Fluoride relay: a new concept for the rapid preparation of anhydrous nucleophilic fluoride salts from KF

Haoran Sun and Stephen G. DiMagno*

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Fluoride relay is used to generate exceptionally nucleophilic fluoride reagents from KF on a time scale commensurate with radiotracer synthesis.

Positron emission tomography (PET) is a powerful *in vivo* imaging technique for healthcare and drug development.[1–4] Provided the appropriately labeled radiotracers can be synthesized, the sensitivity of PET makes it useful to study physiology, pharmacokinetics and modes of action of novel and established drugs.[5,6] The most common positron emitting radioisotopes for the labeling of organic molecules are ^{11}C ($\tau_{1/2}$ = 20.4 min.) and ^{18}F ($\tau_{1/2}$ = 109.7 min.). Nucleophilic fluorination is the reaction of choice for [^{18}F] radiotracer synthesis,[7,8] despite the attenuated reactivity of hydrated fluoride salts obtained after proton bombardment of the [^{18}O] H_2O target. The convenience and high yield of the nuclear reaction ($^{18}O(p,n)^{18}F$) outweigh the reactivity disadvantages of working with hydrated fluoride salts.[9] Potassium salts of [^{18}F]-fluorides so obtained are often "activated" by addition of cryptands, such as Kryptofix 222, to complex the cation and to boost fluoride nucleophilicity.

Recently we reported the synthesis of anhydrous tetrabutylammonium fluoride (TBAF*) by nucleophilic aromatic substitution of hexafluorobenzene with TBACN.[10] TBAF* has proven to be a highly efficient reagent for Halex and fluorodenitration reactions.[11] In head-to-head experiments, we have also found that KF-Kryptofix 222 is a poor reagent compared to anhydrous TBAF*; *room-temperature* aromatic fluorodenitration reactions proceed with TBAF* at rates comparable to those conducted with KF-Kyrptofix 222 in DMSO *heated at reflux*. TBAF* also offers dramatically enhanced selectivity in substrates prone to hydrolysis. These data suggest that [^{18}F] anhydrous ammonium fluoride salts could expand the scope of radiotracers available from nucleophilic substitution reactions, provided such salts could be prepared rapidly and efficiently.

Here we describe a new concept for the synthesis of anhydrous tetraalkylammonium fluoride salts from KF: aromatic fluoride relay. In fluoride relay, fluoride is first transferred from KF to an easily purified hydrophobic arene. An anhydrous fluoride salt is subsequently generated from this fluoroarene by a S_NAr reaction with an appropriate cyanide salt.

Implementation of this concept is shown in Fig. 1. Electron-deficient chlorobenzenes are cleanly and rapidly (10 min) fluorinated using KF in polar aprotic solvents. Although many electron-deficient arenes would suffice for this reaction, we selected

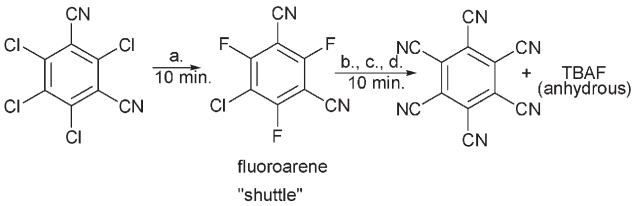

Fig. 1 Fluoride shuttling from KF to TBAF*.

2,6-disubstituted chlorobenzenes to enhance the reaction rate. Polyhalogenation (Fig. 1) also excludes the possibility of detrimental arene deprotonation side reactions at the carbon atoms adjacent to the electron-withdrawing cyano groups. The fluorinated isophthalonitrile is simultaneously purified and dehydrated by flash chromatography, and then subject to a nearly instantaneous (<5 min) S_NAr reaction with tetrabutylammonium cyanide. This final reaction generates TBAF* in good yields from KF (>60%). Cogenerated TBACl is an innocuous byproduct generated from this process (*vide infra*).

Three examples of the use of this process for fluorination of challenging heterocyclic substrates are shown in Fig. 2 and 3. For each reaction, anhydrous TBAF was generated *in situ* and used without isolation or purification. These reactions were conducted using 1 : 1 molar ratios of TBAF* and substrate: 0.2 mmol of heterocyclic aromatic precursor and TBAF* were simply mixed together in 0.5 mL of DMSO-d_6. Yields were determined by integration of ^1H NMR spectra, using the signals from the TBA

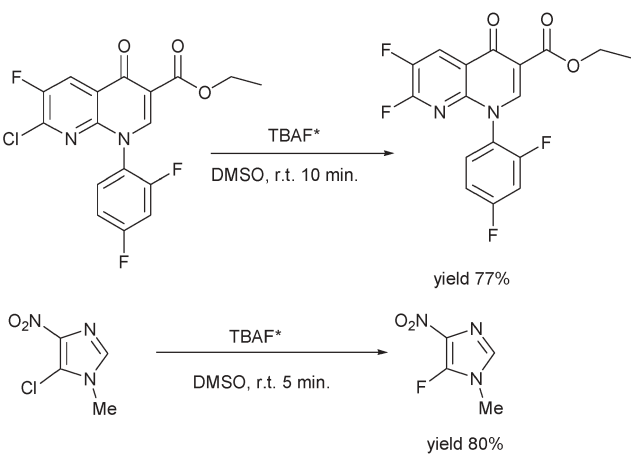

Fig. 2 Rapid preparation of fluorinated heterocycles from KF.

Department of Chemistry & Nebraska Center for Materials and Nanoscience, University of Nebraska, Lincoln, NE, 68588-0304, USA. E-mail: sdimagno1@unl.edu; Fax: 402 472-9402; Tel: 402 472-9895

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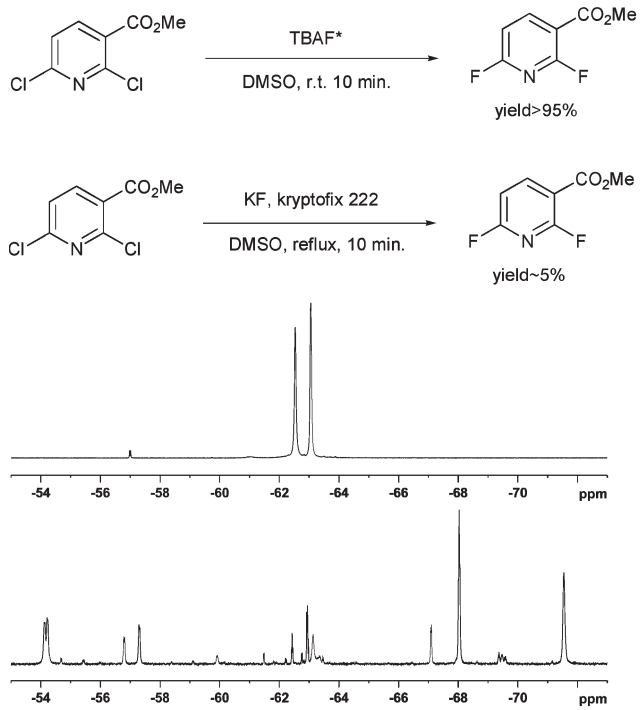

Fig. 3 ^{19}F NMR spectra of fluorination of methyl 2,6-dichloronicotinate with TBAF* (top) and KF-Kryptofix 222 (bottom).

cation as an internal standard. For the first example in Fig. 2, fluorination of the naphthyridine antibiotic precursor ethyl 1-(2,4-difluorophenyl)-6-fluoro-7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate,[12] the product was also isolated to confirm the NMR yield assignments.

Examples in Fig. 2 and 3 show that TBAF* generated in this manner from KF does not cleave methyl or ethyl esters. This is an important point, since the inherent basicity of fluoride ion often leads to ester saponification if water is present. A comparison of the crude ^{19}F NMR spectra of the fluorination of methyl 2,6-dichloronicotinate with TBAF* and KF-Kryptofix 222 (Fig. 3) demonstrates the superiority of TBAF* in this regard.

The smooth fluorination of the commercially available compound 5-chloro-1-methyl-4-nitroimidazole to form the previously unknown, water-sensitive 5-fluoro-1-methyl-4-nitroimidazole provides another example of the power of this technique. This hitherto unreported compound offers access to a wide variety of unusual 4-substituted-5-fluoroimidazoles in two steps (reduction/diazotization).[13]

Finally, while DMSO is a convenient solvent for S_NAr fluorinations, it should be noted this technique is readily transferable to other polar aprotic solvents such as THF or acetonitrile.† Use of these more volatile reaction solvents is warranted when an aqueous workup to remove DMSO is undesirable.

Here we have introduced the concept of fluoride relay for the preparation of nucleophilic fluorinating agents, and demonstrated its utility. Anhydrous fluoride salts may now be prepared on a timescale congruent with the stringent demands of radiotracer synthesis and ^{18}F PET. Importantly, this technique should be applicable for the preparation of diverse anhydrous fluoride salts never before used in radiotracer synthesis. Consequently, this process should expand dramatically the diversity of readily synthesized [^{18}F]-labeled fluorinated radiotracers and radiopharmaceuticals.

Notes and references

† *Typical experimental procedures*: 5-chloro-2,4,6-trifluoroisophthalonitrile was synthesized by refluxing tetrachloroisophthalonitrile (1.43 g, 5 mmol) with KF (1.16 g, 20 mmol) in 15 mL dry DMF for 10 min. The reaction mixture was quenched with 60 mL 1 M HCl and the resulting gray precipitate was collected, washed with deionized water (3 × 5 mL), and dried to yield 0.92 g (85%) of product. For smaller scale reactions, the precipitated fluoroaromatic is simply dissolved in ethyl acetate–hexane (3 : 7) and passed through a plug of silica gel.

*Generation of TBAF**: 5-chloro-2,4,6-trifluoroisophthalonitrile (21.6 mg, 0.1 mmol) in 0.1 mL DMSO was added to a DMSO solution of TBACN (104 mg, 0.4 mmol, 0.4 mL). Anhydrous TBAF formed immediately upon addition. This *in situ* generated anhydrous TBAF solution was used directly for the fluorination reactions reported here.

5-Fluoro-1-methyl-4-nitroimidazole: this was synthesized by adding TBAF* (65 mg, 0.25 mmol, in 0.3 mL DMSO) to a solution of 5-chloro-1-methyl-4-nitroimidazole (65 mg, 0.4 mmol) in 0.2 mL DMSO at room temperature. ^{1}H and ^{19}F NMR spectra indicated that the reaction was complete within 5 min (81% yield). An analytical sample of this water-sensitive fluoroimidazole was obtained by performing the reaction in THF (−20 °C, 5 min reaction time). The THF solution was passed directly through a short silica column to remove the salts, and the solvent was evaporated. Characterization data: NMR (DMSO-d_6): ^{1}H: δ 7.767 (1H, d, 1.52), 3.684 (3H, d, 0.61); ^{19}F: δ −132.2; ^{13}C (proton decoupled): δ 144.68 (d, 286.65), 141.31, 129.92 (d, 4.72), 31.31. Low-resolution MS (*m*/*z*): exptl. M + H = 146, calc. *M* = 145. R_f (silica gel TLC, ethyl acetate) = 0.38 (starting material, R_f = 0.32).

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