



# Fluorination of $\alpha$ -bromomethyl aryl ketones with fluorohydrogenate-based ionic liquids

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## ARTICLE INFO

### Article history:

Received 2 September 2015  
Received in revised form 27 October 2015  
Accepted 28 October 2015  
Available online 10 November 2015

### Keywords:

Fluorination  
Fluorohydrogenate ionic liquids  
 $\alpha$ -Fluoromethyl aryl ketones  
Hydrogen fluoride

## ABSTRACT

Fluorination of  $\alpha$ -bromomethyl aryl ketones using fluorohydrogenate-based ionic liquids as fluorinating reagent is described. Reaction of various  $\alpha$ -bromomethyl aryl ketones (**1a–g**) with fluorohydrogenate-based ionic liquids such as EMIMF·(HF)<sub>2,3</sub>, PYR<sub>13</sub>F·(HF)<sub>2,3</sub> or PYR<sub>14</sub>F·(HF)<sub>2,3</sub> as a fluoride ion source in anhydrous THF led to the formation of the corresponding  $\alpha$ -fluoromethyl aryl ketones (**2a–g**) in very good yield. Compared to alternative fluorinating agents for this reaction, fluorohydrogenate-based ionic liquids are safer to handle and have the potential to be less expensive and more selective.

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## 1. Introduction

Fluorinated organic compounds are widely used in the pharmaceutical, agrochemical and material science industries, and for this reason, selective fluorinating agents are of high interest to both research and industry. It is widely known that the incorporation of fluorine into organic molecules has a significant effect on their physical, chemical, and biological properties [1–3].

$\alpha$ -Fluoromethyl aryl ketones are one class of organofluorine molecules found in bioactive molecules and are often used as building blocks for other organofluorine compounds. For example, it has been well recognized that the electron-withdrawing effect of the fluorine atom can increase the susceptibility of carbonyl groups to hydration. In fact, this property has been exploited in the design of inhibitors of hydrolytic enzymes [4–7]. Due to their importance, efficient and practical strategies to synthesize  $\alpha$ -fluoromethyl aryl ketones have long been pursued. A number of approaches to synthesize these molecules have been described, including electrophilic fluorination, nucleophilic displacement, Friedel–Crafts chemistry, and coupling chemistry. Some of these suffer from drawbacks including poor yield and difficult-to-handle reagents.

In general, there are two synthetic approaches to  $\alpha$ -fluoromethyl aryl ketones. The first approach involves the introduction of fluorine atom into non-fluorinated substrate with electrophilic fluorinating reagents, such as *N*-fluorosulfonimide or Selectfluor

[8–14]. Unfortunately, these reagents are very expensive for use in large scale production and/or are difficult to prepare due to the need for elemental fluorine. The second approach towards  $\alpha$ -fluoromethyl aryl ketones is the nucleophilic substitution of  $\alpha$ -bromomethyl aryl ketones with fluorine using KF/Ph<sub>3</sub>SnF [15], KF/18-crown-6 [16,17], KF/PEG-1000 [18], KF/PEG-400, or ZnF<sub>2</sub>/KF or TBAF/ZnF<sub>2</sub> with DES, DCDMH [19]. However, these combinations of fluorinating reagents have low solubility, thereby limiting their usefulness in a large-scale or continuous processes.

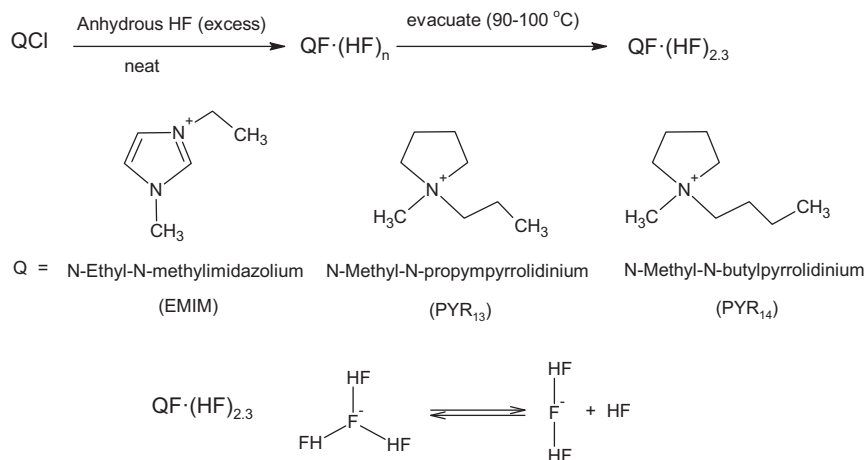
Hydrogen fluoride is the most basic nucleophilic fluorinating reagent [20,21]. Unfortunately, due to difficulties associated with handling hydrogen fluoride, its general applicability as a fluorinating agent is severely limited. Other fluorinating reagents include pyridinium poly(hydrogen fluoride) (Py·nHF) [22,23], and triethylamine trihydrogen fluoride (Et<sub>3</sub>N·3HF) [24]. However, these reagents also require careful handling as they fume in air.

Therefore, there is a need for relatively safe and/or non-fuming fluorinating reagent to produce  $\alpha$ -fluoromethyl aryl ketones. In this paper, we report a new process using fluorohydrogenate-based ionic liquids such as EMIMF·(HF)<sub>2,3</sub>, PYR<sub>13</sub>F·(HF)<sub>2,3</sub> or PYR<sub>14</sub>F·(HF)<sub>2,3</sub> to fluorinate  $\alpha$ -bromomethyl aryl ketones. These materials do not fume, are highly stable, and represent a new class of safer and easier-to-handle fluorinating agents for this reaction [25].

## 2. Results and discussion

Ionic liquids have attracted much attention as reaction media because of their low volatility, especially in the field of green and

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**Scheme 1.** Synthesis of fluorohydrogenate-based ionic liquids.

combinatorial chemistry [26]. Fluorohydrogenate-based ionic liquids such as EMIMF·(HF)<sub>2,3</sub> (1-ethyl-3-methylimidazolium fluorohydrogenate), PYR<sub>13</sub>F·(HF)<sub>2,3</sub> (1-methyl-1-propylpyrrolidinium fluorohydrogenate), and PYR<sub>14</sub>F·(HF)<sub>2,3</sub> (1-methyl-1-butylpyrrolidinium fluorohydrogenate) are stable in air and moisture, and do not fume in air due to their extremely low vapor pressure. These can be used as a reaction media or in fluorinating reactions as a hydrogen fluoride source. It has been shown that there is a rapid exchange of HF occurring between F(HF)<sub>2</sub><sup>-</sup> and F(HF)<sub>3</sub><sup>-</sup> anions [27], with a vacuum stable ratio of 7:3, leading to the empirical anion stoichiometry of F·(HF)<sub>2,3</sub>. Fluorohydrogenate-based ionic liquids were synthesized by the reaction of quaternary ammonium chloride salts with anhydrous hydrogen fluoride in our laboratory (Scheme 1) [28]. The fluorohydrogenate ionic liquids are air- and water-stable, and do not etch borosilicate glass at room temperature. They can be handled in glassware, although fluorinated polymer vessels are recommended for long-term storage and to remove the possibility of contamination.

Scheme 2 shows the general reaction approach.  $\alpha$ -Bromo-methyl aryl ketones were reacted with the fluorohydrogenate ionic liquids in THF solvent. Initially, the reaction of  $\alpha$ -bromo-1-phenylethanone with three equivalents of EMIMF·(HF)<sub>2,3</sub> was carried out without any solvent at room temperature to 100 °C for 20 h. The reaction was found to be slow and only a trace amount of product was formed. Then the reaction was carried out in anhydrous THF at the reflux temperature for 20 h. The isolated

product was obtained in very good yield. Experiments of 5, 10 and 20 h were conducted. Partial conversion was obtained at 10 h and yields above 80% were obtained for most substrates in 20 h. Similar reactivity was observed when PYR<sub>13</sub>F·(HF)<sub>2,3</sub> and PYR<sub>14</sub>F·(HF)<sub>2,3</sub> were used as fluorinating reagents. Reactions of various substrates are shown in Scheme 2 and Table 1. The work up of the reaction was performed by removing THF at reduced pressure and isolating the desired product by extraction with diethyl ether and washing with dilute HCl water solution to remove water-miscible ionic liquids byproducts. Pure product was isolated by using silica gel chromatography. Products were characterized by the <sup>19</sup>F and <sup>1</sup>H-NMR spectroscopy and GC–MS analysis and also compared with literature data.

In summary, fluorohydrogenate ionic liquids are able to fluorinate a wide range of  $\alpha$ -bromomethyl aryl ketones with good yield (typically 85% or more). Ionic liquids with both pyrrolidinium and ethyl-methylimidazolium cations were used successfully.

**Table 1**

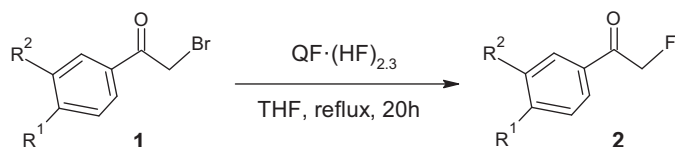
Fluorination of  $\alpha$ -bromomethyl aryl ketones with fluorohydrogenate-based ionic liquids.

Entry <sup>a</sup>	Substrate	QF·(HF) <sub>2,3</sub>	Product	Yield (%) <sup>b</sup>
1	<b>1a</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2a</b>	85
2	<b>1a</b>	PYR <sub>13</sub> F·(HF) <sub>2,3</sub>	<b>2a</b>	87
3	<b>1a</b>	PYR <sub>14</sub> F·(HF) <sub>2,3</sub>	<b>2a</b>	90
4	<b>1b</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2b</b>	82
5	<b>1b</b>	PYR <sub>13</sub> F·(HF) <sub>2,3</sub>	<b>2b</b>	80
6	<b>1b</b>	PYR <sub>14</sub> F·(HF) <sub>2,3</sub>	<b>2b</b>	88
7	<b>1c</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2c</b>	86
8	<b>1c</b>	PYR <sub>13</sub> F·(HF) <sub>2,3</sub>	<b>2c</b>	85
9	<b>1c</b>	PYR <sub>14</sub> F·(HF) <sub>2,3</sub>	<b>2c</b>	88
10	<b>1d</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2d</b>	79
11	<b>1d</b>	PYR <sub>13</sub> F·(HF) <sub>2,3</sub>	<b>2d</b>	80
12	<b>1d</b>	PYR <sub>14</sub> F·(HF) <sub>2,3</sub>	<b>2d</b>	81
13	<b>1e</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2e</b>	82
14	<b>1e</b>	PYR <sub>13</sub> F·(HF) <sub>2,3</sub>	<b>2e</b>	86
15	<b>1e</b>	PYR <sub>14</sub> F·(HF) <sub>2,3</sub>	<b>2e</b>	85
16	<b>1f</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2f</b>	72 <sup>c</sup>
17	<b>1f</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2f</b>	85
18	<b>1f</b>	PYR <sub>14</sub> F·(HF) <sub>2,3</sub>	<b>2f</b>	84
19	<b>1g</b>	EMIMF·(HF) <sub>2,3</sub>	<b>2g</b>	82
20	<b>1g</b>	PYR <sub>13</sub> F·(HF) <sub>2,3</sub>	<b>2g</b>	86
21	<b>1g</b>	PYR <sub>14</sub> F·(HF) <sub>2,3</sub>	<b>2g</b>	85

<sup>a</sup> All reactions were carried out using 5.0 mmol substrates, 15.0 mmol of fluorinating reagents (QF·(HF)<sub>2,3</sub>) in 50 ml of anhydrous THF at reflux temperature for 20 h in a Teflon reaction vessel.

<sup>b</sup> Isolated by silica gel chromatography.

<sup>c</sup> Reaction was carried out using 5 mmol substrates, 15 mmol of EMIMF·(HF)<sub>2,3</sub> in 50 ml of anhydrous THF at reflux temperature for 20 h in a glass reaction vessel.



QF·(HF)<sub>2,3</sub> = EMIMF·(HF)<sub>2,3</sub>, PYR<sub>13</sub>F·(HF)<sub>2,3</sub>, PYR<sub>14</sub>F·(HF)<sub>2,3</sub>

a: R<sup>1</sup> = H, R<sup>2</sup> = H                      e: R<sup>1</sup> = NO<sub>2</sub>, R<sup>2</sup> = H

b: R<sup>1</sup> = Me, R<sup>2</sup> = H                      f: R<sup>1</sup> = H, R<sup>2</sup> = NO<sub>2</sub>

c: R<sup>1</sup> = OMe, R<sup>2</sup> = H                      g: R<sup>1</sup> = Cl, R<sup>2</sup> = Cl

d: R<sup>1</sup> = Cl, R<sup>2</sup> = H

**Scheme 2.** Fluorination of  $\alpha$ -bromomethyl aryl ketones with fluorohydrogenate-based ionic liquids.

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