

1-Ethyl-3-methylimidazolium halogenoaluminate ionic liquids as solvents for Friedel–Crafts acylation reactions of ferrocene

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Friedel–Crafts acylations of ferrocene in 1-ethyl-3-methylimidazolium halogenoaluminate ionic liquids, $[\text{emim}]\text{I}-(\text{AlCl}_3)_x$, are described.³ The effect of varying the “bulk” Lewis acidity of the ionic liquids used as solvents in these reactions and the effect of varying the relative amounts of acylating agent with respect to the amount of ferrocene in these reactions is also described. The use of a variety of different acylating agents in our studies demonstrates the scope of this reaction performed in these ionic liquid systems.

The use of ambient temperature ionic liquids as solvents and catalysts for Friedel–Crafts reactions was first reported in 1976.¹ These very interesting solvent systems were derived from the mixture of an organic halide and aluminium chloride to form a low melting ionic liquid. Since this report, few examples have appeared in the literature in which synthetic chemistry has been conducted in ambient temperature ionic liquids. Interesting examples of the use of these solvent systems in synthetic chemistry include acidic ionic liquids that are utilized simultaneously as solvent and catalyst for Friedel–Crafts reactions, polymerization of ethene using titanocene dichloride derived catalysts, and ligand exchange reactions of ferrocene.^{2–5} Other interesting applications of ionic liquids include their use as novel media for liquid–liquid extractions.⁶

We have recently reported that the Friedel–Crafts acetylation of ferrocene can be conducted in the ionic liquid derived from 1-ethyl-3-methylimidazolium iodide, $[\text{emim}]\text{I}$, (Fig. 1) and two equivalents of aluminium chloride or in the liquid clathrate that is formed from the addition of toluene to these novel reaction media.³ Under the conditions utilized in this preliminary communication, synthetically useful amounts of monoacetylated product, namely acetylcyclopentadienyl(cyclopentadienyl)iron(II) **1a**, could be isolated. It was noted that when acetic anhydride was used as the acetylating reagent no diacetylated product, bis(acetylcyclopentadienyl)iron(II) **2a**, was detected when the reactions were two hours in duration. However, if longer reaction times were employed, some diacetylated product, **2a**, could be detected. In the course of our continuing investigations of this reaction system it was noticed that the ratio of compounds **1a** to **2a** was variable depending upon the source of aluminium chloride (*i.e.* an old bottle *versus* a fresh bottle of highly pure aluminium chloride). It soon became obvious that the outcome of these Friedel–Crafts reactions was dependent upon not only the degree of Lewis acidity of the ionic liquid, but also the amount of acylating agent present and reaction time (Scheme 1).

In this paper we provide a detailed account of our studies involving the Friedel–Crafts acylations of ferrocene in 1-ethyl-3-methylimidazolium halogenoaluminate ionic liquids.³ We also report herein the effect of varying the “bulk” Lewis acidity of the ionic liquids used as solvents in these reactions and the effect of varying the relative amounts of acylating agent with respect to the amount of ferrocene in these reactions. The use of a variety of different acylating agents in our studies demonstrates the scope of this reaction performed in these ionic liquid systems.

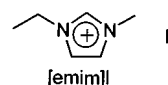
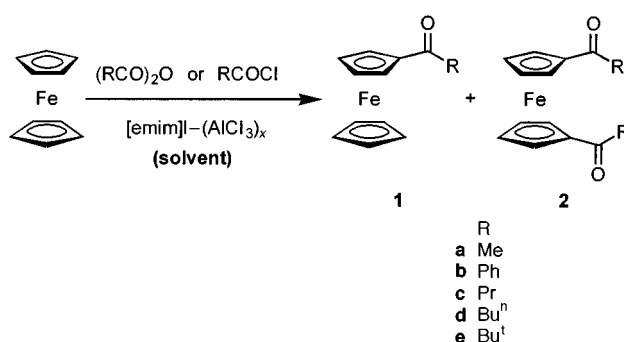


Fig. 1 1-Ethyl-3-methylimidazolium iodide.



Scheme 1 $[\text{emim}]\text{I}-(\text{AlCl}_3)_x$ as reaction media/solvents for Friedel–Crafts acylations of ferrocene.

Results and discussion

The ionic liquids used in this study are derived from the addition of varying amounts of AlCl_3 to 1-ethyl-3-methylimidazolium iodide, abbreviated as $[\text{emim}]\text{I}-(\text{AlCl}_3)_x$ (where x = number of equivalents of AlCl_3 added).⁷ Depending on the mole ratio, x , of AlCl_3 added with respect to the imidazolium salt, $[\text{emim}]\text{I}$, these ionic liquids have been shown to have variable Lewis acidities as described by the equilibrium shown in Scheme 2.⁸ If $x < 1.0$ then the predominant anionic species



Scheme 2 Equilibrium describing acid–base properties of $[\text{emim}]\text{I}-(\text{AlCl}_3)_x$ ionic liquids.²

present are AlX_4^- and Cl^- and the ionic liquid is said to be Lewis basic. If $x = 1.0$, then AlX_4^- is the predominating anionic species and the ionic liquid is said to be Lewis neutral. If $x > 1.0$, the Lewis acid Al_2X_7^- becomes increasingly more prevalent in solution and the ionic liquid is said to be Lewis acidic (in fact, when $x = 2.0$, Al_2X_7^- is the predominant anionic species present and the ionic liquid is referred to as “strictly acidic”).

The methods reported in the literature for the acetylation of ferrocene often use a large excess of the acylating agent (*i.e.* acetic anhydride or acetyl chloride) under refluxing conditions or involve otherwise vigorous reaction conditions to afford mixtures of mono- and diacetylated ferrocene.⁹ The use of [emim]I-(AlCl₃)_x ionic liquids as both solvent and catalyst, as described in this study, allows much more mild conditions (*i.e.* 0 °C) and stoichiometric quantities of reactants to be used. Furthermore, since ferrocene is very soluble in the [emim]I-(AlCl₃)_x ionic liquids, much smaller reaction volumes can be used. Indeed, such mild reaction conditions may enable Friedel-Crafts chemistry to be performed with metallocenes (*i.e.* ruthenocene)¹⁰ and metal arenes that is otherwise difficult or inaccessible *via* conventional means.

Typical reaction conditions involve dissolution of ferrocene in the ionic liquid prepared from the addition of 1.2 equivalents of highly pure AlCl₃ to 1.0 equivalent of [emim]I. Two equivalents of acetic anhydride (with respect to ferrocene) are then added *via* syringe at 0 °C and the reaction is stirred under scrupulously dry conditions for two hours before only monoacetylated ferrocene, **1a**, is isolated in excellent yield after workup (Table 1) and chromatographic purification.

When a Lewis neutral ionic liquid was used no Friedel-Crafts acylation was observed (Table 1). This is to be expected since no Lewis acid catalyst is present in these solutions when $x \leq 1.0$ and the formation of the electrophilic acylium ion does not occur. As the relative proportion of AlCl₃ is increased for the acidic ionic liquid solutions, the relative proportion of

diacetylated ferrocene, **2a**, isolated from these reactions also increases (Table 1). It is evident from this study that as the Lewis acid present in solution becomes available in excess quantities the electrophilic species generated *in situ* must also become more prevalent and hence more highly reactive.¹¹ As a result, the monoacetylated ferrocene, **1a**, can be acetylated a second time to afford compound **2a**. Noteworthy is the fact that when the ionic liquid is prepared from a 3 : 1 admixture of AlCl₃ and [emim]I (Table 1) the proportion of compound **2a** to compound **1a** remains approximately the same as in the 2 : 1 case (Table 1); however, the overall chemical yield goes down substantially in the 3 : 1 case. We attribute this decrease in overall yield of mono- and di-acetylated adducts to the presence of large quantities of intractable "oily", and perhaps polymeric, by-products that form in these highly Lewis acidic reactions.

As alluded to in the Introduction, both the nature of and relative proportion of acylating agent, with respect to ferrocene, play an important role in the outcome of Friedel-Crafts acylation reactions performed in [emim]I-(AlCl₃)_x ionic liquids (Table 2). In general, alkanoyl chlorides show higher reactivity in these systems and afford predominantly diacetylated products. This is particularly the case when a ten-fold excess of alkanoyl chloride is used as the acylating agent. Interestingly, when benzoyl chloride is used as the acylating agent, the monoacylated product is preferred (Table 2). This has been attributed to the lower reactivity/higher stability of the electrophile formed from benzoyl chloride, Ph-C⁺O, *versus* those formed from the alkanoyl chlorides, R-C⁺O (where R = alkyl).^{2,11} When pivaloyl chloride was used as the acylating agent only very small quantities of diacylated product were isolated. Other than the small quantities of compound **2e**, only intractable mixtures of compounds insoluble in standard organic solvents were isolated from the reactions involving pivaloyl chloride.

The use of acid anhydrides as acylating agents in the Friedel-Crafts acylations of ferrocene conducted in [emim]I-(AlCl₃)_x ionic liquids met with limited success (Table 1 and Table 2). Only when acetic anhydride was used as the acylating agent were any Friedel-Crafts acylation products isolated from the reaction mixtures. Conditions in which acetic anhydride is employed in the weakly acidic [emim]I-(AlCl₃)_x derived ionic liquid afford monoacetylated ferrocene, acetylcyclopentadienyl(cyclopentadienyl)iron(II) **1a**, as the only product (Table 1). Conditions in which a ten-fold excess of acetic anhydride is

Table 1 Effect of Lewis acidity on Friedel-Crafts acylation of ferrocene in [emim]I-(AlCl₃)_x ionic liquids

[emim]I : AlCl ₃	Monoacylated Product 1a (%)	Diacetylated Product 2a (%)	Ratio Di : Mono ^a 2a : 1a
1.0 : 1.0	0	0	0
1.0 : 1.2	89	0	0
1.0 : 1.4	38	38	1
1.0 : 1.8	26	29	1.1
1.0 : 2.0	16	40	2.5
1.0 : 3.0	9	19	2.1

^a Unless otherwise stated, balance of material recovered during purification consisted of unreacted ferrocene.

Table 2 Effect of acylating agent on Friedel-Crafts acylations of ferrocene in [emim]I-(AlCl₃)₂ ionic liquids^{a,b}

Acylating agent	Equiv. of acylating agent w.r.t. ferrocene	Yield monoacylated (%)	Yield diacylated (%) ^c
Valeryl chloride	1	25	57
	2	22	65
	10	0	89
Isobutyryl chloride	1	12	30
	2	6	47
	10	0	85
Benzoyl chloride	1	14	0
	2	23	4
	10	83	12
Trimethylacetyl chloride	1	0	4
	2	0	8
	10	0	0
Acetyl chloride	1	26	27
	2	18	34
	10	13	66
Acetic anhydride	1	16	43
	2	16	40
	10	10	58
Succinic anhydride	All proportions	N.R. ^d	
Maleic anhydride	All proportions	N.R.	
Diethylcarbonyl chloride	All proportions	N.R.	

^a Prepared from 1 equiv. [emim]I + 2 equiv. AlCl₃, ^b All reactions were 2 h at 0 °C. ^c Unless otherwise stated, balance of material recovered during purification consisted of unreacted ferrocene. ^d N.R. = no reaction.

employed as the acylating agent in the strictly acidic [emim]I–(AlCl₃)_x derived ionic liquid afford diacetylated ferrocene, bis(acetylcyclopentadienyl)iron(II) **2a**, in a reasonable yield (Table 2).

The cyclic anhydrides, succinic anhydride and maleic anhydride, afforded no Friedel–Crafts products (Table 2). In these reactions unreacted starting material, ferrocene, was isolated after work-up and chromatographic separation.

An increasingly higher number of chiral cyclopentadienyl complexes of transition metals are being prepared and used as catalysts or ligands in asymmetric synthesis.¹² Frequently, the precursors to these chiral catalysts, such as bis(diethylcarbamoylcyclopentadienyl)iron(II) **3**, can be difficult and expensive to prepare using conventional methods. Hence, we endeavored to prepare **3** in a more facile manner using [emim]I–(AlCl₃)_x derived ionic liquids as solvents. Unfortunately, our attempts to prepare **3** by the reaction of ferrocene with *N,N*-diethylcarbamoylchloride in [emim]I–(AlCl₃)_x derived ionic liquids failed (Table 2).

Studies directed at the synthesis of important synthetic precursors to chiral transition metal catalysts, such as **3**, continue in our laboratory. Investigations into other Lewis acid catalyzed reactions, including Friedel–Crafts reactions with other metallocenes and metal arenes, that can be performed in these reaction media as well as development of methods in which the ionic liquid reaction media can be recycled are currently underway in our laboratories.

Experimental

General methods

All glassware and syringes were dried in an oven overnight at 120 °C and glassware was flame dried and flushed with argon or nitrogen immediately prior to use. Transfer of solid reagents and formation of ionic liquids was performed inside a glove box (VAC HE-63-P) under argon atmosphere or with syringes equipped with stainless steel needles. Methylimidazole, iodoethane and AlCl₃ (99.99%) were used as purchased from Aldrich Chemical Company, Inc. Ferrocene (Caledon Laboratories Ltd.) was purified by sublimation just prior to use. Acetic anhydride (Caledon Laboratories Ltd.), acetyl chloride (Fisher Scientific), and benzoyl chloride (Kodak) were distilled shortly before use. Isobutryl chloride and valeryl chloride were used as purchased from Aldrich Chemical Company, Inc. Maleic anhydride (Kodak) and succinic anhydride (Aldrich Chemical Company, Inc.) were dissolved in chloroform, filtered to remove any insoluble impurities, and the solvent removed *in vacuo* prior to use. Purification of all the products was done using column chromatography with Silica Gel 60 (Caledon Laboratories LTD., 63–200 mesh). ¹H and ¹³C NMR spectra were recorded in ppm relative to tetramethylsilane at 250.13 MHz or 400.13 MHz for ¹H and 62.9 MHz or 100.6 MHz for ¹³C.

Preparation of 1-ethyl-3-methylimidazolium iodide, [emim]I

To an oven dried round bottomed flask containing 200 mL of freshly dried and distilled THF was added methylimidazole (31.9 mL, 0.400 mol) and iodoethane (38.4 mL, 0.480 mol) *via* syringe. The mixture was allowed to stir while refluxing for 4 hours. Removal of THF *in vacuo*, resulted in a white solid that was protected from the light by wrapping the round bottomed flask in an aluminium foil. The white solid was then heated *in vacuo* at 100 °C for 6 hours to remove residual solvent and any unreacted starting materials (yield: 95.0 g, 100%; mp 79–80 °C).¹³

Preparation of 1-ethyl-3-methylimidazolium halogenoaluminate ionic liquids, [emim]I–(AlCl₃)_x

An oven dried round bottomed flask in a glove box was charged

with 1-ethyl-3-methylimidazolium iodide (5.0 g, 21 mmol). While the powdery white solid was agitated with a magnetic stirbar, AlCl₃ (2.8 g to 8.4 g, 21 mmol to 63 mmol) was added very slowly to afford the ionic liquids of variable Lewis acidity to be used for the acidity study. For [emim]I–(AlCl₃)₂: δ_H(CDCl₃): 0.84 (t, 3H, *J* = 7.3), 3.2 (s, 3H), 3.5 (q, 2H, *J* = 7.3 Hz), 6.6 (s, 1H), 6.7 (s, 1H), 7.6 (s, 1H).

Typical reaction of ferrocene with acetic anhydride in ionic liquids

Ferrocene (0.25 g, 1.35 mmol) was added to the ionic liquid (as prepared above to afford a ratio of [emim]I–(AlCl₃)₂:AlCl₃ = 1.0:2.0) in a glove box to afford a greenish-brown solution that was allowed to stir for 10 minutes. The reaction vessel was sealed with a septum, removed from the glove box, and placed in an ice bath at 0 °C. Acetic anhydride (0.254 mL, 2.70 mmol, 2 equiv. with respect to ferrocene) was added *via* syringe to afford a purple solution that was allowed to stir for 2 hours at 0 °C. The reaction was then quenched using 10 mL of 2 M hydrochloric acid and extracted with 3 × 25 mL dichloromethane. The combined organic phases were dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting crude oil was purified using column chromatography with silica gel and hexanes–ethyl acetate (10:1). The polarity of the solvent system was increased gradually to hexanes–ethyl acetate (1:1) to elute any diacetylated product. Spectra recorded for both **1a** and **2a** were in agreement with those reported in the literature.¹² Monoacylated ferrocene, **1a** (0.050 g, 16%): δ_H(CDCl₃): 2.39 (s, 3H), 4.20 (s, 5H), 4.50 (dd, 2H, *J* = 1.83), 4.77 (dd, 2H, *J* = 1.83 Hz). δ_C(CDCl₃): 27.5, 69.6, 69.9, 72.4, 79.3, 202.2. Mass spectrum (EI, 70 eV): *m/z* (%): 228 (M⁺, 90), 213 (35), 185 (100), 152 (3), 129 (35), 121 (14). Diacylated ferrocene, **2a** (0.145 g, 40%): δ_H(CDCl₃): 2.35 (s, 6H), 4.51 (m, 4H), 4.77 (m, 4H). δ_C(CDCl₃): 27.8, 71.2, 73.8, 80.9, 201.3. Mass spectrum (EI, 70 eV): *m/z* (%): 270 (M⁺, 100), 255 (36), 227 (6), 199 (28), 163 (2), 121 (6).

Typical reaction of ferrocene with acid chlorides in ionic liquid

An oven dried round bottomed flask in a glove box was charged with 1-ethyl-3-methylimidazolium iodide (5.0 g, 21 mmol). While the powdery white solid was agitated with a magnetic stirbar, AlCl₃ (5.6 g, 42 mmol) was added very slowly to afford the ionic liquid. Ferrocene (0.25 g, 1.35 mmol) was added to the ionic liquid in the glove box to afford a greenish-brown solution that was allowed to stir for 10 minutes. The reaction vessel was sealed with a septum, removed from the glove box, and placed in an ice bath at 0 °C. The acylating agent (1, 2 or 10 equiv.) (Table 2) was added *via* syringe to afford a purple solution that was allowed to stir for 2 hours at 0 °C. The reaction was then quenched using 10 mL of 2 M hydrochloric acid and extracted with 3 × 25 mL dichloromethane. The combined organic phases were dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting crude oil was purified using column chromatography with silica gel and hexanes–ethyl acetate (10:1) as eluent. The polarity of the eluent was increased gradually to hexanes–ethyl acetate (1:1) to elute any diacylated product. Spectra recorded for all compounds were in agreement with those reported in the literature.¹²

Benzoylcyclopentadienyl(cyclopentadienyl)iron(II) **1b**

δ_H(CDCl₃): 4.2 (s, 5H), 4.6 (s, 4H), 4.9 (s, 4H), 7.5–7.9 (m, 5H). δ_C(CDCl₃): 70.5, 71.8, 72.8, 78.3, 128.3, 128.5, 131.7, 104.1, 199.4. Mass spectrum (EI, 70 eV): *m/z* (%): 290 (M⁺, 100), 261 (4), 213 (3), 105 (4), 77 (1).

Bis(benzoylcyclopentadienyl)iron(II) **2b**

δ_H(CDCl₃): 4.6 (m, 4H), 4.9 (m, 4H), 7.3–7.8 (m, 10H). δ_C(CDCl₃): 73.1, 74.6, 79.6, 128.1, 128.4, 132.0, 139.2, 198.0.

Mass spectrum (EI, 70 eV): m/z (%): 394 (M^+ , 100), 289 (9), 261 (7), 225 (1), 105 (5), 77 (2).

2-Methylpropanoylcyclopentadienyl(cyclopentadienyl)iron(II) 1c

δ_H (CDCl₃): 1.2 (d, 6H, $J = 6.85$), 3.1 (septet, 1H, $J = 6.85$ Hz), 4.2 (s, 5H), 4.5 (m, 2H), 4.7 (m, 2H). δ_C (CDCl₃): 19.6, 37.3, 69.5, 69.6, 72.2, 77.2, 208.7. Mass spectrum (EI, 70 eV): m/z (%): 256 (M^+ , 100), 213 (28), 185 (6), 129 (12), 121 (2).

Bis(2-methylpropanoylcyclopentadienyl)iron(II) 2c

δ_H (CDCl₃): 1.1 (d, 12H, $J = 6.1$), 3.0 (septet, 2H, $J = 6.1$ Hz), 4.4 (m, 4H), 4.7 (m, 4H). δ_C (CDCl₃): 19.3, 37.4, 70.7, 73.5, 79.195, 207.8. Mass spectrum (EI, 70 eV): m/z (%): 326 (M^+ , 93), 283 (23), 255 (100), 213 (2), 185 (7), 129 (7), 121 (6).

Pentanoylcyclopentadienyl(cyclopentadienyl)iron(II) 1d

δ_H (CDCl₃): 0.97 (t, 3H, $J = 7.49$), 1.4 (m, 2H), 1.7 (m, 2H), 2.7 (t, 2H, $J = 7.49$ Hz), 4.2 (s, 5H), 4.5 (s, 2H), 4.8 (s, 2H). δ_C (CDCl₃): 14.0, 22.7, 26.8, 39.5, 69.3, 69.7, 72.1, 79.4, 204.6. Mass spectrum (EI, 70 eV): m/z (%): 270 (M^+ , 100), 228 (36), 213 (23), 185 (29), 129 (16), 121 (12).

Bis(pentanoylcyclopentadienyl)iron(II) 2d

δ_H (CDCl₃): 0.89 (t, 3H, $J = 7.49$), 1.3 (m, 2H), 1.6 (m, 2H), 2.6 (t, 2H, $J = 7.49$ Hz), 4.4 (s, 4H), 4.70 (s, 4H). δ_C (CDCl₃): 1.0, 14.0, 22.5, 26.4, 39.6, 70.6, 73.4, 80.3, 204.0. Mass spectrum (EI, 70 eV): m/z (%): 354 (M^+ , 100), 312 (22), 297 (9), 270 (3), 213 (4), 186 (3), 129 (2).

Bis(tert-butanoylcyclopentadienyl)iron(II) 2e

δ_H (CDCl₃): 1.3 (s, 18H), 4.4 (m, 4H), 4.8 (m, 4H). δ_C (CDCl₃): 27.9, 77.8, 73.5, 72.1, 44.4, 27.9. Mass spectrum (EI, 70 eV): m/z (%): 354 (M^+ , 100), 297 (66), 279 (9), 251 (7), 205 (12), 185 (3), 121 (4).

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