

# Green and moisture-stable Lewis acidic ionic liquids (choline chloride · $x\text{ZnCl}_2$ ) catalyzed protection of carbonyls at room temperature under solvent-free conditions

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Received 20 July 2005; received in revised form 6 February 2006; accepted 6 February 2006

Available online 31 March 2006

## Abstract

Choline chloride ·  $x\text{ZnCl}_2$  ( $x = 1-3$ ) or benzyltrimethylammonium chloride ·  $2\text{ZnCl}_2$  have been used as efficient and recyclable catalysts for protection of carbonyls to 1,3-dioxolanes and 1,3-dioxanes at room temperature under solvent-free conditions. FT-IR investigation demonstrates the four ionic liquids have similar Lewis acid strength, which is in agreement with the activities observed in the acetalization reaction. The catalytic system choline chloride ·  $2\text{ZnCl}_2$  can be reused up to five times without appreciable loss of activity. The simple procedures as well as easy recovery and reuse of this novel catalytic system are expected to contribute to the development of more benign acetalization procedure of carbonyl compounds.

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**Keywords:** Choline chloride ·  $x\text{ZnCl}_2$ ; Acetalization; Solvent-free; Reusability; Lewis acidity; Green chemistry

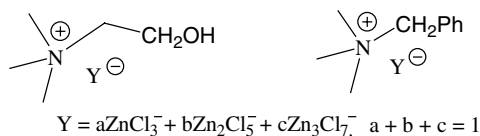
## 1. Introduction

The acetalization or ketalization reaction is a process that is widely used in organic synthesis to protect the carbonyl group of aldehydes and ketones [1]. The acetals are important reactants for synthesis of enantiomerically pure compounds, which were widely used as steroids, pharmaceuticals, and fragrances [2–6]. Previously, the catalysts used in the acetalization or ketalization reactions were generally protonic acids, Lewis acids, and a number of transitional metal complexes including Rh, Pd, and Pt [7–11]. Although good results were obtained, the separation of the product from the catalyst system was still difficult and the noble metal catalysts used were quite expensive and usually unstable [12]. Moreover, the preparations of acetals and ketals have been usually carried out in molecular solvents such as acetonitrile, THF, toluene, and DMF leading to complex isolation and recovery procedures.

These processes also generate waste-containing solvent and catalyst, which have to be recovered, treated, and disposed of. Therefore, the development of a catalytic system that may be green, cost-effective, mild, easily separable, and reusable has long been awaited.

Recently, acidic ionic liquids have been successfully used in this reaction due to their unique properties such as vaporless and reusability [13–15]. However, for practical utilization, these imidazolium-based ionic liquids still suffer from the relatively expensive cost. In the case of chloroaluminate ionic liquid, their poor stability to moisture can lead to undesired side reactions and causing considerable potential for corrosion (due to the release of HCl). More recently, a series of inexpensive and moisture-stable Lewis acidic ionic liquids have been prepared from choline chloride and  $\text{ZnCl}_2$  [16], and used in Diels–Alder and Fischer indole reactions [17,18]. Choline chloride ·  $x\text{ZnCl}_2$  are generally accessible, easy to handle, relatively cheap and moisture-stable, which fulfill several of the principles of green chemistry. In this paper, we report the use of choline chloride ·  $x\text{ZnCl}_2$  or benzyltrimethylammonium

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Choline chloride ·  $xZnCl_2$       Benzyltrimethylammonium chloride ·  $2ZnCl_2$

Scheme 1. Structures of the prepared ionic liquids.

chloride ·  $2ZnCl_2$  as efficient catalysts for protection of carbonyls to 1,3-dioxolanes and 1,3-dioxanes under mild and solvent-free conditions (Scheme 1).

## 2. Experimental

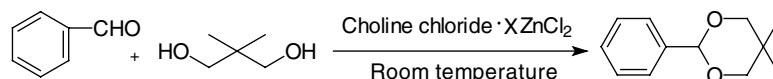
### 2.1. Preparation of the catalysts

Choline chloride, benzyltrimethylammonium chloride and  $ZnCl_2$  were used as received. Quaternary ammonium salt (50 mmol) was mixed with zinc chloride ( $50x$  mmol,  $x = 1-3$ ) and heated to ca.  $100^\circ C$  in air with stirring until a clear colorless liquid was obtained.

### 2.2. Acetalization or ketalization of carbonyl compounds with diols

All the reactions were performed in a 25 mL round-bottom flask with a magnetic stirrer. For a typical experiment, 4 mmol chloride ·  $xZnCl_2$ , 30 mmol neopentyl glycol and benzaldehyde (20 mmol) were charged into the reactor. Then the mixture was stirred for 10 h at room temperature. After reaction, the mixture was extracted with  $Et_2O$  (3 mL  $\times$  2). The organic phase was combined, and analyzed by HP 1790 GC and HP 6890/5973 GC/MS. The concentration of reactant and product was directly given by the system of GC chemstation according to the area of each chromatograph peak. The residue choline chloride ·  $xZnCl_2$  phase could be easily recovered and reused in the next run after heat treatment under vacuum at  $70^\circ C$  for 2 h.

Table 1  
Choline chloride ·  $xZnCl_2$  and benzyltrimethylammonium chloride ·  $2ZnCl_2$  catalyzed reaction between benzaldehyde and neopentyl glycol at room temperature ( $25^\circ C$ )



Entry	Catalyst	Neopentyl glycol/benzaldehyde (M/M)	Conversion <sup>a</sup> (%)	Selectivity <sup>b</sup> (%)
1	Choline chloride · $2ZnCl_2$	1:1	81	~100
2	Choline chloride · $2ZnCl_2$	1:1	83	~100
3	Choline chloride · $3ZnCl_2$	1:1	80	~100
4	Benzyltrimethylammonium chloride · $2ZnCl_2$	1:1	83	~100
5	Choline chloride	1:1	Trace	–

<sup>a</sup> Conversion of benzaldehyde.

<sup>b</sup> Selectivity to 1,3-dioxane.

### 2.3. Evaluation of the Lewis acidity of choline chloride · $xZnCl_2$

Pyridine was dried with KOH and distilled over  $5\text{ \AA}$  molecular sieves and solid KOH before use. All IR samples were prepared by mixing probe liquids and ionic liquids in a given mass ratio of pyridine/ILs = 1:3, and then spreading into liquid films on KBr windows. The spectra were recorded on a NicoLET 5700 Fourier transform infrared spectrophotometer at room temperature.

## 3. Results and discussion

### 3.1. Effect of different mole ratios of choline chloride to $ZnCl_2$

Initially, the reaction between benzaldehyde and neopentyl glycol was used as model reaction to test the catalytic activities of choline chloride ·  $xZnCl_2$  ( $x = 1-3$ ) and benzyltrimethylammonium chloride ·  $2ZnCl_2$ , and the results were listed in Table 1. The reaction was carried out at room temperature for 10 h under solvent-free conditions using equimolar amount of neopentyl glycol and benzaldehyde. It was found that choline chloride ·  $xZnCl_2$  ( $x = 1-3$ ) efficiently promoted the acetalization reaction as did benzyltrimethylammonium chloride ·  $2ZnCl_2$  80–85% benzaldehyde conversions were obtained over four different ionic liquids, and the only product is the corresponding 1,3-dioxane (entries 1–4). When choline chloride was used alone, only trace amount of product was formed (entry 5). We speculate that the acetalization reaction was promoted by some Lewis acidic species ( $ZnCl_3^-$ ,  $Zn_2Cl_5^-$ , and  $Zn_3Cl_7^-$ ) [16] in the ionic liquids. Compared with benzyltrimethylammonium chloride ·  $2ZnCl_2$ , the real advantage of choline chloride ·  $2ZnCl_2$  came in the phase separation. Because of the low melting point ( $12^\circ C$ ) of choline chloride ·  $2ZnCl_2$ , the organic phase could be easily isolated by decantation. Moreover, choline chloride ·  $2ZnCl_2$  is better choice from the viewpoint of economy compared with benzyltrimethylammonium chloride ·  $2ZnCl_2$ .

### 3.2. Optimization of reaction conditions

The reaction between benzaldehyde and neopentyl glycol was then investigated over choline chloride · 2ZnCl<sub>2</sub> ionic liquid under different conditions and the results were listed in Table 2. As the ratio of neopentyl glycol to benzaldehyde was increased from 1.0 to 1.5, benzaldehyde conversions were increased from 83% to 95% correspondingly (entries 1 and 2). When the shortened reaction time or decreased catalyst amount (10 mol% of choline chloride · 2ZnCl<sub>2</sub>) was used, the results were slightly decreased, and 78% and 82% of benzaldehyde conversions were observed, respectively (entries 4 and 6). The subsequent condition optimization experiments revealed that both 10 h reaction time and 20 mol% of catalyst amount were necessary to complete the reaction (entries 4–7). Thus, the optimized conditions should be 1.5 for the ratio of neopentyl glycol to benzaldehyde, 20 mol% of choline chloride · 2ZnCl<sub>2</sub> and 10 h for reaction time. Under this optimized condition, benzaldehyde could be consumed in 95% conversion without formation of any undesired product.

### 3.3. Choline chloride · 2ZnCl<sub>2</sub> catalyzed reaction between carbonyl compounds and different protection reagents

To examine the generality of substrate, various carbonyl compounds were then used to react with neopentyl glycol over choline chloride · 2ZnCl<sub>2</sub> system. The results in Table 3 clearly demonstrate that choline chloride · 2ZnCl<sub>2</sub> is very efficient catalyst for protection of aldehydes when using neopentyl glycol as protection reagent. For example, 91% aldehyde conversion could be observed when using hexanal as substrate to react with neopentyl glycol, and the only product is corresponding 1,3-dioxane (entry 1). Cinnamaldehyde, an acid-labile substrate, was smoothly converted to the corresponding product without any damage of the double bond (entry 2). Under the same condition, aromatic aldehydes, such as *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde could also be acetalized to afford the corresponding 1,3-dioxanes in 97% and 95% aldehyde

conversions (entries 3 and 4). The heterocyclic compounds, 2-furaldehyde and 2-pyridinecarboxaldehyde, were then examined in our system. Much to our delight, choline chloride · 2ZnCl<sub>2</sub> was found to be also effective for these two aldehydes, and the aldehyde conversions were reached to 87% and 75%, respectively for 2-furaldehyde and 2-pyridinecarboxaldehyde (entries 5 and 6). For reactions of some less reactive ketones, such as cyclohexanone and acetophenone, no ketalization was observed at room temperature in choline chloride · 2ZnCl<sub>2</sub> system. Fortunately, moderate ketone conversions could be observed at higher temperature (60 °C, entries 7, 8). Other protection reagents such as ethylene glycol, 1,2-propanediol, 2,3-butanediol, 1,3-propanediol and 1,4-butanediol were also tested using benzaldehyde as model carbonyl compound (entries 9–15). All the examined diols, with an exception of 1,4-butanediol, could smoothly react with benzaldehyde in moderate to good benzaldehyde conversions. Especially, when 2,3-butanediol was used as protection reagent to react with butyraldehyde and benzaldehyde, more than 90% conversions were obtained after certain periods. These good results may profit from the hindrance of two methyl groups in the molecule structure.

### 3.4. Lewis acidity of choline chloride · *x*ZnCl<sub>2</sub>


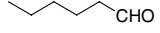
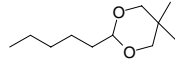

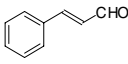
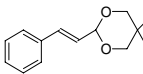


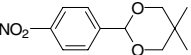

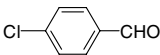
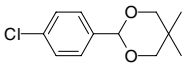

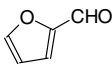
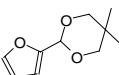

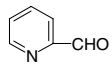
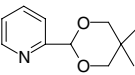


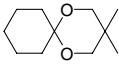


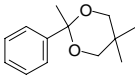

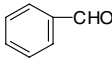
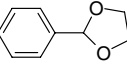


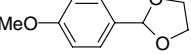

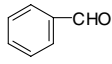
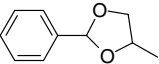
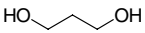
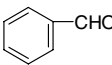
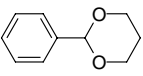
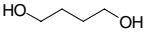
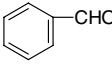
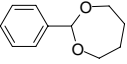


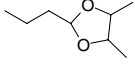

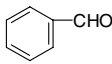
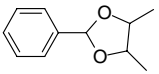
It was evident that various Lewis acidic chlorozincate clusters (ZnCl<sub>3</sub><sup>-</sup>, Zn<sub>2</sub>Cl<sub>5</sub><sup>-</sup>, and Zn<sub>3</sub>Cl<sub>7</sub><sup>-</sup>) are present in chloride · *x*ZnCl<sub>2</sub> ionic liquids by the record of FAB-MS [16]. Pyridine has been widely used as a probe molecule for determination of the Lewis and Brønsted acidity of some solid acids by monitoring the bands in the range of 1400–1700 cm<sup>-1</sup> arising from its ring vibration modes [19]. Recently, this method has proved to be applicable to determine the Lewis acidity of the acidic ionic liquids [20]. The presence of a band near 1450 cm<sup>-1</sup> is an indicative of pyridine coordination to Lewis acid sites, whilst a band near 1540 cm<sup>-1</sup> is an indication of the formation of pyridinium ions resulting from the presence of Brønsted acidic sites. It was well known that the wavenumber of the band near 1450 cm<sup>-1</sup> was increased slightly with increase of the Lewis acidity [20]. To estimate the Lewis acidities of our catalytic systems, pyridine was added to choline chloride · *x*ZnCl<sub>2</sub> and benzyltrimethylammonium chloride · 2ZnCl<sub>2</sub> ionic liquids followed by FT-IR scanning. As shown in Fig. 1, neat pyridine represents a well resolved single band at 1437 cm<sup>-1</sup> (Fig. 1(a)). In choline chloride · *x*ZnCl<sub>2</sub> or benzyltrimethylammonium chloride · 2ZnCl<sub>2</sub> (Fig. 1(b)–(e)), band shifts from 1437 to 1448 cm<sup>-1</sup> were observed, indicating the coordination of pyridine to Lewis acid sites [20]. Because the four ionic liquids cause same band shift of pyridine molecule, we can conclude that they have similar Lewis acid strength. This is in agreement with those catalytic activities obtained in protection of benzylaldehyde with neopentyl glycol (Table 1). It is also noteworthy that

Table 2  
Choline chloride · 2ZnCl<sub>2</sub> catalyzed reaction between benzaldehyde and neopentyl glycol

Entry	Neopentyl glycol/ benzaldehyde (M/M)	Time (h)	Amount of catalyst (%)	Conversion (%) <sup>a</sup>
1	1	10	20	83
2	1.5	10	20	95
3	3	10	20	95
4	1.5	4	20	78
5	1.5	20	20	96
6	1.5	10	10	82
7	1.5	10	50	96

<sup>a</sup> Conversion of benzaldehyde, selectivities are all near 100% to 1,3-dioxane.

Table 3  
Results of acetalizations of diols with aldehydes (acetones) over choline chloride · 2ZnCl<sub>2</sub>

Entry	Alcohol	Aldehyde/acetone	Products	Temperature (°C)	Time (h)	Conversion (%) <sup>a</sup>
1				r.t	10	90
2				r.t	10	92
3				r.t	10	97
4				r.t	10	95
5				r.t	10	87
6				r.t	20	75
7				60	20	68
8				60	20	55
9				r.t	20	52
10				r.t	20	44
11				r.t	20	57
12				r.t	20	55
13				r.t	20	11
14				r.t	10	92
15				r.t	10	96

<sup>a</sup>Conversion of benzaldehyde; selectivities are all near 100%.

no band was observed at approximately 1540 cm<sup>-1</sup>, indicating the fact that there is no Brønsted acid site in choline chloride · xZnCl<sub>2</sub> and benzyltrimethylammonium chloride · 2ZnCl<sub>2</sub>.

### 3.5. Recovery and reuse of choline chloride · 2ZnCl<sub>2</sub>

As described in the experimental section, choline chloride · 2ZnCl<sub>2</sub> could be easily recovered by extraction and

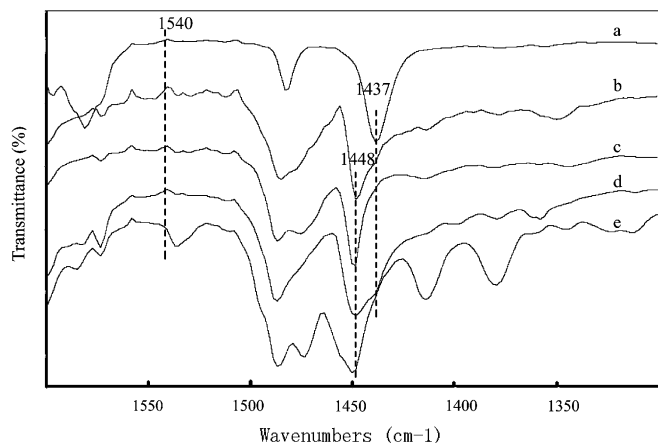


Fig. 1. FT-IR spectra of: (a) pure pyridine; (b) pyridine + choline chloride · ZnCl<sub>2</sub>; (c) pyridine + choline chloride · 2ZnCl<sub>2</sub>; (d) pyridine + choline chloride · 3ZnCl<sub>2</sub>; and (e) pyridine + benzyltrimethylammonium chloride · 2ZnCl<sub>2</sub> (pyridine/ionic liquid = 1:3 by weight in b–e).

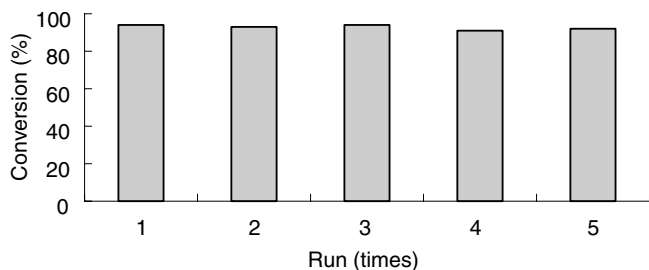


Fig. 2A. Recycling of choline chloride · 2ZnCl<sub>2</sub>.

decantation. After washing with Et<sub>2</sub>O and drying at 70 °C in vacuum for 2 h, the recovered choline chloride · 2ZnCl<sub>2</sub> was used in the next run. Fig. 2A shows the catalyst can be reused at least five times without appreciable loss of activity.

Infrared spectra of choline chloride, fresh choline chloride · 2ZnCl<sub>2</sub> and recovered choline chloride · 2ZnCl<sub>2</sub>

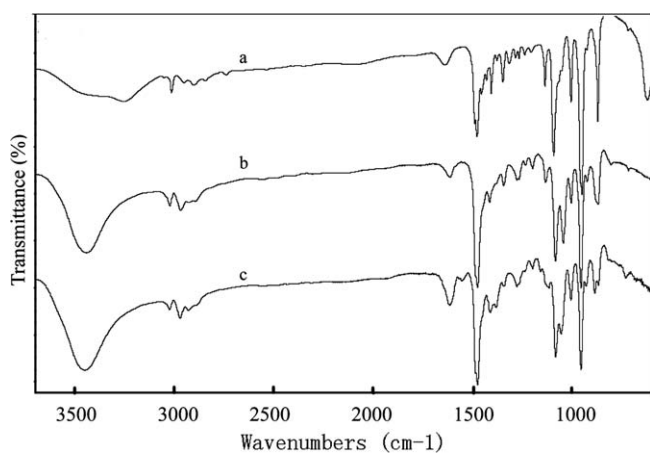


Fig. 2B. FT-IR spectra of: (a) choline chloride; (b) choline chloride · 2ZnCl<sub>2</sub>; (c) choline chloride · 2ZnCl<sub>2</sub> reused five times.

(reused five times in protection of benzaldehyde with neopentyl glycol) are shown in Fig. 2B. Observation of a broad band in 3450 cm<sup>-1</sup> (Fig. 2B(b, c)) clearly indicate the presence of water in the fresh and reused ionic liquids. The bands near 3300–3500, 1090, 1050 cm<sup>-1</sup> could be assigned to the –OH part or C–C–O stretching vibration associated with the N–C<sub>2</sub>H<sub>4</sub>–OH group of choline cation. Furthermore, the characteristic bands of mono-substituted benzene in the range 3100–3000, 1600, 1500, and 770–680 cm<sup>-1</sup> were not observed in the recovered choline chloride · 2ZnCl<sub>2</sub>, obviating our worry about the possible reaction between the hydroxyl in the catalyst and benzaldehyde.

#### 4. Conclusion

Choline chloride · xZnCl<sub>2</sub> and benzyltrimethylammonium chloride · 2ZnCl<sub>2</sub> were used as cost-effective and moisture-stable Lewis acidic catalysts for protection of many carbonyl compounds. Various aldehydes could be successfully converted to corresponding acetals using neopentyl glycol as protection reagent at mild and solvent-free conditions. FT-IR investigation demonstrates that, the four ionic liquids have similar Lewis acid strength, which is in agreement with the activities observed in the protection of carbonyls. The simple procedures as well as easy recovery and reuse of this novel catalytic system are expected to contribute to the development of more benign acetalization procedure of carbonyl compounds.

#### Acknowledgment

This work was financially supported by National Natural Science Foundation of China (Nos. 20225309 and 20533080).

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