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Short Communication

Microwave-assisted Friedel–Crafts acylation of indole with acetic anhydride over tungstophosphoric acid modified Hβ zeolite

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ABSTRACT

Friedel–Crafts acylation of indole with acetic anhydride has been carried out over zeolites under microwave and conventional heating, respectively. A tungstophosphoric acid modified Hβ (PW-Hβ) zeolite showed better catalytic performance than parent Hβ zeolite due to its higher amount of strongly acidic sites and lower amount of Lewis acid sites, confirmed from NH_3 temperature-programmed desorption (NH_3-TPD) and Fourier Transform Infrared Spectrometer after adsorption of pyridine (Py-IR). Particularly, microwave radiation was found to make this transformation not only more efficient but also selective to 3-acetylindole compared with conventional heating. Furthermore, PW-Hβ has shown good stability in this reaction.

1. Introduction

The synthesis of indoles, especially 3-substituted indoles, has attracted much interest, not only because they are important intermediates and chiral auxiliaries in organic reactions, but also because they have been found wide applications in many biological areas including antibacterial, anticancer, and antibiotic activities [1]. Though a wide variety of 3-substituted indoles has been prepared by several well-known synthetic methods such as Friedel–Crafts acylation, Vilsmeier–Haack reaction, and Grignard reaction [2], these methods are restricted by the use of expensive or toxic reactants and catalysts. There has been great demand to develop a green method due to environmental and economical concerns.

Solid acid catalysts, such as zeolites, clays, and ionic resins, are important in green processes [3,4]. Friedel–Crafts acylations of aromatic compounds such as anisole, 2-methoxynaphthalene, and isobutylbenzene have been reported over different kinds of zeolites [5,6]. For example, Derouane et al. have reported an efficient protocol for the synthesis of *p*-methoxyacetophenone from the acetylation of anisole by acetic anhydride over Hβ zeolite [6]. Furthermore, acid modifications have been proven to be important for improving the activity of zeolites [7,8]. On the other hand, microwave-assisted processes have become popular in recent years due to the dramatic reduction in reaction time and higher product yields for a wide range of synthetic transformations, compared with the traditional heating method [9]. However, to the best of our knowledge, few results are available on the Friedel–Crafts acylation under microwave and over zeolites.

Herein, we report our recent studies on the synthesis of 3-acetylindole via the Friedel–Crafts acylation of indole with acetic anhydride over zeolites under microwave and conventional heating, respectively. A tungstophosphoric acid modified Hβ (PW-Hβ) zeolite was found to have the best catalytic performance under microwave in this reaction. The activities of the modified and parent Hβ zeolites were investigated and were found to correlate well with their structures using a range of characterizations.

2. Experimental

2.1. Catalyst preparation

Tungstophosphoric acid modified Hβ zeolite was prepared by impregnating 4.0 g of the parent Hβ zeolite (Tianjin Chemist Catalyst Co., Ltd.) into 40 mL of an aqueous solution of 1.0 mol/L tungstophosphoric acid at 80 °C for 1 h. After that, the samples were filtered, washed with deionized water, dried at 120 °C and then calcined at 500 °C for 4 h. The prepared catalyst was labeled as PW-Hβ. Moreover, oxalic acid, tartaric acid, and hydrochloric acid modified Hβ zeolites were prepared with the same method and labeled as OA-Hβ, TA-Hβ, HCl-Hβ, respectively.

2.2. Catalyst characterization

X-ray diffraction (XRD) analysis was carried out on a Bruker D8 advance diffractometer using Cu Kα radiation. Bulk compositions were

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determined by inductively coupled plasma (ICP) on a Thermo VISTA-MPX spectrometer. BET surface areas and total pore volume of the catalysts were identified using a Micromeritics Tristar II 3020 surface area and pore analyzer. NH_3 temperature-programmed desorption (NH_3-TPD) experiments were performed on a TP-5000 instrument with a thermal conductivity detector. Fourier Transform Infrared Spectrometer after adsorption of pyridine (Py-IR) was recorded using a Bruker EQUINOX55 spectrometer coupled to a conventional high vacuum system.

2.3. Catalyst activity test

Friedel–Crafts acylations of indole were carried out by two methods. In a typical run of conventional heating, 2.5 mmol indole, 5 mmol acetic anhydride, and 0.05 g zeolite were charged to a 25 mL round flask and reacted at 120 °C for 3 h with stirring. The microwave-assisted reactions were performed on a CEM Discover S-class. In a typical run, 2.5 mmol indole, 5 mmol acetic anhydride, and 0.05 g zeolite were charged to a 10 mL microwave vessel equipped with a standard cap. After the vessel was sealed, the sample was irradiated at 120 °C for 8 min, which was plotted in Synergy software applying the power of 150 W or 200 W. Reaction mixtures were analyzed by a gas chromatography using a 30 m SE-54 capillary column. The product structures were confirmed using GC-MS (Agilent 5975C) and ^{1}H NMR (Bruker Avance III 600 MHz).

3. Results and discussion

3.1. Catalyst selection

Friedel–Crafts acylation of indole leads to 1,3-diacylated material as the major product, due to the rapid *N*-acylation of the 3-acylated intermediate, so the selection of a suitable catalyst is crucial to the highly efficient monoacylation of indole [10]. Therefore, we first chose several different kinds of parent zeolites to investigate their catalytic activities in this reaction and the results are listed in Table 1. Among the zeolites studied, Hβ zeolite was found to show the best catalytic performance. Noticeably, the reaction rate increased significantly when the reaction was carried out in the presence of microwave radiation, compared with conventional heating. With the combination of microwave radiation and Hβ zeolite, the conversion of indole can achieve 77.8% and the selectivity to 3-acetylindole is 70.7%, but still below our expectation.

Considering the benefits of acid modification, a series of acid modified Hβ zeolites were prepared and investigated under the same reaction conditions (Table 2). As can be seen, some acid modified zeolites, especially a PW-Hβ zeolite, exhibited higher activities than parent Hβ zeolite. Particularly, the conversion of indole and the selectivity to 3-acetylindole are 100% and 82.9% over the PW-Hβ zeolite under microwave radiation at 200 W. Combined with the mechanism of microwave-assisted organic reactions [11], we speculated that microwave radiation favors generation of 3-acetylindole by reducing side reactions as a consequence of shortening the reaction time. In comparison, the conversion of indole to and the selectivity for 3-acetylindole are only 76.2% and 73.4% over pure tungstophosphoric acid under microwave radiation. So there must be some synergistic effect between tungstophosphoric acid and Hβ zeolite to cause the PW-Hβ zeolite to have the highest activity in this reaction. Thus, PW-Hβ zeolite was chosen as the appropriate catalyst for further investigation and microwave radiation was selected as the best heating method for this reaction.

Table 1
Effect of different zeolites and heating methods on Friedel–Crafts acylation of indole.

Catalyst	Heating method	Conversion (%)	Selectivity (%)		
			1-acetylindole	3-acetylindole	1,3-diacetylindole
MCM-41	A	30.7	15.1	64.0	13.4
	B	35.5	26.4	42.4	15.1
ZSM-5(38)	A	7.7	13.9	44.2	16.4
	B	12.3	27.8	30.3	5.0
ZSM-5(50)	A	17.8	13.1	55.9	17.9
	B	17.1	43.2	32.7	11.0
HY	A	36.9	14.7	66.6	12.2
	B	43.8	22.9	46.7	17.9
Hβ	A	77.8	9.3	70.7	14.0
	B	76.5	6.1	54.5	13.7

Reaction conditions: indole (2.5 mmol), acetic anhydride (5 mmol), catalyst (0.05 g), 120 °C.

[A] Microwave heating 8 min at 150 W.

[B] Conventional heating 3 h.

Moreover, a service life test was performed under the optimum reaction conditions. It was found that the regenerated catalyst showed stable catalytic activity in five subsequent cycles. The conversion of indole remained above 95.0% and the selectivity to 3-acetylindole was up to 78.0% during the whole test. Thus, PW-Hβ zeolite was proven to have good stability in this reaction.

A possible mechanism for indole acylation is proposed based on the GC-MS results and previous literature [12] (Scheme 1). 3-Acetylindole is the initial product as a result of preferential acetylation of the indole nucleus. Further *N*-acetylation of 3-acetylindole will yield 1,3-diacetylindole as the major by-product. On the other hand, if *N*-acylation occurs first, the resultant *N*-acetylindole produced is resistant to further *C*-acylation giving *N*-acetylindole as another possible by-product. Furthermore, considering the polydentate strong nucleophilic nature of indole, competing side reactions such as Mannich-type indole oligomerizations, acylation of oligomerized products, and the less common formation of diindolylmethanes or the oxidation products are also possible competing pathways that could reduce the yield of the desired 3-acetylindole. Although it is documented that the 3-position of the indole nucleus is most susceptible to electrophilic attack, the selectivity for 3-acetylindole was still low under the conventional heating method. In contrast, microwave radiation is shown to favor 3-acetylation of the indole nucleus, reducing formation of 1,3-diacetylindole both over parent and acid modified zeolites. Exactly why this should be so is not absolutely clear to us but we suggest that the increased rate of reaction under microwave heating conditions simply reduces the amount of side reactions occurring, as also reported by Kappe et al. [13].

3.2. Catalyst characterization

XRD patterns of Hβ and PW-Hβ zeolites are shown in Fig. 1. The characteristic diffraction peaks of PW-Hβ zeolite were at about 7.5° and 22.5°, just like parent Hβ zeolite, indicating that no obvious structural changes occurred under this acid treatment. Moreover, a characteristic diffraction peak of WO_3 was also detected at about 25° in the curve of PW-Hβ

Table 2
Effect of different acid modified zeolites and heating methods on Friedel–Crafts acylation of indole.

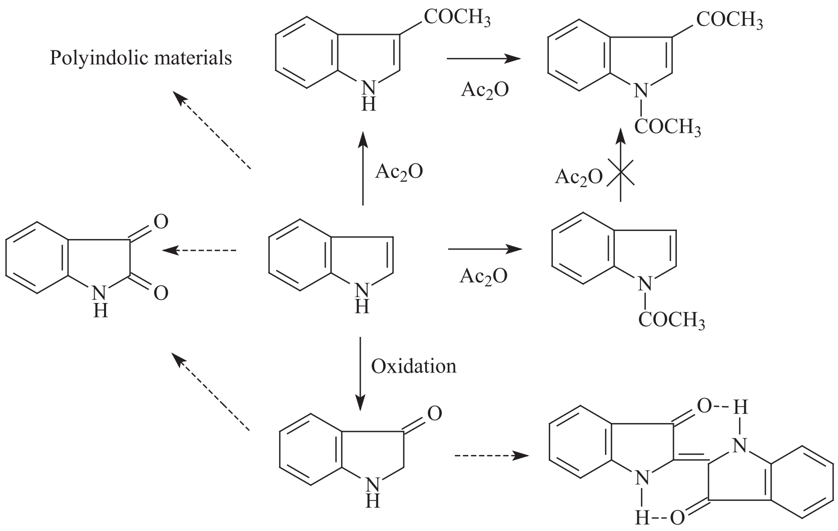
Catalyst	Heating method	Conversion (%)	Selectivity (%)		
			1-acetylindole	3-acetylindole	1,3-diacetylindole
HCl-Hβ	A	99.8	9.6	67.9	15.7
	B	99.1	6.8	59.4	23.9
OA-Hβ	A	97.7	7.7	76.7	10.0
	B	93.6	9.0	65.7	17.0
TA-Hβ	A	47.0	9.9	70.0	1.4
	B	98.6	12.6	68.2	8.4
PW-Hβ	A	100	7.8	71.7	17.4
	B	100	35.4	28.7	27.0
	C	100	9.9	82.9	0.9
PW	A	76.2	7.6	73.4	13.9
	B	93.8	33.8	25.6	16.5

Reaction conditions: indole (2.5 mmol), acetic anhydride (5 mmol), catalyst (0.05 g), 120 °C.

[A] Microwave heating 8 min at 150 W.

[B] Conventional heating 3 h.

[C] Microwave heating 8 min at 200 W.



Scheme 1. Proposed side reactions competing with 3-acylation of indole.

zeolite, implying that tungstophosphoric acid has decomposed to WO_3 during the calcination process [14] and WO_3 should play an important role in this reaction.

The bulk Si/Al molar ratios of Hβ and PW-Hβ zeolites were calculated from ICP results and are listed in Table 3. As can be seen, the Si/Al molar ratio increased from 12.06 to 26.50 after the tungstophosphoric acid modification and thus dealumination of the zeolite occurred during this process, and in turn, offered more active centers in the modified catalyst. Furthermore, it was also found that BET surface area of the zeolite increased from 381 m^2/g to 440 m^2/g, and the pore volume increased from 0.25 cm^3/g to 0.28 cm^3/g after exposure to tungstophosphoric acid (Table 3), which can be attributed to dealumination during the modification process. Thus, the better catalytic performance of PW-Hβ zeolite should be ascribed to the dealumination of Hβ zeolite caused by tungstophosphoric acid modification.

NH_3-TPD profiles of Hβ and PW-Hβ zeolites are presented in Fig. 2. There is only one large peak in the range of 150–400 °C in the NH_3 desorption profile of the parent Hβ zeolite, which could be assigned to weakly acidic sites. In contrast, there are two peaks in the NH_3 desorption profile of the PW-Hβ zeolite. The peak in the range of 150–400 °C is assigned to the weakly acidic sites and the peak in the range of 400–600 °C to the strongly acidic sites, in accordance with previous reports in the literatures [8,15]. It was obvious that the amount of weakly acidic sites decreased notably, while the amount of strongly acidic sites increased markedly after tungstophosphoric acid modification. Furthermore, the total amounts of desorbed NH_3 decreased after this acid modification. Thus, it is suggested that the lower number of weakly acidic sites and higher number of strongly acidic sites are responsible for the effect observed.

Py-IR was carried out to study the effect of tungstophosphoric acid modification on the Lewis and Brønsted acid properties of the Hβ zeolite. The spectra of Hβ and PW-Hβ zeolites are shown in Fig. 3. It is clear that the amount of Lewis acid sites decreased markedly; whereas the amount of Brønsted acid sites increased slightly after the tungstophosphoric acid modification, indicating that the tungstophosphoric acid modification causes different variation on the acid sites. Thus, combined with the reaction data (Table 2) and NH_3-TPD results, we suggested that a catalyst having lower amount of Lewis acid sites and higher amount of Brønsted acid sites is effective for this transformation, as also reported by Selvin et al. [16].

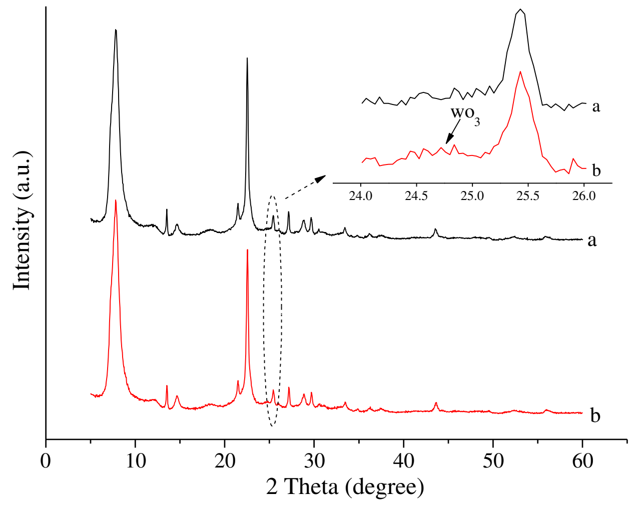


Fig. 1. XRD patterns of Hβ (a) and PW-Hβ (b) zeolites.

4. Conclusions

In conclusion, a simple, efficient and eco-friendly protocol for the synthesis of 3-acetylindole has been reported in this paper. A PW-Hβ zeolite was found to have the best activity and selectivity due to the synergistic effect between tungstophosphoric acid and Hβ zeolite. Particularly, the reaction rate of this microwave-assisted method is 50 to 75 times faster than that of the conventional heating method using $AlCl_3$ as a catalyst [17]. Thus, due to its good activity and stability, this green process involving a PW-Hβ zeolite is potentially applicable to large-scale reactions for the selective synthesis of 3-acetylindole.

Table 3
Morphological properties of zeolites.

Catalyst	Bulk Si/Al[a]	BET surface area (m^2/g)	Pore volume (cm^3/g)	Pore size (nm)
Hβ	12.06	381	0.25	26.3
PW-Hβ	26.50	440	0.28	25.9

[a] Calculated from the ICP results.

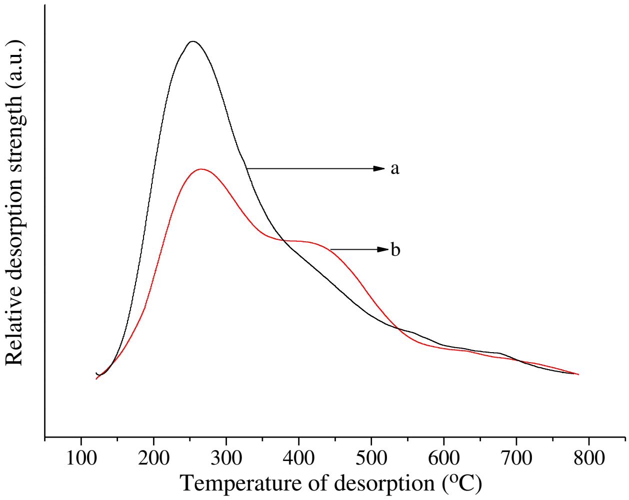


Fig. 2. NH_3-TPD profiles of Hβ (a) and PW-Hβ (b) zeolites.

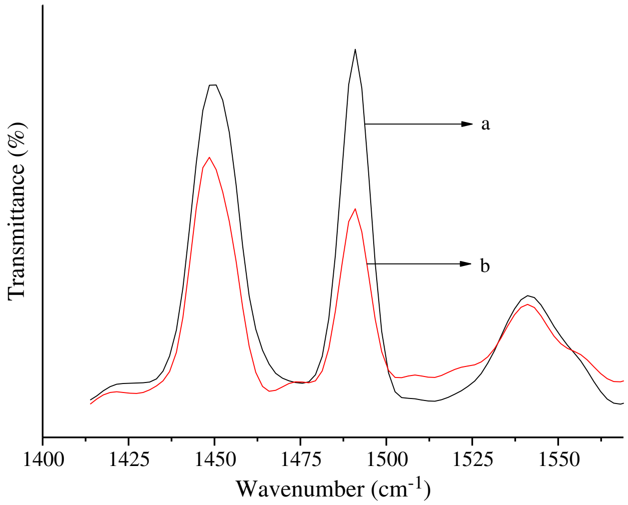


Fig. 3. Py-IR spectra of Hβ (a) and PW-Hβ (b) zeolites.

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