SHORT PAPER

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$FeCl_3{\cdot}6H_2O$ catalysed condensation of aldehydes and ketones in ionic liquid: a novel green synthesis of chalcones†

Xinying Zhang, Hongying Niu and Jianji Wang*

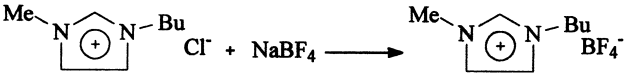
School of Chemical and Environmental Sciences, Henan Normal university, Key Laboratory of Environmental Science and Technology of High Education of Henan Province, Xinxiang, Henan 453002, P. R..China

Using iron(III) chloride hexahydrate as a catalyst, chalcones were efficiently prepared from acetophenone and benzaldehyde in ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate) for the first time. Compared with the known methods, this novel access to chalcones has the advantage of being a green process together with good yields and mild reaction conditions.

Keywords: ionic liquid, chalcone derivatives, iron(III) chloride hexahydrate

Chalcones and their derivatives are important intermediates in organic synthesis.[1] In addition, many chalcone derivatives display interesting pharmacological and biological activities.[2] Therefore, much attention has been paid to the synthesis of chalcones. Classically, chalcone derivatives are obtained with NaOH, KOH or $Ba(OH)_2$ in aqueousalcoholic medium from benzaldehyde and ketones.[3] Unfortunately, under such a strong alkaline condition the enones so formed may undergo further condensation and the uncondensed aldehyde may undergo dismutation, both leading to undesired byproducts. Since then, several other methods have been put forward for improvements to the preparation of chalcones.[4] In recent years, the development of novel synthetic methods remains an active research area[5] due to their great importance.

Ionic liquids have recently been found to be excellent environmentally benign solvents for a variety of reactions.[6] These liquids are non-volatile, non-flammable, non-explosive, non-toxic, and can be recycled . They offer an attractive alternative to conventional organic solvents. Of particular interests are air and moisture stable imidazolium ionic liquids, which have been used as solvents for a variety of transition metal catalysed reactions (*e.g.* oxidation,[7a] allylation,[7b] living radical polymerisation[7c] and hydrogenation[7d]). Herein we wish to report our preliminary results on the efficient preparation of calcone derivatives from benzaldehyde and acetophenone promoted by $FeCl_3{\cdot}6H_2O$ using an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), as the solvent. This was readily prepared through ion exchange from 1-butyl-3-methylimidazolium chloride with $NaBF_4$ according to the literature[8] (shown in Scheme 1).



Scheme 1

In a typical experimental procedure, a solution of acetophenone (1 mmol) and benzaldehyde (1 mmol) in [bmim][BF_4] was heated in the presence of a catalytic amount (0.5 mmol) of $FeCl_3{\cdot}6H_2O$ for a certain period of time as required to complete the reaction (monitored by TLC). Then, the reaction mixture was allowed to cool to room temperature. The precipitate was isolated by filtration, washed with water and ethanol and dried to give the desired chalcones in high purity. The reaction was shown in Eqn (1) and the results were listed in Table 1.

$$\underset{\mathbf{1}}{Ar^1CHO} + \underset{\mathbf{2}}{Ar^2COCH_3} \xrightarrow[\text{[BMIM][BF}_4\text{], 100°C}]{FeCl_3\ .\ 6H_2O} \underset{\mathbf{3}}{Ar^1CH = CHCOAr^2} \quad (1)$$

Table 1 Preparation of chalcones promoted by $FeCl_3{\cdot}6H_2O$

Entry	Ar[1]	Ar[2]	Yield/%[a]
1	C_6H_5	C_6H_5	78
2	4-$NO_2C_6H_4$	C_6H_5	91
3	3-$NO_2C_6H_4$	C_6H_5	87
4	4-ClC_6H_4	C_6H_5	82
5	2-ClC_6H_4	C_6H_5	80
6	3-BrC_6H_4	C_6H_5	81
7	4-$CH_3C_6H_4$	C_6H_5	75
8	4-$CH_3OC_6H_4$	C_6H_5	72
9	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	71
10	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	85

[a] Isolated yields of chalcone derivatives; only the *trans* form products were obtained.

As showed in Table 1, this process provides an efficient access to chalcones. Generally, the yields are affected to some extent by the substituents on the phenyl ring of benzaldehydes. Substrates bearing strong electron withdrawing groups (entries 2-3) could be obtained with higher yields than those bearing electron donating groups (entries 7-9).

To our knowledge, this is the first example for the preparation of enones in which $FeCl_3{\cdot}6H_2O$ is used in ionic liquid medium to facilitate the aldol condensation of ketones with aldehydes. Other Lewis acids, such as $ZnCl_2$,[4e] have also been used in this kind of reaction. However, they need anhydrous or microwave conditions, which have limited their application. As for the amount of the catalyst used, we found that 50 mol% of $FeCl_3{\cdot}6H_2O$ is sufficient to accelerate reaction efficiently. It should be emphasised that Fe(III) ion was immobilised in [bmim][BF_4] at the end of the reaction. After filtration of the product, the solvent [bmim][BF_4] and the catalyst could be recovered easily by drying the mixture at 100°C for several hours , and reused for many times without any detriment to the yield of the product.

Although the detailed mechanism of the above reaction has not been clarified yet, it is proposed that chalcones **(3)** may be formed through an iron(III) enolate intermediate (**A**, Scheme 2), which is formed from acetophenone with the aid of iron(III). Meanwhile, the keto group in benzaldehyde may

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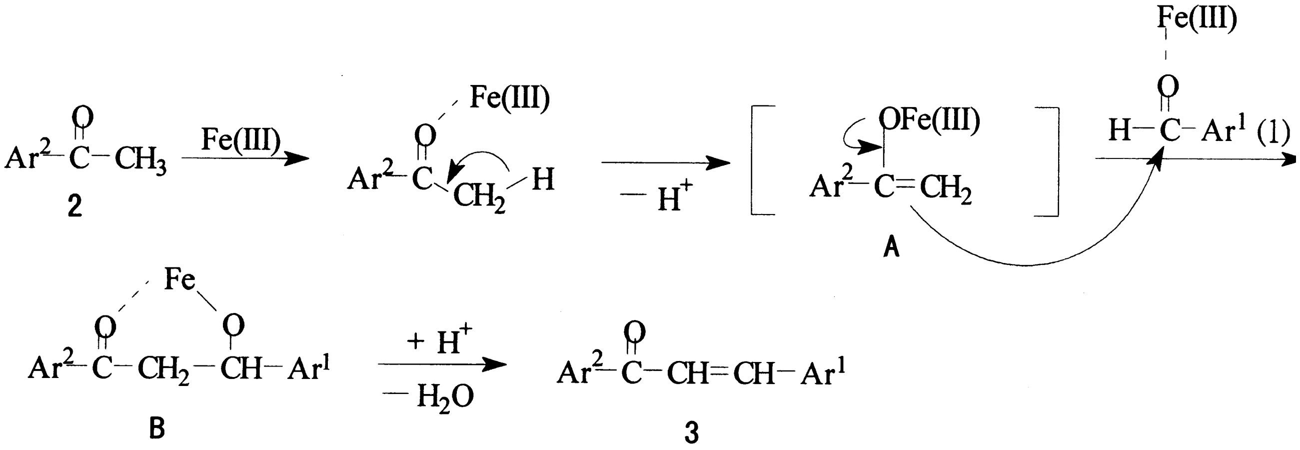
* To receive any correspondence. E-mail: Jwang@henannu.edu.cn

† This is a Short Paper, there is therefore no corresponding material in J Chem. Research (M).



Scheme 2

also be activated by iron(III) due to the strong oxophility of iron(III). The enolate **A** may react with the activated keto group in benzaldehyde to give intermediate **B**. By subsequent protonation and dehydration, intermediate **B** gives **3** as the final product.

In conclusion, we have developed an efficient and much improved modification of the cross coupling reaction of non-cyclic ketones with benzaldehydes, which provides a simple access to chalcones in high yields. Furthermore, the advantages of this methodology still include: (1) easy procedure. Using Fe(III) as catalyst does not require inert or anhydrous conditions and [bmim][BF_4] is also air and moisture stable. These make the reaction procedure reasonably easy. (2) Green and clean to the environment. Not only is [bmim][BF_4] an environmental benign solvent with non-volatile and non-toxic, but also Fe(III) has environmentally friendly nature. (3) A process with atomic economy. Since Fe(III) can facilitate the aldol condensation under mild and neutral conditions, side-reactions resulted from basic conditions are avoided. Moreover, the solvent [bmim][BF_4] and the catalyst can be recovered conveniently and reused efficiently. With all the advantages mentioned above, the method presented in this paper may provide an attractive alternative to the preparation of chalcones.

Further studies on the application of ionic liquid used as reaction solvent in organic synthesis are currently underway in the author's laboratory.

Experimental

Melting points were measured by a Kofler micromelting point apparatus. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC 80 spectrometer as $CDCl_3$ solutions. Chemical shifts were expressed in ppm downfield from the internal standard tetramethylsilane.

Typical procedure for the preparation of 3-(4-nitrophenyl)-1-phenyl-2-propen-1-one **(3b):** A mixture of acetophenone (1mmol), 4-nitrobenzaldehyde (1mmol) and $FeCl_3{\cdot}6H_2O$ (0.5mmol) was added to the ionic liquid ([bmim][BF_4], 2 ml). The solution was stirred at 100°C for 6 hours. After cooling, the solid precipitated was isolated by filtration, washed with water and ethanol and dried to give **3b** with high purity. Other chalcone products were obtained in a similar process.

After the filtration of the chalcone products, the ionic solution containing the catalyst could be easily recovered for reuse by washing with diethyl ether (2×5 ml) to remove the minor amount of unreacted acetophenone and substituted benzaldehydes, and then heating at 100°C for several hours.

1,3-Diphenyl-2-propen-1-one **(3a):** Crystal, m.p. 53.5–54.5°C (lit. [9]55–56°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.20–7.98(m, ArH, =CH); IR (KBr) ν: 1660 (C=O) cm^{-1}.

3-(4-Nitrophenyl)-1-phenyl-2-propen-1-one **(3b):** Crystal, m.p.164.5–166°C (lit.[9]165°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.35–8.30 (m, ArH, =CH); IR (KBr) ν: 1659 (C=O) cm^{-1}.

3-(3-Nitrophenyl)-1-phenyl-2-propen-1-one **(3c):** Crystal, m.p. 144–145°C (lit. [10] 145–146°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.30–8.10 (m, ArH, =CH); IR (KBr) ν: 1662 (C=O) cm^{-1}.

3-(4-Chlorophenyl)-1-phenyl-2-propen-1-one **(3d):** Crystal, m.p. 111–112°C (lit. [9] 112–113°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.20–8.02 (m, ArH, =CH); IR (KBr) ν: 1660 (C=O) cm^{-1}.

3-(2-Chlorophenyl)-1-phenyl-2-propen-1-one **(3e):** Crystal, m.p. 49–50°C (lit. [9] 49–51°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.10–7.90 (m, ArH, =CH); IR (KBr) ν: 1660 (C=O) cm^{-1}

3-(3-Bromophenyl)-1-phenyl-2-propen-1-one **(3f):** Crystal, m.p. 82–84°C (lit. [9] 83–85°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.20–7.98 (m, ArH, =CH); IR (KBr) ν: 1658 (C=O) cm^{-1}.

3-(4-Methylphenyl)-1-phenyl-2-propen-1-one **(3g):** Crystal, m.p. 93–94°C (lit. [11] 94–96°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 2.30 (s, 3H, CH_3), 7.12–8.17 (m, 11H, ArH, =CH); IR (KBr) ν: 1663 (C=O) cm^{-1}.

3-(4-Methoxyphenyl)-1-phenyl-2-propen-1-one **(3h):** Crystal, m.p. 74–76°C (lit.[11] 70–75°C) ^1H NMR ($CDCl_3$, 80 MHz) δ: 3.70 (s, 3H, OCH_3), 6.75–8.05 (m, 11H, ArH, =CH); IR (KBr) ν: 1650 (C=O) cm^{-1}.

1,3-Di (4-methylphenyl)-2-propen-1-one **(3i):** Crystal, m.p. 93–94°C (lit. [9] 94–95°C); ^1H NMR ($CDCl_3$, 80 MHz) δ: 2.40 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.22–8.00 (m, 10H, ArH, =CH); IR (KBr) ν: 1600(C=O) cm^{-1}.

1-(4-Methylphenyl)-3-(4-nitrophenyl)-2-propen-1-one **(3j):** Crystal, m.p. 169–171°C; ^1H NMR ($CDCl_3$, 80 MHz) δ: 2.48 (s, 3H, CH_3), 7.35–8.35 (m, 10H, ArH, =CH); IR (KBr) ν: 1668 (C=O) cm^{-1}.

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