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Catalytic nucleophilic fluorination by an imidazolium ionic liquid possessing trialkylphosphine oxide functionality

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ABSTRACT

The synthesis of a new alkylmethylimidazolium ionic liquid wherein the alkyl group is functionalized with dihexylphosphine oxide moiety at the terminal position has been achieved in four steps from 1-methylimidazole. This hybrid ionic liquid effectively catalyzed the nucleophilic fluorination of primary alkyl mesylates under mild conditions using CsF as the fluoride source with a faster rate compared to butylmethylimidazolium mesylate. The hybrid catalyst was recycled 5 times without compromising the yield and purity of the product. The nucleophilic fluorination has been used for the synthesis of diethyl 2-(5-fluoropentyl)-2-methyl malonate, a precursor of ^{18}F isotopomer of an apoptosis imaging agent and the protected form of *O*-(2′-fluoroethyl)-L-tyrosine, a ^{18}F isotopomer of a tumor imaging agent.

1. Introduction

Fluorinated organic molecules show improved properties especially in increasing solubility, bioavailability and metabolic stability compared to their non-fluorinated analogs [1–5]. Therefore, they have great importance in pharmaceuticals, agrochemicals, solvents, liquid crystals, dyestuffs, polymers and novel materials [6–10]. A large number of methods have been developed over last few decades for the selective introduction of fluorine into target molecules [11]. Nevertheless, development of mild, selective and environmentally more acceptable fluorination method still remains a challenge. Besides fluorinated starting materials, fluorine can be incorporated into organic molecules in a nucleophilic manner, an electrophilic manner, or electrochemically. Introduction of single fluorine into aliphatic organic compounds is very important for making ^{18}F-labeled compounds and this has been typically carried out by nucleophilic substitution of sulfonates such as tosylates, mesylates and triflates utilizing alkali-metal/tetraalkylammonium fluorides as reagents [12,13]. The limited solubility and low nucleophilicity of the fluoride salts in organic solvents require generally vigorous conditions [14]. Phase-transfer catalysis involving crown ether derivatives and quaternary ammonium salts have been used to enhance the solubility and nucleophilicity of the metal salt in organic solvent systems consequently accelerating the reaction rate [15]. Although the problem of solubility and reactivity has been solved, 'naked' fluoride generated from these phase-transfer processes can induce side reactions such as elimination and hydroxylation reactions due to strong basicity of the fluoride [16–21]. Phase-transfer catalysis is also ineffective when the metal and nucleophile form a tight ion pair [22,23].

Recently, 1,3-dialkylimidazolium salts-based ionic liquids (ILs) have frequently been used as alternative reaction media instead of conventional volatile organic solvents for reaction acceleration and easy partitioning of products and catalysts [24–28]. It was found that ionic liquids can remarkably enhance the reactivity of alkali metal fluorides in the nucleophilic fluorination [29–34]. While anionic counterparts including BF_4, PF_6, SbF_6, NTf_2, and OTf play a critical role in determining different physical properties, such as melting point, polarity and solubility, functionality in the alkyl chains has been introduced for hybrid ILs to do specific functions [35–43].

Trialkylphosphine oxides are well known to complex various cations thus enhancing the solubility of their salts in organic media [44,45]. ILs have been used as both reaction media and phase transfer catalysts, and it has been found that nucleophilic fluorination is accelerated in ILs [29–34]. We were therefore curious to uncover the outcome of hybridization of ILs and

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trialkylphosphine oxide in the nucleophilic fluorination. Also, it would be interesting to check whether this combined functionality would provide dual advantages for the acceleration of the reaction rate by IL component and interruption of tight metal fluoride ion pair to lose ion pair but not "naked one" [46]. Herein, we describe the design and synthesis of a novel, imidazolium IL-trialkylphosphine oxide hybrid and its application to nucleophilic fluorination of primary alkyl mesylates.

2. Results and discussion

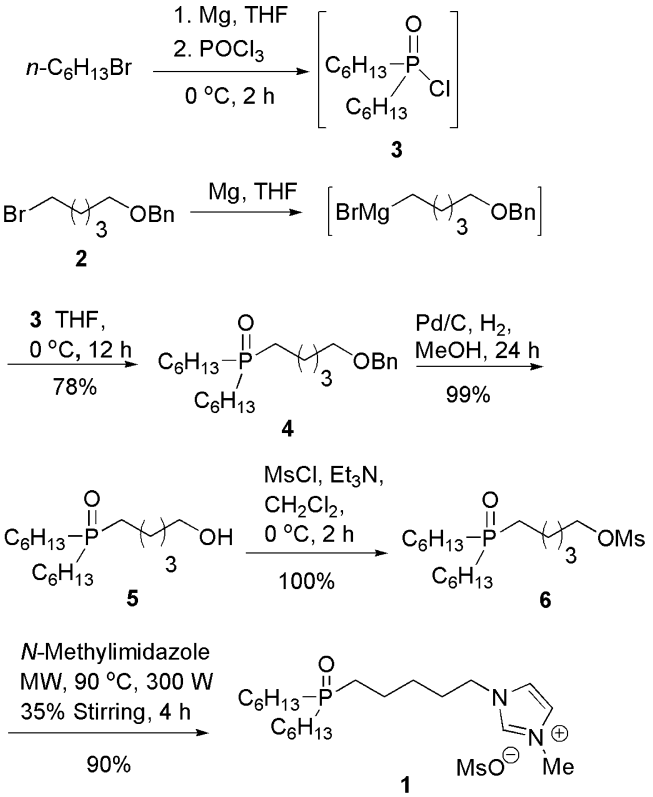
The imidazolium IL-trialkylphosphine oxide hybrid **1** having a dihexylpentylphosphine oxide moiety and methanesulfonate as a counter ion, was prepared from *N*-methylimidazole as shown in Scheme 1. For this the Grignard reagent derived from 5-benzyloxy-1-bromopentane **2** [47] was reacted with *in situ* generated dihexylphosphoryl chloride **3** in THF to give the trialkyl phosphine oxide **4** which on hydrogenolysis gave alcohol **5**. Reaction of this alcohol with methanesulfonyl chloride in the presence of triethylamine gave the mesylate **6** which on reaction with *N*-methylimidazole gave the desired hybrid IL **1** in excellent yield and purity.

For screening and optimization of nucleophilic fluorination protocol, we prepared the primary mesylate **7a** from 5-benzyloxypentanol using methanesulfonyl chloride and in the presence of triethylamine (Scheme 2). Cesium fluoride was chosen as the fluoride source as it has been reported [48–51] to give best results. We chose *t*-BuOH as the reaction medium as it is known [48–52] to suppress basicity of fluoride ion by the way of H-bonding thus minimizes the side reactions due to elimination.

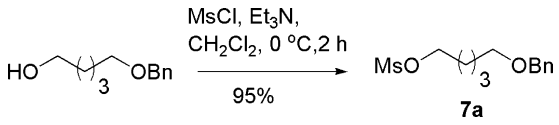
When the solution of mesylate **7a** in *t*-BuOH was heated at 60 °C with 3 equiv. of added cesium fluoride, no reaction took place (Table 1, entry 1). When the same reaction was repeated after addition of 0.5 equiv. of hybrid IL **1**, an incomplete but clean reaction took place with 48% conversion (Table 1, entry 2) of mesylate **7a** to fluoride **8a**. For comparison purpose, the fluorination reaction was carried out with 0.5 equiv. of butylmethylimidazolim mesylate ([BMIm] [OMs]) **9** instead of hybrid IL **1** under the same reaction conditions. Only 5% conversion of mesylate **7a** to fluoride **8a** was observed (Table 1, entry 3). Interestingly, when the reaction was carried out with 0.5 equiv. of phosphine oxide **4** as an additive, no fluorination took place. Only the starting mesylate **7** was recovered (Table 1, entry 4). When a mixture containing 0.5 equiv. each of [BMIm] [OMs] **9** and phosphine oxide **4** was used as an additive, a marginal rate enhancement was noticed and about 10% fluorination took place (Table 1, entry 5). Clearly, a distinctive rate enhancement was observed in the hybrid IL **1**. For establishment of optimum conditions for the catalytic fluorination using hybrid IL **1**, the reaction temperature was increased and at 100 °C within 10 min, 90% of **7a** was transformed into fluoride **8a** and the reaction was completed in 45 min (Table 1, entries 6 and 7).

To check the reusability of the hybrid IL **1**, the fluorination reaction was repeated using same ionic liquid recovered after fluorination. After 45 min, the reaction mixture was triturated with hexanes and the hexane layer was decanted. After evaporation of the hexane solution, pure fluoride **8a** was isolated and the ionic liquid associated with CsF/CsOMs remained in the reaction pot was subjected under high vacuum and reused. In each cycle, an additional 1 equiv. of CsF was added and the yield of the fluoride **8a** was uniformly high in all the cycles (Table 2).

To enhance the utility, the IL **1** catalyzed nucleophilic fluorination was investigated with substrates having halides ($Cl^-/Br^-/I^-$) as leaving groups under the optimized conditions (Scheme 3). The reaction of chloride **10a** [53] and bromide **2** were slow and required 75 min and 60 min, respectively to undergo completion. A trace of elimination product **11** (~5%) could be seen in case of chloride substrate **10a** while bromide **2** gave about 10% of **11**. Interestingly, the reaction of iodide **10b** [54] was faster and completed within 35 min but accompanied with about 30% of alkene **11**. Although the elimination product **11** is easily separable from the desired fluoride **8a**, its yield was affected to varied extent depending on the substrate.

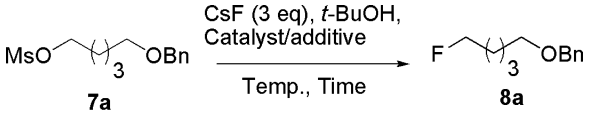


Scheme 1.



Scheme 2.

Table 1
Fluorination of mesylate **7a** with CsF in *t*-BuOH[a].



Entry	Catalyst/additive (equiv.)	Temperature (°C)/time (min)	% conversion[b]
1	Nil	60/30	0
2	**1** (0.5)	60/30	48
3	**9** (0.5)	60/30	5
4	**4** (0.5)	60/30	0
5	**9** (0.5) and **4** (0.5)	60/30	10
6	**1** (0.5)	100/10	90
7	**1** (0.5)	100/45	100

[a] All reactions were carried out using **7a** (1 mmol), cesium fluoride (3 mmol) and catalyst **1** (0.5 mmol) in *t*-BuOH (0.25 mL).
[b] Determined from ^{1}H NMR of the crude reaction mixture by integrating the peak area of CH_2 in CH_2OMs and CH_2F resonances.