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RADIOCHEMICAL YIELD DEPENDENCE OF 3'-DEOXY-3'-[^{18}F]FLUOROTHYMIDINE IN VARIOUS PROTIC SOLVENT SYSTEMS

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Introduction: [^{18}F]Fluorination method with protic solvents showed the possibility of high [^{18}F]fluorination yield and reproducibility. In this experiment, we evaluated various alcohol solvent possibility for [^{18}F]fluorination in the [^{18}F]fluorothymidine ([^{18}F]FLT) synthesis and we also developed an automatic synthesis of [^{18}F]FLT with a protic solvent.

Experimental: We used t-BuOH (2,2-dimethyl-1-propanol), t-amyl alcohol (2-methyl-2-butanol), 2,3-dimethyl-2-butanol, 3,3-dimethyl-2-butanol, 3,3-dimethyl-1-butanol, and 2-trifluoromethyl-2-propanol for [^{18}F]fluorination. After trapping of 185 MBq/0.5 mL of [^{18}F]F^- on PS-HCO_3 cartridge, we eluted it with TBAHCO_3 20 μL, 300 μL CH_3CN and 300 μL H_2O mixture solution. We have a [^{18}F]fluorination at 100°C for 5–30 min with 20 mg of precursor as (5'-*O*-DMTr-2'-deoxy-3'-*O*-nosyl-β-D-threo-pentofuranosyl)-3-*N*-BOC-thymine and evaluated [^{18}F]fluorination yield with radioTLC. Commercially available GE TracerLab MX was used for the automatic synthesis of [^{18}F]FLT. This MX module has blue, red, yellow and green reagent vials. We added 7 mL of CH_3CN to the blue vial; 20 mg of precursor, 2 mL t-amyl alcohol and 200 μL of CH_3CN to the red; 1.75 mL 2 N NaOH and 0.7 mL citrate buffer to the yellow; and 3 mL 1 N HCl and 0.25 mL acetonitrile to the green vial. We have 10 minutes of [^{18}F]fluorination at 120°C. For hydrolysis, we have 5 minutes at 85°C. The reaction mixture was moved to HPLC purification system automatically, and we purified [^{18}F]FLT with EtOH:H_2O=10:90 solution at 5ml/min. Quality control procedures were evaluated according to the previous reported methods.

Results and Discussion: Each alcohol solvent showed different [^{18}F]fluorination yield on radioTLC analysis. The highest [^{18}F]fluorination yield was 94.09±4.42% with 2,3-dimethyl-2-butanol at 5 min on radioTLC (n=3). Tertiary alcohol solvent except 2-trifluoromethyl-2-propanol showed > 85% of radiochemical yield on the radioTLC analysis after hydrlysis, but primary and secondary alcohol showed 26.27-71.79% of low radiochemical yield. In the automatic synthesis, t-amyl alcohol showed 64.6±6.1% of radiochemical yield after HPLC purification. (n=43) The highest radiochemical yield was 74.0% and the lowest radiochemical yield was 53.0%. After HPLC purification from automatic preparation, [^{18}F]FLT showed same retention time with cold FLT and no residual alcohol solvent in the gas chromatography analysis.

Conclusion: We evaluated various alcohol solvents for high radiochemical yield [^{18}F]FLT synthesis and bulky tertiary alcohol showed high radiochemical yield except 2-trifluoromethyl-2-propanol. In the automatic synthesis, t-amyl alcohol showed stable and high radiochemical yield to synthesize [^{18}F]FLT.

NEW NUCLEOPHILC ^{18}F-FLUORINATION IN PROTIC SOLVENTS – *TERT*-ALCOHOLS

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Introduction: Aliphatic nucleophilic [^{18}F]fluorinations are the most common method for the synthesis of radiopharmaceuticals for PET. In general, polar aprotic solvents such as acetonitrile and DMF have been used for this reaction. Recently, we reported new [^{18}F]fluorination in protic solvent.[1] This abstract is introduced history and background of new fluorination method including of cold reaction with demonstration of the synthesis of most common PET radiochemical.

Results and Discussion: We introduce the phenomenal efficiency of using tertiary alcohols as a reaction media for the nucleophilic fluorination with alkali metal fluoride or tetrabutylammonium fluoride. The non-polar, protic *tert*-alcohol media–in the absence of any kind of catalyst–actually enhances the nucleophilicity of the alkali metal fluoride dramatically, increasing the rate of nucleophilic fluorination compared with conventional methods, and reducing formation of typical byproducts (e.g., alkenes, alcohols, or ethers). To denote the unusual behavior of fluoride ion under these conditions, we use the term "*flexible*" fluoride. The fluorination of a model compound, 2-(3-methanesulfonyloxypropoxy)naphthalene, with various alkali metal fluorides under various reaction conditions were performed. The fluorination of mesylate with 3 equiv of CsF under typical reaction conditions produced the 2-(3-fluoropropoxy)naphthalene product in *tert*-alcohol (*flexible* fluoride conditions) proceeded almost to completion within 6 h, providing the fluoroalkane in very high yield (92%), together with only small amounts of the ether byproduct. It is of note that under these conditions, the reaction mixture forms a solid at 30 min. We also have applied this new fluorination method to synthesize [^{18}F]FDG, [^{18}F]FLT, [^{18}F]FES, [^{18}F]FMISO, and others. We achieved a high radiochemical yield of [^{18}F]FDG (83-97%) with 20-40 mg of precursor at 110°C for 5-10 min (n = 14).

Conclusion: A new radiofluorination method has been developed providing high radiochemical yield. The mild and efficient synthesis of all aliphatic fluorine-18 labeled radiopharmaceuticals by nucleophilic substitution in protic solvent will be demonstrated.

Acknowledgement: We acknowledge the National Research and Development Program of MOST, Korea (2005-03184).

Reference: [1] Kim DW, Ahn D-S, Oh Y-H, Lee S, Kil HS, Oh SJ, LeeSJ, Kim JS, Ryu JS, Moon DH, Chi DY. *J. Am. Chem. Soc.* **2006**, *128*, 16394-16397.

Keywords: [^{18}F]Fluorination, Nucleophilic Fluorination, Tert-Alcohol, New Fluorination Method, Aliphatic Fluorination

(^{18}F)CF_3H, A VERSATILE SYNTHON FOR THE PREPARATION OF (^{18}F)TRIFLUOROMETHYLATED RADIOPHARMACEUTICALS

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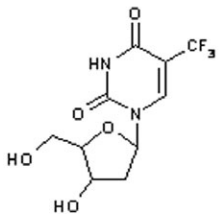
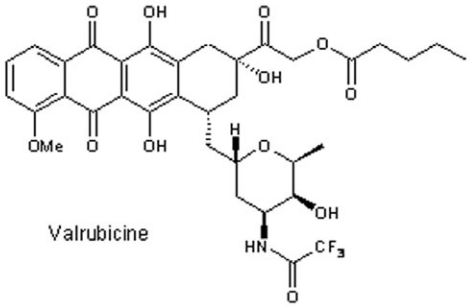
Introduction: The importance of fluorine in medicinal chemistry is well recognized. Indeed, an increasing number of drugs on the market contain fluorine. Fluorinated drugs can greatly alter various biological steps: binding with enzyme or receptor, metabolism leading to the clearance of the exogenous substance, absorption and transport and interference with enzymatic reactions. Many biologically active compounds have already been labeled with fluorine-18 for PET research ([^{18}F]CFR_3, R ≠ F). However, radiotracers with an ^{18}F-labeled trifluoromethyl group ([^{18}F]CF_3R) are very rare. The aim of our research is to develop methods for the preparation of [^{18}F]trifluoromethylated ligands and as a result increase the structural diversity of ^{18}F-labeled radiopharmaceuticals for PET research.



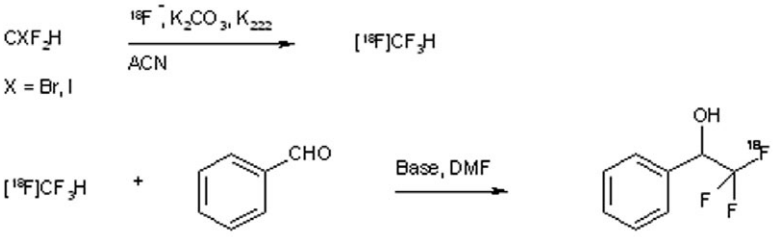
Trifluridine



Valrubicine

Experimental: Difluoromethyl halide was (Br or I) reacted under standard labeling conditions with [^{18}F]fluoride to give [^{18}F]trifluoromethane. The radiochemical yields were 80-90%.

[^{18}F]Trifluoromethane was deprotonated with base and coupled to benzaldehyde affording α-(trifluoromethyl) benzyl alcohol in quantitative yield.



Results and Discussion: The anion of [^{18}F]trifluoromethane was used in a whole range of SN_2-type reactions of which the coupling with benzaldehyde as described above is one example. High radiochemical yields were also obtained for the [^{18}F]trifluoromethylation of ketones and esters.

Conclusion: [^{18}F]Trifluoromethane was successfully applied for the labeling of aldehydes, ketones and esters in high radiochemical yields. Therefore, [^{18}F]trifluoromethane is considered to be a versatile synthon for the preparation of [^{18}F]trifluoromethylated radiopharmaceuticals.

Keywords: [^{18}F]Trifluoromethane, [^{18}F]Trifluoromethylation

DECARBONYLATION OF HIGHLY SUBSTITUTED ^{18}F-LABELED BENZALDEHYDES AS MODEL COMPOUNDS FOR AROMATIC AMINOACIDS

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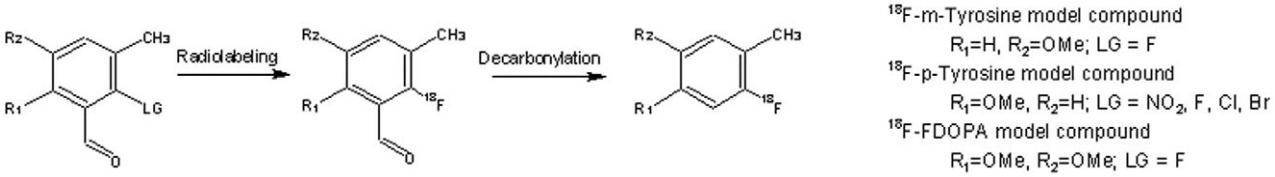
Introduction: Synthesis of ^{18}F-labeled aromatic aminoacids using [^{18}F]fluoride via nucleophilic aromatic substitution (S_{NAr}) is of high interest [1-3]. Electron rich aromatic systems can be substituted in presence of an appropriate electron withdrawing leaving group (LG) and an auxiliary substituent, e.g. aldehyde group. The latter can be removed easily via decarbonylation by e.g. Wilkinson's catalysts [2-4]. Here, decarbonylation was tested in multiple substituted benzenes as model compounds for [^{18}F]-*m*-tyrosine, [^{18}F]-*p*-tyrosine and [^{18}F]FDOPA (Figure).



Experimental: Nucleophilic ^{18}F-fluorination was performed at 140°C in K/222, K_2CO_3 and DMF during 10 – 20 min. After cartridge purification (Alumina, C18) radiochemical purity was > 95% (HPLC and TLC).

The [^{18}F]fluorobenzaldehyde derivative was dissolved, transferred into a sealed vessel containing the catalyst and heated. $RhCl(pph_3)_3$ was chosen as catalyst for decarbonylation due to short reaction times and mild conditions. Reaction yields were estimated from the reaction mixture by HPLC and TLC. All experiments were $n \geq 3$.

Results and Discussion: Dioxane was reported [2,3] as solvent for this decarbonylation reaction (RCY = 59–85%) as well as benzonitrile [4] for highly substituted aromatic systems. First, we investigated the solvent effect on decarbonylation (2 equiv. catalyst, 150°C, 1 ml solvent, 15–20min). Yields were 81.0 ± 0.8% (benzonitrile); 64.7 ± 1.3% (DMSO); 62.1 ± 1.7% (dioxane); 52.6 ± 1.7% (toluene) and 29.8 ± 3.0% (DMF). Further optimizations were performed in benzonitrile, best results were obtained within 10 min at 150°C, 3 equiv. catalyst (90.4 ± 0.3%) or at 180°C, 2 equiv. catalyst (89.1 ± 1.3%).

Decarbonylation of the other two model compounds (150°C, 2 equiv. catalyst, 30 min) gave highest yields for the [^{18}F]-*p*-tyrosine model of 88.9 ± 1.2% (LG: NO_2) and the [^{18}F]FDOPA model of 91.8 ± 1.6%.

Conclusion: Decarbonylation of [^{18}F]fluorotyrosine and [^{18}F]FDOPA model compounds could be performed in good yields under mild conditions using $RhCl(pph_3)_3$ as catalyst in benzonitrile.

References: [1] Krasikova RN et al., Nucl. Med. Biol. 31, 597-603, 2004. [2] Plenevaux A. et al., Appl. Radiat. Isot. 43, 1035-1040, 1992. [3] Kaneko S. et al., Appl. Radiat. Isot. 50, 1025-1032, 1999. [4] Ohno K. et al., J. Amer. Chem. Soc. 90, 99-107, 1968.

Keywords: Decarbonylation, Benzaldehyde, Nucleophilic Aromatic Substitution, ^{18}F-Labeled Aromatic Aminoacids

(^{18}F)FLUORINATION OF ALKYL SULFONATE IS ENHANCED BY ARYLSULFONATES-BASED NUCLEOPHILE ASSISTING LEAVING GROUPS (NALGS) UNDER MICROWAVE IRRADIATION

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Introduction: NALGs contain acyclic or cyclic polyether units in the *ortho* position of the arylsulfonyl ring. They display enhanced S_N2 type reactivity towards metal halides through the cation-chelating moiety that attracts nucleophilic metal salts to the site of attack and stabilizes the newly-forming leaving group through internal chelation.[1] We wished to test whether such advantages might also be realized in radiofluorination under thermal and microwave conditions.

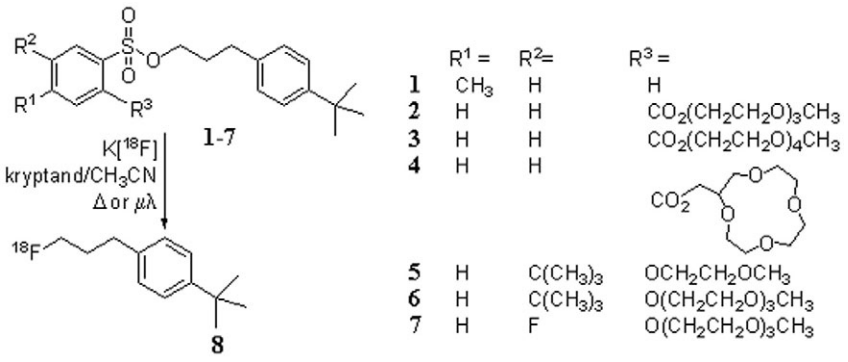
Experimental: Compounds **1**-**7** were synthesized based on a published method.[1] Thermal and microwave drying of [^{18}F]fluoride ion and subsequent reaction were carried out with a modified Synthia radiochemistry module equipped with a thermal heating unit and a RI 521 microwave cavity.[2] Typically, NALG compound (5.0 mg) in MeCN (0.5 ml) was heated with dried [^{18}F]fluoride ion and appropriate base/kryptand at 110°C for 10 min or irradiated for 3 × 2 min at 90 W microwave power. The reaction mixture was diluted with water (0.7 ml) and injected onto preparative HPLC using isocratic MeCN-10 mM HCO_2NH_4 (65:35) as mobile phase at 4 ml/min. The ^{18}F-labeled product (**8**) was collected with retention time of 24.5-27 min.

Results and Discussion: Contrarary to results from bromination,[1] Li^+ or Na^+ as counter ion did not promote ^{18}F-fluorination, most likely due to insufficient basicity and poor solubility of the respective [^{18}F]fluoride salt. With K_2CO_3 and K222, the desired product was obtained under both thermal and microwave conditions. RCYs are better under microwave irradiation. In the absence of K222, **8** was only obtained under microwave conditions. Bulkier groups, at either *ortho*, or *meta* positions seem to hinder ^{18}F-fluorination. Three ethylene glycol units in the side chain gave better results.

Table 1. [^{18}F]Fluorination of NALGs under thermal *vs* microwave conditions*

Compound	Thermal Rxn RCY (%)		Microwave Rxn RCY (%)	
	K_2CO_3	K_2CO_3-K222	K_2CO_3	K_2CO_3-K222
1	0	65	9	76
2	0	62	22	79
3	0	44	4	66
4	0	2	0	4
4	0	32	0#	80
6	0	31	16	64
7	0	72	12	75

* For each RCY, n ≥ 2. # Unidentified product (RCY, 7%) obtained at retention time of 14-16 min



Conclusion: NALGs can be ^{18}F-fluorinated under microwave conditions without K222.

Acknowledgement: This research was supported by the IRP of the NIH, NIMH.

References: [1] Lepore SD *et al*, J Org Chem, 2005, 70, 8117. [2] Lazarova N *et al*, J Label Compd Radiopharm, 2007, 50, in press.

Keywords: Fluorine-18, Sulfonate, NALG, Microwave

DEVELOPMENT OF NEW SILICON-BASED BUILDING BLOCKS FOR ^{18}F-LABELING OF BIOMOLECULES

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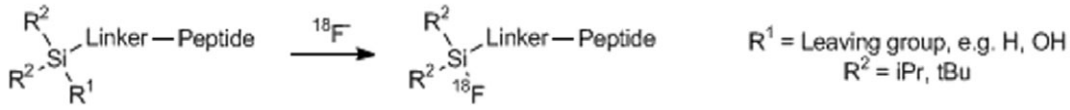
Introduction: Current methods for ^{18}F-labeling of biomolecules require generally a multi-step reaction sequence and thus are time-consuming. As ^{18}F has a relatively short half-life (110min) more efficient methods are required. Silicon has a high affinity for fluorine as a consequence of the strength of the Si-F bond (135kcal/mol vs. 116kcal/mol for C-F), therefore it should be possible to introduce ^{18}F in silicon-containing biomolecules under mild conditions in a single high-yielding step. In order for the silicon-based ^{18}F imaging agent to be effective as a PET probe, the Si-F bond must be stable under physiological conditions. It is known that the hydrolytic stability of the silicon-halogen bond is determined by the nature of the substituents on silicon. Based on these considerations, different organosilanes were proposed in the literature as labeling precursors[1,2,3]. However, so far only one example for the direct radiolabeling of an organosilicon-modified peptide was accomplished by isotopic exchange.[3] We report our recent work on the synthesis and radiolabeling of silicon-based building blocks for the ^{18}F-labeling of biomolecules.



Experimental: Several model precursors varying in their alkyl substitution, leaving group and linker for peptide conjugation were synthesized. Radiolabeling with K^{18}F/K222 was carried out under various conditions. The crude reaction mixtures were analyzed by HPLC. Subsequently the ^{18}F-labeled products were tested for their hydrolytic stability.

Results and Discussion: After optimization of the radiolabeling conditions up to quantitative yields were achieved. The building blocks yielding the most stable radiolabeled products were coupled to peptides. Radiofluorination of these peptides proceeded also with very good conversion under a wide range of reaction conditions (pH 4.5-7.5, RT-90°C, 15-30min). Careful choice of the leaving group allowed for easy HPLC separation of precursor and radiolabeled product.

Conclusion: In conclusion, we have developed a unique silicon-based method for facile ^{18}F-labeling of biomolecules under mild conditions and with high specific activity.

References: [1] Walsh JC, et al. *J Labelled Compd Radiopharm* 1999; **42:** S1-S3. [2] Choudhry U, et al. *34th BNMS meeting abstract* 2006. Choudhry U, et al. *EANM Congress abstract* 2006. [3] Schirrmacher R, et al. *Angew Chem Int Ed* 2006; **45:** 6047-6050.

Keywords: Fluorine-18, Organofluorosilanes, Peptides, PET

TOWARDS A GENERAL STRATEGY FOR PROTEIN LABELING WITH ^{18}F USING BORONATE DERIVATIVES

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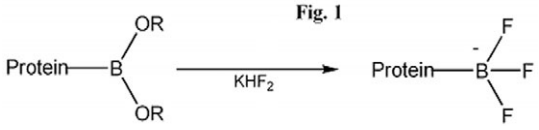
Introduction: Proteins can not be directly labeled with ^{18}F by nucleophilic fluorination. The indirect labeling techniques typically involve synthesis of ^{18}F labeled prosthetic groups or synthons with a reactive function that can be used subsequently for selective conjugation with a specific functional group in the protein. These multi-step labeling procedures are not necessarily very practical. The routine one step direct labeling of proteins with ^{18}F represents a challenge for the field of radiochemistry. Recently, several techniques have been reported for efficient and straightforward preparation of ^{18}F labeled peptides and proteins. We have been working on extending an elegant method developed by Ting et al (1) towards a general strategy for labeling proteins (Fig. 1). Essentially, this exploits the reactivity of boronic acids and derivatives thereof towards fluoride in aqueous and organic solutions, as originally developed by Vedejs et al (2).

Fig. 1



Experimental: We have used model aryl boronic acids (Fig 2A) and esters (Fig 2B) to optimize the labeling of these compounds. The substrate boronic acids and esters were dissolved in water and water/DMF mixtures and reacted with aqueous solution containing H^{18}F and KHF_2 in sodium acetate buffer. The reaction mixtures were analyzed by TLC and autoradiography.

Fig. 2A

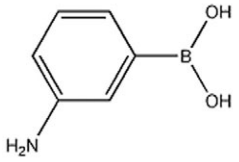
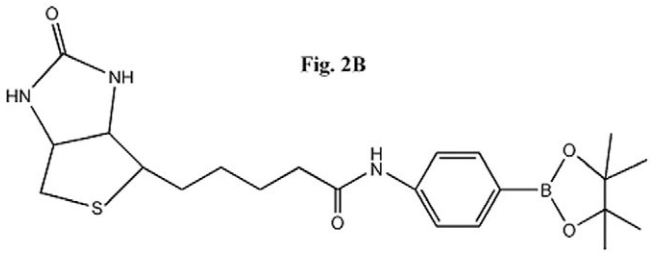


Fig. 2B



Results and Discussion: The labeling yields at RT and in aqueous solution were minimal minimal (<1%). But at higher temperature (37-45°C), there was significant increase in labeling efficiency (5-75%), depending on water:DMF ratio and reaction time. With 50% DMF and 1 hr incubation labeling yields were reasonable (10-40%).

Conclusion: The pilot data with model boronic acid and esters indicate that one step ^{18}F labeling of proteins can be accomplished by optimizing the reaction conditions such as solvent mixture, temperature and incubation time.

References: [1] Ting R, Adam MJ, Ruth TJ, Perrin DM. J Am Chem Soc 2005;127:13094-13095. [2] Vedejs E, Chapman RW, Fields SC, Lin S, Schrimpf MR. J Org Chem 1995;60:3020-3027.

Keywords: F-18 Labeled Proteins, Boronic Acid