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Deep eutectic solvents choline chloride·2CrCl₃·6H₂O: an efficient catalyst for esterification of formic and acetic acid at room temperature

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A highly efficient and selective method for esterification of formic and acetic acid with alcohols has been achieved at room temperature, with the choline chloride (ChCl)/ chromium(iii) chloride hexahydrate (CrCl₃·6H₂O) deep eutectic solvent as catalyst. High yields and good selectivities of organic esters are obtained using DES [ChCl][CrCl₃·6H₂O]₂ with the molar ratio 5:1 (carboxylic acids: alcohols) at room temperature in 24h. The ease of recovery and reusability of DES with high catalytic activity makes this method efficient and practical.

Introduction

Esterification is one of the fundamental reactions in organic synthetic chemistry, and the product organic esters are important chemicals and valuable intermediates in the cosmetic and pharmaceutical industries.¹ The esterification reaction is an equilibrium reaction and liquid inorganic acids such as H₂SO₄, HF, and H₃PO₄ were widely used as catalysts to achieve organic esters in most cases.² However, these acids, which need to be neutralized at the end of the reactions, are extremely corrosive and very difficult to reuse. Moreover, the removal of adsorbed products from the catalyst is quite complex and requires large excess of volatile organic solvents. Furthermore, the reaction temperature is generally too high. These above-mentioned drawbacks all are not environmental friendly.³ Finding a new simple synthetic process which is environment begin and is of high yield as well as easy operation is still a hot issue in this field.

Deep eutectic solvents (DESs) are composed of mixing a quaternary ammonium salt with a metal salt or a hydrogen bond donor (HBD).⁴ DESs can be easily prepared from safe and low cost chemical materials, and through an atom economical approach. In 2001, Abbott⁵ reported firstly that choline chloride and MCl₂ (M = Zn and/or Sn) could form a moisture-stable deep eutectic solvents and the melting points of these liquids were measured. It was found that the decrease in the melting point of the mixture relative to the melting points of

the individual components. In recent decades, DESs have been used widely as Lewis acid catalysts and reaction medium for O-acetylation of cellulose and monosaccharides⁶, Diels–Alder reactions⁷, the synthesis of pillararenes⁸, and Kabachnik-Fields reaction⁹. In 2007, Prasad and coworkers¹⁰ reported that DES [ChCl][ZnCl₂]₂ as a Lewis acid catalyst as well as reaction medium to prepare long chain wax esters in high yields, but they used high temperature (110°C) with need of heat supply. Later, Feng¹¹ have used DES [ChCl][SnCl₂]₂ as a Lewis acid catalyst to prepare phytosteryl esters, however the scope of reaction is limit. Germani's group¹² reported a new Brønsted acidic deep eutectic solvent which prepared by mixing new quaternary ammonium methanesulfonate salts with p-toluenesulfonic acid (PTSA) as reaction media for esterification of carboxylic acid with alcohols in good yields, but it needs a large amount of DESs (e.g., 0.3 mol DES per 1 mol carboxylic acid). Recently, Cvjetko¹³ reported the esterification reaction in DESs, which took Novozym 435 (immobilized *Candida Antarctica* lipase B) as catalyst. In this case, however, deep eutectic solvents only used as green solvents instead of the catalysts. Therefore, esterification under mild conditions is of a great interest and importance in application of deep eutectic solvents.

Up to now, chromium based DESs have been widely used in electrochemistry¹⁴, nanoscience¹⁵ and leather production processes¹⁶, but there are only few examples about application of organic synthesis. Herein, we initiate a new and distinct method for the esterification of formic and acetic acid with alcohol. The reaction is catalyzed by choline chloride (ChCl)/ chromium(iii) chloride hexahydrate (CrCl₃·6H₂O) DES at room temperature, and gives out good efficiency and selectivity. This method meets with the principles of green chemistry and will stimulate and broaden the applications of DESs in different relative fields.

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†Electronic Supplementary Information (ESI) available: Experimental details, preparation of deep eutectic solvents, the synthesis process of organic esters,

Results and discussion

Firstly, esterification of acetic acid with n-butanol was chosen as a model reaction. Then, a series of DESs including [ChCl][MCl]₂ (M = Fe, Zn and Sn) and [ChCl][MCl·H₂O]₂ (M = Mg, Al, Cr, Mn, Co, Ni and Cu) were selected to study their performance on the synthesis of n-butyl acetate. The activity of these catalyst was evaluated by the yield of n-butyl acetate and the results were summarized in Table 1. As shown in the table, DES originated from choline chloride (ChCl) and chromium(iii) chloride hexahydrate (CrCl₃·6H₂O) had the highest activity of the tested DESs and the yield of n-butyl acetate was 93.0% at room temperature. The yield of n-butyl acetate (64.5%) with [ChCl][FeCl₃]₂ was acceptable. Moreover, the yield improved with a little increases of temperature (Table S1, Electronic Supplementary Information). However, the rest of DESs showed extremely poor efficiency in the esterification reaction as compared to CrCl₃·6H₂O-based DES. Interestingly, the DES formed by choline chloride and ZnCl₂¹⁰, which was good at synthesizing long chain wax esters at 110°C, gave extremely low product under our milder conditions. Moreover, excellent selectivities were obtained and no by-products, such as olefins or ethers, were detected in all cases at room temperature. These results indicated that DES [ChCl][CrCl₃·6H₂O]₂ could be a very potential catalyst for the synthesis of organic esters under mild conditions.

Table 1 Preparation of n-butyl acetate with different deep eutectic solvents^a

Entry	DES	Yield of n-butyl acetate ^b	Selectivity to n-butyl acetate ^b
1	[ChCl][CrCl ₃ ·6H ₂ O] ₂	93.0% 85.7% ^c	100%
2	[ChCl][FeCl ₃] ₂	64.5%	100%
3	[ChCl][AlCl ₃ ·6H ₂ O] ₂	49.1%	100%
4	[ChCl][MgCl ₂ ·6H ₂ O] ₂	18.0%	100%
5	[ChCl][MnCl ₂ ·4H ₂ O] ₂	6.3%	100%
6	[ChCl][CoCl ₂ ·6H ₂ O] ₂	7.8%	100%
7	[ChCl][NiCl ₂ ·6H ₂ O] ₂	10.4%	100%
8	[ChCl][CuCl ₂ ·2H ₂ O] ₂	3.7%	100%
9	[ChCl][ZnCl ₂] ₂	3.0%	100%
10	[ChCl][SnCl ₂] ₂	3.6%	100%

a Reaction conditions: n-butanol (0.01 mol), acetic acid (0.05 mol), and DES (0.25 mmol) at room temperature (25°C) for 24h
b Yield and selectivity are based on GC. 1,4-dimethyl-benzene as internal standard

c isolated yield

Table 2 The effect of molar ratio of [ChCl][CrCl₃·6H₂O]₂ to butanol on the esterification reaction^a

Entry	DES amount n(DES):n(n-butanol)	Yield of n-butyl acetate ^b
1	1:100	78.4%
2	1:50	87.5%
3	1:40	93.0%
4	3:100	94.3%
5	1:25	95.8%
6	1:20	96.3%

a Reaction conditions: n-butanol (0.01 mol) and acetic acid (0.05 mol) at room temperature (25°C) for 24h

b Yield are based on GC. 1,4-dimethyl-benzene as internal standard

The effect of molar ratio of [ChCl][CrCl₃·6H₂O]₂ to n-butanol on the esterification of acetic acid with n-butanol was investigated. As shown in Table 2, yield of n-butyl acetate increased rapidly with molar ratio of DES/n-butanol below 1/40. When the ratio is over 1/40, however, the yield of n-butyl acetate remained almost unchanged, so the optimal DES amount should be 1/40. The data showed that the reaction could reach high yield of ester at low catalyst amount using [ChCl][CrCl₃·6H₂O]₂, while other DESs, including Brønsted acidic DESs and [ChCl][ZnCl₂]₂, required a large amount in the esterification to reach the maximum catalytic activity (generally the amount was above 0.3 of carboxylic acids or alcohols)¹⁰⁻¹². So, DES [ChCl][CrCl₃·6H₂O]₂ was an economic catalyst with high efficiency for the esterification of acetic acid and n-butanol.

Esterification reaction was an equilibrium reaction and generally required the usage of excess amount of the reactants for satisfactory conversion rate. Therefore, the effect of molar ratio of acetic acid to n-butanol was also studied in the presence of [ChCl][CrCl₃·6H₂O]₂. The molar ratio of acetic acid to n-butanol was varied in the range of 1:4 to 10:1 and the results were given in Table 3. When acetic acid and n-butanol was added as stoichiometrically according to the reaction equation, the n-butyl acetate formation only reached 72.6% after 24h. Although equimolar ratio substrate could appear as ideal in terms of economical aspect of the process, it was observed that such ratio was not advantageous for the formation of n-butyl acetate. When the amount of n-butanol was increased, the yield of ester was increased slightly as well. The highest yield of n-butyl acetate only reached 82.0% using the molar ratio of 1:2 (acetic acid to n-butanol). Interestingly, with the increasing the molar ratio of acetic acid to n-butanol from 1:1 to 5:1, the yield of ester increased greatly. The yield of 93.0% could be obtained using acetic acid/n-butanol ratio of 5:1. While the molar ratio of acetic acid/n-butanol was above 5:1, the yield of n-butyl acetate became slightly decreasing.

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These data indicated that the excess of acetic acid was in favor of the formation of n-butyl acetate and the optimal molar ratio of acetic acid/n-butanol was 5:1. What is more, the acetic acid price was relatively cheaper and the purification of n-butanol Table 3 The effect of molar ratio of acetic acid to n-butanol on the esterification reaction ^a

Entry	n(acid):n(n-butanol)	Yield of n-butyl acetate ^b
1	1:4	81.4%
2	1:3	81.4%
3	1:2	82.0%
4	1:1.5	80.0%
5	1:1	72.6%
6	1.5:1	78.1%
7	2:1	80.9%
8	3:1	88.2%
9	4:1	91.2%
10	5:1	93.0%
11	6:1	91.8%
12	8:1	90.5%
13	10:1	87.3%

a Reaction conditions: n-butanol (0.01 mol) and DES (0.25 mmol) at room temperature (25°C) for 24h

b Yield are based on GC. 1,4-dimethyl-benzene as internal standard

would also be easier, it made the process more industrial application value.

The yield of n-butyl acetate was also monitored with the reaction time. The results were shown in Figure 1. The formation of n-butyl acetate was increased continuously with the reaction time up to 24h. From 24h to 48h, the yield of

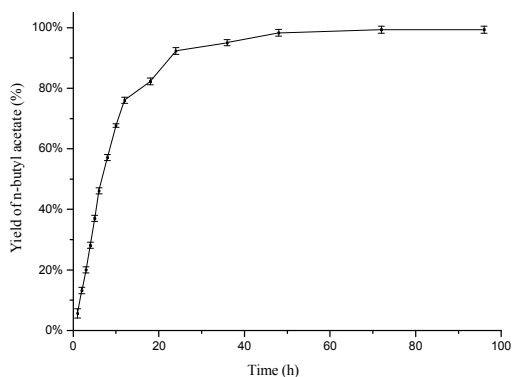


Figure 1 The effect of reaction time on the esterification reaction: n-butanol (0.01 mol), acetic acid (0.05 mol), and DES (0.25 mmol) at room temperature (25°C). Error bars represent the SD.

ester changed a little, only from 93.0% to 98.9%. After 48h of reaction, the yield of n-butyl acetate almost reached 100% and were almost unchanged. Considering the economic factor, the best time for the esterification of alcohols by carboxylic acids with the DES [ChCl][CrCl₃·6H₂O]₂ was 24h.

In order to investigate the scope and limitation of the DES [ChCl][CrCl₃·6H₂O]₂ as a catalyst for esterification, various alcohols and acids as the substrates were also tested, and the results were outlined in Table 4. As can be seen, the length of the alkyl chains of the alcohols did not affect the yield of ester much. In the reaction of n-octanol and acetic acid, the yield of n-octyl acetate was still above 76%(Table 4, Entry 1-9). While with the increase of chain length of the carboxylic acids, the rate of esterification decelerated dramatically and the yield of n-butyl butyrate was poor (Table 4, Entry 10-12). In addition, the alcohols with a branched chain, which had a huge steric hindrance, reacted with acetic acid and had slower reaction rate. Among the alcohols mentioned in Table 4, cyclohexanol had the biggest steric hindrance, so it had the lowest yield.

Table 4 Results of esterification for different acids and alcohols in [ChCl][CrCl₃·6H₂O]₂ DES ^a

Entry	Alcohols	Carboxylic acids	Yield of esters ^b
1	Methanol	Acetic acid	95.1%
2	Ethanol	Acetic acid	93.2%
3	Propanol	Acetic acid	92.8%
4	Isopropanol	Acetic acid	88.7%
5	n-Butanol	Acetic acid	93.0%
6	Isoamyl alcohol	Acetic acid	85.7% ^c
7	n-Hexanol	Acetic acid	85.1%
8	n-Octanol	Acetic acid	82.5%
9	Iso-octyl alcohol	Acetic acid	76.4%
10	n-Butanol	Formic acid	64.9%
11	n-Butanol	Propanoic acid	97.1%
12	n-Butanol	Butyric acid	59.8%
13	Cyclohexanol	Acetic acid	29.4%
14	Benzyl alcohol	Acetic acid	31.1%
15	2-Chloro-1-ethanol	Acetic acid	74.7%
16	Propargyl alcohol	Acetic acid	68.2% ^c
17	Isoamyl alcohol	Acetic acid	79.2%
18	Propargyl alcohol	Formic acid	65.4%
19	n-Hexanol	Formic acid	92.2%
20	n-Octanol	Formic acid	90.9%
	Benzyl alcohol	Formic acid	87.5%
			85.6%
			77.9% ^c

a Reaction conditions: alcohols (0.01 mol), carboxylic acids

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(0.05 mol), and DES (0.25 mmol) at room temperature (25°C) for 24h

b Yield are based on GC-MS

c isolated yield

Table 5 Recycling of [ChCl][CrCl₃·6H₂O]₂ DES in the synthesis of n-butyl acetate^a

Recycle times	Yield of n-butyl acetate ^b
0	93.0%
1	91.8%
2	90.7%
3	90.0%
4	89.5%

a Reaction conditions: n-butanol/acetic acid/ DES =1:5:0.025 at room temperature (25°C) for 24h

b Yield are based on GC. 1,4-dimethyl-benzene as internal standard

Benzyl alcohol's hydroxide radical formed the conjugated system with the benzene ring decreasing the strict hindrance, and its methylene was mobilizable, so the yield of methyl phenylacetate was higher than cyclohexyl acetate (Table 4, Entry 13-14). Also, the alcohols with electron-withdrawing groups had poorer reactivity (Table 4, Entry 15-16). Moreover, esterification of alcohols and formic acid (Table 4, Entry 17-20), catalyzed by DES also had high efficiency. These results indicated that [ChCl][CrCl₃·6H₂O]₂ DES could be a very potential catalyst for the synthesis of formate and acetate.

Once the reactions were complete, more attention was paid to separate esters from the reaction system and recycle the DES. In fact, the product can be very easily isolated, DES and water formed the lighter phase while the ester product and reactants remained in the upper liquid phase and it was simply and conveniently separated by decanting. After that, the reusability test was conducted by using the former model reaction. As shown in Table 5, although the yield of n-butyl acetate slightly decreased, the reused DES [ChCl][CrCl₃·6H₂O]₂ still had higher activity for the yield of n-butyl acetate after reusing 4 times. The slight decrease of activity might be ascribed to the slight deactivation and loss of DES during the process of reuse.

Deep eutectic solvents are formed by mixing metal halides and choline chloride. So, it shows both Lewis acidity and polar solubility in an esterification reaction. During the reaction, the reactants alcohols and carboxylic acids are dissolved in the DES phase, and the product ester are separated to a non-polar phase. As a result, the chemical equilibrium of the esterification was pulled forward, and the reaction occurred simultaneously without removing the by-product water.

As a conclusion, the DES [ChCl][CrCl₃·6H₂O]₂ showed good catalytic ability in the reaction between organic acids and alcohols, and the unique solubility of the DES was beneficial to generate more products. Further experiments, aiming at the specific reaction mechanism, are now ongoing in our labs.

Experimental

Materials. All reagents and solvents for syntheses were purchased from commercial sources and used without further purification.

Measurements. The analysis of the reaction mixture was carried out on a gas chromatograph (SP-6890) equipped with a flame ionization detector (FID) and a capillary column (HP-5, 30 m × 0.25 mm × 0.25 mm). The column temperature was 80 °C. The temperatures of the injector and detector were maintained at 320°C and 320°C, respectively. The products were further identified by GC (Varian 3900)-MS (Varian Saturn 2100 T) equipped with a flame ionization detector (FID) and a capillary column (DB-5, 30 m × 0.25 mm × 0.25 mm). The ¹H and ¹³C NMR spectra were recorded on a Bruker 400MHz NMR spectrometer at 298K. The chemical shifts (δ) were given in part per million relative to internal tetramethylsilane (TMS, 0 ppm for ¹H), CDCl₃ (77.3 ppm for ¹³C).

General preparation of deep eutectic solvent (see ESI for more details). A mixture of the metal halides and choline chloride in a molar ratio of 2:1 was heated to 70-100 °C with gentle stirring until a liquid formed.

General synthetic process of organic esters (see ESI for more details). A typical reaction mixture consisted of 0.01 mol alcohols and 0.05 mol carboxylic acids without solvent. The deep eutectic solvent was added to initiate the reaction. The molar ratio of deep eutectic solvent/alcohol was 1/40. The reaction mixture was stirred at 25°C for 24h. After the reaction was completed, liquid samples were analyzed on a gas chromatograph after addition of the internal standard.

Recycle process of DES. After the reaction was completed, two clearly separated phases are formed, the upper liquid layer was spilled off with a Pasteur pipette, the lower layer formed by DES, water and excess starting material was extracted with diethyl ether three times. A drying in vacuo at 60°C overnight was carried out on DES for further cycles.

Conclusions

In summary, a new method for the esterification of carboxylic acids with alcohols catalyzed by [ChCl][CrCl₃·6H₂O]₂ deep eutectic solvent under mild conditions have been achieved. This method makes it possible to synthesize organic esters easily and efficiently at room temperature. The effect of different Lewis acids DESs and the amount of DES on the esterification reaction are investigated. The CrCl₃ based DES stands out among other catalysts. The effect of molar ratio of carboxylic acids to alcohols and reaction time on the esterification reaction are also studied. Furthermore, different organic esters are obtained through this method, and the chain length of reactants can obviously influence the reaction rate and yield. Compared with traditional methods, using the DES [ChCl][CrCl₃·6H₂O]₂ as catalyst has following advantages: (a) the DES [ChCl][CrCl₃·6H₂O]₂ has excellent activity, high

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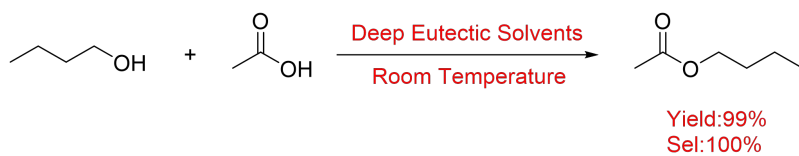
efficiency and selectivity; (b) the preparation of DES is very easily operated and the cost is rather low; (c) the esterification procedure can be achieved at room temperature; (d) the DES can be reused directly with the initial activity.

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