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# Ionic liquids as media for nucleophilic fluorination

Christopher B. Murray[a], Graham Sandford[a,*], Stewart R. Korn[b]

[a]Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK
[b]Avecia, P.O. Box 521, Leeds Road, Huddersfield HD2 1GA, UK

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Dedicated to Professor Eric Banks on the occasion of his 70th birthday

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## Abstract

The use of Room Temperature Ionic Liquids (RTILs) for a variety of halogen exchange (Halex) fluorination processes using alkali metal fluorides is assessed. Whilst fluorination of a range of halogenated substrates is possible in good yield, the utility of RTILs as reusable, inert media for such reactions is limited by the gradual decomposition of the RTIL in the presence of highly basic fluoride ion.

*Keywords:* Ionic liquids; Fluoride ion; Nucleophilic fluorination; Green chemistry

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## 1. Introduction

Methodology for the regio- and stereo-selective introduction of fluorine atoms into organic systems, that is both suitable for scale up and economically realistic, remains a significant and important challenge to organofluorine chemists [1–3]. In general, the synthesis of carbon fluorine bonds may be accomplished by functional group interconversion of carbon hydrogen or carbon–halogen bonds, using either an electrophilic fluorinating agent such as Selectfluor™ [4] or elemental fluorine [5], or a source of fluoride ion, using an alkali metal fluoride, hydrogen fluoride or amine hydrofluoride [6,7], respectively. In particular, halogen exchange (Halex) processes involving nucleophilic substitution of halogens by fluorine, upon reaction of a suitably activated halogenated substrate with an alkali metal fluoride, have been used extensively for the synthesis of various fluorinated aliphatic [3], aromatic [8] and heterocyclic systems [8,9].

Whilst the Halex approach has been used effectively for a number of fluorination reactions, the low solubility of KF and CsF even in polar aprotic solvents, such as sulpholane, *N*-methylpyrrolidinone and *N*,*N*-dimethylformamide, generally means that harsh reaction conditions (high temperatures) are required for significant fluorination to occur. Consequently, Halex methodology can be unsuitable for the fluorination of less thermally robust systems. Furthermore, extraction and purification of fluorinated products from aprotic media is often very difficult and such environmentally hazardous solvents are not generally recycled, leading to large waste streams for disposal.

There is growing interest in the development of "green" chemical processes that are more environmentally benign [10,11] and, in particular, do not lead to any hazardous by-products or solvent waste. The development and application of new inert reaction media, that may be recycled, is a primary goal and, in this context, Room Temperature Ionic Liquids (RTILs) have been widely investigated as potential replacement solvents for a variety of chemical processes [12,13]. RTILs, such as butylmethylimidazolium hexafluorophosphate, [BMIM][$PF_6$] (**1**), may, potentially, be advantageous reaction media because they are essentially non-toxic, recyclable and have a limited vapour pressure, allowing efficient recovery of organic products by simple distillation under vacuum or conventional liquid–liquid extraction techniques. Indeed, many classes of chemical reactions [13,14], such as nucleophilic substitution, Heck reactions, etc. have been carried out in RTILs, exemplifying these facts.

In the light of recent reports [15–18], in this paper we report our investigations into the use of RTIL media for Halex processes involving reaction of caesium fluoride with a variety of halogenated organic substrates.

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[*] Corresponding author. Tel.: +44-191-334-2039;
fax: +44-191-384-4737.
*E-mail address:* graham.sandford@durham.ac.uk (G. Sandford).

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## 2. Results and discussion

We have investigated the use of the readily accessible [19] hydrophobic RTIL, [BMIM][$PF_6$] (**1**), as a medium for a range of Halex processes, involving substitution of bromine or chlorine located at various $sp^2$ and $sp^3$ carbon sites, and these experiments are collated in Table 1.

In all reactions, both the CsF and **1** were rigorously dried before use by heating under vacuum, except where indicated in Table 1. CsF is not appreciably soluble in ionic liquid **1** and so all fluorination reactions were carried out with CsF suspended in the reaction medium. After heating and stirring the reaction mixtures overnight under an inert atmosphere at the temperature required, product mixtures were isolated by simple vacuum transfer directly from the RTIL fluid. Yields of fluorinated products and by-products were assessed by NMR spectroscopy with reference to a weighed quantity of an NMR standard which was added to the weighed product mixture. Identification of all products was carried out by $^{19}F$ and $^{1}H$ NMR and GC–MS, with reference to authentic samples [20]. In most cases, recovery of organic material by vacuum transfer was satisfactory.

After completion of the reaction and transfer of the organic products, the RTIL was washed with water, filtered, dried under vacuum and could be reused over a limited number of reaction cycles. Unfortunately, repeated use of the RTIL gradually led to significant discoloration and decreased performance. Fluorinations of 1-bromooctane using KF, $KHF_2$ and $CaF_2$ were attempted but only starting material was recovered after heating in RTIL overnight.

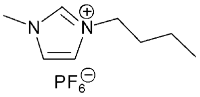
The results of the experiments outlined in Table 1 suggest that fluorination of very activated systems such as benzoyl chloride and benzyl bromide occur efficiently in the RTIL media at room temperature and a reasonable yield of products may be obtained. Less reactive substrates such as bromoalkanes give lower yields of the corresponding fluoroalkanes because elimination, where the fluoride ion acts as a base, is a competing process and a common feature of Halex processes. Increasing the temperature of many of the fluorination reactions does not lead to significant increase in the yield of fluorinated product but, instead, leads to a discoloration of the RTIL to give a brown, tarry oil.

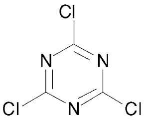
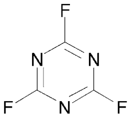
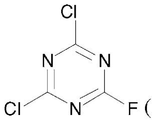
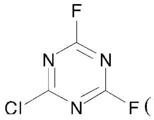
The discoloration of the RTIL upon heating and repeated use suggested that **1** was not compatible with the highly basic reaction conditions. Therefore, we heated samples of **1** with KF and CsF in Carius tubes at 150 °C to assess the long-term stability of the medium towards fluoride ion. After 18 h, the RTIL had visibly decomposed and volatile

Table 1
Halogen exchange processes using RTIL reaction media

$$\text{R—X} + \text{M—F} \xrightarrow[\text{overnight}]{\text{temperature}} \text{R—F} + \text{M—X} + \text{other products}$$

RTIL **1**

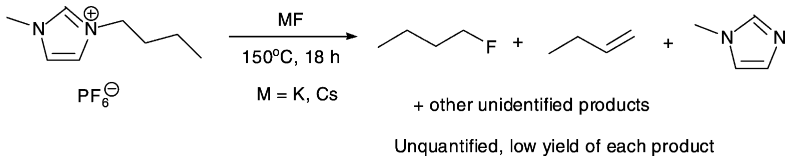
RTIL **1** =


| R–X | CsF | T (°C) | Conversion (%) | R–F (%)[a] | Others (%) |
|---|---|---|---|---|---|
| $PhCH_2Br$ | CsF | 20 | 63 | $PhCH_2F$ (47) | – |
| $n$-$C_8H_{17}Br$ | CsF | 20 | 17 | $n$-$C_8H_{17}F$ (12) | $C_6H_{13}CH{=}CH_2$ (3) |
| $n$-$C_8H_{17}Br$ | CsF | 70 | 26 | $n$-$C_8H_{17}F$ (19) | $C_6H_{13}CH{=}CH_2$ (5) |
| $n$-$C_8H_{17}Br$ | 2 CsF | 80 | 98 | $n$-$C_8H_{17}F$ (55) | $C_6H_{13}CH{=}CH_2$ (7) |
| $n$-$C_8H_{17}Br$ | 2 CsF[b] | 80 | 76 | $n$-$C_8H_{17}F$ (65) | $C_6H_{13}CH{=}CH_2$ (11) |
| $C_6H_{13}CHBrCH_3$ | CsF | 20 | 11 | 0 | $C_5H_{11}CH{=}CHCH_3$ (10) |
| $C_6H_{13}CHBrCH_3$ | 2 CsF | 20 | 17 | $C_6H_{13}CHFCH_3$ (1) | $C_5H_{11}CH{=}CHCH_3$ (1) |
| $C_6H_{13}CHBrCH_3$ | CsF | 70 | 5 | 0 | $C_5H_{11}CH{=}CHCH_3$ (4) |
| $C_6H_{13}CHBrCH_3$ | CsF | 70 | 38 | $C_6H_{13}CHFCH_3$ (3) | $C_5H_{11}CH{=}CHCH_3$ (13) |
| PhCOCl | CsF | 20 | 74 | PhCOF (40) | – |
|  | 3 CsF | 80[c] | – |  (10) |  (3)<br> (11) |

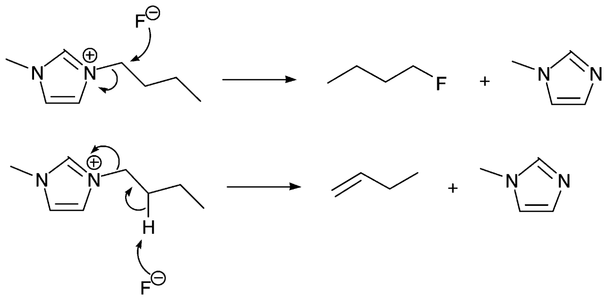
[a] Yields based on conversion of starting material.

[b] CsF used as received from suppliers without further drying.

[c] Carius tube.



Scheme 1.



Scheme 2.

decomposition products could be isolated, albeit in very small quantities, from the Carius tube by vacuum transfer. GC–MS analysis of this very volatile material showed the presence of several species including alkyl imidazoles, fluoroalkanes and alkenes (Scheme 1).

Possible mechanisms for the formation of these volatile decomposition products are outlined in Scheme 2, in which fluoride ion acts as a base to promote elimination or substitution processes.

These findings demonstrate that Halex fluorination in RTILs is possible for various systems in which relatively low temperatures are adequate for successful reaction. However, there are some significant difficulties due to the decomposition of **1** upon heating with fluoride ion, either in the reaction or vacuum transfer stages. Recycling of the ionic liquid, a primary driving force for using these systems is, therefore, limited to some extent when using alkali metal fluorides as the source of fluoride ion for nucleophilic fluorination reactions.

## 3. Experimental

All starting materials were obtained commercially (Aldrich) or synthesised according to published procedures [19] and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Mass spectra were recorded on either a VG 7070E spectrometer or a Fissons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph.

### *3.1. Halogen exchange reactions in RTIL **1***

#### *3.1.1. General procedure*

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar and septa under an inert atmosphere. The vessel was charged with alkali metal fluoride and RTIL **1** (15 ml) and then degassed for 10 min under vacuum to allow distribution of the alkali metal fluoride in the liquid media. The halogenated substrate was added under an inert atmosphere and the mixture stirred vigorously at the required temperature overnight. Volatile fractions were removed by vacuum transfer to yield a weighed crude product which was analysed by $^{19}$F and $^{1}$H NMR (after a weighed amount of internal standard had been added) and GC–MS. Products were identified with reference to literature values ($^{19}$F, $^{1}$H NMR) and authentic samples (GC–MS).

#### *3.1.2. Reaction of **1** with caesium fluoride*

A Carius tube was charged first with CsF (3.60 g, 23.4 mmol) under argon and then **1** (3.1 ml, 15 mmol). The tube was then evacuated and frozen in liquid nitrogen before being sealed. After the tube had been heated at 150 °C for 96 h, it was opened and the volatile materials isolated by vacuum transfer. A small quantity of colourless liquid was collected in the trap, the residue in the Carius tube being a deep brown-yellow colour. The volatile fraction was analysed by GC–MS and the following products were detected:

- but-1-ene: $m/z$ (EI$^+$) 56 ($M^+$, 87%);
- 1-fluorobutane: $m/z$ (EI$^+$) 75 ($M^+ - 1$, 1.5 %), 56 ($M^+$ – HF, 100%), 47 ($CH_2CH_2F^+$, 15%), 33 ($CH_2F^+$, 55%);
- *N*-methylimidazole: $m/z$ (EI$^+$) 81 ($M^+ - 1$, 2%), 56 (N–CH–N–$CH_3^+$, 13%), 55 (CH–CH–N–$CH_3^+$, 8%), 42 (CH–N–$CH_3^+$, 9%), 40 (N–CH–$CH^+$, 92%), 41 (N–CH–$N^+$, 100%), 28 (N–$CH_3^+$, 22%);

as compared to authentic samples.

By a similar procedure, KF (0.58 g, 10 mmol) and **1** (0.83 ml, 4 mmol) were heated to 150 °C in a Carius tube overnight and visual examination indicated that the [BMIM]-[$PF_6$] had decomposed due to its increased viscosity and deep yellow-brown colour. No further analysis was conducted.

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