

## Manganese Dioxide Allylic and Benzylic Oxidation Reactions in Ionic Liquids

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Ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate [bmIm][BF<sub>4</sub>] and 1-butyl-3-methylimidazolium hexafluorophosphate [bmIm][PF<sub>6</sub>] were evaluated as reaction media for allylic and benzylic oxidation reactions using manganese dioxide. The use of ionic liquids as an extractant in the reaction work-up was also investigated. Procedures for recycling of the [bmIm][PF<sub>6</sub>] ionic liquids used in these MnO<sub>2</sub> oxidation reactions were also developed.

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Ionic liquids have been the subject of intense interest as 'green solvents' with several potential advantages to industry including low volatility, high polarity, and stability over a wide temperature range.<sup>[1–6]</sup> Ionic liquids have been used as solvents for classical organic reactions (such as the Friedel–Crafts and Diels–Alder reactions, hydrogenation, *N*- and *O*-alkylations, and epoxidation reactions) as well as catalytic and biocatalytic processes. Several 'task specific' ionic liquids have also been developed.<sup>[1]</sup> Research in this area has been the subject of several comprehensive reviews.<sup>[2–6]</sup>

Recently ionic liquids have been employed as media for a range of oxidation reactions.<sup>[7–13]</sup> This list includes the asymmetric epoxidation of alkenes,<sup>[7]</sup> the oxidation of aromatic aldehydes using [Ni(acac)<sub>2</sub>],<sup>[8]</sup> oxidation of alcohols using ruthenium catalysts,<sup>[9]</sup> selective oxidation of benzyl alcohol and alkyl benzenes,<sup>[10]</sup> palladium-catalyzed oxidation of styrene (the Wacker reaction),<sup>[11]</sup> the TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy radical) catalyzed aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones,<sup>[12]</sup> and the osmium tetroxide dihydroxylation of alkenes.<sup>[13]</sup>

Manganese dioxide has proven to be a useful and versatile reagent for the oxidation of  $\alpha,\beta$ -unsaturated alcohols (e.g. allylic, acetylenic, and benzylic alcohols), as well as several other classes of compound.<sup>[15,16]</sup> Manganese dioxide has also been employed as a selective reagent for dehydrogenation. The reaction solvent is known to have an important effect on MnO<sub>2</sub> oxidations, influencing the rate of adsorption of the reactants and desorption of the products. A wide range of solvents including saturated and chlorinated hydrocarbons,

benzene, toluene, diethyl ether, tetrahydrofuran, ethyl acetate, acetone, acetonitrile, glacial acetic acid, dimethyl sulfoxide, dimethylformamide, and pyridine have been employed for these reactions.<sup>[15,16]</sup> We recently reported the application of the ionic liquid [bmIm][BF<sub>4</sub>] in the MnO<sub>2</sub> oxidation of codeine methyl ether (CME) to thebaine.<sup>[14]</sup> In this case, [bmIm][BF<sub>4</sub>] gave poor results when used as the reaction solvent, but proved to be a useful additive in the extractive work-up, significantly increasing the isolated yield.

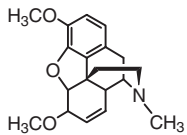
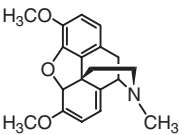
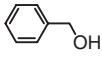
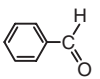
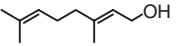
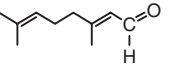
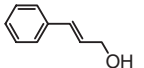
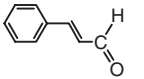
In order for oxidation reactions in ionic liquids to be of use to the chemical industry, the issue of recycling must be addressed. Ionic liquids are relatively expensive, generally in the same price range as fine chemicals rather than bulk solvents, and little is known about their biodegradability and environmental impact.<sup>[17,18]</sup>

We now report the use of the ionic liquids [bmIm][BF<sub>4</sub>] and [bmIm][PF<sub>6</sub>] as solvents and extractants in other manganese(IV) oxide oxidation reactions as well as procedures for recycling [bmIm][PF<sub>6</sub>].

### Manganese Dioxide Oxidations

Ionic liquids were evaluated as solvents, co-solvents and extractants in the MnO<sub>2</sub> oxidation of CME and a series of allylic alcohols (Table 1). The use of the ionic liquid as a solvent involved suspending MnO<sub>2</sub> in an ionic liquid and performing the oxidation in the ionic liquid, followed by product extraction using a suitable organic solvent such as diethyl ether or ethyl acetate. The second approach employed a biphasic mixture consisting of a lower ionic liquid layer and an

**Table 1.** MnO<sub>2</sub> oxidation outcomes

Entry	Substrate	Product	Conditions	Yield [%]
1			THF	24
			[bmIm][BF <sub>4</sub> ]	38
			[bmIm][BF <sub>4</sub> ]/Et <sub>2</sub> O (biphasic)	36
			THF; [bmIm][BF <sub>4</sub> ] extraction	95
2			[bmIm][BF <sub>4</sub> ]	47
			[bmIm][BF <sub>4</sub> ]/THF (biphasic)	75
			THF; [bmIm][BF <sub>4</sub> ] extraction	42
			[bmIm][PF <sub>6</sub> ]	68
			[bmIm][PF <sub>6</sub> ]/Et <sub>2</sub> O (biphasic)	66
Et <sub>2</sub> O; [bmIm][PF <sub>6</sub> ] extraction	39			
3			[bmIm][BF <sub>4</sub> ]	85
			[bmIm][BF <sub>4</sub> ]/THF (biphasic)	75
			THF; [bmIm][BF <sub>4</sub> ] extraction	45
			[bmIm][PF <sub>6</sub> ]	56
			[bmIm][PF <sub>6</sub> ]/Et <sub>2</sub> O (biphasic)	91
Et <sub>2</sub> O; [bmIm][PF <sub>6</sub> ] extraction	45			
4			[bmIm][BF <sub>4</sub> ]	74
			[bmIm][BF <sub>4</sub> ]/THF (biphasic)	68
			THF; [bmIm][BF <sub>4</sub> ] extraction	74
			[bmIm][PF <sub>6</sub> ]	67
			[bmIm][PF <sub>6</sub> ]/Et <sub>2</sub> O (biphasic)	42
Et <sub>2</sub> O; [bmIm][PF <sub>6</sub> ] extraction	73			

upper organic solvent layer (diethyl ether or tetrahydrofuran). MnO<sub>2</sub> was added which became suspended in the ionic liquid phase and the reaction was performed in this system with vigorous stirring, again followed by product extraction using a suitable organic solvent. In the third variation, the MnO<sub>2</sub> oxidation was performed in an organic solvent and the ionic liquid was added once the reaction was complete to facilitate product extraction. All of these methods were performed under stirring or sonicating conditions. We found that sonication at room temperature had no effect on the non-opiate oxidations and rapid stirring gave the same results. However, oxidation of CME was improved with sonication by decreasing reaction times and facilitating product isolation, perhaps through desorbing product from MnO<sub>2</sub> particles.

In the case of codeine methyl ether, the use of the ionic liquid in the extractive work-up provided significant improvements in the isolated yield. We postulated that the ionic liquid is facilitating desorption of the product from the MnO<sub>2</sub> particles, though the exact nature of this interaction is unknown. However, for the simple benzylic/allylic oxidation of benzyl alcohol, geraniol, and cinnamyl alcohol no improvement in the isolated yield was observed under any of the conditions trialled; interestingly, the best result in each case was obtained under different conditions. In each case, different conditions produced the most favourable outcome. The highest yield of benzaldehyde was obtained using biphasic conditions ([bmIm][BF<sub>4</sub>]/THF; 75% yield), while the oxidation of geraniol also worked best using biphasic conditions involving [bmIm][PF<sub>6</sub>] and diethyl ether (yield 91%). Cinnamaldehyde was prepared in comparable yields using neat [bmIm][BF<sub>4</sub>]

as the reaction solvent (74%), or by using organic solvents and employing either [bmIm][BF<sub>4</sub>] or [bmIm][PF<sub>6</sub>] in extractive reaction work up procedures (74% and 73%, respectively). These yields are comparable or better than those obtained using a recently reported TEMPO-catalyzed aerobic oxidation of these substrates in ionic liquids.<sup>[12]</sup> The TEMPO-catalyzed procedure gave yields of 72%, 85%, and 75% for the oxidation of benzyl alcohol, geraniol, and cinnamyl alcohol, respectively. Although our product yield in these MnO<sub>2</sub> oxidations are only a few percent better than those when using TEMPO, it is noteworthy that our method is far less expensive. For example, TEMPO is listed in the 2003 Aldrich catalogue at C\$ 38.30 per 1 g whereas finely divided, activated MnO<sub>2</sub> good for organic oxidations is listed at C\$ 25.90 per 5 g (C\$ 5.18 per 1 g).

#### *Ionic Liquid Regeneration/Recycling*

One of the many interesting properties of ionic liquids is their potential for recycling. Since ionic liquids have no measurable vapour pressure they do not evaporate. Both [bmIm][BF<sub>4</sub>] and [bmIm][PF<sub>6</sub>] are only slightly soluble in many different organic solvents and [bmIm][PF<sub>6</sub>] is also only slightly soluble in water, which allows them to be easily washed free of many contaminants. However, washing the ionic liquid is problematic in the case of MnO<sub>2</sub> reactions as a large excess of the oxidant is generally used (which turns the ionic liquid into a viscous black oil) and MnO<sub>2</sub> is not soluble in many solvents.

We have found that washing the [bmIm][PF<sub>6</sub>] ionic liquid with phosphoric acid solutions effectively cleaned the

ionic liquid. As noted previously, manganese dioxide has been traditionally used as an oxidant under heterogeneous reaction conditions due to its poor solubility in most solvents. However, the solubilization of manganese(IV) using various strategies has a long history, which was discussed by Pastor and Pastor in a review on the oxidant's role in analytical chemistry.<sup>[19]</sup> In the mid-1970s, Jáky and co-workers postulated that soluble manganese(IV) species may have been present as intermediates during the oxidation of unsaturated carboxylic acids with acidic permanganate.<sup>[20–23]</sup> Subsequently, this group prepared manganese(IV) solutions by shaking freshly precipitated manganese dioxide with aqueous phosphoric acid (3 M) and investigated the kinetics of the oxidation of a range of organic compounds, including  $\alpha,\beta$ -unsaturated alcohols, formaldehyde, formic acid, oxalic acid, and other bifunctional substrates.<sup>[24–27]</sup> Additionally, soluble manganese(IV) has recently been evaluated as a chemiluminescence reagent<sup>[28]</sup> and this experience led us to consider the use of phosphoric acid to sequester the manganese dioxide after product extraction to afford a simple and effective ionic liquid regeneration process.

There were three factors which needed to be considered when choosing the molarity of the phosphoric acid used in the extraction process: (a) the stability of the ionic liquid to the concentrated acid solutions,<sup>[29]</sup> (b) the solubility of the ionic liquid in the aqueous acid solution,<sup>[30]</sup> and (c) the density of the acid solution. Treatment of [bmIm][PF<sub>6</sub>] with 14.5 M phosphoric acid led to the appearance of degradation products as measured by <sup>19</sup>F NMR. These degradation products were considerably less in more dilute phosphoric acid solutions (trend 14.5 M  $\gg$  10 M  $\approx$  5 M  $\approx$  1 M). The presence of [bmIm][PF<sub>6</sub>] in the acid layer was also assayed by <sup>19</sup>F NMR. Concentrated acid solutions contained considerably less ionic liquid than the dilute acid solutions (trend 14.5 M  $\approx$  10 M  $\gg$  5 M  $>$  1 M). During the extraction of the MnO<sub>2</sub> from the ionic liquid considerable oxidant settles to the bottom of the flask. It was preferential to have the acid solution as the lower phase to facilitate uptake of the oxidant. The density of [bmIm][PF<sub>6</sub>] is 1.37 g mL<sup>-1</sup>,<sup>[31]</sup> 14.5 M phosphoric acid is 1.69 g mL<sup>-1</sup>. We were pleased to find that 10 M phosphoric acid has a suitable density of 1.47 g mL<sup>-1</sup>. Based on the studies above, 10 M phosphoric acid was chosen as the acid solution of choice.

Oxalic acid solutions also proved to be effective for the washing/recycling of the [bmIm][PF<sub>6</sub>] ionic liquid used in MnO<sub>2</sub> oxidation reactions. Thus, after performing oxidations of benzyl alcohol and geraniol in biphasic [bmIm][PF<sub>6</sub>]/Et<sub>2</sub>O systems and working-up the reactions,  $\sim$ 20 mL of a 1.0 M oxalic acid solution was stirred with the [bmIm][PF<sub>6</sub>]/MnO<sub>2</sub> suspension overnight. The result was a clear upper aqueous layer containing a white precipitate and a tan lower ionic liquid layer. The aqueous layer was decanted, leaving some of the white precipitate in the ionic liquid. This was dissolved in acetone and filtered. The acetone was evaporated and the cloudy tan oil was washed with water several times until the washings were pH-neutral, then once with diethyl ether, after which the ionic liquid became clear. The ionic liquid was clean according to <sup>1</sup>H and <sup>13</sup>C NMR measurements

after removing residual solvent under vacuum. The oxidations were then repeated in the recycled ionic liquids to afford the corresponding aldehydes with no decrease in the yield.

The best percent recovery we obtained in our ionic liquid recycling experiments described above were through use of phosphoric acid solutions. Recoveries reached between 78% and 81% (see Experimental section for details) for this method of recycling whereas use of the oxalic acid solution recycling method afforded only a 60% to 70% recovery of ionic liquids used. These levels of recovery are not yet satisfactory in the industrial context and we are conducting further studies to increase recovery and re-use of ionic liquids used in these reactions. The slight solubility of [bmIm][PF<sub>6</sub>] in water used in these methods is the likely source of ionic liquid loss.

## Experimental

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker 250 MHz spectrometer at the Atlantic Regional Magnetic Resonance Centre (ARMRC); unless otherwise stated, the solvent was CDCl<sub>3</sub> for all NMR spectra. Gas chromatography was performed using a Varian 3800 GC-FID unit. Mass spectra were recorded in conjunction with the GC using a Varian 2000 GC/MS electron impact system with an ion trap. All solvents were used as obtained. Diethyl ether and tetrahydrofuran were dried and distilled from a potassium/benzophenone kettle immediately before use.  $\gamma$ -MnO<sub>2</sub> was dried in an oven and heated to 110°C under vacuum before use. Flash chromatography was performed using silica gel 60, 230–400 mesh. Thin-layer chromatography was performed using Kieselgel 60 F<sub>254</sub> on aluminium-backed plates. <sup>1</sup>H and <sup>13</sup>C NMR of aldehyde products and thebaine were in agreement with the literature.

### Manganese Dioxide Oxidations

#### Method A

5.0 mL of [bmIm][BF<sub>4</sub>] were heated under vacuum in an oven-dried flask at 60°C for 2 h.  $\gamma$ -MnO<sub>2</sub> (0.87 g, 10.0 mmol, 5 eq.) was added to the ionic liquid under a nitrogen stream, heated for 1 h, then allowed to cool to room temperature. THF (15 mL) and benzyl alcohol (0.21 mL, 2.0 mmol) were added and the flask placed in a sonicating bath or stirred for 2 days, after which time a further MnO<sub>2</sub> (0.87 g, 10.0 mmol, 5 eq.) were added to the flask under a nitrogen stream. After 4 days in total, the upper THF layer was decanted. The ionic liquid was extracted with ethyl acetate (6  $\times$  15 mL) then washed with water (50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated to a clear oil. Flash column chromatography was performed using 5 : 1 hexanes/ethyl acetate as an eluent. The product was isolated as a clear oil (0.159 g, 1.50 mmol, 75%).

### Ionic Liquid Regeneration

#### Method A

After the geraniol had been isolated, H<sub>3</sub>PO<sub>4</sub> (10 M, 10 mL) was added to the MnO<sub>2</sub>/[bmIm][PF<sub>6</sub>] phase. After standing overnight, the MnO<sub>2</sub> was suspended in the lower acid layer and the top layer was clear colourless [bmIm][PF<sub>6</sub>]. The ionic liquid was decanted and the acid layer was extracted with dichloromethane : hexane (8/2, 3  $\times$  25 mL). The combined ionic liquid extracts were washed with saturated NaHCO<sub>3</sub> until the aqueous extracts were basic, then washed with water (25 mL). Solvents were removed in vacuo at room temperature and clear colourless [bmIm][PF<sub>6</sub>] was recovered in 78–81% yield.

#### Method B

After the geraniol had been isolated oxalic acid (1.0 M, 25 mL) was added to the MnO<sub>2</sub>/[bmIm][PF<sub>6</sub>] phase, which formed a reddish upper layer and bubbles were produced. After 2 h, the upper layer was clear with a white precipitate. The lower layer was a clear tan oil. The aqueous layer was decanted, and the ionic liquid dissolved in acetone. The precipitate was filtered from the organic phase and the filtrate evaporated. The tan

oil was washed with water (3 × 20 mL) until pH 7 was reached. The cloudy ionic liquid was washed with diethyl ether (20 mL) then residual solvent removed in vacuo at room temperature; [bmIm][PF<sub>6</sub>] was recovered in 60–70% (i.e. 3.0–3.5 mL recovered based on initial 5.0 mL) and was then re-used to provide geranial in comparable yield.

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