

## Green Protocol for Conjugate Addition of Thiols to $\alpha,\beta$ -Unsaturated Ketones Using a [Bmim]PF<sub>6</sub>/H<sub>2</sub>O System

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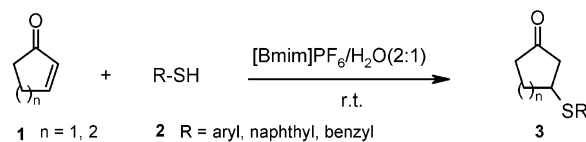
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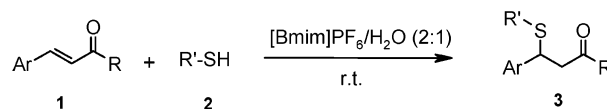
**Abstract:**  $\alpha,\beta$ -Unsaturated ketones undergo conjugate addition rapidly with thiols in a hydrophobic ionic liquid [bmim]PF<sub>6</sub>/H<sub>2</sub>O solvent system (2:1) in the absence of any acid catalyst to afford the corresponding Michael adducts in high to quantitative yields with excellent 1,4-selectivity under mild and neutral conditions. The enones show enhanced reactivity in ionic liquids, thereby reducing reaction times and improving the yields significantly. The use of ionic liquids helps to avoid the use of either acid or base catalysts for this conversion. The recovered ionic liquid was reused four to five times with consistent activity.

The conjugate addition of thiols to  $\alpha,\beta$ -unsaturated ketones to form carbon–sulfur bond constitutes a key reaction in biosynthetic processes as well as in organic synthesis.<sup>1,2</sup> Consequently, a large number of methods have been reported for the 1,4-addition of thiols to electron-deficient olefins through the activation of thiols by bases.<sup>3,4</sup> In contrast, there are only a few reports of thiol addition to enones activated by Lewis acids.<sup>5</sup> Asymmetric versions of Michael addition of thiols to  $\alpha,\beta$ -unsaturated ketones have also been reported using cinchona alkaloids and proline-derived chiral amines to produce enantiomerically enriched organosulfur compounds.<sup>6</sup> More recently, tetrabutylammonium bromide has been reported as an efficient catalyst for this conversion.<sup>7</sup> However, many of these methods often involve the use of an acid or a base catalyst which always demand

### SCHEME 1

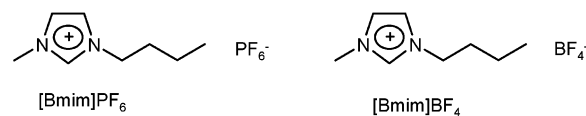


### SCHEME 2



aqueous workup for the catalyst separation, recycling and disposal. Furthermore, some of them involve the use of harsh conditions and expensive reagents. In many cases, the yields and selectivities are far from satisfactory due to the occurrence of several side reactions. Since organosulfur compounds have become increasingly useful and important in the synthesis of biologically active compounds such as the calcium antagonist diltiazem,<sup>8</sup> the development of simple, convenient, and environmentally benign approaches are desirable.

In recent times, ionic liquids have emerged as an alternative reaction media for the immobilization of transition-metal catalysts, Lewis acids, and enzymes.<sup>9</sup> They are being used as green solvents with unique properties such as a wide liquid range, good solvating ability, tunable polarity, high thermal stability, negligible vapor pressure, and ease of recyclability. They are referred to as “designer solvents” as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity, and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion, and the length of alkyl chain attached to an organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering to the needs of any particular process.<sup>10</sup>



Their high polarity and ability to solubilize both organic and inorganic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.<sup>11</sup>

With an ever-increasing quest for exploration of newer reactions in ionic liquids, we report herein the use of ionic liquids as green solvents for the conjugate addition of thiols to  $\alpha,\beta$ -unsaturated ketones to afford Michael

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



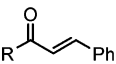
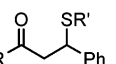

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TABLE 1. Conjugate Addition of Thiols to Enones in 1-Butyl-3-methylimidazolium Ionic Liquids/H<sub>2</sub>O

Entry	Enone 1	Product <sup>a</sup> 3	Conversion (%) <sup>b</sup>	[bmim]PF <sub>6</sub> -H <sub>2</sub> O		[bmim]BF <sub>4</sub> -H <sub>2</sub> O	
				Time (min)	Yield (%) <sup>c</sup>	Time (min)	Yield (%) <sup>c</sup>
							
<b>a</b>	"	R = Phenyl	100	10	95	15	93
<b>b</b>	"	R = p-Cl-phenyl	99	15	93	10	92
<b>c</b>	"	R = p-MeO-phenyl	100	10	97	15	95
<b>d</b>	"	R = Benzyl	98	25	91	20	90
<b>e</b>	"	R = 2-Naphthyl	99	20	90	25	89
							
<b>f</b>	"	R = Phenyl	99	15	95	20	93
<b>g</b>	"	R = 2-Naphthyl	97	20	90	30	88
<b>h</b>	"	R = p-Me-phenyl	100	10	94	15	91
							
<b>i</b>	R = Phenyl	R' = Phenyl	100	15	95	20	93
<b>j</b>	R = Phenyl	R' = p-Me-phenyl	99	10	92	15	95
<b>k</b>	R = Methyl	R' = p-Me-phenyl	100	20	92	25	90
<b>l</b>	R = Styryl	R' = p-Me-phenyl <sup>d</sup>	97	25	89	30	87
<b>m</b>	R = Phenyl	R' = 	95 <sup>e</sup>	45	90	60	85

<sup>a</sup> All the products were reported previously in the literature.<sup>12</sup> <sup>b</sup> Conversions (obtained by [bmim]PF<sub>6</sub>/H<sub>2</sub>O) were determined by GC analysis. <sup>c</sup> Yield refers to the isolated pure products after column chromatography. <sup>d</sup> Monoadduct was obtained (when 1 equiv of thiocresol was used). <sup>e</sup> The product was filtered by diluting the ionic liquid with water.

adducts in high to quantitative yields under mild and neutral conditions (Scheme 1).

Accordingly, treatment of 2-cyclohexen-1-one with thiophenol in 1-butyl-3-methylimidazolium hexafluorophosphate/water (2:1) solvent system in the absence of catalyst gave the corresponding 1,4-adduct in 97% yield. The reaction proceeded efficiently at room temperature without the need of any acid or base catalyst. The reaction went to completion in a short time (10–15 min). 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 cyclohexenone and thiophenol, we turned our attention to various thiols and substituted enones. Inter-

estingly, numerous cyclic and acyclic enones including chalcones underwent 1,4-addition with a range of thiols under mild reaction conditions to afford the corresponding Michael adducts (Scheme 2).

It is noteworthy to mention that readily available thiosalicylic acid afforded the 1,4-adduct in 90% yield after crystallization (entry **m**, Table 1). Sterically hindered 2-thionaphthol also gave the desired 1,4-adducts in excellent yields (entries **e** and **g**, Table 1). No byproducts resulting from 1,2-addition or bis-addition were observed. Moreover, the reactions are clean, high yielding, and sometimes quantitative. Compared to conventional methods, enhanced reaction rates, improved yields, and high 1,4-selectivity are the features observed in ionic liquids. For instance, treatment of 1,3-diphenyl-(*E*)-2-

propen-1-one with thiophenol in a [bmim]PF<sub>6</sub>/H<sub>2</sub>O solvent system (2:1) afforded the corresponding Michael adduct **3i** in 95% yield within 15 min, whereas the same reaction in commonly used organic solvents such as acetonitrile and methanol after 8 h gave the desired product in 52% and 67% yield, respectively. However, in the absence of ionic liquid, the product **3i** was obtained in 60% yield in water after 8 h at room temperature. The addition of phase transfer catalyst, i.e., benzyltriethylammonium bromide, the product **3i** was isolated in 85% yield after 6 h. Thus, the combination of ionic liquid and water was found to be the most effective solvent system for this conversion. In this reaction, the efficiency of ionic liquid was strongly influenced by the nature of the anion. The reactivity of various thiols and enones was studied in both hydrophobic [bmim]PF<sub>6</sub> and hydrophilic [bmim]BF<sub>4</sub> ionic liquids and the results are presented in the Table 1. Among them, [bmim]PF<sub>6</sub> was found to be superior in terms of conversion. The yields are generally high to quantitative in a few minutes. The recovered ionic liquid was reused several times without loss of activity, even after fourth cycle the product **3a** was obtained with the similar yield and purity of those obtained in the first cycle. In further reactions, the efficacy of various quaternary ammonium salts was tested. The reactions, however, did not proceed at room-temperature either in *n*-tetrabutylammonium chloride/water (2:1) or in 1-*n*-butyl-3-methylimidazolium chloride/water (2:1) solvent system, but the reactions were successful at 65 °C with moderate yields (45–69%). The commercially available ionic liquids were used in this study. They have also been prepared in our laboratory from the readily available and inexpensive *N*-methylimidazole, 1-chlorobutane, and hexafluorophosphoric acid or sodium tetrafluoroborate,<sup>12</sup> and their purity was determined by comparing their <sup>1</sup>H NMR spectra with commercial samples. The purity of [bmim]PF<sub>6</sub> ionic liquid is ≥97.0% (NMR). The use of ionic liquids as the reaction media for this transformation helps to avoid the use of moisture sensitive reagents or

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heavy metal Lewis acids or solid acids or bases as promoters, thereby minimizing the production of toxic waste during workup.

In summary, we describe a simple, convenient, and efficient protocol for the 1,4-conjugate addition of thiols to  $\alpha,\beta$ -unsaturated ketones using ionic liquids as green solvents under mild and neutral conditions. The ionic liquids play the dual role of solvent and the promoter. The enones exhibit enhanced reactivity in ionic liquids thereby 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 of thiols to enones.

## Experimental Section

**General Methods.** Melting points are uncorrected. TLC was performed using precoated silica gel 60 F<sub>254</sub> (0.25 mm) glass plates. Chromatography was performed using silica gel (100–200 mesh). IR spectra were recorded neat on refractive spectrophotometer. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> at 200 MHz. Chemical shifts are given in ppm with respect to internal TMS, and *J* values are quoted in Hz. Mass spectra were recorded at 70 eV.

**General Procedure for the Conjugate Addition of Thiols to  $\alpha,\beta$ -Unsaturated Ketones.** A mixture of the enone (1 mmol) and aryl- or alkanethiol (1 mmol) in 1-butyl-3-methylimidazolium hexafluorophosphate/water (2:1, 3 mL) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated in vacuo, and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate/*n*-hexane to afford the pure 1,4-adduct. The products thus obtained were characterized by comparison of their NMR, IR, mass, TLC, and mixed TLC analysis and physical data with those of authentic samples. The spectral data of all the products were identical with those of authentic samples.<sup>5,6</sup>

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