Tetrahedron Letters 51 (2010) 432–434

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile nucleophilic fluorination of primary alkyl halides using tetrabutylammonium fluoride in a *tert*-alcohol medium

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ARTICLE INFO

Article history:
Received 25 September 2009
Revised 6 November 2009
Accepted 13 November 2009
Available online 18 November 2009

Keywords:
Nucleophilic fluorination
TBAF
tert-Alcohol
Solvent effect
Fluorinated compounds

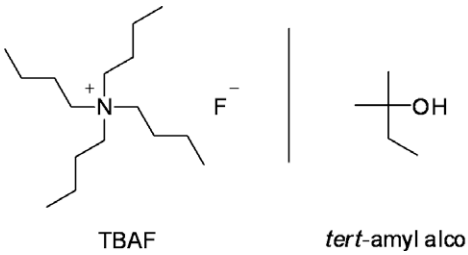
ABSTRACT

Nonpolar protic reaction media such as *t*-amyl alcohol allow the aliphatic, nucleophilic fluorination reaction of primary haloalkane systems to fluoroalkanes, using tetrabutylammonium fluoride (TBAF), to proceed chemo-selectively at a reasonable reaction rate under mild conditions to afford the fluoro-product in high yield. As an example, the nucleophilic fluorination of 2-(3-iodopropoxy)naphthalene (**1a**) as the primary haloalkane model compound, with TBAF in acetonitrile as a polar aprotic solvent, CsF in *t*-amyl alcohol as a nonpolar protic solvent, and TBAF in *t*-amyl alcohol for 1 h provided 2-(3-fluoropropoxy)naphthalene (**2a**) in 38, 5 and 76% yields, respectively.

The nucleophilic replacement reaction of the C–X functional groups (X = Cl, Br, I) with C–F is a typical method for single fluorine substitution at a specific aliphatic molecular site.[1] Due to their medicinal importance, including molecular imaging probes for positron emission tomography (PET), selective and mild fluorination methods for targeted preparation are desirable.[1] Thus, a number of nucleophilic fluorination methods and reagents based on phase-transfer protocols,[2] such as crown ether derivatives[3] and quaternary ammonium fluorides,[4] metal fluoride/ionic liquid systems,[5] and polymer-supported ionic liquids methods,[6] have been developed over the past several decades.

Among the various phase-transfer type reagents used, tetrabutylammonium fluoride (TBAF), capable of generating a '*naked*' fluoride source, is the most popular reagent for nucleophilic fluorination given its good nucleophilicity and solubility in organic reaction media. In particular, recently, highly reactive '*anhydrous*' TBAF ($TBAF_{anh}$), generated in situ from the treatment of hexafluorobenzene with tetrabutylammonium cyanide (TBACN), was developed by DiMagno.[7] However, despite its good reactivity, the '*naked*' fluoride source generated from the TBAF (especially $TBAF_{anh}$) can cause elimination, which is base-catalyzed, forming olefin by-products in the fluorination reaction as it can act as a good nucleophile as well as a strong base.[4d]

Although polar aprotic solvents such as dimethylformamide (DMF) and acetonitrile are generally regarded as good solvents for nucleophilic displacement reactions, including fluorination, by enhancing the reactivity of the anionic nucleophiles through selective solvation of their counter cations in polar aprotic reaction media,[8] the fluorination of haloalkanes, especially iodoalkanes, using the '*naked*' fluoride, performs poorly because of the competing.[4d] Recently, it was found that nonpolar protic tertiary alcohol solvents such as *t*-butyl alcohol and *t*-amyl alcohol show unexpected, good performance in the nucleophilic fluorination of sulfonate ester substrates (mesylate, tosylate, triflate), thereby enhancing reactivity of alkali metal fluorides and suppressing formation of olefin and alcohol by-products. However, this *tert*-alcohol reaction media protocol is inefficient and requires harsh reaction conditions, particularly in the case of the reaction of substrates containing a halide as a leaving group, such as bromoalkanes and iodoalkanes.[9] Herein, we wish to introduce an effective fluorination method for the transformation of the halide functional



TBAF *tert*-amyl alcohol

Figure 1. Structure of tetrabutylammonium fluoride (TBAF) and *tert*-amyl alcohol.

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.058

group to the fluoride group in a primary aliphatic system using commercially available TBAF as a '*naked*' fluoride source in a *tert*-alcohol medium (Fig. 1). This *t*-alcohol/TBAF fluorination proceeded smoothly under relatively mild conditions, reducing the formation of olefin by-products compared with previous methods.

Figure 2 illustrates the dependence of the reactivity and selectivity of commercially available TBAF on two different solvent systems, nonpolar protic (*t*-amyl alcohol) and polar aprotic (CH_3CN). Although the reaction rate of the fluorination in *t*-amyl alcohol was slower than that in CH_3CN (reaction time: 48 and 6 h, respectively), this protic medium reaction proceeded chemo-selectively, affording the corresponding fluoro-product (**2a**) in very high yield (95%). However, the same reaction in CH_3CN afforded product **2a** (59%) with both olefin (36%) and alcohol (4%) by-products (see: entries 11 and 12 in Table 1).

To investigate the relative selectivity of nucleophilic fluorination using the various proposed methods, fluorination of primary halide model compounds, 2-(3-iodopropoxy)naphthalene (**1a**), 2-(3-bromopropoxy)naphthalene (**1b**), and 2-(3-chloropropoxy)naphthalene (**1c**) was carried out and compared with fluorination with TBAF in *t*-amyl alcohol. Table 1 summarizes the results of the fluorinations under various reaction conditions with the results reported in the literature for comparison. Entries 1, 2, and 8 show nucleophilic fluorination using traditional phase-transfer protocols such as 18-crown-6/KF or commercially available TBAF in traditional polar aprotic solvents such as CH_3CN or DMF. Whereas the fluorination of iodoalkane **1a** with 3.0 equiv of KF in the presence of 0.5 equiv 18-crown-6 in acetonitrile at 70 °C barely proceeded after 1 h (entry 1), the same reaction using 2.0 equiv of TBAF was completed within 1 h, affording 38% of 2-(3-fluoropropoxy)naphthalene (**2a**) with 5% of alcohol **2b** and 57% of olefin **2c** formed as by-products (entry 2). Thus, elimination of iodoalkane **1a** to olefin **2c** was the dominant reaction in this method. Moreover, the use of '*anhydrous*' TBAF ($TBAF_{anh}$), generated in situ from the treatment of hexafluorobenzene with TBACN in CD_3CN,[5] gave very low selectivity fluorination (entry 3, only 12% of fluoroalkane **2a** was obtained with 87% of alkene **2c**). Although the *tert*-alcohol/CsF method afforded a highly chemo-selective fluorination of the iodoalkene, by greatly reducing the formation of the olefin as a by-product, harsh reaction conditions were required for a complete reaction, as shown in entries 4 and 5. In an effort to increase this reaction rate, fluorination using TBAF as a '*naked*' fluoride source instead of CsF in *t*-amyl alcohol medium was attempted. Interestingly, the use of TBAF in *t*-amyl alcohol not only significantly increased reaction yield, but also enhanced slightly the selectivity of the fluorination,

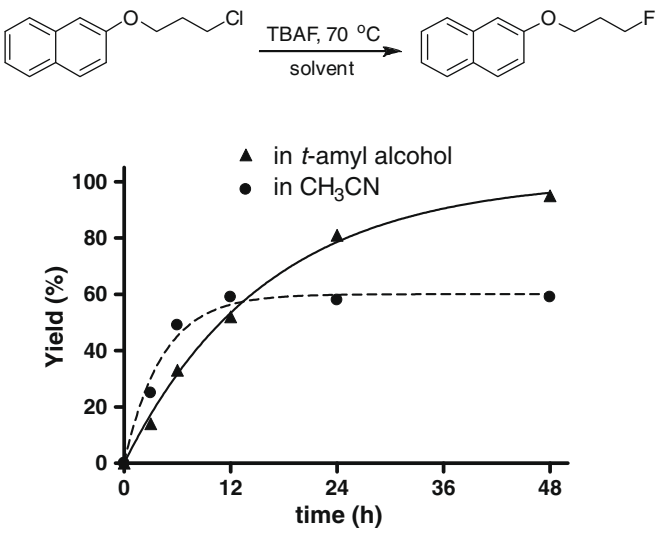
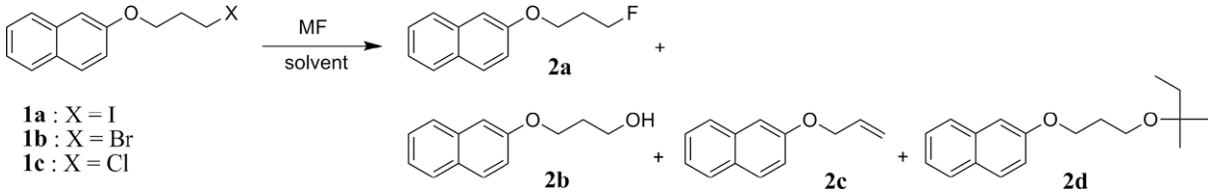


Figure 2. Solvent dependence of the reactivity and selectivity of TBAF in nucleophilic fluorination. All reactions were carried out on a 0.1 mmol reaction scale of alkyl chloride **1c**, using 2.0 equiv of TBAF in 0.5 mL of solvent at 70 °C; fluoro-product yields determined by ^{1}H NMR.

Table 1
Fluorination of alkyl halides (**1**) under various reaction conditions[a]



Entry	X	MF/Catalyst	Solvent	Temp. (°C)	Time (h)	Yield of product[b] (%)				
						1	**2a**	**2b**	**2c**	**2d**
1	I	KF/18-crown-6[c]	CH_3CN	70	1	98[d]	—	—	—	—
2	I	TBAF	CH_3CN	70	1	—	38	5	57	—
3[e]	I	$TBAF_{anh}$	CD_3CN	25	1	Trace	12	—	87	—
4[f]	I	CsF	*t*-Amyl alcohol	Reflux	12	—	72	—	22	Trace
5	I	CsF	*t*-Amyl alcohol	70	1	93	5	—	Trace	—
6	I	TBAF	*t*-Amyl alcohol	70	1	—	76 (74[d])	3	19	2
7	I	TBAF	H_2O/CH_3CN[g]	70	1	94 [d]	Trace	Trace	—	—
8	Br	TBAF	DMF	70	1	—	62	6	32	—
9	Br	CsF	*t*-Amyl alcohol	70	2	92	7	—	—	—
10	Br	TBAF	*t*-Amyl alcohol	70	2	—	88 (85[d])	3	7	Trace
11	Cl	TBAF	CH_3CN	70	6	—	59	4	36	—
12	Cl	TBAF	*t*-Amyl alcohol	70	48	—	95	3	—	Trace

[a] Unless otherwise noted, all reactions were carried out on a 1.0 mmol scale of haloalkane **1a**, **1b**, or **1c** with 2.0 mmol of fluoride source in 5.0 mL of solvent for 1 h at 70 °C.
[b] Yield determined by ^{1}H NMR integration.
[c] 3.0 equiv of KF and 0.5 equiv of 18-crown-6 were used.
[d] Isolated yield.
[e] The reaction was carried out on a 0.2 mmol scale of substrate with 2.0 equiv of $TBAF_{anh}$ generated in situ in CD_3CN at 25 °C.
[f] Ref. 9a.
[g] 2.5 mL of H_2O and 2.5 mL of CH_3CN were used.

providing fluoroalkane **2a** in high yield (76%, entry 6[10]) compared with the use of CsF in *t*-amyl alcohol. As shown in entry 7, however, employing TBAF in the presence of polar protic solvents (water) proceeded negligibly as TBAF becomes almost chemically inert in polar protic solvents.[9b]

The second example (entries 8–10) of the primary alkyl bromide substrate **1b** showed a similar trend. Fluorination of **1b** using TBAF in *t*-amyl alcohol proceeded smoothly and chemo-selectively, affording desired fluoro-product **2a** in higher yield (88%) than other reactions.

In summary, a highly efficient method for the nucleophilic fluorination of primary haloalkane systems to fluoroalkanes, using commercially available TBAF in nonpolar protic *t*-amyl alcohol reaction medium has been demonstrated. In this method, as the protic environment of the *tert*-alcohol reduced the basicity of the TBAF, still maintaining its good nucleophilicity, fluorination of the haloalkanes showed a reasonable reaction rate under mild conditions, effectively inhibiting the inherent base-catalyzed eliminations and consequently enhancing the selectivity of the fluorination reaction.

Further studies on the application of this TBAF/*tert*-alcohol medium fluorination method for the preparation of short-lived positron emitting radionuclide fluorine-18 labeled radiopharmaceuticals for PET studies are in progress in our laboratories.

Acknowledgment

This work was supported by Nuclear Research & Development Program of the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korean government (MEST) (grant code: 2009-0078422 and 2009-0062472 to D.W.K).

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10. *Typical procedure* (entry 6). TBAF (523 mg, 2.0 mmol) was added to the mixture of 2-(3-iodopropoxy)naphthalene (**1a**) (312 mg, 1.0 mmol) in *t*-amyl alcohol (5.0 mL). The mixture was stirred over 1.0 h at 70 °C. The residue was dissolved in water (5.0 mL) and extracted from the aqueous phase with ethyl ether (5.0 mL × 3). The organic layer was dried (sodium sulfate) and evaporated under reduced pressure. The flash column chromatography (5% EtOAc/hexanes) of the filtrate afforded 151 mg (74%) of 2-(3-fluoropropoxy)naphthalene (**2a**) as a colorless oil.