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Manganese(III) acetate mediated radical reactions in the presence of an ionic liquid

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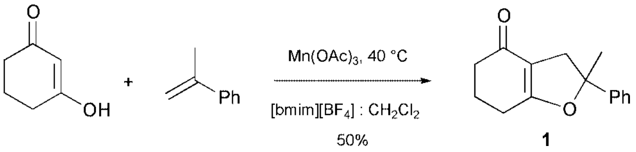
A new, mild and practical method for conducting manganese(III)-mediated radical reactions, which lead to the formation of carbon–carbon bonds, has been developed using the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]).

Manganese(III) acetate is known to oxidise a variety of carbonyl compounds, including β-diketones and β-keto esters, to form radicals.[1] These α-carbonyl radicals can undergo cyclisation or intermolecular addition reactions to form radical adducts, which may be oxidised by a second equivalent of manganese(III) acetate. The resultant cations can undergo nucleophilic attack or β-deprotonation reactions leading, for example, to acetates or alkenes. These carbon–carbon bond forming reactions are synthetically attractive because manganese(III) acetate is inexpensive and, in contrast to related tributyltin hydride reactions, this oxidative method of radical generation leads to functionalised products.

One significant drawback to the use of manganese(III) acetate, however, is the harsh reaction conditions. As manganese(III) acetate has poor solubility in organic solvents, acetic acid is invariably used and this severely limits the range of substrates which can be employed, especially as many reactions require heating (often to ⩾70 °C). An additional drawback to the use of acetic acid involves the separation and recovery of the manganese acetate at the end of the reaction. The standard workup procedure involves addition of large quantities of water and/or aqueous sodium hydrogen carbonate to remove the acetic acid and so large-scale reactions would generate considerable amounts of aqueous waste. With a view to establishing milder reaction conditions, as well as facilitating the recovery of the manganese acetate, we have investigated the novel use of an ionic liquid in manganese(III)-mediated radical reactions.

Ionic liquids have recently been found to be excellent, environmentally benign solvents for a variety of reactions.[2] These liquids offer an attractive alternative to conventional organic solvents because, for example, they are easy to recycle and are non-volatile. Of particular note 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,[3] allylation,[4] living radical polymerisation[5] and hydrogenation[6]). This suggested that ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]), which is miscible with polar solvents (*e.g.* methanol, dichloromethane) but immiscible with less polar solvents (*e.g.* ethyl acetate, diethyl ether, toluene), could be compatible with manganese(III)-mediated radical reactions.

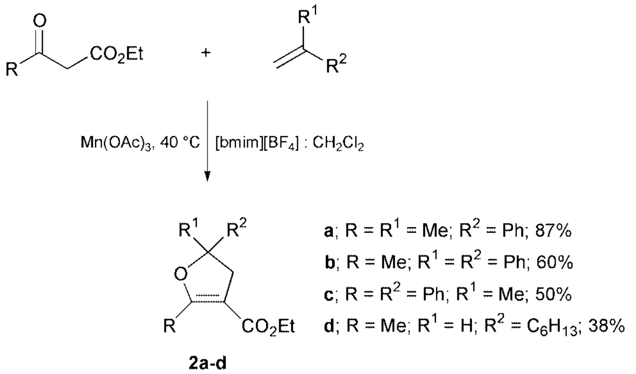
Although our initial manganese(III) acetate reactions in neat [bmim][BF$_4$] were low yielding, we found that cyclised products could be isolated in good yield when 1,3-dicarbonyl compounds and alkenes were reacted in a mixed [bmim][BF$_4$]–dichloromethane solvent system (Scheme 1). Thus, reaction of cyclohexane-1,3-dione (1 equiv.), α-methylstyrene (5 equiv.) and manganese(III) acetate (2.1 equiv.) in a 1:4 mixture of [bmim][BF$_4$]–dichloromethane produced tetrahydrofuranone **1** in 50% yield after column chromatography.†‡ Similar yields of **1** were obtained when using different ratios of starting materials and different amounts of the ionic liquid and dichloromethane. This showed that only small amounts of the ionic liquid are required for the reaction to proceed. For example, when a 1:19 mixture of [bmim][BF$_4$]–dichloromethane was used, **1** was isolated in 45% yield. The reaction could also be carried out using [bmim][BF$_4$] in the presence of alternative solvents to dichloromethane, including methanol, acetone or acetonitrile and **1** was isolated in 27–58% yield. Even solvents that are immiscible with [bmim][BF$_4$] can be employed. For instance, when the reaction was carried out in a 1:19 mixture of [bmim][BF$_4$]–ethyl acetate, **1** was isolated in 30% yield. It should also be noted that cerium(IV) ammonium nitrate (CAN), another efficient one-electron oxidant, can be used in place of manganese(III) acetate and when [bmim][BF$_4$]–dichloromethane was used as the solvent with this reagent, tetrahydrofuranone **1** was isolated in an excellent 82% yield. This is an interesting result because CAN, like manganese(III) acetate, has only limited solubility in organic solvents and so CAN oxidations are usually carried out in aqueous acetonitrile.



Scheme 1

Related manganese(III)-mediated reactions can also be carried out using acyclic 1,3-dicarbonyl precursors (Scheme 2). Hence, β-keto esters can be reacted with electron-rich alkenes in the presence of 2.0 equiv. of manganese(III) acetate to give dihydrofurans **2a–d**. These types of reactions do not require a nitrogen atmosphere. For example, **2c** was isolated in 46 and 50% yield from reactions carried out in the presence or absence of a nitrogen atmosphere, respectively.

The yields of **1** and **2a–d** are similar or higher than those reported for related manganese(III) acetate/acetic acid reactions or alternative cyclisation methods.[7] This was also apparent using quinolone precursors when reaction of **3** (1 equiv.) with oct-1-ene (10 equiv.) in a mixed [bmim][BF$_4$]–chloroform



Scheme 2

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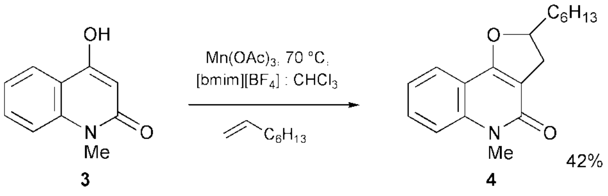
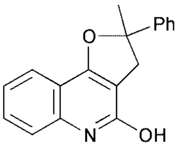


Scheme 3

solvent system produced the dihydrofuroquinolone **4** in 42% yield (Scheme 3).§ This can be compared to the corresponding manganese(III) acetate/acetic reaction at 60 °C, which required ultrasonic irradiation (because of the poor solubility of **3** in acetic acid) to give quinolone **4** in 50% yield.[8] A similar manganese(III)-mediated reaction using quinoline-2,4-diol (1 equiv.) and α-methylstyrene (5 equiv.) in $[\mathrm{bmim}][\mathrm{BF}_4]$–dichloromethane gave a 1:1 mixture of the angular and linear tricycles **5** and **6**, respectively, in a combined 78% yield.



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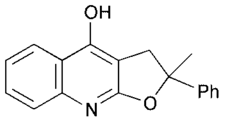

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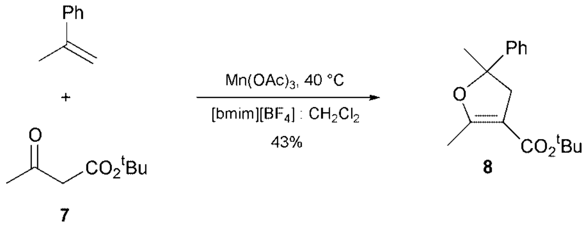
This work has shown, for the first time, that manganese(III)-mediated radical reactions can be carried out in alternative solvents to acetic acid in the presence of the ionic liquid $[\mathrm{bmim}][\mathrm{BF}_4]$. The ability to carry out manganese(III) reactions in a variety of solvents, under much milder reaction conditions than when using acetic acid, should extend the range of precursors which can be employed in these types of reactions. For example, we have shown that the *tert*-butyl ester **7** can be reacted with α-methylstyrene in $[\mathrm{bmim}][\mathrm{BF}_4]$–dichloromethane to give **8** in 43% yield (Scheme 4). The same reaction at 50 °C in acetic acid afforded **8** in a much lower yield of 25%, presumably because of the harsher (acidic) reaction conditions.

At the end of the reaction, the manganese acetate can be easily recovered (on precipitation) by addition of further organic solvent to the reaction mixture. After filtration, the manganese acetate was reacted with potassium permanganate to re-oxidise the manganese(II) back to manganese(III).[9] The manganese(III) acetate can therefore easily be recycled although this does depend on the nature of ionic liquid. For example, when the related ionic liquid $[\mathrm{bmim}][\mathrm{PF}_6]$ was used, complete removal of the manganese byproducts was problematic. The ionic liquid $[\mathrm{bmim}][\mathrm{BF}_4]$, which is believed to act as a co-solvent in these reactions,¶ can also be recovered on workup (in ⩾95% yield) and we have shown that this can be reused without any detriment to the product yields. For example, dihydrofuran **2c** was isolated in similar yields (*ca*. 50%) when using freshly prepared ionic liquid or ionic liquid recovered from other reactions. This work offers the potential for carrying out a variety of metal-mediated radical reactions in ionic liquids and this is currently under investigation.



Scheme 4

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Notes and references

† To a solution of $[\mathrm{bmim}][\mathrm{BF}_4]$[10] (2 cm^3) and dichloromethane (8 cm^3) containing cyclohexane-1,3-dione (0.10 g, 0.89 mmol) and α-methylstyrene (0.53 g, 2.63 mmol, 5 equiv.) was added manganese(III) acetate dihydrate (0.50 g, 1.88 mmol, 2.1 equiv.) under an atmosphere of nitrogen. The reaction mixture was then heated overnight until the solution changed from brown to yellow. Dichloromethane (40 cm^3) was then added and manganese(II) acetate was removed by filtration. The filtrate was then washed with water (4 × 10 cm^3) to remove the ionic liquid from the organic phase. (The ionic liquid can be recovered by extracting the aqueous phase with dichloromethane). The organic phase was then dried (MgSO_4), evaporated and purified using column chromatography (silica) to give 2-methyl-2-phenyl-3,5,6,7-tetrahydro-2*H*-benzofuran-4-one **1** (0.10 g, 50%) as an oil.

‡ All spectral data were in accord with the structures assigned. *Selected data* for **1**: δ_{H}(300 MHz, CDCl_3) 7.30–7.15 (5H, m, aromatics), 2.98 and 2.89 (2H, dt, *J* 14.5, 1.9, $\mathrm{C}H_2$CPh), 2.45–2.40 (2H, m, CH_2), 2.29–2.23 (2H, m, CH_2), 2.02–1.91 (2H, m, CH_2), 1.62 (3H, s, CH_3); δ_{C}(75 MHz, CDCl_3) 196.0 (C=O), 176.4 (O–*C*=C), 146.0 (PhC^1), 128.9, 127.9, 124.6 (PhC^{2-6}), 113.0 (*C*=C–O), 93.0 (OCPh), 41.0 (PhC$C\mathrm{H}_2$), 36.8 ($C\mathrm{H}_2$C=O), 30.2 (CH_3), 24.5, 22.1 ($\mathrm{CH}_2C\mathrm{H}_2\mathrm{CH}_2$).

§ When the reaction was carried out in dichloromethane in the absence of the ionic liquid, quinolone **4** was not formed even after heating in an ultrasonic bath (300 W, 30–40 kHz) for 24 h.

¶ Addition of the ionic liquid presumably increases the polarity of the medium and similar reactions can be carried out using dichloromethane in the presence of $\mathrm{Et}_4\mathrm{N}^{+-}\mathrm{OTs}$. Reaction of cyclohexane-1,3-dione with α-methylstyrene in a 0.1 M solution of $\mathrm{Et}_4\mathrm{N}^{+-}\mathrm{OTs}$ in dichloromethane also gave tetrahydrofuranone **1** in 50% yield.

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