

Friedel–Crafts acylation of aromatics and heteroaromatics by beta zeolite

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Abstract

Friedel–Crafts acylation of aromatic compounds such as anisole, 2-methoxynaphthalene, veratrole, isobutylbenzene and aromatic heterocycle compounds such as pyrrole, furan, thiophene, benzothiophene with different acid anhydrides is carried out in the batch mode with different forms of beta zeolite. The micronized beta zeolite shows manifold activity over normal zeolite in acylation reactions of aromatics. © 2004 Elsevier B.V. All rights reserved.

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1. Introduction

Friedel–Crafts acylation of aromatic compounds and aromatic heterocycle compounds is an ubiquitous reaction in the production of aromatic ketones largely used as intermediates in the synthesis of pharmaceuticals, naproxen, dextromethorphan, ibuprofen and dyes, fragrances, and agrochemicals [1–6]. The acylated aromatics and aromatic heterocycle compounds are conventionally prepared by the acylation of corresponding aromatics with acid chlorides using Lewis acids such as AlCl_3 , BF_3 as reagents or protic acids [7–9]. However, these Lewis acids are consumed in more than stoichiometric amounts due to the formation of 1:1 molar adduct with aromatic ketones and the subsequent separation of the product by hydrolysis, which is cumbersome, generates a large amount of hazardous, corrosive, environmentally unfriendly waste approximately more than 4 mol of Cl^- per mole of the ketone produced. The major draw back in this process is that the Lewis acid is non-regenerable. Similarly, HF is used commercially more than stoichiometric amounts in the acy-

lation of isobutylbenzene to obtain 4-isobutylacetophenone, an intermediate for ibuprofen. The major impediment is the handling of extremely toxic and corrosive HF that requires utmost care and an expensive inconel reactor. In view of the current environmental restrictions, there is a long felt need and demand for the replacement of conventional Lewis acids and HF with easily recyclable and regenerable solid acid catalysts.

Zeolites, with their shape selective properties and good regenerability, have been found to be viable alternatives to liquid acids in numerous reactions in recent years. Acylation of aromatic compounds like anisole, veratrole, 2-methoxynaphthalene, isobutylbenzene was reported using different kinds of zeolites [10–18]. Sustained efforts in this direction culminated into the development of two of the commercial processes for the production of 4-methoxy acetophenone and 3,4-dimethoxy acetophenone by the acylation of anisole and veratrole, respectively. The first industrial application of a zeolite-promoted acylation for the production of an aromatic ketone was recently reported by researchers at Rhone-Poulenc [11]. Acylation of 2-MN was studied with various zeolites and clays [19] and found that the beta zeolite is found superior to others. Further, the acylation was studied

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with beta zeolite by several authors, but the conversions and selectivities towards 6-acyl-2-methoxynaphthalene, a desired regiomers is poor to moderate. The acylation of isobutylbenzene over beta zeolite has been reported by Davis and co-workers [12]. Acylation of heterocycle compounds was also studied with various zeolites and clays [20,21]. Holderich described a procedure for the vapor phase acylation of heterocycle compounds in the presence of zeolite catalyst [22]. Although the high selectivity towards the desired product 2-acyl heteroaromatic compound is achieved, the limitations are the low conversions and high-energy requirements for the vapor phase reactions.

Thus, the results described in earlier publications either fell short of expectations for commercial reality or needed improvement. We report in this article the acylation of aromatics and aromatic heterocycle compounds using acid anhydrides as acylating agents, beta zeolite and microcrystalline beta zeolite as catalysts dispensing the use of stoichiometric amounts of the corrosive, toxic aluminium chloride as Friedel–Crafts reagent.

2. Experimental

2.1. Materials

All chemicals were purchased from Aldrich and used as such. Acetic anhydride was dried and distilled before use.

2.2. Catalyst preparation

2.2.1. Beta zeolite

Tetraethylorthosilicate and aluminium nitrates of appropriate molar ratios were used to get desired ratio of Si/Al. Water was added to tetraethylorthosilicate and stirred for 30 min. To this solution, a solution of aluminium nitrate non-hydrate in tetraethylammonium hydroxide was added dropwise by a pressure-regulating funnel under stirring. After the addition, the solution was kept at 50 °C and later on cooked at 135 °C in an autoclave for 1 week for crystallization. Then the crystalline solid was filtered and air-dried. The resultant solid was calcined at 500 °C. This is denoted as (BZ)

2.2.2. Microcrystalline beta zeolite-I

Microcrystalline beta zeolite-I (BZ-I) used in this process was obtained with particle size 1–10 µm (95%) by mechanical disintegration of the beta zeolite obtained as described above or by adopting the following synthetic method.

2.2.3. Microcrystalline beta zeolite-II

Microcrystalline beta zeolite-II (BZ-II) was synthesized with the particle size of 10–50 µm (85%) by decreasing the ageing time to 48 h instead of 1 week during the synthesis of beta zeolite according to the procedure in Section 2.2.1.

2.2.4. Preparation of metal exchanged beta zeolite

Beta zeolite of 10 g was subjected to an ion-exchange procedure by stirring with 5 wt.% metal chloride solution at 80 °C for 6 h. The resultant zeolite was washed with deionised water until chloride ions disappeared, and dried at 120 °C. After that the metal exchanged zeolite was calcined at 500 °C for 6 h.

2.3. Characterization

The particle diameter of microcrystalline beta zeolite samples was analyzed by Malvern instrument. The acidity of the samples was established by the standard pyridine adsorption–desorption method. In order to compare the acidic properties of each beta zeolite samples, NH₃-TPD has been used. The surface area of the catalyst was calculated by the BET/BJH method with N₂ adsorption/desorption performed at 77 K in a Micromeritics ASAP 2000 instrument. The acidity data of beta zeolite samples is shown in Table 1.

2.4. Reaction procedures

The acylation reactions were carried out in a 50 ml round-bottomed flask under argon equipped with a magnetic stirrer under heating in an oil bath with acetic anhydride as an acylating agent. Prior to use, the catalyst was calcined in situ in air at 500 °C.

2.4.1. Acylation of anisole and veratrole

A mixture of anisole (50 mmol), acetic anhydride (10 mmol), catalyst (0.25 g) was stirred in a round-bottomed flask (50 ml) under argon at 80 °C. After completion of the reaction as indicated by GC (using nitrobenzene as internal standard), the reaction mixture was filtered and distilled to obtain the product.

2.4.2. Acylation of 2-methoxy naphthalene

A mixture of 2-methoxynaphthalene (10 mmol), acetic anhydride (20 mmol), catalyst (0.5 g) and 5 ml of nitrobenzene solvent were stirred in a round-bottomed flask (50 ml) under nitrogen atmosphere at 136 °C. After completion of the reaction as indicated by GC (using dodecane as internal standard), the reaction mixture was filtered and distilled to obtain the product.

2.4.3. Acylation of isobutylbenzene

A mixture of isobutylbenzene (40 mmol), acetic anhydride (10 mmol) and catalyst (0.5 g) were stirred in a round-bottomed flask (50 ml) under nitrogen atmosphere at 130 °C. After completion of the reaction as indicated by GC (using nitrobenzene as internal standard), the reaction mixture was filtered and distilled the reaction mixture to obtain the crude product.

Table 1
Physico-chemical properties of different crystalline sizes of beta zeolite

Catalyst	Surface area (m ² /g)	Particle size (μm)	Temperature (°C)	Acidity (μmol Py) ^a	
				1563–1510 cm ⁻¹	1469–1422 cm ⁻¹
BZ	350	250–350	100	9.38	11.53
			200	5.55	4.42
			300	5.55	5.36
			400	5.50	5.33
BZ-I	590	1–10 (95%)	100	14.82	19.00
			200	7.47	7.23
			300	6.88	7.02
			400	7.16	7.94
BZ-II	620	5–50 (85%)	100	16.5	21.87
			200	8.4	8.14
			300	7.92	8.31
			400	8.00	9.75
Ce-BZ-II	–	–	100	9.844	24.05
			200	5.290	10.56
			300	5.88	10.48
			400	5.89	10.67

^a Determined from the infra red spectra of adsorbed pyridine after evacuation at 100, 200, 300, 400 °C.

2.4.4. Acylation of aromatic heterocycle compounds

A mixture of heterocycle compound (10 mmol), acetic anhydride (20 mmol), catalyst (0.5 g) and 10 ml of 1,2-dichloroethane were stirred in a round-bottomed flask (50 ml) under nitrogen atmosphere at 80 °C. After completion of the reaction as indicated by GC (using nitrobenzene as internal standard), the reaction mixture was filtered and distilled to obtain the product.

Aliquots of the reaction mixture were sampled and analyzed by gas chromatography equipped with a FID detector on a 30 m HP-5 column. The products were identified by comparing their retention time with commercial compounds or by GC–MS analysis.

3. Results

3.1. Acylation of anisole and veratrole with different crystallites of beta zeolite

Acylation of anisole and veratrole are conducted with different crystalline sizes of beta zeolite catalyst. Anisole and veratrole gave *p*-isomers exclusively with acid anhydrides (C2–C8) in the presence of all different crystalline sizes of beta zeolite. Table 2 shows the effect of crystal size in the acylation of anisole. The conversion of acetic anhydride is 98% at 6 h with BZ and 99% at 2.0 h with BZ-II. The selectivity of 4-methoxyacetophenone in both cases is greater than 99%. The acylation of anisole was carried out with different acid anhydrides using microcrystalline beta zeolite (BZ-II). In all cases the selectivity towards 4-acetylated product is >99% (Table 3).

Various solvents were tried for the acylation of anisole and veratrole. However, there is no significant effect of solvent in the acylation of anisole and veratrole. The best result was ob-

Table 2
Acylation of anisole with acetic anhydride by beta zeolite catalysts of different crystalline sizes

Catalyst	Isolated yield ^a (%)	STY ^b
Beta zeolite	45 ^c , 98 ^d	0.9 ^d
Microcrystalline beta zeolite-I (BZ-I)	78 ^c , 99 ^e	2.3 ^e
Microcrystalline beta zeolite-II (BZ-II)	99 ^c	2.9 ^c

^a Based on acetic anhydride.

^b STY: kg product/kg cat./h.

^c After 2 h.

^d After 6 h.

^e After 2.5 h.

tained when aromatic ethers were used as self-solvents. The acylation of anisole was conducted with different ratios of anisole and acetic anhydride (Fig. 1). When equimolar concentrations of anisole and anhydride are used, the conversion of acetic anhydride to 4-methoxyacetophenone decreases to 75%. The deactivation of the catalyst might be due to the strongly adsorbed acetic acid and the product on the acid sites. It is known that acetic acid is generally strongly absorbed on the acidic sites of zeolite [10]. In order to avoid the adsorption of organic products on the catalyst, it is necessary to conduct

Table 3
Acylation of anisole and veratrole with various acid anhydrides by microcrystalline beta zeolite-II

Acid anhydride	Time (h)	Temperature (°C)	Isolated yield ^a (%)
Acetic ^b	2.5	110	95
Propionic	3	90	97
Butyric	3	130	98
Valeric	3	130	89
Hexanoic	6	130	75
Benzoic	6	130	70

^a Based on acid anhydride.

^b Veratrole and remaining examples are for anisole.

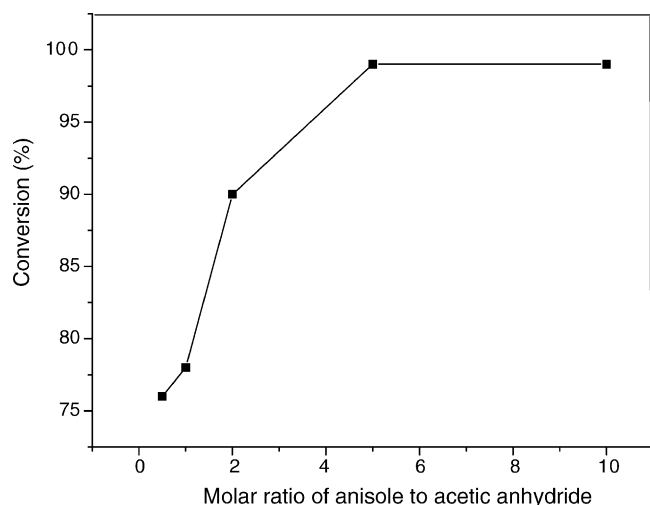


Fig. 1. Conversion vs. molar ratios of anisole/anhydride for acylation of anisole at 80 °C with beta zeolite.

the reaction in a solvent medium or by taking excess of anisole as self-solvent. In further experiments, where anisole is taken as a self-solvent (5:1), the anhydride conversion is quantitative. The increasing conversion of acetic anhydride to 4-methoxyacetophenone is attributed to the easy diffusion of product through the zeolite pores with sufficient washing of the excess anisole. Microcrystalline beta zeolite catalysts showed higher activity in the acylation reaction due to their higher acidity than the beta zeolite (Fig. 2). A comparative data is provided to illustrate the activity versus particle size (Tables 1 and 2). The surface area of these particles is also increased due to reduction of the particle size of zeolites as evidenced from the BET surface area given in Table 1.

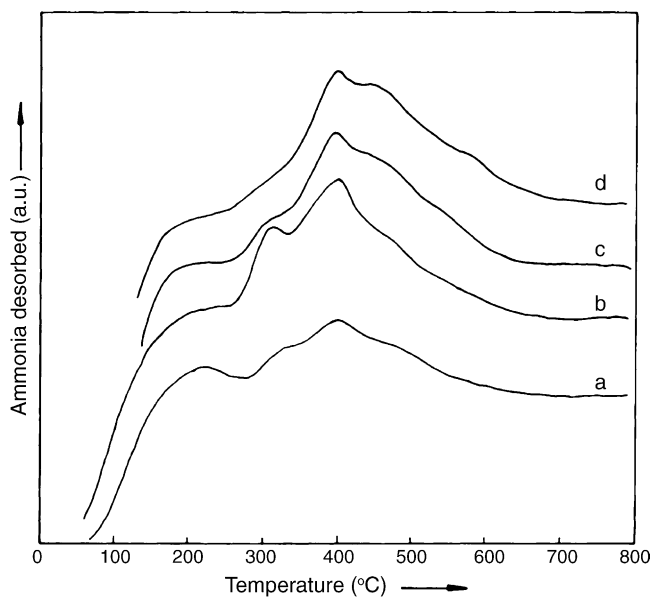


Fig. 2. TPD patterns of beta zeolite samples: (a) beta zeolite (BZ), (b) microcrystalline beta zeolite-I (BZ-I), (c) microcrystalline beta zeolite-II (BZ-II) and (d) Ce^{3+} -microcrystalline beta zeolite-II (Ce^{3+} -BZ-II).

Table 4
Acylation of 2-methoxynaphthalene with different crystalline sizes of beta zeolite

Catalyst	Conversion (%) ^{a, b}	Product distribution	
		1-Ac-2Mn	6-Ac-2Mn
BZ	68, 82 ^c	30, 18 ^c	70, 82 ^c
BZ	75 ^d	8	92
BZ	75 ^e	24	76
BZ-I	81	35	65
BZ-I	86 ^d	25	75
BZ-II	82	35	65
Ce^{3+} -BZ-II	88	22	78

^a Based on 2-methoxynaphthalene by GC.

^b Based on ¹H NMR and GC.

^c After 12 h.

^d Propionic anhydride.

^e Calcined at 750 °C.

3.2. Acylation of 2-methoxynaphthalene by different crystalline sizes of beta zeolite

The acylation of 2-methoxynaphthalene with acetic anhydride in the presence of different crystalline sizes of beta zeolite catalysts is presented in Table 4. The other processes reported earlier with beta zeolite offered either lower selectivity towards 2-acyl-6-naphthyl ether, a desired intermediate at higher conversions or vice versa. The sterically hindered bulky product, 1-acyl-2-methoxynaphthalene was preferentially formed on the outer surface of beta zeolite. Although the micronized beta zeolite offered higher conversions in shorter times, the selectivities towards 6-acyl-2-methoxynaphthalenes are only moderate. These lower selectivities, when compared to that with beta zeolite, are due to the increased external surface area that invariably promotes the formation of bulky 1-acyl-2-methoxynaphthalenes. Microcrystalline beta zeolite enhances the activity for acylation of 2-methoxynaphthalene due to the increasing number of acidic sites and broken edges of surface pores, which are more accessible to the reactants for easier formation of products for higher conversion. However, micronized Ce^{3+} beta zeolite afforded good yields and selectivity towards the desired isomer. Introduction of Ce^{3+} increases Lewis acidity of beta zeolite to afford higher selectivity towards 6-acyl-2-methoxynaphthalene, because it promotes the reversible reaction of the formed 1-acyl-2-methoxynaphthalene to 6-acyl-2-methoxynaphthalene.

3.3. Catalyst activity

The yield of the acylated product increases considerably with the calcined (750 °C) beta zeolite and microcrystalline beta zeolite (Table 4). During the synthesis of beta zeolite, dealumination usually occurs even under very mild condition [23], the increased Bronsted sites gained during formation of H^+ are likely to offset by dealumination process as described earlier. Moreover, the framework of aluminium in beta zeolite is very sensitive towards calcination due to the

Table 5
Acylation of isobutylbenzene with acetic anhydride by different crystalline sizes of beta zeolite

Catalyst	Time (h)	Yield (%)
BZ	8	6
BZ-I	6	20
BZ-II	3	25
Fe ³⁺ -BZ	8	12
La ³⁺ -BZ	6	15
Ce ³⁺ -BZ-II	3	30 ^a
Fe ³⁺ -BZ-II	4	29
Zn ²⁺ -BZ-II	4	28
La ³⁺ -BZ-II	4	28

^a Isolated yield: 0.52 g.

loss of some aluminium from the framework [24]. It can be concluded that increasing yield and selectivity towards bulky product which formed on external surface of the beta zeolite calcined at 750 °C shows that even after dealumination active sites are still present. Therefore, beta zeolite as synthesized is a better option, in particular, for the synthesis of 6-acyl naphthyl ethers, since it does not encumber post-treatment. Microcrystalline beta zeolite catalysts show higher activity in the acylation reaction due to their higher acidity than the beta zeolite. Temperature programmed desorption of microcrystalline zeolites (I and II) and beta zeolite synthesized are shown in Fig. 2.

3.4. Acylation of isobutylbenzene

The acylation of isobutylbenzene was carried out with different crystalline sizes of beta zeolite. Table 5 shows that the conversion of isobutylbenzene was higher with BZ-II catalyst than BZ. In this case, a high external surface has no effect on the reaction selectivity, as the acylation does not require the shape selective properties of zeolite. The advantage of the present reaction is the use of microcrystalline (BZ-II) and metal exchanged microcrystalline beta zeolite (Ce³⁺-BZ-II) for the acylation of isobutylbenzene to 4-isobutylacetophenone gives better yields than beta zeolite (BZ). Decrease in particle size of beta zeolite, enhances the density of acidic sites and surface area

of the zeolites, which are essential factors to increase the activity of acylation reaction. The higher density of acidic sites eventually increases number of acyl cations generated in the reaction in the electrophilic substitution of the Friedel–Crafts acylation and thus enhances activity of the reaction. The Bronsted acidic site generates an acyl carbonium ion, which in turn affects the electrophilic substitution with the isobutylbenzene to provide the 4-isobutylacetophenone.

3.5. Acylation of aromatic heterocycle compounds over beta zeolite

Acylation of heterocyclic compounds such as pyrrole, furan and thiophene are conducted with different crystalline sizes of beta zeolite catalyst (Table 6). 3-Acetyl and 2,5-diacetyl heteroaromatic compounds are the major byproducts in these reactions.

4. Conclusions

The decrease in particle size of beta zeolite enhances the density of acidic sites and surface area of zeolites, which are essential factors to increase the activity of the acylation reaction. As a result of this, the acylation of aromatics and heteroaromatics is accomplished successfully in reasonable yields for the first time. Thus the microcrystalline beta zeolite enhances the activity in the acylation of aromatics and heteroaromatics due to the increasing number of acidic sites and the broken edges of surface pores which are more accessible to the reactants for easier formation of products for higher conversion. The higher density of acidic sites eventually increases the number of acyl cations generated in the electrophilic substitution of the Friedel–Craft acylation of aromatics and aromatic heterocyclic compounds and thus enhances the activity of the reaction. The process described here has the assets of total simplicity, easier filtration of the catalyst, reusability for a number of cycles, waste minimization and possibility of regeneration. Thus, the present studies indicate that the zeolite catalyzed reactions having distinct and

Table 6
Acylation of aromatic heterocycle compounds with acetic anhydride by different crystalline sizes of beta zeolite

Heteroaromatic	Catalyst	Temperature (°C)	Time (h)	Conversion. (%) ^a	2-Acyl heteroaromatic (selectivity) ^b (%)
Thiophene	BZ	25	12	20	100
Thiophene	BZ	80	8	70	92
Thiophene	BZ-I	80	3	91	70
Thiophene	BZ-II	80	6	35	67
Pyrrole	BZ	80	6	40	100
Pyrrole	BZ-I	80	2.5	73	58
Pyrrole	BZ-II	80	2.0	78	64
Furan	BZ	40	8	40	88
Furan	BZ-II	25	12	26	100
Benzofuran	BZ-II	130	6	20	100
Benzothiophene	BZ-II	130	6	30	100

^a Based on heterocycle compound.

^b Based on ¹H NMR and GC.

characteristic features are more advantageous over the AlCl_3 promoted reaction.

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