

Acylation of Anisole with Methylsuccinic Anhydride Catalysed by Zeolites

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The zeolite-catalysed acylation of anisole with methylsuccinic anhydride gave a mixture of products. The main component was 4-hydroxy-4,4-bis-(4-methoxyphenyl)-2-methyl- γ -butyrolactone, which was isolated in 25% yield; the expected keto acids were not formed. In the zeolite-catalysed reaction between 3-(4-methoxybenzoyl)-2-methylpropionic acid and anisole, the γ -butyrolactone was isolated in 82% yield, indicating that the initially formed keto acid undergoes cyclisation to the lactone. When these reactions were performed with a zeolite deactivated with triphenylphosphine, the lactone was not formed, suggesting that acid sites on the external surface of the zeolite catalyse these reactions.

Friedel–Crafts acylation is a reaction in which an active and selective heterogeneous catalyst might replace more traditional homogeneous systems. Zeolites are crystalline aluminosilicates that have been found to be interesting alternatives to the conventional catalysts, and the first industrial application of zeolite-catalysed acylation in the production of aromatic ketones was recently reported by researchers at Rhône-Poulenc.¹ The key opportunity for the use of zeolites as catalysts relies on their unique pores, which can control the selectivity of the reaction. The zeolite functions as a Brønsted acid catalyst, and the electronic effects have been shown to be analogous to those reported for classical electrophilic aromatic substitution.² In earlier work we presented results from the Friedel–Crafts acylation of anisole by acetyl chloride and acetic anhydride catalysed by modified zeolites.³ The yield of acylated product was studied as a function of various catalyst modifications. Subsequent studies have focused on a more refined application of the shape-selective properties of the zeolites. Two isomeric γ -keto acids may be obtained in the Friedel–Crafts acylation of anisole **1** with methylsuccinic anhydride **2**.⁴ Even though the α -isomer **3** is the predominant product, different ratios between the two isomers **3** and **4** have been reported, and have been found to depend on the substituent on the anhydride and the dielectric constant of the solvent.^{4–7} It was of interest therefore to see if the shape-selective properties of the zeolites could influence the isomer ratio.

For a complete reaction with the formation of a keto

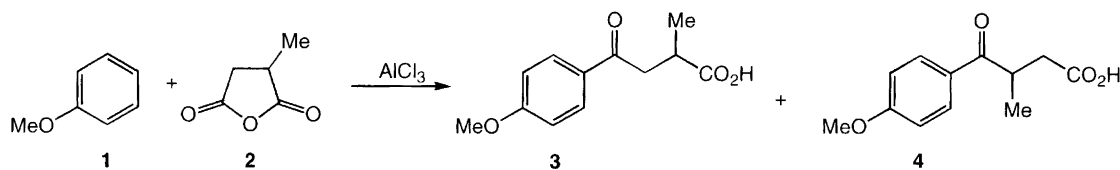
acid, one molecule of anhydride requires two of aluminium chloride; thus it is not a true catalyst.⁴ The products can only be obtained by hydrolysis, which leads to the loss of the catalyst and the environmental consequences of its disposal. The main features of a zeolite-catalysed reaction are the ease of work-up and the regenerability of the catalyst. In accordance with increasing environmental concern, new applications for zeolites in organic synthesis are of particular interest.

Results and discussion

The AlCl₃-catalysed acylation of anisole with methylsuccinic anhydride resulted in two isomeric keto acids, as indicated in Scheme 1. The crude product was obtained in 91% yield, and consisted essentially of the acids **3** and **4** in a 6:1 ratio (¹H NMR). The α -methyl isomer **3** was isolated by recrystallisation of the crude product from glacial acetic acid. The β -methyl isomer **4** was not isolated due to higher solubility and the low yield.

The zeolite used in this work was a commercial sample of Zeolite Y, the synthetic analogue of the naturally occurring mineral faujasite. The zeolite had been dealuminated ($\text{Si}/\text{Al}_{\text{framework}} = 15.9$), which indicated that few and strong Brønsted acid sites were present. The building units in the zeolite framework are tetrahedra of $[\text{SiO}_4]^{4-}$ and $[\text{AlO}_4]^{5-}$. Charge-neutralising cations are necessary to obtain a neutral framework, and in this zeolite the charge balancing cations were ammonium. The Brønsted acid sites are so-called bridging OH groups, which consist of hydroxy protons associated with lattice oxygen ions. These Brønsted acid sites are generated by thermal

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Scheme 1.

Table 1. Reaction of methylsuccinic anhydride and anisole.

$T/^\circ\text{C}$	Conversion ^a (%) 5 h	Conversion ^a (%) 24 h	Yield (%) 3+4	Yield ^b (%) 5	Yield ^b (%) 6	Yield ^b (%) 7
100	9	17	0	—	—	—
120	24	29	0	—	—	—
150	35	—	0	9	< 1	2
150	43	73	0	25	4	4

^aGLC. ^bIsolated.

decomposition (calcination) of the ammonium cations at 500 °C with the loss of ammonia, as indicated in Fig. 1. The calcined zeolite is called HY.

As described above, the AlCl_3 -catalysed reaction resulted in high yields of keto acids. It was therefore anticipated that a Brønsted acid would also catalyse this reaction and give the same products. However, in the reaction between anisole and methylsuccinic anhydride catalysed by HY, the keto acids **3** and **4** were not present in the product. The reaction was performed at 150 °C with the substrate anisole as the solvent; lowering the temperature resulted in reduced conversion of the anhydride (Table 1). After 24 h the conversion reached 73%, and TLC showed that many products had been formed. Three products were isolated by flash chromatography on silica (Fig. 2).

The main product was the substituted γ -butyrolactone **5**, which was isolated in 25% yield. Its structure was identified by comparing the NMR and IR spectra with those of the literature.⁸ It is interesting to note that not all the ^{13}C signals of the two aromatic rings in the lactone coincide, which is probably due to hindered rotation. The ester **6** and the substituted furan **7** were also formed,

although in lower yields. Most of the anhydride was converted into polymeric material and products which could not be separated on the column. The structures of compounds **6** and **7** were established mainly on the basis of their NMR spectra.

The formation of a lactone as the main product was quite surprising. However, formation of lactones in reactions with succinic anhydride has been reported. In the condensation between resorcinol and succinic anhydride catalysed by ZnCl_2 at 170–180 °C, the lactone was the main product, isolated in 60% yield.⁹ Different mechanisms for the formation of these lactones have been suggested.⁴ According to Scheme 2, the lactone may be formed without acylation of anisole or ring-opening of the anhydride. Protonation of the anhydride, followed by nucleophilic addition of anisole to the resulting cation, may give the hydroxylactone **8**. The product **5** may then be formed by subsequent dehydration and addition of a second molecule of anisole. However, the hydroxylactone **8** could also originate from the acid-catalysed cyclisation of the acid **3**. Formation of **5** according to the latter mechanism would imply initial formation of the keto acid **3**. In order to differentiate between these two reaction modes, a reaction of the keto acid **3** and anisole catalysed by HY was performed. Conversion of the acid was found to be quantitative after 2 h, and the lactone **5** could be isolated in 82% yield. Both the ester **6** and the furan **7** were formed as by-products. This result indicates strongly that the lactone **5** is formed from the keto acid **3**. The rapid conversion, under the reaction conditions, of the keto acid into the lactone explains why the former is not a product of the reaction. However, we cannot exclude that the lactone **5**, at least in part, is formed from anisole and the anhydride without ring-opening.

A possible mechanism for the formation of the methyl ester **6** is presented in Scheme 3. This compound may result from ring-opening of the γ -lactone, in which one of the aromatic substituents has the methoxy group in an *ortho* position. A similar isomerisation of 4,4-di(*o*-

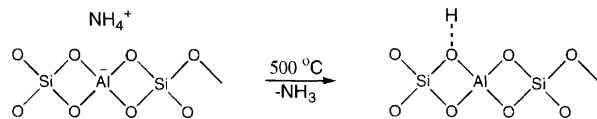


Fig. 1. Generation of acid sites in the zeolite.

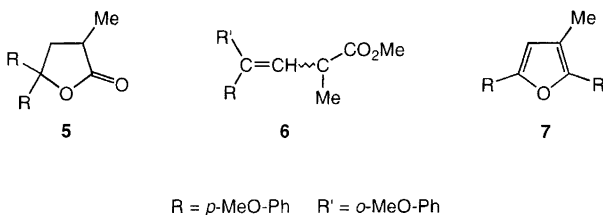
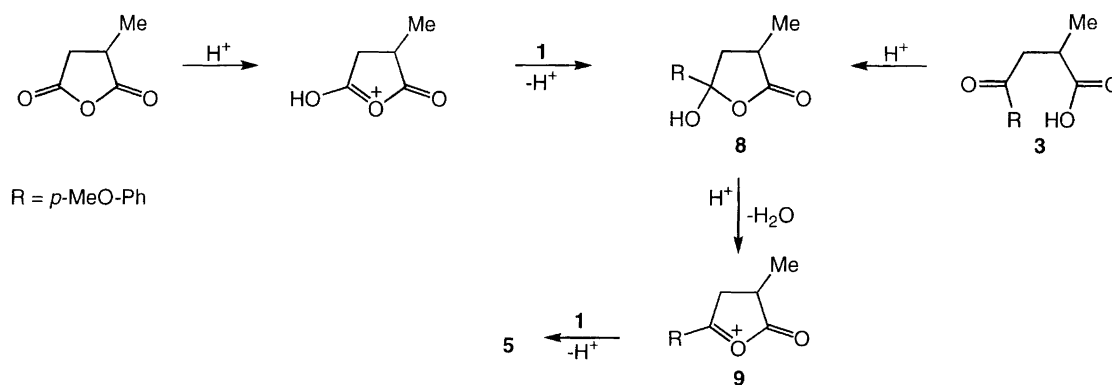


Fig. 2. The products obtained in the zeolite-catalysed reaction of anisole and methylsuccinic anhydride.



Scheme 2.

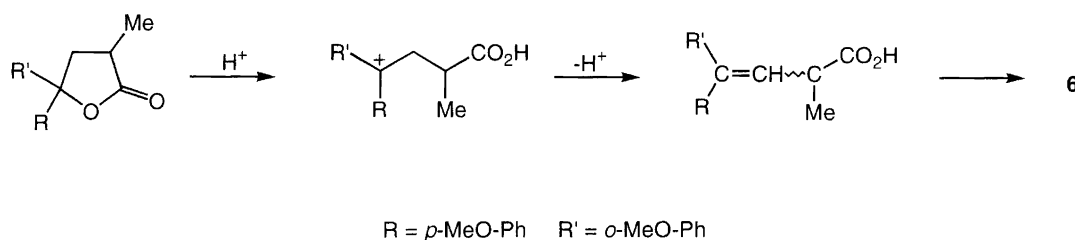
methoxyphenyl)-2-methylbutyrolactone in boiling HCl (conc.) has been reported.¹⁰ The *ortho* position of the methoxy group was deduced from the coupling pattern in the ¹H NMR spectrum and from the number of different carbon signals in the ¹³C NMR spectrum.

However, the configuration around the double bond was not determined. The origin of the methyl species was probably demethylation of anisole. The formation of phenols in the reaction between succinic anhydride and anisole has been reported.¹¹ The condensation of anisole and methylsuccinic anhydride has been reported to give 4,4-di(*p*-methoxyphenyl)butene-2-carboxylic acid in 13–14% yield, and the low yield of keto acids often obtained in these reactions has been attributed to this competing reaction.¹² Surprisingly, the butenoic acid derivative with both the methoxy groups in the *para* position was not observed in the present work. However, the formation of this product cannot be excluded; the separation by flash chromatography was complicated, and it was not possible to isolate all the different products.

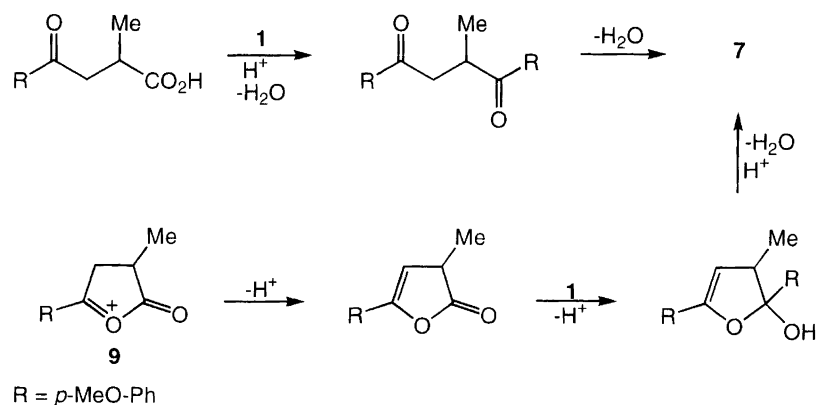
The formation of the 2,3,5-trisubstituted furan **7** may be explained by the two different routes outlined in Scheme 4. One possible reaction path is the dehydration of 1,2-di(4-methoxybenzoyl)-1-methylpropane. The diketone was not observed in this work, but it may have undergone dehydration immediately after its formation. The dehydration properties of zeolites are well known, and acid-catalysed dehydration of γ -diketones is a common method for the preparation of 2,5-disubstituted furans.¹³ Another possible mechanism for the formation of **7** is deprotonation of the cation **9** formed according

to Scheme 2, resulting in an unsaturated lactone. The furan may then be formed by addition of a second molecule of anisole followed by dehydration.

The location of the acid sites in the zeolite is important for the catalytic activity. They may be located both inside the zeolite channels and on the external surface of the crystallites. In shape-selective catalysis there is a combination of the molecular sieve effect and catalysis, and these reactions are therefore catalysed by acid sites inside the pore system. Bulky reactants may be hindered from diffusing into the pores and reaching the active sites, and products that are too bulky cannot leave the pore system. However, in shape-selective catalysis there is sometimes a contribution from catalysis on the external surface. This catalysis is non-shape-selective, since there will be no molecular sieving. It was of interest to establish whether the products **5**, **6** and **7** resulted from shape-selective catalysis, or if they were formed on the outer surface. Deactivation of the external Brønsted sites is possible by poisoning the catalyst with triphenylphosphine,¹⁴ which is too bulky to enter the pores, and therefore will not deactivate the internal acid sites. When deactivated HY was used in the reactions of anisole with either methylsuccinic anhydride or the keto acid **3**, no reaction was observed. Possible explanations for this observation could be (i) the reactions were catalysed by acid sites on the external surface, now deactivated by PPh₃, or (ii) PPh₃ had poisoned all the acid sites in the zeolite. Although we regarded alternative (ii) as less likely, it was tested by using the deactivated HY as a catalyst in a reaction in which the shape-selective properties of the non-deactivated catalyst were known. In earlier



Scheme 3.



Scheme 4.

work we showed that the zeolite-catalysed acylation of anisole by acetic anhydride resulted in a high yield of *para* product.³ When this reaction was catalysed with the deactivated HY, 4-methoxyacetophenone was obtained in a yield of 67%. Accordingly, the high catalytic activity was retained after deactivation, and only the acid sites on the external surface were deactivated by PPh₃. Hence, formation of the products **5**, **6** and **7** was a result of outer-surface catalysis.

Experimental

The NMR spectra were recorded in CDCl₃ at 300 MHz (¹H) and 75 MHz (¹³C). The mass spectra were recorded at 70 eV; the spectra are presented as *m/z* (% rel. int.). The IR spectra were recorded on a Perkin Elmer model 2000 FT-IR spectrometer.

GC-analysis. The samples were analysed by GLC [14% (cyanopropylphenyl)methylpolysiloxane capillary column] and FID. The samples were filtered through a syringe filter (SRP 15 from Sartorius) before analysis to avoid deposits of solid material on the capillary column. The conversion of methylsuccinic anhydride and the yield of 4-methoxyacetophenone were calculated from the GLC trace using hexadecane as an internal standard. The acid **3** had to be derivatised with BSTFA [bis(trimethylsilyl)trifluoroacetamide] after the following procedure: 250 μl of the reaction mixture were mixed with 250 μl of BSTFA, and the solution was heated at 60 °C for 30 min.

The zeolite used in the present work was commercial zeolite Y (CBV-712, Si/Al_{framework} = 15.9, Si/Al_{bulk} = 5.9) supplied by PQ. HY was obtained from NH₄Y by calcination at 500 °C for 7 h in an air flow. Further characteristics of this zeolite are given in an earlier publication.³

Anisole and nitromethane were dried by means of molecular sieves (4 Å). Acetic anhydride was used without further purification. Light petroleum b.p. 40–60 °C was used in the chromatographic separations.

3-(4-methoxybenzoyl)-2-methylpropionic acid (3**).**^{5–7} A solution of methylsuccinic anhydride (5.0 g, 0.04 mol) and anisole (4.74 g, 0.04 mol) in nitromethane (100 ml) was added dropwise to AlCl₃ (12.85 g, 0.096 mol) in nitromethane (100 ml) at 0 °C. The reaction was stirred at ambient temperature overnight before it was poured into a mixture of water and ice, acidified with 3 M HCl and extracted with diethyl ether. Evaporation of the ether gave the acids **3** and **4** in 91% yield in a ratio of 6:1, respectively. Recrystallisation of the crude product from glacial acetic acid gave 3.98 g (41%) of **3**. ¹H NMR (CDCl₃): δ 1.30 (CH₃, d, *J* 7.1 Hz), 2.95–3.45 (side chain, 3 H, m), 3.88 (OCH₃), 6.95 (ArH, 2 H, d, *J* 8.9 Hz), 7.95 (ArH, 2 H, d, *J* 9.0 Hz). ¹³C NMR (CDCl₃): δ 17.0 (CH₃), 34.7 and 41.2 (side chain), 55.4 (OCH₃), 113.6, 129.4, 130.2, 163.5 (ArC), 181.9 (COOH), 196.3 (CO).

Pretreatment of the zeolite. The calcined zeolite was weighed and rapidly transferred while hot to the reaction vessel. The system was subsequently evacuated at 130 °C overnight to eliminate any water adsorbed during the transfer.

Methylsuccinic anhydride as acylating agent. A solution of anisole (150 ml) and methylsuccinic anhydride (1.14 g, 10 mmol) containing hexadecane as an internal standard was added to the cooled zeolite (0.5 g). The suspension was stirred for 24 h at 150 °C before it was filtered and anisole evaporated off under oil-pump vacuum. The crude product was purified by flash chromatography on silica gel with gradient elution, starting with light petroleum–ethyl acetate (9:1) and finishing with light petroleum–ethyl acetate (1:1). Three products were isolated.

4-Hydroxy-4,4-bis(4-methoxyphenyl)-2-methylbutyric acid γ -lactone (5**).**⁸ Yield 0.80 g (25%). ¹H NMR (CDCl₃): δ 1.29 (CH₃, d, *J* 6.9 Hz), 2.38–3.18 (H-2 and 2 × H-3, 3 H, m), 3.79 (2 × OCH₃), 6.85 (ArH, 4 H, m), 7.30 (ArH, 4 H, m). ¹³C NMR (CDCl₃): δ 14.5 (CH₃),

35.2 (CH₂), 43.9 (CH), 55.1 (OCH₃), 87.0 (C-O), 113.6, 126.6, 134.7, 136.2, 158.8 (ArC), 178.7 (C=O). IR (KBr): 1774 cm⁻¹ (CO). MS (EI): 313 (14), 312 (68, M), 294 (89), 267 (100), 251 (34), 243 (49), 159 (34), 135 (74).

Methyl 4-(4-methoxyphenyl)-4-(2-methoxyphenyl)-2-methyl-3-butenolate (6). Yield 113 mg (3%). ¹H NMR (CDCl₃): δ 1.27 (CH₃, d, *J* 7.0 Hz), 3.32 (CHCH₃, m), 3.69, 3.80 and 3.85 (3 × OCH₃), 5.97 (CH=, d, *J* 10.2 Hz), 6.79–7.23 (ArH, m, 8 H). ¹³C NMR (CDCl₃): δ 18.7 (CH₃), 40.4 (C-2), 51.9 (OCOCH₃), 55.3 (ArOCH₃), 113.6, 125.9, 128.6 and 130.9 (ArC), 131.9 and 135.0 (ArC and C=CH), 142.1 (Ar₂C=C), 158.9 (ArC), 175.7 (C=O). IR (KBr): 1735 cm⁻¹ (CO). MS (EI): 327 (8), 326 (33, M), 267 (100), 251 (9), 237 (6), 159 (33), 135 (14).

2,5-(4-Methoxyphenyl)-3-methylfuran (7). Yield: 113 mg (4%). Found: *M*⁺, 294.1246. Calc. for C₁₉H₁₈O₃: *M*, 294.1256. ¹H NMR (CDCl₃): δ 2.30 (CH₃, s), 3.85 (2 × OCH₃), 6.46 (H-4,s), 6.88–7.02 (Ph, 4 H, m), 7.60–7.68 (Ph, 4 H, m). ¹³C NMR (CDCl₃): δ 12.0 (CH₃), 55.4 (OCH₃), 109.2 (C-4), 114.1 (Ph), 117.0 (C-3), 124.1, 124.9, 125.0, 126.6 (Ph), 147.7 (C-2), 151.2 (C-5), 158.4 and 158.9 (Ph). MS (EI): 295 (21), 294 (100, M), 280 (13), 279 (64), 236 (3), 208 (3), 147 (15), 135 (4), 77 (5).

3-(4-Methoxybenzoyl)-2-methylpropionic acid (3) as acylating agent. A solution of anisole (100 ml) and 3-(4-methoxybenzoyl)-2-methylpropionic acid (3) (1.0 g, 4.48 mmol) containing hexadecane as an internal standard was added to the cooled zeolite (0.25 g). The suspension was stirred for 5 h at 150 °C before it was filtered and anisole evaporated off under oil-pump vacuum. The crude product was purified by flash chromatography on silica gel with gradient elution, starting with light petroleum–ethyl acetate (9:1) and finishing with light petroleum–ethyl acetate (1:1). The product consisted of 1.14 g (82%) of the lactone 5, 28 mg (2%) of the ester 6 and 30 mg (2%) of the furan 7.

Poisoning of the zeolite with triphenylphosphine. Poisoning of the zeolite by triphenylphosphine was performed according to a literature procedure.¹⁴ After evacuation of the zeolite at 130 °C overnight the zeolite was cooled before a solution of PPh₃ in anisole was added (PPh₃/Al_{bulk} = 1). This suspension was stirred at ambient temperature for 45 min before a solution of the acylating

agent in anisole was added and the temperature raised to the desired level.

Acylation of anisole by acetic anhydride catalysed by HY deactivated with PPh₃. Calcined zeolite (0.51 g) was weighed out and evacuated at 130 °C overnight as described above. A solution of PPh₃ (0.3411 g, 1.3 mmol) in anisole (75 ml) was added to the cooled zeolite at room temperature, and the suspension was stirred for 45 min. Acetic anhydride (1.023 g, 10 mmol) in anisole (75 ml) was then added, and the reaction was stirred at 70 °C for 5 h. The yield of 4-methoxyacetophenone was 67% (GLC).

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