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Phase-Transfer Protocol-TBAF In Ter-Alcohol Medium for Nucleophilic Fluorination of Alkyl Halides

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ABSTRACT

We have used commercially available TBAF in a non-polar protic t-amyl alcohol reaction medium to demonstrate a very effective nucleophilic fluorination technique of primary haloalkane systems to fluoroalkanes. It has recently been discovered that ter-alcohols, as nonpolar protic reaction media, exhibit unexpectedly strong performance in nucleophilic fluorination of sulfonate substrate, despite the fact that polar aprotic solvents such as acetonitrile and DMF are good for nucleophilic fluorination reactions. Using commercially available TBAF in a ter-alcohol medium, we present the efficient fluorination method for converting halide (particularly iodide) functional groups to fluoride at the primary aliphatic system.

Keywords: nucleophilic fluorination, TBAF, tert-alcohol, and fluorinated compounds

INTRODUCTION

Despite their rarity in nature, low fluorinated organic compounds have attracted a lot of attention due to their unique physiological properties and the potential of fluorine-18 labeled organic molecules as molecular imaging probes for positron emission tomography (PET) studies. The typical method for single fluorine substitution at a particular aliphatic molecular site is the nucleophilic replacement reaction of C-X functional groups with C-F [1, 2]. Selective and mild fluorination techniques are preferred for their preparation because of their therapeutic value. Thus, over the past few decades, a variety of nucleophilic fluorination techniques or reagents have been developed [3, 4].

Phase-transfer methods, including crown ether derivatives [5, 6] and quaternary ammonium fluorides [7-10], are conventionally employed for this purpose, with tetrabutylammonium fluoride (TBAF) produced from a phase-transfer protocol being the most favored reagent for nucleophilic fluorination because of its excellent nucleophilicity and solubility in organic reaction environments. Specifically, DiMagno recently developed highly reactive “anhydrous” TBAF (TBAFanh), produced in situ by treating hexafluorobenzene with tetrabutylammonium cyanide (TBACN) [11, 12]. Nevertheless, even with its favorable reactivity, "naked"

fluoride produced from TBAF (particularly TBAFanh) can lead to elimination, which is base-catalyzed, resulting in by-products of olefins during the fluorination reaction since it acts as a strong base and a good nucleophile [10]. When crown ether derivatives act as phase-transfer catalysts for fluorination, these crown ether/alkali metal fluoride complexes do not work well if the metal fluoride creates a strong ion pair [5, 6].

Imidazolium-containing ionic liquids and their counter anions have been thoroughly researched for a variety of applications in numerous chemistry disciplines in the past ten years due to their distinct physical and chemical characteristics [13-16]. It was discovered that using ionic liquid as a substitute reaction medium can significantly improve the reactivity of alkali metal fluorides and the selectivity of fluorination [17-20]. Nonetheless, separation issues arose between the ionic liquid and polar products with numerous heteroatoms during the reaction process [21]. To address the limitation of the ionic liquid fluorination approach, polystyrene-based polymer supported ionic liquids (PSILs) have been created as catalysts for nucleophilic fluorination with alkali metal fluorides in polar aprotic solvents [22].

While polar aprotic solvents like acetonitrile and DMF are typically recognized for their effectiveness in nucleophilic displacement reactions, including fluorination due to their ability to heighten the reactivity of anionic nucleophiles through selective solvation of counter cations, it has recently been discovered that tertiary alcohols, serving as nonpolar protic reaction media, exhibit surprisingly good results in the nucleophilic fluorination of sulfonate substrates, subsequently boosting the reactivity of alkali metal fluorides and minimizing the creation of byproducts like olefins or alcohols. Nevertheless, this tert-alcohol reaction media method is ineffective for reactions involving substrates with a halide leaving group, like alkyl bromides and iodides [24, 25]. The fluorination of haloalkanes, particularly iodoalkanes, with “naked” fluoride is recognized as challenging due to the competing elimination that produces the olefin byproduct. In this paper, we aim to present the efficient fluorination technique for converting halide (particularly iodide) functional groups into fluoride groups within primary aliphatic systems using commercially obtainable TBAF in a tert-alcohol solvent. This t-alcohol/TBAF fluorination occurred efficiently under relatively mild conditions, decreasing the formation of elimination byproducts in comparison to other earlier methods.

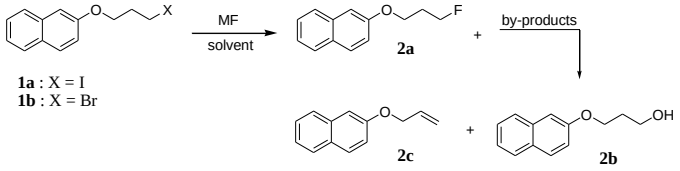
METHODS AND MATERIAL

Unless otherwise noted all reagent and solvents were commercially available. Reaction progress was followed by TLC on 0.25 mm silica gel glass plates containing F-254 indicator. Visualization on TLC was monitored by UV light. Flash chromatography was performed with 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 600 MHz spectrometer, and chemical shifts were reported in δ units (ppm) relative to tetramethylsilane. Solid-state ^{13}C, and ^{19}F NMR spectra were also recorded on 600 MHz spectrometer at rt. Low- and high-resolution electron impact (EI, 70 eV) spectra were obtained. The preparation of PSILs, PS[hmim][BF_4] as a catalyst.

RESULTS AND DISCUSSION

To investigate the relative selectivity of nucleophilic fluorinations using various methods of them, we carried out the fluorination of primary halide model compounds, 2-(3-iodopropoxy)naphthalene (1a) and 2-(3-bromopropoxy)naphthalene (1b), using various fluorination methods as shown in scheme 1 and compared with the fluorination reaction with TBAF in t-amyl alcohol. Table 1 summarizes the results of fluorination reactions under various reaction conditions.

Scheme 1. Fluorinations of Alkyl Halides (I & Br).



All reactions were carried out on a 1.0 mmol scale of haloalkane 1a or 1b with 2 mmol of fluoride source in 5.0 mL of solvent for 1 h at 70 °C. Yield determined by 1H NMR integration. 3.0 equiv of KF and 0.5 equiv of 18-crown-6 were used. The reaction was carried out on a 0.2 mmol scale of substrate with 2.0 equiv of TBAFanh generated in situ in CD_3CN at 25 °C. 3.0 equiv of CsF and 0.5 equiv of PS[hmim][BF_4] were used5 mL of H_2O and 2.5 mL of CH_3CN were used.

Table 1. Fluorinations of Alkyl Halides 1(a & b) in Various Reaction Condition.

entry	X	MF/catalyst	Solvent	temp. (°C)	time (h)	yield of product (%)			
						1(a, b)	**2a**	**2b**	**2c**
1	I	KF/18-crown-6	CH_3CN	70	1	98	-	-	-
2	I	TBAF	CH_3CN	70	1	-	38	6	56
3	I	$TBAF_{anh}$	CD_3CN	25	1	trace	14	-	87
4	I	CsF/PSIL[f]	CH_3CN	90	2	-	27	-	75
5	I	CsF	*t*-amyl alcohol	Reflux	12	-	75	-	21
6	I	CsF	*t*-amyl alcohol	70	1	93	6	-	Trace
7	I	TBAF	*t*-amyl alcohol	70	1	-	76	3	21
8	I	KF	IL/CH_3CN	100	3	-	76	[i]	21
9	I	TBAF	H_2O/CH_3CN[j]	70	1	96	trace	Trace	-
10	Br	TBAF	DMF	70	1	-	61	7	34
11	Br	TBAF	*t*-amyl alcohol	70	2	-	91	4	6
12	Br	CsF	*t*-amyl alcohol	70	2	94	7	-	-
13	Br	KF	IL/CH_3CN[i]	100	4	-	83	-	15

For comparison, results reported in the literature using other fluorination methods have been shown in Table 1. Entry 1, 2 and 10 show the nucleophilic fluorination using traditional phase transfer protocols such as 18-crown-6/KF or commercially available TBAF in traditional polar aprotic solvents such as CH3CN or DMF. Whereas the fluorination of iodoalkane 1a with 3 equiv of KF in the presence of 0.5 equiv of 18-crown-6 in acetonitrile at 70 °C barely proceeded after 1 h, the same reaction using 2 equiv of TBAF was completed within 1 h, affording 39% of 2-(3-fluoropropoxy)naphthalene (2a), with 6% of alcohol 2b and 55% of olefin 2c being formed as by-products; thus, the elimination of this iodoalkane 1a to olefin 2c was the dominant reaction in this reaction method. Moreover, the use of "anhydrous" TBAF (TBAFanh), which was generated in situ from the treatment of hexafluorobenzene with TBACN in CD_3CN,5 gave very low selectivity of the fluorination reaction (entry 3, only 12% of fluoroalkane 2a was obtained with 86% of alkene 2c). In entry 4, PSIL system (0.5 equiv of PS[hmim][BF_4]/3.0 equiv of CsF in acetonitrile) also did not show good performance in the selective fluorination of iodoalkane 1a. Although tert-alcohol/CsF method afforded good chemo-selective fluorination of iodoalkene, greatly reducing the formation of olefin as a by-product, harsh condition was required for the reaction to be completed as shown entry 5. In an effort to increase this reaction rate, we tried

to perform this fluorination using TBAF instead of CsF in t-amyl alcohol medium. Interestingly, a comparison of entries 6 and 7 showed that the use of TBAF in t-amyl alcohol could allow not only this reaction rate to increase significantly, but also the selectivity of fluorination to be enhanced slightly compared with the use of CsF, with providing the fluoroalkane 2a in 74% yield. Although, in the literature, ionic liquid fluorination method could provide the Fluor product in similar yield as shown entry 8, however, this ionic liquid method has been known to have the possibility of the problem in purification and extraction of product from ionic liquid. Because TBAF becomes almost chemically inert in polar protic solvent such as water, this transformation using TBAF in water proceeded hardly (entry 9).

The second example (entries 10 -13) of primary alkyl bromide substrate 1b showed a similar trend. The fluorination of 1b using TBAF in t-amyl alcohol proceeded smoothly, affording the desired fluoro-product 2a in higher yield (90%) than other reactions. In particular, this fluorination system showed much faster reaction rate as well as higher selectivity than ionic liquid fluorination protocol in the nucleophilic fluorination.

CONCLUSION

In this method, as the protic environment of the tert-alcohol reduces the basicity of TBAF, with almost maintaining its strong nucleophilicity, this fluorination of haloalkanes showed the reasonable reaction rate under mild condition, effectively inhibiting the elimination that are base catalyzed, and consequently enhancing the selectivity of fluorination reaction. Further studies on the applications of this TBAF/tert-alcohol medium fluorination method for the preparation of the short lived positron emitting radionuclide fluorine-18 labeled radiopharmaceuticals for PET studies are in progress in our laboratories.

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