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Catalytic Synthesis of Diethyl Pimelate with Functionalized Ionic Liquids

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An acidic ionic liquid, [Emim]HSO_4, was prepared and used as solvent and catalyst in the esterification reaction of 1,7-pimelic acid and ethanol. The esterification products could be easily separated from the reaction system. The effects of the reaction conditions on the reaction results, such as the amount of catalyst, molar ratio of acid and ethanol, reaction time, were examined and the optimal conditions were obtained through orthogonal tests based on single-factor experiments. The optimal conditions were as follows: n(C_2H_5OH):n($C_7H_{12}O_4$) = 3:1, 2 mL of catalyst, reaction time for 5 h at 383.15 K. Under the optimal reaction conditions, the diethyl pimelate was obtained in 96.37 % yield. The acidic ionic liquid, [Emin]HSO_4 could be reused for 5 times and the yield of diethyl pimelate were more than 95.18 % after repeating 5 times of catalyst applications. Compared with the traditional catalyst of concentrated sulfuric acid, the ionic liquids had the advantages of good chemical stability, non-pollution, less side reaction, good repeatability and not using organic solvent as hydrated solvent, *etc*.

Key Words: Ionic liquids, Diethyl pimelate, Catalytic synthesis, Single-factor experiments, Orthogonal experiments.

INTRODUCTION

Diethyl pimelate and its derivatives are an important fine chemical raw materials and intermediates. Widely used in pharmaceuticals, perfume, polyester and other organic synthesis[1-3]. They are the important intermediate for synthesis of macrocyclic compounds in drug research[4] and act as the cephalosporin intermediate for synthesis of quinolone drugs.

At present, diethyl pimelate is synthesized mainly with concentrated sulfuric acid as catalyst, which has many disadvantages such as environmental pollution, serious corrosion of equipment, difficult recovery and utilization of catalyst[5,6]. As an environmentally friendly green solvent and catalyst, the ionic liquids have been widely used for catalytic or uncatalytic reaction. Acidic ionic liquids have not only the advantages of ionic liquids, but also can change and modify anion and cation of ionic liquids according to the reaction demand, which have flexible acidic adjustability and high density of acid sites of the catalysts, uniform acid strength and more easy for recovery and utilization of catalyst[7,8]. In this paper, [Emin]Br was synthesized starting with N-methyl imidazole and ethyl bromide and then [Emin]HSO_4 was synthesized with concentrated sulfuric acid and [Emin]Br through single-factor experiments and orthogonal experiments. The effects of the reaction conditions on the reaction results, such as the amount of catalyst, molar ratio of acid and ethanol, reaction time, were experimented and the optimal conditions were obtained.

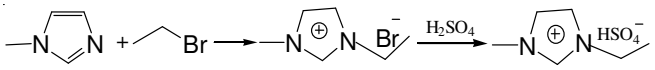
EXPERIMENTAL

All reagents including pimelic acid, bromine ethane, N-methylimidazolium, methylene chloride, ethanol, methanol, sulfuric acid and ethyl acetate were all of AR grade and were obtained from Shanghai Chemical Reagent Co. with purities of 0.995 in mass fraction.

GC9800 TFP Gas chromatograph (Shanghai chromatographic instrument Co. Ltd.), Infrared spectrometer (IR-200 Nicolet America).

[Emin]HSO_4 preparation process: Weighing 28.96 g of N-methylimidazolium dissolved in 25 mL methanol, while ethyl bromide and methanol solution was prepared with 37 mL ethyl bromide dissolved in 30 mL of methanol. Ethyl bromide and methanol solution was added *via* the dropping funnel within 3 h at a suitable stirred rate and the mixture was continually agitated and reacted for 10 h. The ionic liquid [Emin]Br is obtained by removing the ethyl bromide, methanol and water by using a rotary evaporator. The [Emin]Br dissolved in dichloromethane and then ionic liquid [Emin]HSO_4 was prepared by adding dropwise equal amount concentrated sulfuric acid, with constant stirring and heated for 5 h. After

extraction and distillation, ionic liquid [Emin]HSO_4 was obtained. The reaction equation was as follows:



Preparation of diethyl pimelate: A mixture of ethanol and 1,7-pimelic acid (n(C_2H_5OH):n($C_7H_{12}O_4$) = 3:1) and 2 mL [Emin]HSO_4 was stirred in a 50 mL 3-neck round bottom flask equipped with a cold-water condenser, water divider and thermometer. The reaction temperature was kept at 378.15-383.15 K for 5 h. The reaction equation was as follows:

$$HOOC(CH_2)_5COOH + C_2H_5OH \xrightarrow{[Emin]HSO_4} H_5C_2OOC(CH_2)_5COOC_2H_5$$

After reaction, mixture was cooled down to room temperature and stood to obtain two phase liquids, the upper is diethyl pimelate by infrared analysis, the lower is the ionic liquid phase. The upper phase was extracted with 5 mL ethyl acetate for three times, combined upper phase and then washed to neutral by anhydrous sodium sulfate, dried with anhydrous sodium sulfate for overnight, then filtered and distillated with a rotary evaporator and diethyl pimelate was obtained. In the lower phase, the ionic liquids was obtained by a rotary evaporator to remove the water and the ionic liquids could be reused. The content of the diethyl pimelate was analyzed by gas chromatography and the yield was calculated as follows: Yield (%) = (experimental value/theoretical value) × 100 = (mass of extracts × the content of the diethyl pimelate/theoretical value) × 100.

RESULTS AND DISCUSSION

Esterification is a reversible reaction. The catalyst can only accelerate the reaction rate, but can not increase the yield of esterification. To improve the yield,we often added excess methanol and remove water continuously from the product, which also can inhibit the hydrolysis reaction of the ester. Through several experiments, we found amount of catalyst, molar ratio of acid and ethanol and reaction time were important factors that influenced the reaction.

Effect of reaction time on the yield: The methods employed as above, only reaction time was changed. The conditions of the reaction were observed and tested by gas chromatography when the reaction time was 3.5, 4, 4.5, 5, 5.5 and 6h, respectively. The effects of different reaction time on yield were showed in Fig. 1.

From the Fig. 1, it is clear that with the increase of reaction time, the yield increased. When the reaction time was 5.0 h, the yield was 95.01 %, which illustrated that the [Emin]HSO_4 has good catalytic activity for esterification reaction. When the reaction time was more than 5.0 h, the yield kept constant. If the reaction time was too long, side effects and the reverse reaction might possibly happen, the yield even decreased instead, therefore, the optimal reaction time was about 5.0 h.

Effect of the reaction temperature on the yield: When the reaction temperature was 368.15, 373.15, 378, 383.15 and 388.15 K, respectively, the effects of the reaction temperature on the yield are shown in Fig. 2.

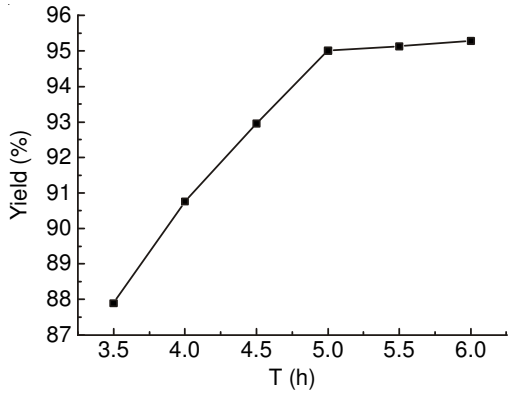


Fig. 1. Effect of reaction time on the yield of diethyl pimelate

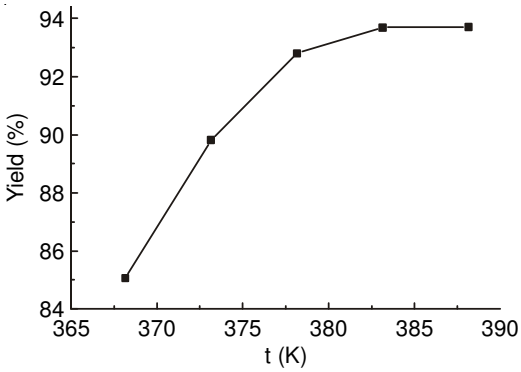


Fig. 2. Effect of the reaction temperature on the yield of diethyl pimelate

From Fig. 2 it is suggesated that with the reaction temperature increased, the yield increased, when the reaction temperature was at 383.15 K, the yield was 93.69 %, continually to increase the reaction temperature, the yield even descend instead and the colour of the liquid change into yellow, which would affect the quality of the product. Therefore, considered the energy consumption and product quality into account, the optimum temperature was 378.15-383.15 K.

Effect of the amount of catalyst on the yield: The effects of the amount of catalyst on the yield are shown in Fig. 3.

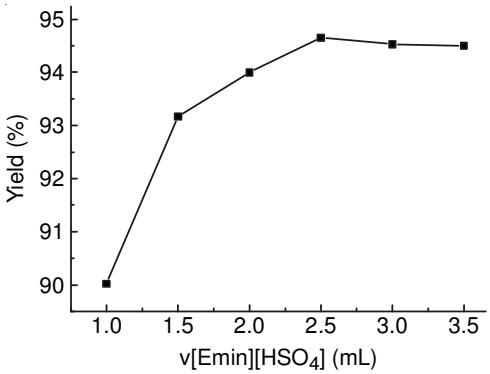


Fig. 3. Effect of the catalyst amount on the yield of diethyl pimelate

From Fig. 3, it is observed that with the increase of catalyst amount, the yield increased. When the dosage of [Emin]HSO_4 was 2.5 mL, the yield was 94.65 %, continually to increase catalyst amount, the yield would decreased slightly. Because [Emin]HSO_4 is a surfactant, which has both hydrophobic group and hydrophilic group. With the increase of catalyst amount, some product would be soluble in water.

Effect of ethanol to acid ratio on the yield: The effects of the ethanol to acid ratio on the yield are shown in Fig. 4.

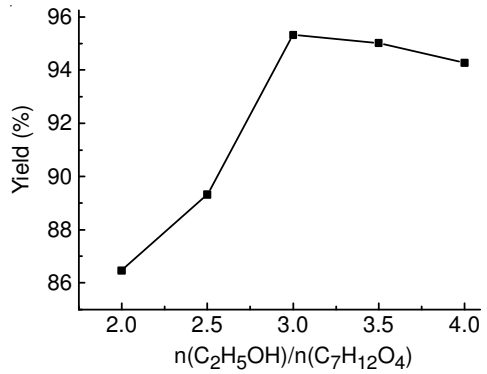


Fig. 4. Effect of the ethanol to acid ratio on the yield of diethyl pimelate

From the Fig. 4, we could find that with the increase of alkyd ratio, the yield increased, reached a maximum value 95.32 % at about $n(C_2H_5OH):n(C_7H_{12}O_4)$ = 3:1 and then decreased, continue to add ethanol, the reaction temperature would be lower than 383.15 K and the yield of diethyl pimelate decreased.

Orthogonal experiments: Based on the single factor experiments, the orthogonal experiment for synthesis of diethyl pimelate was arranged. Considering three levels of every factor, the factor-level table of orthogonal experiment for synthesis of diethyl pimelate with $[Emin]HSO_4$ is given in Table-1. Based on $L_9(3^4)$ orthogonal test table, orthogonal experiments for synthesis of diethyl pimelate with $[Emin]HSO_4$ were arranged, the results are listed in Table-2.

TABLE-1
FACTOR-GRADE TABLE OF ORTHOGONAL EXPERIMENT FOR SYNTHESIS OF DIETHYL PIMELATE WITH $[Emin]HSO_4$

Level	Factor			
	A	B	C	D
	Reaction time (h)	Reaction temp. (K)	Catalyst (mL)	Ethanol to acid ratio
1	4.5	373.15	1.5	2.5
2	5.0	378.15	2.0	3.0
3	5.5	383.15	2.5	3.5

TABLE-2
ORTHOGONAL EXPERIMENT FOR SYNTHESIS OF DIETHYL PIMELATE WITH $[Emin]HSO_4$

No.	A	B	C	D	Yield (%)
1	1	1	3	2	92.35
2	2	1	1	1	93.05
3	3	1	2	3	95.42
4	1	2	2	1	93.56
5	2	2	3	3	95.37
6	3	2	1	2	95.69
7	1	3	1	3	93.36
8	2	3	2	2	96.37
9	3	3	3	1	95.61
K_1 (Sum of grade I)	279.27	280.82	282.10	282.22	–
K_2 (Sum of grade II)	284.79	284.62	285.35	284.41	–
K_3 (Sum of grade III)	286.72	285.34	283.33	284.15	–
R (Extreme difference)	7.45	4.52	3.25	2.19	–

The results indicate that the major factor affecting the yield is A (reaction time), the sub major factor B (reaction temperature); while C (the amount of $[Emin]HSO_4$) and D (ethanol to acid ratio) have little influence. From Table-2, the optimum yield was obtained at 5 h of reaction time, 383.15 K of reaction temperature, 2 mL of catalyst, 3:1 of ethanol to acid ratio.

Recycle of catalyst: Under the above optimum conditions, the recycle of $[Emin]HSO_4$ catalyst was studied and the result was shown in Fig. 5. From Fig. 5, we could find that the yield of diethyl pimelate slightly decreased from 96.37 to 95.18 %. The yield of diethyl pimelate was more than 95.18 % after repeating 5 times of catalyst applications, which indicate that catalyst could still maintain fairly good selectivity and activity after repeating many times.

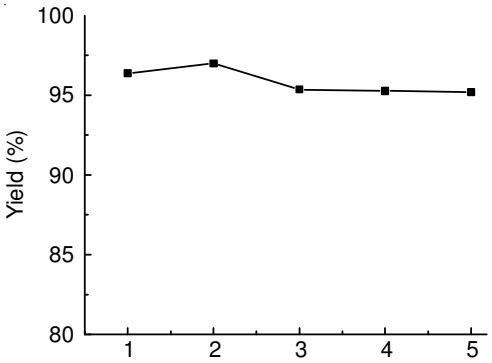


Fig. 5. Effect of reusing catalyst on the esterification of diethyl pimelate

Conclusion

An acidic ionic liquid, $[Emim]HSO_4$, was prepared and used for catalytic synthesis of diethyl pimelate. The results indicated that $[Emin]HSO_4$ had good catalytic activity for esterification reactions. The effects of amount of $[Emin]HSO_4$, reaction time, temperature and acid ethanol ratio to the yield were researched. The optimum yield was obtained at 5 h of reaction time, 383.15 K of reaction temperature, 2 mL of catalyst, 3:1 of ethanol to acid ratio, the yield could reach to 96.37 %. Compared with the traditional catalyst of concentrated sulfuric acid, ionic liquids had the advantages of good chemical stability, non-pollution, less side reaction, good repeatability and not using organic solvent as hydrated solvent, *etc*.

$[Emin]HSO_4$ catalyst could be recycled easily and the yield of diethyl pimelate were more than 95.18 % after repeating 5 times of catalyst applications, which indicated that catalyst could still maintain fairly good selectivity and activity after repeating many times.

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