An improved synthesis of 2',3',5,'6'-tetrafluorophenyl-6-[F-18]fluoronicotinate, an amine reactive bifunctional agent.

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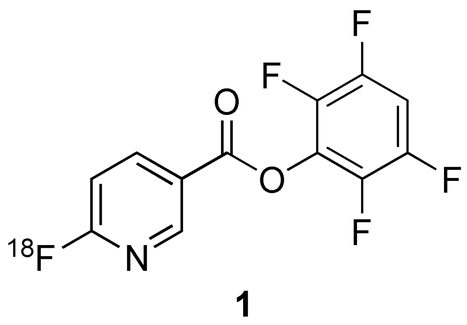
INTRODUCTION: Bioactive peptides and proteins are very important key regulators of cell growth and cellular functions in living organisms. Radiolabeling of these sensitive biomolecules including nucleotides, antibodies and antibody fragments has been used in nuclear medicine for imaging tumors and inflammatory processes. A very few direct radiofluorination reactions of these biomolecules are known as it involves drastic reaction conditions that would entail the denaturing of the proteins and antibodies. Radiochemists have circumvented this problem by using F-18 prosthetic groups to label these molecules. An example of such a reactive prosthetic group is [F-18]SFB[1]. Its radiosynthesis requires two to three steps and HPLC purification prior to conjugation with peptide. Furthermore, following conjugation with [^{18}F]SFB an additional purification step is often required to obtain the [F-18]peptide with sufficient specific activity and purity for in vivo studies. Olberg and co-workers[2] have reported the synthesis of 6-[F-18]fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester using trimethylammonium triflate precursor that was prepared in two steps and trimethylamine gas was continuously bubbled through the reaction mixture in the first step. We wish to report one step synthesis of DMAP precursor 2, that does not involve any use of gas, followed by radiofluorination to obtain the title compound

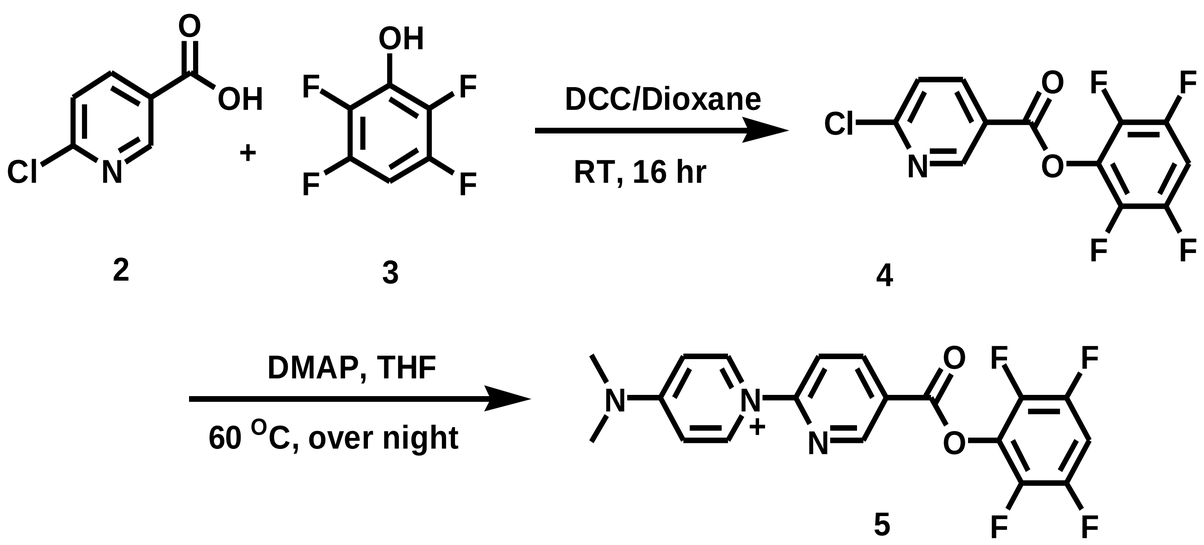


1

Figure-1

RESULTS and DISCUSSION:

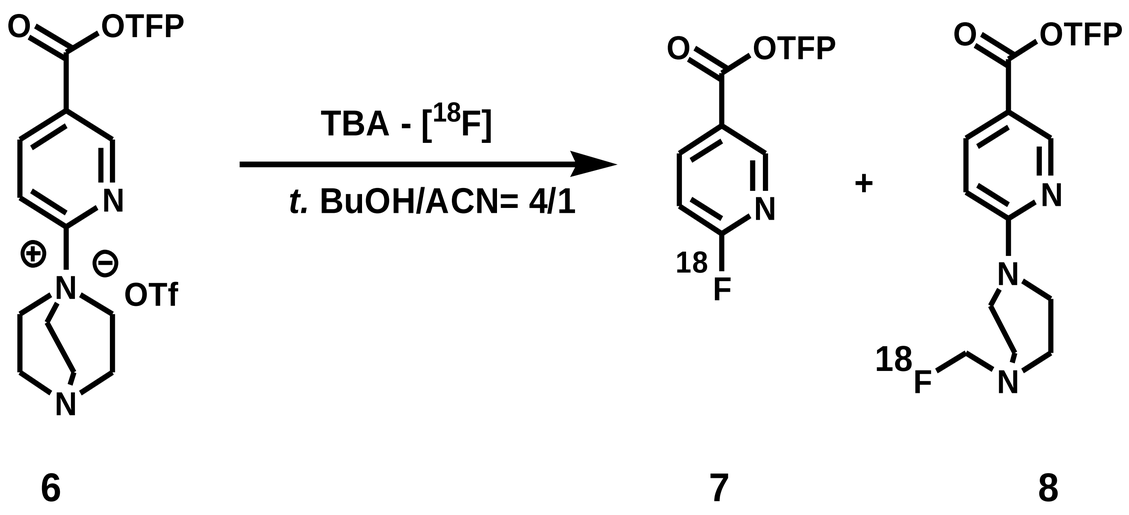
The DMAP precursor **5** was prepared from 6-chloronicotinic acid, **2**. Esterification of the acid **2** with 2,3,5,6-tetrafluorophenol, **3**, using DCC and dioxane at RT for 16 hr afforded the ester **4.** Nicotinic acid ester 4 was converted to DMAP salt by heating at 60 ^{o}C it with dimethylaminopyridine in THF for overnight as white crystalline powder.



2 **3** **4** **5**

Scheme 1

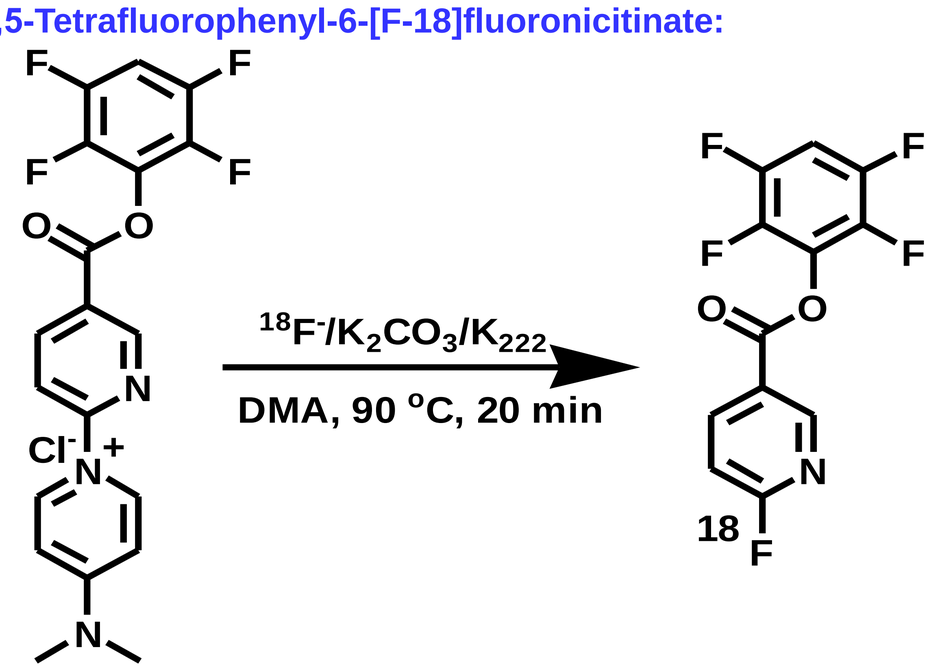
Previously we reported[3] similarly prepared DABCO salt **6** underwent radiofluorination to yield the required product, **7**, along with undesired minor product **8 [Scheme 2]**.



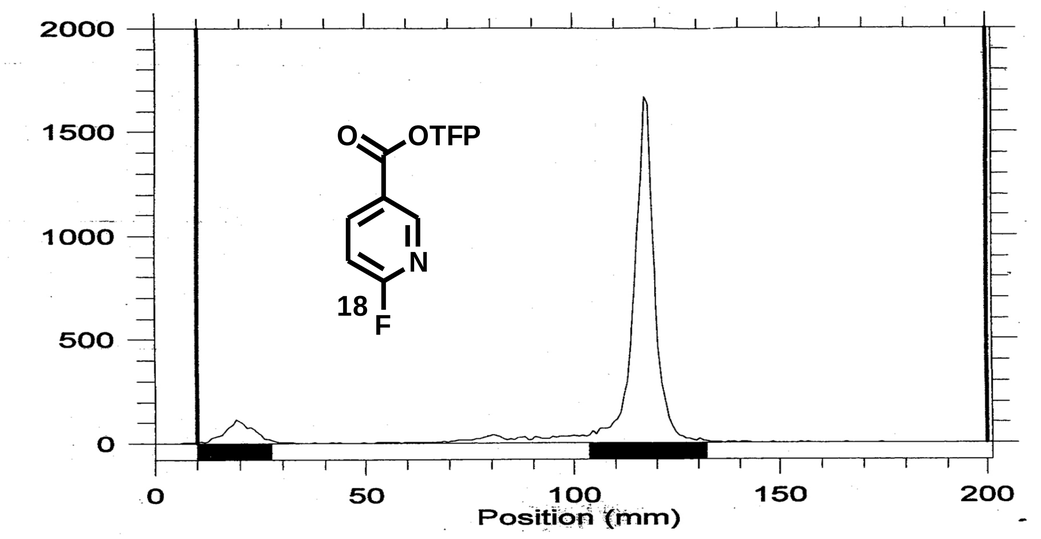
6 **7** **8**

Scheme 2

2',3',4',5-Tetrafluorophenyl-6-[F-18]fluoronicitinate:



Cyclotron produced fluoride (50 mci) was trapped on QMA cartridge, eluted with a mixture of K_{222}/K_2CO_3 and azeotropically dried using drying sequence in Sofie Elixys Synthetic Platform. Precursor **5** (5 mg) was dissolved in dimethyl acetamide (1 mL) and added to anhydrous fluoride, heated at 90 ^{o}C for 20 min. The reaction mixture was diluted with water (30 mL) and passed it through C_{18} Sep-Pak to remove unreacted isotope. Fluorinated product was released from the cartridge using ethyl acetate and the solvent was removed under a stream of nitrogen to obtain 18 mCi of the desired product EOS.



Bioscan of the title compound

CONCLUSION:

An improved synthesis of the tile compound was achieved from dimethlaminopyridonium salt in 74 % radiochemical yield and 97 % radiochemical purity. Unlike DABCO salt no side product was noticed. Also this procedure involves only two steps as compared to 3 steps reported previously.

ACKNOWLEDGEMENTS:

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REFERENCES:

1. Lang, L and Eckelman, W; *Appl. Radiat. Iso.* **1994; *45***:1155.
2. Olberg, D; Arukwe, J and Grace, D. *J. Med. Chem.* **2010 *53***:1732**.**
3. Akula, M; Blevins, D; Kabalka, G and Osborne, D. 21 st International Symposium on Radiopharmaceutical Sciences, *Columbia,MO, USA*, May 26-30, **2015.**

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