m*-substituted phenol is required as well as Michael activation of the β-carbon. Regenerability of the catalyst, zeolite H-Beta, is excellent.

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