

Baeyer–Villiger Oxidations in Ionic Liquids. A Facile Conversion of Ketones to Esters and Lactones

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A variety of cyclic and acyclic ketones underwent readily oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF₄ to afford esters/lactones with high selectivity, ease of product separation and in excellent chemical yields. The reaction proceeded smoothly in ionic liquid without the need of any additional acid or base catalyst. The ketones show enhanced reactivity in ionic liquids thereby reducing reaction times and improving the yields significantly.

The Baeyer–Villiger oxidation of ketones into esters and lactones by peroxy acid is an important functional group transformation in organic synthesis.¹ It is a useful synthetic tool for the stereocontrolled construction of heterocycles and functionalized carbon framework.² In particular, Baeyer–Villiger oxidation of cyclic ketones into lactones has been widely used for ring expansion in the total synthesis of complex natural products such as antibiotics, steroids, and pheromones.^{3,4} Among various oxidizing agents, *m*-chloroperbenzoic acid (*m*-CPBA) is the most commonly used oxidant for this reaction. Because of its low reactivity towards ketones, generally, it requires prolonged reaction time to achieve high conversions.⁵ A variety of activators such as sulfonic acids, Nafion-H, CF₃COOH, hydrotalcite, SnCl₄ and triflic acid or rare earth metal triflates have been employed to enhance the reactivity of *m*-CPBA.^{6,7} Besides of the acid catalysts, heterogeneous bicarbonate has also been used to accelerate the reaction.⁸ However, these methods often involve the use of an acid or a base catalyst which always demand aqueous work-up for the catalyst separation, recycling and disposal. Since Baeyer–Villiger oxidation has become an increasingly useful and important tool for ring expansion in organic synthesis, 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.⁹ They are being used as green solvents with unique properties such as 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 (Figure 1).

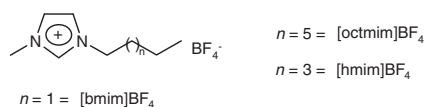














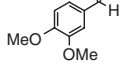
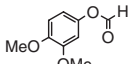


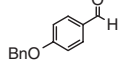
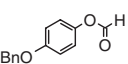








Figure 1.

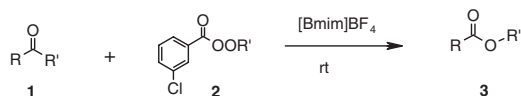
These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering to the needs of any particular process. As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.¹⁰

In view of recent surge in the activity of ionic liquids, we report herein for the first time the use of ionic liquids as recyclable solvents for the conversion of carbonyl compounds into esters and lactones. Initially, we have attempted the oxidation of (–)-menthone with 2 equiv. of *m*-chloroperbenzoic acid (commercial grade 60% *m*-CPBA) in ionic liquid [bmim]BF₄. The oxidation proceeded smoothly at room temperature and the desired lactone was isolated in 90% yield (Entry **3b**, Table 1). The remarkable activation of *m*-CPBA with [bmim]BF₄ prompted us to study it in further reactions with other ketones. *m*-CPBA/[bmim]BF₄ system oxidizes both cyclic and acyclic ketones in very shorter reaction times and in higher chemical yields than with *m*-CPBA alone (Scheme 1).

In all cases, the oxidation proceeds smoothly in ionic liquid [bmim]BF₄ without the need of any additional acid catalyst. In most cases, the desired esters and lactones were obtained in good to excellent yields with high selectivity. Cyclic ketones are generally more susceptible to oxidation than acyclic or aromatic ketones. In majority of cases, the product was obtained as a result of preferential migration of the more substituted carbon atom. However, vinyl group has a preferential migrating ability in α,β -unsaturated carbonyl compounds such as cinnamaldehyde (Entry **3h**, Table 1). 2-Cyclohexen-1-one gave the corresponding epoxide as a major product (Entry **3j**, Table 1). Oxidation of 2-methyl cyclohexanone with *m*-CPBA in ionic liquid afforded 6-methylcaprolactone in a highly regioselective manner (Entry **3c**, Table 1). In case of norcamphor, two regioisomeric products were obtained due to the migration of bridge head carbon as well as methylene carbon (Entry **3l**, Table 1). The products could be easily separated by simple extraction with diethyl ether. No side products arising from over oxidation or transesterification were observed under these reaction conditions. The oxidation is generally quite efficient in ionic medium. Almost 3–4 times rate acceleration was achieved in ionic liquid when compared with the controlled reaction using *m*-CPBA alone. For instance, treatment of cyclohexanone with *m*-CPBA/[bmim]BF₄ gave caprolactone in 87% yield over 2.0 h, whereas the same reaction with *m*-CPBA alone afforded 70% yield after 6.5 h. The oxidation has also been carried out in both hydrophobic [bmim]PF₆ and hydrophilic [bmim]BF₄ ionic liquids. Among them, [bmim]BF₄ was found to be the more effective and giving the best results. Comparable results were also obtained with ionic liquids having longer alkyl chains such as 1-hexyl-3-methylimidazolium tetrafluoroborate [hmim]BF₄ or 1-octyl-3-methylimidazolium tetrafluoroborate [octmim]BF₄. These ionic liquids could be easily recovered by simple extraction. The ionic liquid [bmim]BF₄ thus

Table 1. *m*-CPBA-promoted Baeyer–Villiger oxidation of ketones in [bmim]BF₄

Entry	Substrate 1	Product ^a 3	Reaction time /h	Yield ^b /%
a			2.0	87
b			3.0	90
c			2.5	88
d			3.5	92
e			5.0	85
f			6.0	83
g			5.0	90
h			3.0	75
i			5.5	93
j			4.0	90(60:40)
k			4.5	73
l			3.5	85(90:10)
m			4.0	91

**Scheme 1.**

recovered was recycled for several times with consistent activity. Even after fourth cycle the product **3b** was obtained with the similar yield and purity to those obtained in the first cycle. Ionic liquids used in this study were prepared from the readily available and inexpensive *N*-methylimidazole, 1-chlorobutane and sodium hexafluorophosphate or sodium tetrafluoroborate and their purity was determined by comparing of their ¹H NMR spectra with commercial samples.¹¹ The use of ionic liquids helps to avoid the necessity of strong acids or heavy metal Lewis acids as promoters thereby minimizing the production of toxic or corrosive acid waste during work-up. In order to compare the efficiency of ionic liquids, the reactions were also carried out in acetonitrile and chloroform using *m*-CPBA alone. In these organic

solvents in the absence of Lewis acids, the oxidations took longer reaction times (6.5–24 h) to achieve comparable yields to those obtained in [bmim]BF₄. In ionic liquid even in the absence of acid catalyst, the reactions proceeded rapidly with high efficiency. Furthermore, this method is not only applicable to ketones but also to aldehydes (see, Table). The scope of this new method is illustrated with respect to various acyclic and cyclic ketones and the results are presented in the Table.

In conclusion, the combination of *m*-CPBA and ionic liquid [bmim]BF₄ has been used for the first time for the conversion of carbonyl compounds into esters and lactones. Ionic liquid plays a dual role of solvent and the activator of *m*-CPBA. Taking advantage of the availability of *m*-CPBA and accelerating the oxidation by ionic liquid provides a simple and efficient protocol for conducting Baeyer–Villiger oxidations under mild and neutral conditions. The simple operation combined with ease of recovery and reuse of ionic liquids is expected to contribute to the development of green strategy for the conversion of ketones into esters and lactones.

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- General procedure: A mixture of carbonyl compound (1 mmol) and *m*-CPBA (2 mmol, 60% w/w) in [bmim]BF₄ or [bmim]PF₆ (3 mL) were stirred at 27 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 times with 10 mL). The combined organic extracts were concentrated in vacuo and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (2:8) to afford pure ester or lactone. Excess *m*-chloroperbenzoic acid and the by-product meta-chlorobenzoic acids were also isolated by column chromatography. The remaining ionic liquid was further washed with ether and recycled in subsequent runs. The recovery of [bmim]PF₆ ionic liquid is facilitated by its hydrophobic nature. All the products were characterized by comparison of their NMR, IR, and mass spectra with authentic samples. The spectral data of all the products were identical with those of authentic samples.^{5–7}