Green Chemistry

Cite this: Green Chem., 2011, 13, 1182

www.rsc.org/greenchem

Iron(III)-based ionic liquid-catalyzed regioselective benzylation of arenes and heteroarenes[†]

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Received 14th January 2011, Accepted 11th March 2011 DOI: 10.1039/c1gc15056a

An easily prepared Fe(III)-derived Lewis acid ionic liquid ($[C_4mim][FeCl_4]$), being comprised of 1-butyl-3-methyl imidazolium cation and tetrachloroferrate anion, was found to be an efficient, recyclable catalyst for benzylation of various arenes/heteroarenes into the diarylmethanes derivatives under mild reaction conditions without utilization of additional organic solvent. Interestingly, the acidity of $[C_4mim][FeCl_4]$ could account for its catalytic activity in promoting the Lewis acid-catalyzed alkylation. Notably, this type of Fe(III)-based ionic liquid (IL) shows excellent stability, and could be easily recovered, and reused for five times without significant loss of its catalytic activity.

Introduction

It is well known that fine chemicals, pharmaceuticals, agrochemicals, dyes, commonly contain an aromatic and/or heteroaromatic framework structure. Most aromatic and/or heteroaromatic compounds are conventionally prepared on a large scale by employing classic transformations like Friedel-Crafts alkylations, Friedel-Crafts acylations, nitrations, and halogenations.¹ Although these methods work reliably for a variety of substrates, they often pose major drawbacks such as drastic reaction conditions (high temperature, strong acidic conditions in conjunction with the use of stoichiometric amounts of Lewis acid such as AlCl₃), low regioselectivity along with formation of large amounts of salt by-products. Due to increasing demand for efficient, cost-effective and environmentally friendly processes to prepare the aforementioned aromatic compounds, development of direct catalytic carbon-carbon bond forming reactions of arenes and heteroarenes is of great significance, and has become an important topic in organometallic chemistry and catalysis. In this regard, considerable progress has been made in the metalcatalyzed Friedel-Crafts type alkylation of arenes to prepare the desired products containing a diarylmethane motif, com-



Scheme 1 Selected biologically active compounds containing diarylmethane moiety.

monly showing biological activity (Scheme 1). Recently, various late-transition-metal salts, such as $FeCl_3$,² $IrCl_3$,³ $RhCl_3$,³ or H_2PtCl_6 ,³ $AuCl_3$,⁴ $Bi(OTf)_3$ ⁵ and $[IrCp*(OTf)_2(NHC)]^6$ complexes were found to catalyze the addition reaction of benzyl acetates to arenes and heteroarenes in high yield and selectivity. However, high catalyst loadings and difficulties in recovering the transition-metal catalysts in these processes could lead to high corrosion and increased cost to some extent. Therefore, developing greener protocol would still be highly appealing.

Ionic liquids (ILs) have been attracting rising interest in the last decades with a diversified range of applications because of their potential advantages including negligible vapor pressure,

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[†] Electronic supplementary information (ESI) available: General experimental methods, experimental procedures, characterization for ionic liquids, iron-containing ionic liquids, benzylating reagents and products and copies of the NMR spectra, thermal gravimetric analysis and Raman scattering spectra. See DOI: 10.1039/c1gc15056a

good thermal stabilities, wide liquid temperature ranges and so on.7 In this aspect, ILs have been successfully used as immobilizing reagents for transition-metal catalysts, offering advantages of both homogeneous and heterogeneous catalysis and thus leading to improved catalyst performance.7 Recently, synthesis and application of specific-task ILs containing transition metals have drawn much attention in this thriving research field. The functionalized ILs are regarded as promising materials which would favorably combine spectroscopic, and/or magnetic properties with catalytic activity, presumably originating from incorporated metals. In this context, ILs containing metals such as Fe(II), Fe(III), Zn(II) and Al(III) have been successfully used as catalysts in organic transformations, e.g. Friedel-Crafts type alkylation⁸/acylation⁹ and hydroxymethylation of β-ketoesters.¹⁰ In particular, the Fe(III)-based IL, e.g. [C4mim][FeCl4] which combines the attractive properties of both ionic liquid and FeCl₃ was found to have great application in catalysis.11 As one of the most inexpensive and non-pollutant metals, iron catalysis would be of great interest and is constantly growing from a standpoint of sustainable catalysis.12

As part of our continuous efforts to develop ILs and transition metal-based ILs for catalytic transformations,¹³ we envisioned that the Fe(III)-derived Lewis acid IL could catalyze an electrophilic substitution, for instance, Friedel-Crafts type alkylation. Indeed, [C4mim][FeCl4] proved to be an efficient catalyst for regioselective benzylation of arenes and heteroarenes affording functionalized diarylmethane motif which is an integral part of a number of biologically active compounds and pharmaceuticals such as piritrexim, trimethoprim, avrainvilleol, papaverine, beclobrate, or letrozole^{2,14} (Scheme 1). In addition, the catalyst can be successfully recovered and reused for five times without any loss of its catalytic activity. The protocol presented here provides an alternative and efficacious strategy to achieve both regioselective benzylation and transition-metal recycling and would be particularly promising from a viewpoint of green chemistry.

Results and discussion

The Fe(III)-based Lewis acidic ILs are comprised of 1-butyl-3methylimidazolium cation and different anions such as $FeCl_4^$ or $FeCl_3X^-$ (X = Br) as depicted in Scheme 2. Those ILs were easily prepared from commercially available anhydrous $FeCl_3$ and an imidazolium salt such as C_4 mimCl. They were characterized by Raman scattering spectroscopy (see Supplementary Information†) and proved to be identical with authentic material reported in the literature.¹⁵ The results indicated that $FeCl_4^$ would be the dominating anion species. Furthermore, a small quantity of $Fe_2Cl_7^-$ species also exists in the IL as published results.^{15b}



Scheme 2 Iron-containing ionic liquids used in this study.

It was reported that the Lewis acidic strength of this kind of metal-containing ILs could be adjusted by varying the molar fraction of the metal halide.^{8d,16} Based on the reported principles,

Table 1 Fe(III) based IL-catalyzed coupling reaction of o-xylene with 1-phenylethyl acetate^{*a*}

Entry	Catalyst	Conversion (%) ^b	Yield (%) ^c	Regioselectivity
1	FeCl ₃	98	97	95:5
2	C₄mimCl	0		
3	C₄mimBr	0		
4	C ₄ mimBF ₄	0		
5	$[C_4 mim][FeCl_3Br] (1:1)^e$	0		
6	$[C_4 mim][FeCl_4](1:1)$	0		
7 ^f	C ₄ mimBF ₄ FeCl ₃	4	4	
8	$[C_4 mim][FeCl_4] (1:1.2)$	99	98	96:4
9	$[C_4 mim][FeCl_4] (1:2.0)$	99	98	96:4
10 ^g	$[C_4 mim][FeCl_4](1:1.2)$	20	14	94:6
11 ^h	$[C_4 mim][FeCl_4] (1:1.2)$	69	64	95:5

^{*a*} Reaction conditions: 1-phenylethyl acetate, 1 mmol; *o*-xylene, 8.4 mmol (1 mL); catalyst, 10 mmol% relative to 1-phenyl acetate, 80 °C, 12 h. All the reactions were performed two times, and the data were the average of both results. ^{*b*} Determined by GC. ^{*c*} Total yield of 1 and 2. ^{*d*} Molar ratio of 1 to 2. ^{*c*} Molar ratio of C₄mimX/FeCl₃. ^{*f*}C₄mimBF₄ was used instead of C₄mimCl. ^{*s*} 50 °C. ^{*k*} 6 h.

we used acetonitrile as a basic probe molecule to determine the acidity of the iron-containing ILs mentioned above.17 As can be seen from Fig. 1, acetonitrile itself shows two characteristic v_{CN} stretching vibrations at 2254 and 2293 cm⁻¹ (Fig. 1a). When acetonitrile was mixed with the iron-containing IL with a FeCl₃/C₄mimCl molar ratio of 1:1, no change in the v_{CN} stretching frequencies was observed (Fig. 1b). This indicates that there is no interaction between this relatively weak acidic IL and acetonitrile, a weak Lewis base. Interestingly, when the molar ratio of FeCl₃/C₄mimCl is more than 1:1, a third band appeared at around 2355 cm⁻¹ (Fig. 1c and d), being indicative of Lewis acid-base interactions between the iron-containing ILs and acetonitrile. Moreover, the intensity of the IR band around 2355 cm⁻¹ becomes stronger with the increase of the molar fraction of FeCl₃, implying that the increased fraction of FeCl₃ leads to a stronger Lewis acid-base interaction between the ILs and acetonitrile. Those results indicate that the Lewis acidity of the iron-containing ILs can be modified by varying the fraction of FeCl₃. In other words, a higher molar fraction of FeCl₃ could lead to stronger Lewis acidity of the FeCl₃-based IL, i.e. [C4mim][FeCl4].



Fig. 1 IR spectra of mixtures of acetonitrile and $[C_4mim][FeCl_4]$: (a) acetonitrile; (b) molar ratio of FeCl₃ to $C_4mimCl = 1:1$; (c) molar ratio of FeCl₃ to $C_4mimCl = 1.2:1$; (d) molar ratio of FeCl₃ to $C_4mimCl = 2.0:1$.

	$R^{+} = OH, OAc, CI$					
Entry	(Hetero)Arenes	Benzylating reagent	<i>p</i> -isomer Main product	o-isomer Yield (%) ^b	Regioselectivity (%)	
1	\bigcirc	OAc		21	_	
2	\square	OAc		55	76:11:3 ^r	
3		OAc		98	96:4	
4		OAc		86 ^a	100	
5	MeO	OAc		97	80:20	
6 ^e	HO	OAc		98	67:33	
7 ^e	но	OAc	СССС	84	94:6	
8 ^e	Ś	OAc	C→ S>	65	78:22	
9 ^e		OAc		87	100	
10	\bigcap	ОН		92	98:2	
11		OAc	ÛÛ	87	98:2	
12		ОН		96	96:4	
13		Рһ	Ph	56	95:5	
14		Ç CI		93	97:3	

^{*a*} Reaction conditions: 1-phenylethyl acetate, 1 mmol; (hetero)arenes, 1 mL; $[C_4mim][FeCl_4]$ (1:1.2), 10 mmol%; 80 °C; 12 h. ^{*b*} Determined by GC. ^{*c*} Molar ratio of *p*-:*o*-isomer. ^{*d*} 30 mmol% C₄mim-FeCl₄ (1:1.2). ^{*c*} 4 mmol of arenes or heteroarenes, 2 mL CH₃NO₂. ^{*f*} Molar ratio of *p*-:*o*-:*m*-isomer.

Then the catalytic application of the task-specific ILs for benzylation of arenes was further investigated. In the initial study, the reaction of *o*-xylene and 1-phenylethyl acetate was selected as a model reaction for preliminary study, as shown in Scheme 3. The results are summarized in Table 1.



Scheme 3 Benzylation reaction of o-xylene with 1-phenylethyl acetate.

On one hand, FeCl₃ showed high activity for the reaction, affording the corresponding p-benzylated product 1 [1,2-dimethyl-4-(1-phenylethyl)benzene] quantitatively under the given reaction conditions (entry 1, Table 1). On the other hand, the native ILs, viz. C4mimCl, C4mimBr and C4mimBF4 were inactive at all (entries 2-4). Furthermore, only starting materials were recovered when the reaction was carried out in the presence of 10 mmol% of the FeCl₃-based IL, *i.e.* [C₄mim][FeCl₄] or [C₄mim][FeCl₃Br] with 1:1 molar ratio of C₄mimX/FeCl₃ (entries 5, 6). Additionally, the catalyst system comprising FeCl₃ and the non-complexing IL, viz. C₄mimBF₄ only gave less than 5% conversion (entry 7), suggesting that the neutral FeCl₃ in this study could not be the actual catalytic species. To our delight, 1-phenylethyl acetate was almost quantitatively converted to the desired p-benzylated products 1 with an excellent regioselectivity when the molar ratio of FeCl₃ to C₄mimCl was increased to 1:1.2 and 1:2.0 (entries 8, 9), respectively. This could be understandable because the catalyst activity of [C₄mim][FeCl₄] for the Lewis acid-catalyzed alkylation reactions could be depended on its acidity as mentioned before in Fig. 1. As a consequence, the Fe(III)-based IL with a FeCl₃/C₄mimCl molar ratio of 1.2: 1 was chosen as the catalyst for further investigation. It is also worth mentioning that either decreasing the reaction temperature or shortening the reaction time caused a sharp decrease in the conversion while regioselectivity was almost unchanged (entries 10, 11).

The utility and generality of this approach for various aromatics using 1-phenylethyl acetate as the benzylating reagent were also investigated by performing the reaction under the given conditions. The results are summarized in Table 2. As expected, a variety of electron-rich aromatic substrates such as o-xylene, anisole, phenol, and β -naphthol gave the corresponding benzylated products in excellent yields (entries 3, 5, 6, 7, Table 2). However, toluene was shown to be less active for this reaction (entry 2). In the case of *p*-xylene as a substrate, higher catalyst loading up to 30 mmol% is required to perform the reaction smoothly (entry 4). On the other hand, benzene as a non-activated substrate gave poor results under the reaction conditions (entry 1), and further increasing the reaction temperature or prolonging the reaction time can not improve the reaction. In addition, several heteroarenes such as thiophene and furan could work very well affording the corresponding benzylated products in good to excellent yields (entries 8, 9). It is particularly noteworthy that furan showed the best regioselectivity specifically furnishing the corresponding pbenzylated product. The scope of benzylating reagents was also investigated as shown in Table 2. 1-Phenylethylacetate, benzyl

Table 3	Catalyst	repetition ^a
Table 5	Cataryst	repetition

Run	Conversion (%) ^b	Yield (%) ^c	Regioselectivity $(\%)^d$
1	99	97	96:4
2	99	97	95:5
3	99	96	95:5
4	99	97	95:5
5	99	96	96:4

^{*a*} Reaction conditions: 1-phenylethyl acetate, 1 mmol; *o*-xylene, 8.4 mmol (1 mL); catalyst, 0.1 mmol; $[C_4mim][FeCl_4]$ (1 : 1.2); 80 °C; 12 h. ^{*b*} Based on 1-phenylethyl acetate, determined by GC. ^{*c*} Total yield of 1 and 2. ^{*d*} Molar ratio of 1 to 2.

alcohol, benzyl acetate, 1-phenylethanol, 1,1-diphenylmethanol and benzyl chloride were found to be active benzylating reagents. *O*-xylene could react with the tested benzylating reagents in the presence of C_4 mim/FeCl₄ (1:1.2) to give the corresponding benzylated products in good to excellent yields with high regioselectivity. (entries 3, 10–14).

Catalyst recycling

ILs have been proven to be an excellent medium for the immobilization of transition metal catalysts.7 One feature of this IL-catalyzed benzylation reaction would be facile separation of the catalyst. Although FeCl₃ alone is sensitive to moisture since its hydrolysis easily, the results in this study showed that the catalyst FeCl₃/C₄mimCl is stable to air and moisture. To test catalyst reusability, the initially surveyed benzylation reaction of o-xylene and 1-phenylethyl acetate was carried out under identical reaction conditions in the presence of [C₄mim][FeCl₄]. The products can be simply separated by decantation from the reaction mixture while the catalyst trapped in the IL phase was then subjected to a subsequent run of the reaction by charging fresh substrate. As listed in Table 3, the catalyst [C₄mim][FeCl₄] could be reused for five times without significant loss of its catalytic activity with the retention of high regioselectivity (entries 1-5, Table 3). In addition, determination of the iron content of both fresh and recovered catalyst by using ICP method also confirmed the stability of the catalyst (see Supplementary Information[†]).

Conclusions

In conclusion, we have established an efficient approach to Friedel–Crafts-type benzylation of various arenes and heteroarenes using an iron-containing IL, *viz.* $[C_4mim][FeCl_4]$ as the catalyst. The mild reaction conditions, operational simplicity and practicability render this protocol an attractive approach to diarylmethane derivatives. Furthermore, it is worth noting that this procedure is especially attractive because of its cheap, easy to handle and recyclable catalyst from the point of view of green and sustainable chemistry. When benzyl alcohols are used as the benzylated reagents, it would become a state-of-the-art green access to diarylmethane derivatives because water is the only side-product in this reaction.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grants Nos. 20872073, 21003129), Research Fellowship for International Young Scientists from NSFC (20950110325), the 111 project (B06005), and the Committee of Science and Technology of Tianjin.

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