Copper(II) Triflate Immobilized in [bmim]BF_4 Ionic liquid: An Efficient Reaction Medium for Michael Addition of β-Ketoesters to Acceptor-activated Alkenes

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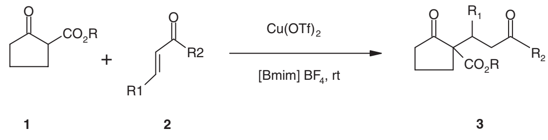
1,3-Dicarbonyl compounds undergo smooth conjugate addition to α,β-unsaturated ketones in the presence of 10 mol % copper(II) triflate immobilized in air and moisture stable [bmim]BF_4 ionic liquid under extremely mild conditions to afford the corresponding Michael adducts in high to quantitative yield.

The Michael reaction is widely recognized as one of the most important carbon–carbon bond forming reactions in organic synthesis.[1] Traditionally, the Michael reaction is conjugate addition of nucleophiles to unsaturated carbonyl compounds performed under the influence of strong bases such as alkali metal alkoxides or hydroxides.[2] The strong basic conditions often leads to a number of undesirable side reactions such as Aldol cyclizations, ester solvolysis, base induced rearrangements, such as retro-claisen or retro Michael reactions, and polymerization reactions. Subsequently, Lewis acids are found to catalyze the Michael reaction under mild conditions.[3] However, most of these catalysts cannot be recovered and reused because they decompose under quenching conditions. The presence of even a small amount of water causes lower yields, probably due to the rapid decomposition or deactivation of the catalyst and also the solvolysis of β-keto esters. Furthermore, many of these methods often involve the use of strong acids which always required aqueous work-up for the catalyst separation, recycling and disposal. Therefore, in recent years, to circumvent these problems, considerable attention has been focused on developing mild and neutral catalysts. The main improvement of these reagents are the ability to limit to catalytic amounts[4] instead of using stoichiometric amounts. Since the Michael adducts have become increasingly useful and important in the field of drugs and pharmaceuticals, the development of simple, efficient, and environmentally benign approaches are desirable.

Room temperature ionic liquids (RTLs) have been recognized as "green" recycle alternatives to the traditional volatile organic solvents, because of their unique chemical and physical properties such as being liquid at room temperature, air, and moisture stability, high solubility and negligible vapor pressure. Their high polarity, Lewis acidity and ability to solubilize both organic and inorganic compounds can result in enhanced rates of chemical process and can provide higher selectivities compared to conventional solvents.

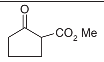
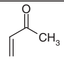
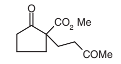
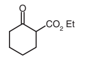
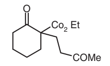
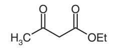
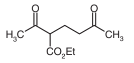
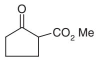
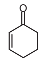
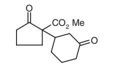
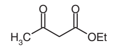
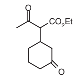
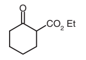
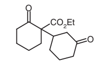
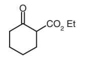
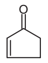
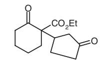
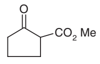
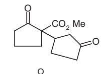
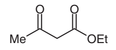
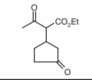
In view of the emerging importance of ionic liquids[5–7] as green solvents in organic synthesis, and as part of our on going programme in developing new synthetic methodologies,[8] we report herein the use of ionic liquid as recyclable solvent for the conjugate addition of 1,3-dicarbonyl compounds to α,β-unsaturated ketones to produce the corresponding 1,4-adducts in high to quantitative yields under mild reaction conditions (Table 1).



Scheme 1.

Accordingly, the treatment of ethyl 2-oxocyclopentane-1-carboxylate with methyl vinyl ketone in the presence of 10 mol % copper(II) triflate immobilized in [bmim]BF_4 resulted the corresponding ethyl 2-oxo-1-(3-oxobutyl)cyclopentane-1-carboxylate **3a** in 90% yield. The reaction proceeded efficiently at room temperature with in a short period (4 h). The product thus obtained was isolated by simple extraction with diethyl ether. The ionic liquid was further washed with ether and reused several times without further purification. Encouraged by the results obtained with ethyl 2-oxocyclopentane-1-carboxylate and methyl vinyl ketone, we turned our attention to various β-keto esters and acceptor-activated alkenes to give the corresponding 1,4-adducts. The yields are generally high to quantitative and the reaction time also few hours. In the absence of catalyst, the reactions did not proceed even after a long reaction time (10–15 h). Interestingly, no byproducts arising from 1,2-addition or bis-addition were observed. Moreover, the reactions were

Table 2. $Cu(OTf)_2$-catalyzed conjugate addition of β-ketoester to enones in [bmim]BF_4 ionic liquid

Entry	β-Ketoester **1**	Enone **2**	Product[a] **3**	Time/h	Yield/%[b]
a				3.5	92
b		,,		4.5	85
c		,,		5.0	83
d				4.5	88
e		,,		5.0	85
f		,,		5.0	82
g				4.5	91
h		,,		5.0	85
i		,,		6.0	89

[a] All the products were characterized by ^1H NMR, IR, and MS.
[b] Isolated and unoptimized yields.

Table 1. Reactivity of $Cu(OTf)_2$ in various solvents for the condensations of methyl 2-oxocyclopentane-1-carboxylate and methyl vinyl ketone[a]

Runs	Copper triflate	Reaction medium	Time /h	Yield /%
1	10 mol % $Cu(OTf)_2$	$[bmim]BF_4$	3.5	92
2	10 mol % $Cu(OTf)_2$	$[bmim]PF_6$	4.0	89
3	10 mol % $Cu(OTf)_2$	CH_3CN	8.0	71
4	10 mol % $Cu(OTf)_2$	MeOH	7.0	71
5	10 mol % $Cu(OTf)_2$	CH_2Cl_2	8.0	68

[a] Reaction was carried out in 1 mmol scale.

clean and high yielding. Compared to conventional solvents enhanced reaction rates and improved yields are the notable features observed by using $Cu(OTf)_2/[bmim]BF_4$ catalytic system. The reactivity of copper triflate in various solvents has been studied in the case of methyl 2-oxocyclopentane-1-carboxylate and methyl vinyl ketone and the results are summarized in Table 1.

In further experiments, the reactivity of various β-ketoesters and enones were studied in both hydrophilic $[bmim]BF_4$ and hydrophobic $[bmim]PF_6$ ionic liquids. Among them, $[bmim]BF_4$ was found to be superior in terms of conversion and reaction rates. The recovered ionic liquid containing copper(II) triflate was reused four times without loss of activity, even after fourth cycle the product **3e** was obtained with the similar yield and purity of those obtained in the first cycle. The commercially available ionic liquids were used in this study. The purity of $[bmim]BF_4$ ionic liquid is $\geq 97.0\%$ (NMR). The use of ionic liquid as the reaction media for this transformation helps to recycle the catalyst there by making the process quite simple, more convenient and environmentally friendly.

In summary, we describe a mild, clean and efficient protocol for the conjugate addition of β-ketoesters to α,β-unsaturated ketones using copper(II) triflate/$[bmim]BF_4$ as novel and recyclable catalytic system. The enones show enhanced reactivity in ionic liquids there by reducing the reaction times and improving the yield significantly. The simple experimental procedure combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of a green strategy for the conjugate addition reactions.

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9 General Procedure for the conjugate addition of β-ketoesters to α,β-unsaturated compounds: A mixture of α,β-unsaturated compounds (1 mmol), β-ketoester (1 mmol) and copper(II)triflate (10 mol %) in 1-butyl-3-methylimidazolium tetrafluoroborate (3 mL) was stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC. The reaction mixture was extracted with diethyl ether (3×10 mL). The combined ether extracts were concentrated under reduced pressure and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane to afford the pure compound. The products thus obtained were characterized by comparison of their ^{1}H NMR, IR, and MS. The spectral data of all the products were identical with those of authentic samples.[3–5] IICT Communication No; 040907.