Acetylation of 2-Methoxynaphtalene with Acetic anhidryde over Zr^{4+}-Zeolite beta

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ABSTRACT

Regioselective acetylation of 2-methoxy naphthalene (2-MN) to 2-acetyl-6-methoxy naphthalene (2,6-ACMN) is the important step in the synthesis of pharmaceutical compounds such as (*S*)-naproxen. The liquid phase acetylation of 2-MN with acetic anhydride over Zr^{4+}-zeolite beta catalyst was investigated under controlled reaction conditions. Catalyst was prepared by ion exchange and impregnation method. Zr^{4+}-zeolite beta(ie) was obtained by ion exchange that done with 0,5 M $ZrCl_4$ then calcined at 550 °C for 3 h and Zr^{4+}-zeolite beta(ip) was obtained by impregnation method. Catalytic activity of catalysts was affected by preparing method, temperature, and reaction solvent. Catalyst that prepared by impregnation showed inactive on acetylation of 2-MN. 1-Acetyl-2-methoxynaphtalene (1,2-ACMN), 1-acetyl-7-methoxy-naphtalene (1,7-ACMN), and 2-acetyl-6-methoxy naphthalene (2,6-ACMN) were identified as the products of 2-MN acetylation over Zr^{4+}-zeolite beta(ie) without solvent. Activity and selectivity of Zr^{4+}-zeolite beta(ie) was increased in dichloromethane solvent at 140 °C for 36 h, 1,8-ACMN was not identified and ratio of 1,2-ACMN to 2,6-ACMN was 1,6:1

Key words: Acetylation; 2-Acetyl-6-methoxynaphthalene;
Zeolite beta; Regioselectivity; Solvent effect.

INTRODUCTION

Acetylation reaction is mostly done in the chemical industry to synthesize a variety of organic compounds. In many cases the acetylation reaction is not easy to obtain the desired product if there is more than one group in the starting material which can undergo the same reaction. To produce the desired product required special conditions that minimize byproducts. One of the factors that can determine the selectivity of the reaction is the catalyst. Drug class nonsteroidal anti-inflammatory

(NSAID) has analgesic effects, antipyretic and anti-inflammatory. Drugs of this class is very effective to reduce the symptomatic pain. From a variety of NSAIDs, each has advantages and disadvantages which looks at the effects of therapeutic and side effects. (S)-Naproxen, or (+)-2-(6-methoxynaphtyl)-propionic acid, is a nonsteroidal anti-inflammatory drug that was introduced under the trade name Synex in 1976. In industry, these compounds were synthesized in four stages, starting with the Friedel-Crafts acylation of 2-methoxyinaphtalene for 2-acetyl-6 methoxyinaphtalene (2,6-ACMN), which

is then converted to acid by Willgerodt reaction. Methylation produces a racemic mixture of an acid *(R,S)* which can be solved efficiently with sinkonidin, to obtain (S)-naproxen (Harrington and Lodewijk , 1997). This process has several interesting problems. First, Friedel-Crafts acylation is not regiospesifik, and in addition not only 2,6-ACMN formed but also 1,2-ACMN isomer obtaioned, which must be separated by crystallization. Second, a significant amount of aluminum hydroxide and hydrochloric acid waste. Third, a number of undesirable reagents used, such as nitrobenzene as solvent acylation, ammonium sulfide for Willgerodt reaction, sodium hydride and methyl iodide. Furthermore, using of $AlCl_3$ in stoichiometric amounts. These problems were combined with the toxicity and trouble some job work procedure, not in accordance with the ongoing process technology (Hoelderich, 1993) . Therefore, studies with alternative procedures which continue to be made more environmentally friendly. Friedel-Crafts acylation reactions are traditionally carried out with reagent $AlCl_3$/chloride acid, alternative procedure that developed is the use of heterogeneous catalysts with acid anhydride. Some examples of heterogeneous catalysts for the synthesis of fine chemicals and intermediates are functionalised polymers such as zeolites or Amberlist A15 or Nafion (Heinichen and Hoelderich, 1999; Heidekum, Harmer, and Hoelderich, 1998; Heidekum, Harmer, and Hoelderich, 1999). Preparation of Zr^{4+}-zeolite beta through ion exchange showed that ion exchange increases the surface area, pore volume but lower pore spokes compared the same parameters on the zeolite beta before treatment. Increase in the concentration of Zr^{4+} ion exchange in general increase the surface area and pore volume solids , but less pore jejeri show a clear trend . In general, ion exchange porosity results better than impregnation (Cahyono, 2011). Pore size and acidity properties of the resulting catalyst will have a good selectivity for the acetylation of 2-methoxy naphthalene.

The acetylation of 2-MN has been investigated over MCM-41, H-Y, ZSM-12 and BEA, and ZSM-5 and mordenite (Andy *et al.* 2000), The products are usually obtained, 1,2-ACMN and 2,6-ACMN. Schuster and Holderich (2008) showed that

in the aceylation reaction the Fe^{3+}- ion-exchanged zeolite beta to a conversion of acetic anhydride of 97%. The selectivity to the desired 2,6-ACMN was 37.4% after 24 h reaction time. A slightly higher selectivity to 2-acyl-6-methoxynaphthalene of 40% at 97% conversion could be achieved in presence of Cu^{2+} ion-exchanged BEA zeolite. The silver ion-exchanged zeolite gave a selectivity of 53% at 67% conversion. After 350 h reaction time the Cu^{2+} and the Fe^{3+} ion-exchanged zeolite led to complete conversion at a selectivity of 93% while the silver ion-exchanged zeolite deactivated after 48 h reaction time. Cahyono *et al.* (2010) has been investigated the activity and stereoselectivity of modified zeolite beta on cyclisation-acetylation of *(R)*-(+)-citronellal. The affect of catalyst preparing method, temperature, mol ratio of reactant, and solvent on the acetylation of 2-MN with acetic anhydride over Zr^{4+}-zeolit beta were studied.

MATERIAL AND METHOD

Zeolite beta was obtained from Tosoh (zeolite 940 NHA) with ratio of SiO_2/Al_2O_3 37. Precursor $ZrCl_{4.}$, solvents toluene and dichloromethane, acetic anhydride were provided by EMerck. Characterization of catalysts was conducted by using pyridyn adsorption -IR method at energy laboratory LP2M ITS and morphology of the catalyst by SEM at Physics Laboratory UM. The reaction was performed in a reflux apparatus with cooler and nitrogen gas flow. Product acetylation analysis was done by GC and GC-MS.

Preparation and Characterization of Catalysts
Catalyts was prepared by impregnation method and ion exchange method. Preparation of Zr^{4+}-zeolite beta(ip) catalyst by impregnation method was adapted from the procedure Yongzhong *et al.* (2004). At 1.0 g of zeolite beta was added 10 % of Zr^{4+} with 0.5 M zirconium chloride and then stirred for 24 hours. After drying at 100 ° C, the samples calcined at 550 ºC for 3 hours, with a low heating rate of 1 ° C / min. Preparation of catalyst by ion exchange method was done by soaking 1 g of zeolite beta in 25 mL of 0.5 M $ZrCl_4$ and then stirred for 24 hours, filtered until free of chloride ions. After drying at 100 ° C, the sample calcined at 550 ºC for 3 h. Acidity of catalysts was determined by pirydin adsorbtion-FTIR method and morphology of

catalysts was performed by using scanning electron micrograph (SEM).

In a 3-neck flask equipped with a magnetic stirrer and a cooler was added acetic anhydride (0.95 mL, 10 mmol) , 0.5 g of catalyst, and 20 mL of toluene and then stirred for 2 min, the mixture was added 1.58 g (10 mmol) of 2-methoxy naphthalene, the mixture heated at 70 ^oC under N_2 gas flow. During the reaction 1 ml sample was taken after 12 hours, 24 hours and 36 hours. Then added 6 mL of distilled water and 3 ml n-hexane and separated by centrifuge. The organic phase was dried by adding of anhydrous Na_2SO_4, the products were analyzed by GC. The same procedure was done at difference temperature of 140 ^oC. Reactions also repeated with dichloromethane solvent, without solvent, and increasing amount of acetic anhydride.

RESULTS AND DISCUSSION

Acidity of Catalysts

Pyridine have been used as probe molecules for the quantitative analysis of surface acidity of modified zeolite beta catalysts by FTIR spectroscopy. A scale of acidity and an evaluation of the relative acid strength were obtained for both Brønsted- and Lewis-acid sites. Table 1 shows the results of acidity analysis by pyridine adsorption-FTIR analysis.

Low total acidity on zeolite beta showed that calcination of NH_4^+-zeolite beta was not perfect released of NH_3 for converted into H-zeolite beta. Zr^{4+}-Zeolite beta (ip) that prepared by impregnation with 10% Zr^{4+} shows lower total acidity than Zr^{4+}-Zeolite beta (ie) that prepared by ion exchange.

**Table 1: Acidity modified zeolite beta with
Pyridine adsorption-FTIR analysis**

No	Sample	Parameter	Results (mmol/g)
1	Zeolite beta	Lewis acid	0,1892
		Bronsted acid	-
		Total acid	0,1892
2	Zr^{4+}-Zeolite beta (ie)	Lewis acid	0,2373
		Bronsted acid	0,0388
		Total acid	0,2761
3	Zr^{4+}-Zeolite beta (ip)	Lewis acid	0,1108
		Bronsted acid	0,0182
		Total acid	0,1290

High concentration of $ZrCl_4$ covered of pores and surface of zeolite beta affected the pyridine adsorption on the active sites solids cannot optimum. Better distribution of Lewis acidity and Bronsted acidity sites is shown by Zr^{4+}-Zeolite beta (ie).

SEM Analysis

Fig. 1 shows the SEM images of zeolite beta before and after adsorption of Zr^{4+}. Comparing the images of virgin (Figure 1(a)) and modified zeolite beta (Figure 1(b)), the difference image of catalysts is not clear, but the surface of Zr^{4+}-zeolite beta shows brighter. than zeolite beta.

Acetylation of 2-Methoxynaphtalene

Catalysts preparation method of the modified beta?zeolite influenced its catalytic activity on acetylation reactions. Both at 70 ?C and 140 ^oC, acetylation of 2-MN with acetic anhydride over Zr^{4+}-zeolite beta(ip) and Zr^{4+}-zeolite beta(ie) in toluene (mole ratio of acetic anhydride:2-MN, 1:1) showed almost no conversion of 2-MN after 24 h. Replacing the solvent and mole ratio of reactant showed better conversion.

Activity of Zr^{4+}-zeolite beta(ie) that showed with conversion of 2-MN of 29%. The selectivity to the desired 2,6-ACMN was 39% after 36 h reaction time. A slightly higher conversion to 2-acetyl-6-methoxynaphthalene could be achieved in dichloromethane solvent and added amount of acetic anhydride. Figure 2 shows the
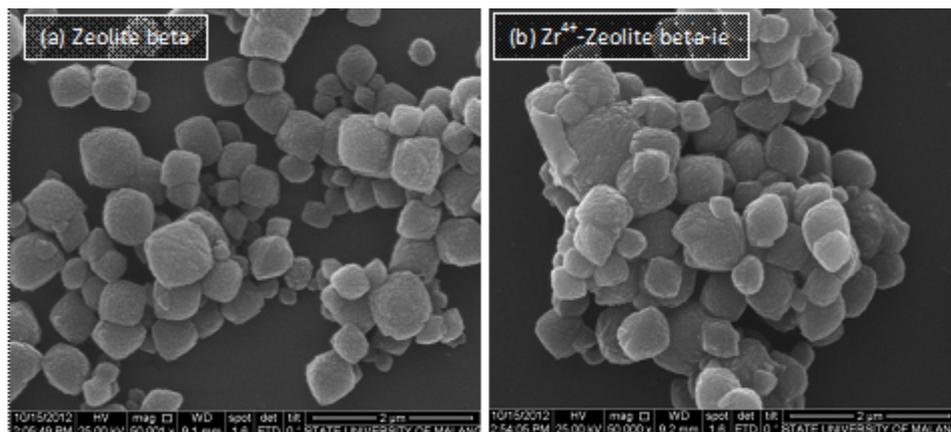
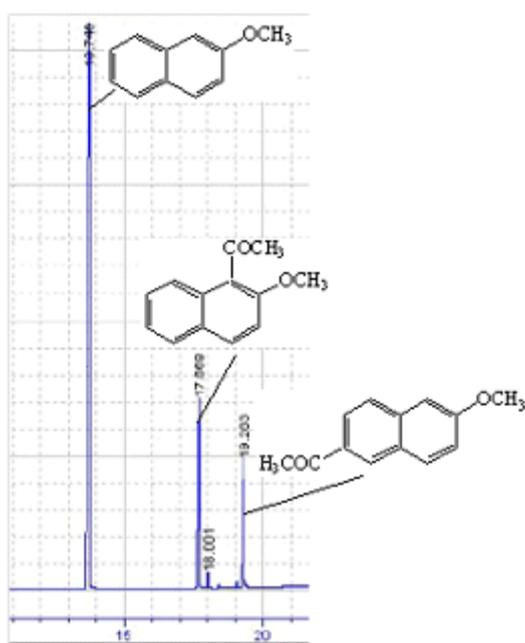**Fig. 1: SEM images of (a) zeolite beta (b) Zr^{4+}-zeolite beta (ie)**

Fig. 2: Chromatogram of acetylation product at 140 ^{o}C, 36 h in dichloromethane solvent
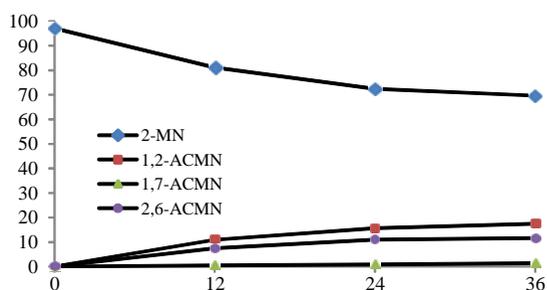

Fig. 3: Acetylation products of 2-MN over Zr^{4+}-zeolite at 140 ^{o}C

chromatograms of reaction product. Based on Schuster and Holderich (2008) report, reaction must be run in longer time for higher conversion.

CONCLUSION

Catalytic activity of catalysts was affected by preparing method, temperature, and reaction solvent. Zr^{4+}-zeolite beta(ip) showed low activity on acetylation of 2-MN. Activity and selectivity of Zr^{4+}-zeolite beta(ie) was increased in dichloromethane solvent at 140°C for 36 h, 1,7-ACMN was not identified and ratio of 1,2-ACMN to 2,6-ACMN was 1,6:1.

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