

# Friedel-Crafts acylation reactions in pyridinium based ionic liquids

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## Abstract

The Friedel-Crafts acylations of representative aromatic compounds with acetic anhydride in pyridinium based ionic liquids (ILs) were investigated. The effect of factors such as reactant composition, catalyst-IL composition, catalyst dosage and reaction temperature were studied. The reactions were found to proceed under relatively mild conditions with excellent conversions; and a simple product isolation procedure was achieved. ILs could also be recycled and reused effectively, thus rendering green characteristic to this reaction.

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*Keywords:* Pyridinium ionic liquid; Friedel-Crafts acylation

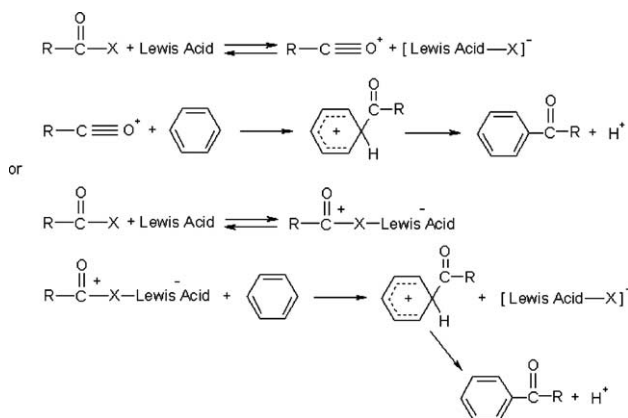
## 1. Introduction

The Friedel-Crafts acylation of aromatic compounds is an important method for the synthesis of aromatic ketones [1]. This method has been widely used in the synthesis of pharmaceuticals, fine chemicals and polymers [2–5]. The acylation reaction involves substitution by an acyl group, RCO–, derived from a carboxylic acid derivative, usually an acid halide or acid anhydride. The carbonyl group in such acid derivatives is sufficiently basic that formation of a complex requires a strong Lewis acid. A general mechanism is shown in Scheme 1 [6]. Generally, acids such as BF<sub>3</sub>, ZnCl<sub>2</sub>, TiCl<sub>4</sub>, SbF<sub>5</sub>, etc., could promote this reaction; however, AlCl<sub>3</sub> is most commonly used as catalyst. Although, this reaction is widely applied in industry, there are some disadvantages such as long reaction time, troublesome product recovery and purification, catalysts can not be reused and formation of environmentally hazardous, corrosive aluminate waste. In contrast, very few examples are reported in the literature where FeCl<sub>3</sub>, an envi-

ronmentally favorable catalyst is applied for this reaction [7,8].

Recently, much attention has been focused on ionic liquids for their advantageous applications in organic reactions [9–12]. The increased interest for their investigations is mainly due to their green characteristics, such as chemical and thermal stability, no measurable vapor pressure, non-flammability, non-coordinating yet solvation properties etc. [13]. They can be readily recycled; have profound effect on the activity and selectivity in reactions and in some cases, facilitate the isolation of products. Therefore, ionic liquids are considered viable substitute for volatile organic solvents. There are literature examples reporting clean synthesis and improved reaction characteristics of the Friedel-Crafts acylation in ILs [14–20]. The conversion and selectivity of the reaction in these studies vary with the catalyst, substrates and reaction conditions. Also, all these studies have focused only on the ILs derived from imidazole. Encouraged by earlier successful investigations with pyridinium based ionic liquids [21,22]; we embarked on the study of Friedel-Crafts acylation in these solvents. Here we wish to report the results of this first study on the Friedel-Crafts acylation using pyridinium based ionic liquids as solvents (Fig. 1).

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Scheme 1. General mechanism of acylations.

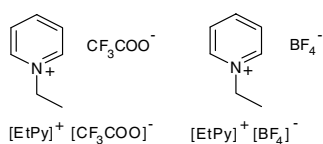
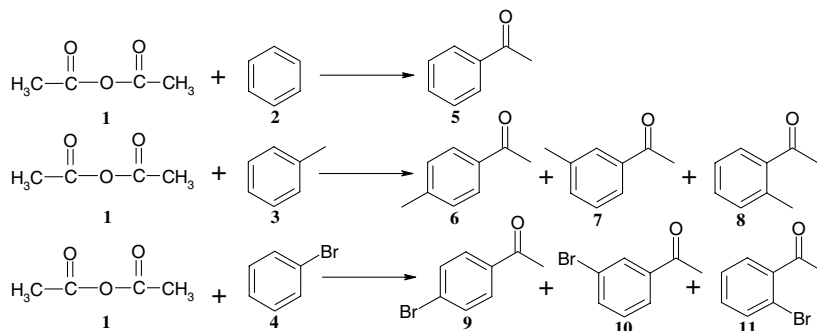


Fig. 1. Pyridinium based ionic liquids.

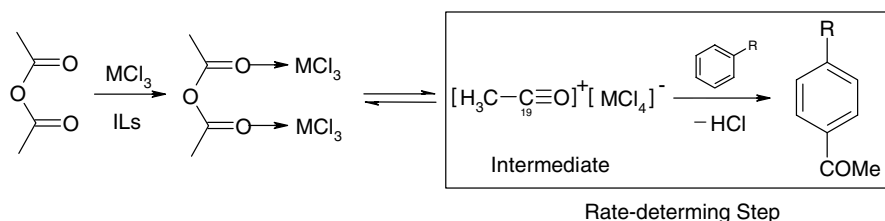
## 2. Results and discussion

Two ionic liquids investigated in this study, 1-ethylpyridinium trifluoroacetate ([EtPy]<sup>+</sup>[CF<sub>3</sub>COO]<sup>-</sup>) and 1-ethylpyridinium tetrafluoroborate ([EtPy]<sup>+</sup>[BF<sub>4</sub>]<sup>-</sup>), are shown in Fig. 1 below.

The utility of these ILs was investigated in the acylation reactions using acetic anhydride **1** and aromatic compounds benzene **2**, toluene **3** and bromobenzene **4** (Scheme 2).



Scheme 2. Friedel-Crafts acylation reaction with acetic anhydride.



Scheme 3. Proposed mechanism.

In a typical reaction, specified amount of catalyst (anhydrous FeCl<sub>3</sub> or AlCl<sub>3</sub>) was slowly added to ionic liquid and mixture was continuously stirred at 45 °C until the catalyst completely dissolved. Acetic anhydride (**1**) and aromatic compound (**2**, **3** or **4**) were added directly to the catalyst-IL mixture. As a result two phases (ionic liquid and organic) were formed, and the mixture stirred (250 rpm) at a desired reaction temperature for 4 h. The molar ratio of aromatic: acetic anhydride: ionic liquid was maintained at 2:1:1. (see Scheme 3).

### 2.1. Acylation of benzene with acetic anhydride

As shown in Scheme 2, Eq. 1, acetophenone was obtained as the major product in acylation of benzene **2** with acetic anhydride **1** in different catalyst-IL systems at various temperatures. The results are listed in Table 1.

The first important observation here is that significant amount product formation was seen in ionic liquid medium (entry 1, 2), even in the absence of any catalyst. This renders truly green characteristics to the reaction procedure. Further, as data shows the reaction yields are dependent on the catalyst-solvent composition. When same reaction was carried out in the presence of a catalyst in ionic liquid, the product yields improved. Both FeCl<sub>3</sub> and AlCl<sub>3</sub> promoted the reaction, giving nearly same yield for the products. This suggests that the FeCl<sub>3</sub>-IL system could efficiently substitute AlCl<sub>3</sub>-IL system for the Friedel-Crafts acylations. Also, a comparative study of different temperatures (rt, 50 and 75 °C) showed that the product conversions were higher when reaction temperature was increased to 50 °C. However, further increasing the temperature to 75 °C

Table 1  
The Friedel-Crafts acylation of acetic anhydride **1** with benzene **2**<sup>a</sup>

Entry	Catalyst–solvent	Conv. (%) rt/50 °C/75 °C	Selectivity to major product (%) rt/50 °C/75 °C
1	[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	51/72/78	100/97/69
2	[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	60/77/81	100/99/71
3	AlCl <sub>3</sub> –[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	77/92/94	100/96/70
4	AlCl <sub>3</sub> –[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	84/98/99	100/99/74
5	FeCl <sub>3</sub> –[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	73/90/93	100/94/73
6	FeCl <sub>3</sub> –[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	82/97/97	100/97/75

<sup>a</sup> Molar ration of benzene:acetic anhydride:catalyst: IL = 2:1:2:1.

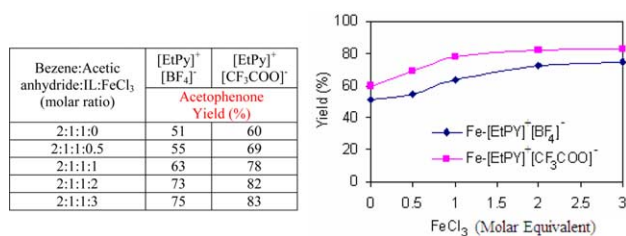


Fig. 2. The acylation of benzene and acetic anhydride with different content of FeCl<sub>3</sub>.

resulted in decreased yield of the desired product, and unidentified byproducts formed. In all case, the results with [EtPy]<sup>+</sup>[CF<sub>3</sub>COO]<sup>−</sup> are better than those with [EtPy]<sup>+</sup>[BF<sub>4</sub>]<sup>−</sup> even though they have the same cation. This indicates the anions of ILs are critical for the acylation reactions.

In order to find a suitable catalyst amount in the FeCl<sub>3</sub>-IL system, this reaction was studied with different FeCl<sub>3</sub> molar ratios at room temperature for 4 h in both ILs. However, the molar ratio of benzene:acetic anhydride:ionic liquid was maintained at 2:1:1. The results are shown in Fig. 2.

As data shows the catalytic activity increases on increasing the amount of FeCl<sub>3</sub> to 2 molar equivalent. However, further increasing the molar ratio of FeCl<sub>3</sub> to 3 equivalent did not have any significant change in product yields. Interestingly, this optimized FeCl<sub>3</sub> amount in ionic liquid, i.e., 2 equivalent is similar to other studies reported in the literature [15,19]. Therefore, further investigations were carried out with these optimized conditions.

## 2.2. Acylation of toluene with acetic anhydride

The acylation of toluene (Scheme 2, Eq. 2) resulted in three products, i.e., *para*- (**6**), *meta*- (**7**) and *ortho*- (**8**). The major product of this reaction was the *para*-compound. Results of this reaction in different catalyst-IL systems at room temperature and at 50 °C are shown in Table 2.

As Table 2 shows higher conversions were seen with toluene compared to that with benzene at room temper-

Table 2  
The Friedel-Crafts acylation of acetic anhydride **1** with toluene **3**

Entry	Catalyst–solvent	Conv. (%) rt/50 °C	Selectivity to major product (%) rt/50 °C
1	[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	55/75	57/66
2	[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	62/80	61/72
3	AlCl <sub>3</sub> –[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	77/89	63/70
4	AlCl <sub>3</sub> –[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	86/98	65/77
5	FeCl <sub>3</sub> –[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	74/89	63/71
6	FeCl <sub>3</sub> –[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	85/96	67/80

ature (Table 1). This could be due to inductive effect of the CH<sub>3</sub>-moiety, which increases the reactivity of the phenyl ring in toluene. However, significant amount of *ortho*-product is also formed, which results in reduced overall selectivity. A comparative study at two different temperatures (rt and 50 °C) showed that higher product conversions are obtained with increased temperature. Similar to previous reaction, these results also show that the catalytic activity FeCl<sub>3</sub>-IL is comparable with AlCl<sub>3</sub>-IL system. The ionic liquid [EtPy]<sup>+</sup>[CF<sub>3</sub>COO]<sup>−</sup> has relatively more influence on acylation reaction compared to [EtPy]<sup>+</sup>[BF<sub>4</sub>]<sup>−</sup>. Again, suggesting that the anion of IL has some influence as well. Therefore, further systematic studies with different anions are required for better understanding of the anion effect.

## 2.3. Acylation of bromobenzene with acetic anhydride

As shown in Scheme 2, Eq. 3, acylation of bromobenzene with acetic anhydride gave three products. In this reaction, *para*-isomer, i.e. (*p*-bromobenzene) methyl ketone **9**, was the major product. Similar to previous examples, the reaction was tested in both ionic liquids at two different temperatures. The results are listed in Table 3.

The data suggests that an electron-withdrawing group Br-renders bromobenzene less reactive than benzene and toluene. As a result, the conversion is slightly lower than the previous reactions. However, the selectivity is relatively higher than for toluene. This could be due to *ortho*- and *para*-directing and deactivating effect

Table 3  
The Friedel-Crafts acylation of acetic anhydride **1** with bromobenzene **4**

Entry	Catalyst–solvent	Conv. (%) rt/50 °C	Selectivity to major product (%) rt/50 °C
1	[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	54/71	61/74
2	[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	63/77	69/82
3	AlCl <sub>3</sub> –[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	76/86	73/86
4	AlCl <sub>3</sub> –[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	84/95	83/92
5	FeCl <sub>3</sub> –[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>−</sup>	73/88	76/87
6	FeCl <sub>3</sub> –[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>−</sup>	82/93	85/93

of Br, seem more predominant on the *para*-position. Also, in this case, steric effect favors the *para*-product. Though, improved conversions are seen with the catalyst-IL system, it is noteworthy that reaction could also proceed in ionic liquid alone. In all cases, the results with [EtPy]<sup>+</sup>[CF<sub>3</sub>COO]<sup>-</sup> are better than those with [EtPy]<sup>+</sup>[BF<sub>4</sub>]<sup>-</sup>, and FeCl<sub>3</sub>-IL show efficiency similar to the AlCl<sub>3</sub>-IL system.

#### 2.4. Recycle and reuse of FeCl<sub>3</sub>-IL

The IL-catalyst system was recycled to investigate the reusability and efficiency of ionic liquids, with or without catalyst. The recycling process involved washing the used ionic liquids with diethyl ether to remove any leftover organic residues. Two layers formed (ionic liquid and organic). The resulted ILs were separated and the ionic liquid dried under reduced pressure at 65 °C. Successive runs were used for acylation between benzene and acetic anhydride (Scheme 2, Eq. 1) at 50 °C for 4 h. Results are shown in Table 4.

Both ionic liquids could be recovered quantitatively with negligible loss of activity. Moreover, the acylation was not affected even after 3rd run with the recovered ionic liquid. Similar study was also carried out with recovered FeCl<sub>3</sub>-IL system, for the acylation of benzene with acetic anhydride. Results are shown in Table 5

In this case, even though FeCl<sub>3</sub>-IL system could be recovered efficiently, the conversion to acylation product dropped dramatically. After 3rd trial, conversions obtained were nearly same as seen with pure IL alone. This could be due to lost catalytic activity of the FeCl<sub>3</sub>-IL system.

Table 4  
Recycling of ionic liquids in the acylation of benzene and acetic anhydride

Recycling #	[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>-</sup>		[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>-</sup>	
	Recovered <sup>a</sup> (wt %)	Acetophenone yield (%)	Recovered <sup>a</sup> (wt%)	Acetophenone yield (%)
0	–	70	–	76
1	93	68	96	75
2	93	67	94	72
3	94	65	95	73

<sup>a</sup> Isolated yield.

Table 5  
Recycling of ionic liquids-FeCl<sub>3</sub> in the acylation of benzene and acetic anhydride

Recycling #	FeCl <sub>3</sub> -[EtPy] <sup>+</sup> [BF <sub>4</sub> ] <sup>-</sup>		FeCl <sub>3</sub> -[EtPy] <sup>+</sup> [CF <sub>3</sub> COO] <sup>-</sup>	
	Recovered <sup>a</sup> (w%)	Acetophenone yield (%)	Recovered <sup>a</sup> (w%)	Acetophenone yield (%)
0	–	85	–	94
1	90	80	88	90
2	87	75	91	83
3	89	73	88	81

<sup>a</sup> Isolated yield.

#### 2.5. Proposed mechanism

The ionic liquids [EtPy]<sup>+</sup>[BF<sub>4</sub>]<sup>-</sup> and [EtPy]<sup>+</sup>[CF<sub>3</sub>COO]<sup>-</sup> are suitable as solvents for the Friedel-Crafts acylation of aromatic compounds. Based on the classical mechanism of acylation (Scheme 1), we propose the following mechanism in IL-MCl<sub>3</sub> (M = Al or Fe) system.

The acetic anhydride reacts with Lewis acid to form a more electrophilic C<sup>+</sup>, an acylium ion. Subsequently, reaction with nucleophilic aromatic ring results in cyclohexadienyl cation. Removal of the proton reforms the aromaticity generating HCl as byproduct. We found that the rate of this reaction is significantly enhanced in ionic liquids compared to organic solvents [17,23]. This enhanced rate of the reactions is due to lowered activation energy of the slow reaction step. This is due to ionic nature of the ionic liquid medium which makes intermediate relatively more accessible for reaction with aromatics.

It has been reported earlier [14,20] that the acetylium cation [CH<sub>3</sub>CO]<sup>+</sup>[MCl<sub>4</sub>]<sup>-</sup> is the key intermediate in the Friedel-Crafts acetylation reactions in ionic liquids, thus using ionic liquids instead of organic solvents does not change the mechanism of the Friedel-Crafts acetylation reaction. Furthermore, the product could be easily extracted with petroleum ether, indicating that the product did not combine with the catalyst. This further renders the reaction “green” characteristics.

### 3. Experimental

All reactions were carried out under nitrogen atmosphere. The reaction samples and products were analyzed using a Varian CP-3800 Gas Chromatograph equipped with SPB<sup>TM</sup>-5 column, 30 m × 0.25 mm × 0.25 μm. The conversion (based on the consumption of acetic anhydride) and the yield of major products were determined by the area ratio of each chromatograph peak as compared with the standard compounds.

#### 3.1. Synthesis of ionic liquids

Two ionic liquids 1-ethyl-pyridinium trifluoroacetate ([EtPy]<sup>+</sup>[CF<sub>3</sub>COO]<sup>-</sup>) and 1-ethyl-pyridinium tetrafluoroborate ([EtPy]<sup>+</sup>[BF<sub>4</sub>]<sup>-</sup>) were prepared following the literature methods [24,25].

##### 3.1.1. General synthetic procedure

Trifluoroacetic acid or tetrafluoroboric acid (0.2 mol) were slowly added to a stirred slurry of silver (I) oxide (0.1 mol) and distilled water (50 ml). To avoid photodegradation of silver (I) oxide, the reaction mixture was fully covered with aluminum foil. The reaction mixture was stirred continuously until the reaction was complete, which was indicated by the formation of a

solution. A solution of *N*-ethyl-pyridinium bromide (0.2 mol) was added to the reaction mixture. As reaction took place and ILs formed, a yellow precipitate of silver (I) bromide started to be observed. The mixture was stirred at room temperature for a certain time until no more precipitate formed. The stirring was stopped and precipitates allowed to settle at the bottom of the beaker with clear water layer at the top. Because *N*-ethyl pyridinium bromide is hygroscopic, silver (I) trifluoroacetate is used in excess. Therefore, we add 1 M solution of *N*-ethyl pyridinium bromide drop by drop. This step is repeated of AgBr are formed. To make sure no excess *N*-ethyl pyridinium bromide in the mixture, we test with 1 M silver (I) trifluoroacetate solution. Finally, the mixture is stirred for 10 min, and the precipitate of silver (I) bromide filtered off. Any color and impurities present in the synthesized ionic liquids could be removed by passing ILs through a charcoal column with distilled water [26]. Finally, the water is removed by rotary evaporation under vacuum at about 65 °C. The resulting ionic liquids are dried in an oven overnight at 65 °C to remove any residual moisture.

### 3.2. Acylation

#### 3.2.1. General experimental procedure

The catalyst, anhydrous AlCl<sub>3</sub> or FeCl<sub>3</sub> (16 mmol), was slowly added to pyridinium based ionic liquid (8 mmol). The mixture was stirred at 45 °C until the catalyst completely dissolved. Acetic anhydride 1 (8 mmol) was added to the mixture and stirred for 15 min then aromatics 2 or 3 or 4 (16 mmol) were added. Two phases were formed and the reaction mixture was allowed to stir (250 rpm) at the desired reaction temperature for 4 h. After the reaction was over, the mixture was diluted with 3 mL water and 3 mL petroleum ether and shaken vigorously. The organic layer was separated from ionic liquid. Any leftover organic material was extracted with ethyl ether and the ionic liquid was dried at 65 °C under vacuum to remove moisture and then reused. The combined organic extracts were washed with water (3 mL) followed by brine (3 mL). Evaporation under vacuum yielded the product and then dried over Na<sub>2</sub>SO<sub>4</sub>.

## 4. Conclusion

The pyridinium based ILs are suitable media for Friedel-Crafts acylation reactions. High conversions were obtained at relatively lower temperature, as compared with the literature studies [17,18,23] which were carried

out at high temperature and obtain similar results. Combination of [EtPy]<sup>+</sup>[CF<sub>3</sub>COO]<sup>-</sup>-FeCl<sub>3</sub> is found to be an excellent solvent–catalyst system, which could efficiently substitute the aluminum catalyst system. Applications of the pyridinium based ILs as solvents for number of other reactions are under investigation in our laboratory.

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