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Nucleophilic Fluorination of aromatic radionuclide compounds for Molecular Imagine technique

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Abstract: Our aim is the synthesis of ^{18}F- radiolabeled drug molecules for the Positron emission tomography (PET), it is a functional imaging technique with important clinical applications in cardiology, oncology, and neurology. Our major work on the selective fluorination of aromatic compounds because of fluoroaromatic are important intermediates in the pharmaceutical especially in molecular imagine technique.

KEYWORDS. *nucleophilic fluorination, TBAF, tert-alcohol, and fluorinated compounds.*

Introduction:

During the last thirty years Organic Fluorine compound have become of considerable economic importance. The initial impetus in this field of chemistry comes during the last war when the ‘Manhatten Project’ demanded the fractionation of the isotopes of uranium hexafluoride [1]. A whole series of perfluoro-organic compounds was synthesized to provide compounds resistant to uranium hexafluoride vapour. In consequence methods of catalytic perfluorination have become well developed and hosts of perfluoro-organic compounds are known in the aliphatic, alicyclic and aromatic series [2].

Therefore the selective fluorinated compounds are used in many areas, including the pharmaceutical, agrochemical and dye industries. Such compound is having applications as herbicides and fungicides as well as being used in the treatment of Cancer (PET). Positron emission tomography (PET) is non-invasive image techniques which allow in vivo measurement and quantification of biological and biochemical process at the molecular level and thus it considered as a molecular image technique [3]. PET is not only a diagnostic tool in oncology, cardiology and neurology but it also become a valuable tool in nuclear medicine

for drug development.

There are number of positron emitting radionuclide of interest such as ^{15}O, ^{13}N, ^{11}C, ^{18}F, ^{76}Br, ^{124}I and metal like ^{68}Ga, ^{69}Cu and ^{64}Cu. They all have properties of interest for various applications, especially ^{11}C, ^{18}F and the other halogen are of interest because of their properties in a synthetic labeling perspective [4]. Additionally, ^{18}F is of interest due to its physical properties. There are also a number of drugs containing one or more fluorine atoms. In some studies within drug development the need of specific radioactivity is less, for example in straightforward distribution studies, so in these cases F-exchange could be used as the labeling method [5].

In general, fluorine is a small atom with a very high electronegativity, Covalent bond fluorine is larger then an H-atom but occupying a small van-der waals volume than methyl, amino or hydroxyl group. Fluorine substituent effect on pharmacokinetics and pharmacodynamics are very obvious. Therefore the replacement of a hydroxyl group by fluorine atom is a strategy frequently applied in both PET tracer and drug development [6, 7].

Theoretical considerations suggest that there should be three difference modes of fluorination of organic molecules depending upon whether Fluorine atoms, Fluorine anions and Fluorine cations. Therefore the selectively fluorinated can be formed by number of methods [8]. The nucleophilic methodologies for aromatic fluorination available, Balz-Scheemann, Direct fluorination (F_2/N_2), Halex Chemistry (KF/450°C), HF diazotization and halogen exchange are well established routes to such compound, Both Balz-Scheemann and HF diazotization are based around the conversion of a diazonium salt to a fluoroaromatic. In halogen exchange reaction, a chloro group displaced by a fluoride ion to yield the corresponding fluoroaromatic it first discovered in 1936 by Gottlieb for the conversion of 2,4-dinitrochlorobenzene to 2,4-dinitrofluorobenzene and then in 1956, Whilst attempting to fluorodechloronitrate by 2,4-dinitrochlorobenzene using KF at 150°C, and then many methods are come for aromatic fluorination using many fluoride source (like metalfluoride, amoniumfluoride). Now in current period No-Carrier-Added Fluoride source are developed for aromatic fluorination [9, 10].

Experimental Section:

General. 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 were performed as described in the literature [11], and the identity was confirmed by comparison of NMR data.

Result and Discussion:

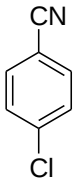
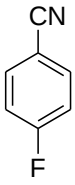
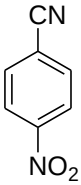
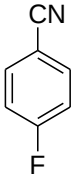
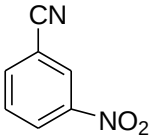
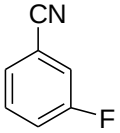
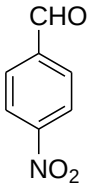
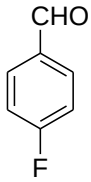
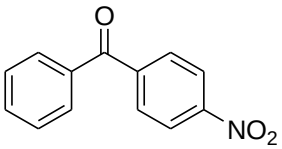
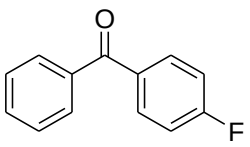
In the past, various ammonium fluorides have been investigated as alternative to metal fluorides in nucleophilic fluorination reactions. Because of ammonium fluorides are more reactive than metal fluoride, these include MeHMTAF2H_2O, TMAF, Ph_4PHF_2, MeHMTAF and TBAF anh [12]. Their solubility in dipolar aprotic solvent can lead to large increasing in activity, although this increase is accompanied by a number of problematic side-reaction producing phenol and ether which can significantly reduce the overall yield of the fluorinated product and most of the aromatic fluorination reaction are doing under anhydrous condition using anhydride amoniumfluoride source, But it is very difficult to maintain unhygroscopic condition during reaction because it possible to formation of hydrolysis product via attack of residual water activated by hydrogen bonding to fluoride [13].

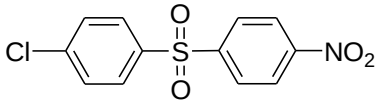
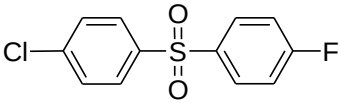
So our aim is to do the aromatic fluorination reaction using Hydrate Tetrabutylammonium fluoride (TBAF nH_2O) and in that condition there is not necessary to maintain the unhygroscopic condition and give the good source of nucleophilic fluoride reaction, it mentioned in paper of *J. Org. Chem., 1998, 63, (25), 9587-9589 by Domenico Albanese, Dario Landin and Michele Penso.* In that they reported the quantitative study of the influence of the specific hydration (n) on the reactivity (nucleophilicty and basicity) of quaternaryammonium fluoride in polar aprotic solvent. In particularly we found that in the same hydration range from 1.5 to 10, the F^- basicity is much more decreased than it nucleophilicty by increased [14].

Our interest is to do the aromatic fluorination reaction using commercially available Hydrated Tetrabutylammonium fluoride (TBAF_3H_2O) using aprotic solvent like DMF, ACN, N,N-Dimethylacetaamide and also use some protic solvent. Generally in nucleophilic fluorination reaction protic solvent is not use because it forms H-F bond and it

reduces nucleophilicty of fluoride. But in paper of *J. Label Comp. Radiopharma 200b, 51,80-82 by Sang Ju Lee, Seung Jun Oh, Dae Yoo Chi.* They showed the use of protic solvent such as t-BuOH, t-amyl alc. And Thexyl alc. Increase the fluorination yield even with smaller amount of precursor at lower reaction temperature and also it essay to purify by chromatography compare to aprotic solvent because it's more soluble than aprotic solvent and it was removed easily by evaporation due to lower boiling temperature (100℃) [15, 16].

Scheme 1:

Sr. No,	Substrate	Method	Product
1		Method A Method B	
2		Method A Method B	
3		Method A Method B	
4		Method A Method B	
5		Method A Method B	

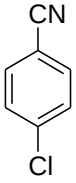
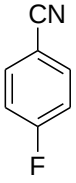
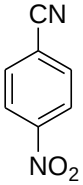
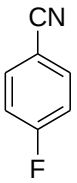
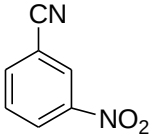
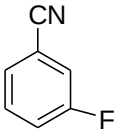
6		Method A Method B	

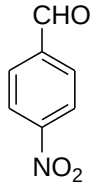
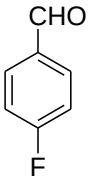
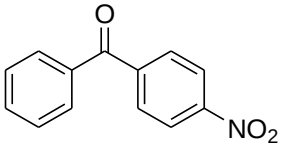
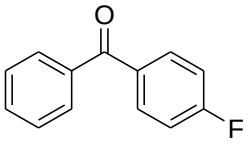
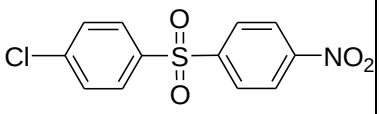
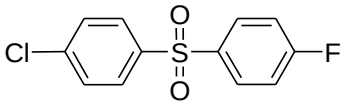
Method A: reaction carried out at 100℃ with aprotic solvent (ACN, DMAc, DMF) using 2 mol equiv. Of $TBAF_3H_2O$.

Method B: reaction carried out at 80℃ with protic solvent (t-BuOH, t-amyl alc., Thexyl alc.) Using 2 mol equiv. Of $TBAF_3H_2O$.

There are many ammonium fluoride source are available for nucleophilic fluorination but recently a new ammonium fluoride source are available is $TBAF(t\text{-}BuOH)_4$ [17]. It showed new ammonium fluoride source $TBAF\ (t\text{-}BuOH)_4$ for the nucleophilic fluorination and they give increasingly fluorinated yield with less side product using aprotic and protic solvent. So I am also interested to do the aromatic fluorination reaction using these conditions [18, 19].

Scheme 2:

Sr. No	**Substrate**	**Method**	**Product**
1		Method C Method D	
2		Method C Method D	
3		Method C Method D	

4		Method C Method D	
5		Method C Method D	
6		Method C Method D	

Method C: reaction carried out at 100℃ with aprotic solvent (ACN, DMAc, DMF) using 2 mol equiv. Of TBAF $(t\text{-BuOH})_4$

Method D: reaction carried out at 80℃ with protic solvent (t-BuOH, t-amyl alc., Thexyl alc.) Using 2 mol equiv. Of TBAF $(t\text{-BuOH})_4$

Further studies on the applications of this TBAF/solvents 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.

Conclusion: In this work, we have demonstrated a highly efficient nucleophilic fluorination method of primary haloalkane systems to fluoroalkanes using commercially available TBAF in non-polar protic *t*-amyl alcohol reaction medium. 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.

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