



Role of Aromatic Fluorine-18 in PET Based Molecular Imaging in Oncology

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Abstract:

In general, fluorine is a small atom with a very high electronegativity; Covalent bond fluorine is larger than H-atom bond but occupying a small Van-der waals volume than methyl, amino or hydroxyl group. Fluorine substituent effect on pharmacokinetics and pharmacodynamics are very obvious. The replacement of a hydroxyl group by fluorine atom is a strategy frequently applied in both PET tracer and drug development. Therefore the selective fluorination of aromatic compounds because of fluoroaromatic are important intermediates in the pharmaceutical especially in molecular imagine technique.

Keywords: Fluorination, Molecular imaging, oncology, personalized medicine, Positron emission tomography (PET), Radiofluorination, fluorine-18.

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 'Manhattan Project' demanded the fractionation of the isotopes of uranium hexafluoride. A whole series of perfluoro-organic compounds was synthesized to provide compounds resistant to uranium hexafluoride vapour. In consequence methods of catalytic per fluorination have become well developed and hosts of perfluoro-organic compounds are known in the aliphatic, alicyclic and aromatic series. 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. 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.

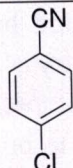
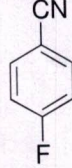
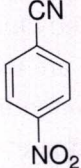
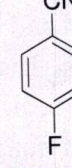
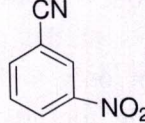
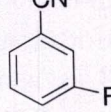
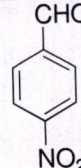
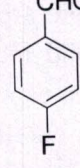
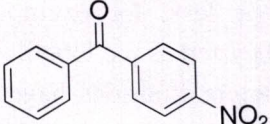
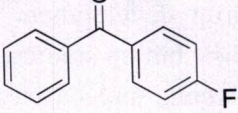
There are number of positron emitting radionuclide of interest such as ^{15}O , ^{13}N , ^{11}C , ^{18}F , ^{76}Br , ^{124}I and metal like ^{68}Ga , ^{69}Cu and ^{64}Cu . They all have properties of interest for various applications; especially ^{11}C , ^{18}F and the other halogen are of interest because of their properties in a synthetic labelling perspective. 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 labelling method.

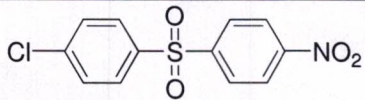
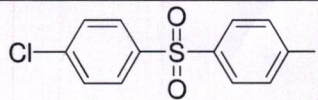
Results and Discussion: In the past, various ammonium fluorides have been investigated as alternative to metal fluorides in nucleophilic fluorination reactions. Because of ammonium fluorides are more reactive than metal fluoride, these include MeHMTAF $_2$ H $_2$ O, TMAF, Ph $_4$ PHF $_2$, MeHMTAF and TBAF anhydride. 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 ammonium fluoride 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.

So our aim is to do the aromatic fluorination reaction using Hydrate Tetrabutylammonium fluoride (TBAF nH₂O) and in that condition there is not necessary 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 (nucleophilicity and basicity) of quaternary ammonium 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 (reduces elimination reaction) than it nucleophilicity by increased (n). As shown in Table 1.

Table 1:

Sr. No,	Substrate	Method	Product
<u>1</u>		Method A Method B	
<u>2</u>		Method A Method B	
<u>3</u>		Method A Method B	
<u>4</u>		Method A Method B	
<u>5</u>		Method A Method B	

<u>6</u>		Method A Method B	
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My interest is to do the aromatic fluorination reaction using commercially available Hydrated Tetrabutylammonium fluoride (TBAF₃H₂O) using aprotic solvent like DMF, ACN, N, N-Dimethylacetamide 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 nucleophilicity of fluoride. But in paper of J. Label Comp. Radiopharma 200b, 51, 80-82 by Sang Ju Lee, Seung Jun Oh, and 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 purified 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°C).

Conclusion: There are many ammonium fluoride source are available for nucleophilic fluorination but recently a new ammonium fluoride source are available is TBAF(t-BuOH)₄ is introduced. In that they showed new ammonium fluoride source TBAF (t-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 the aromatic fluorination reaction using this conditions.

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