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Facile Route to 2-Fluoropyridines via 2-Pyridyltrialkylammonium Salts Prepared from Pyridine *N*-Oxides and Application to ^{18}F-Labeling

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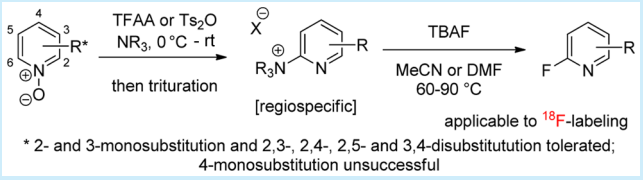
Supporting Information

ABSTRACT: Among known precursors for 2-[^{18}F]-fluoropyridines, pyridyltrialkylammonium salts have shown excellent reactivity; however, their broader utility has been limited because synthetic methods for their preparation suffer from poor functional group compatibility. In this paper, we demonstrate the regioselective conversion of readily available pyridine *N*-oxides into 2-pyridyltrialkylammonium salts under mild and metal-free conditions. These isolable intermediates serve as effective precursors to structurally diverse 2-fluoropyridines, including molecules relevant to PET imaging. In addition to providing access to nonradioactive analogues, this method has been successfully applied to ^{18}F-labeling in the radiosynthesis of [^{18}F]AV-1451 ([^{18}F]T807), a PET tracer currently under development for imaging tau.



2-[^{18}F]Fluoro-substituted pyridines have emerged as a widely used functionality in PET tracers[1] (Figure 1) due to their straightforward, though often inefficient, methods of radiosynthesis and their limited radiodefluorination in vivo.[2]

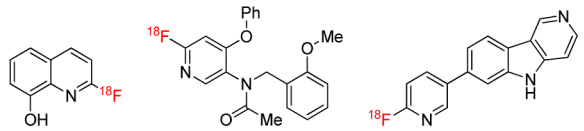
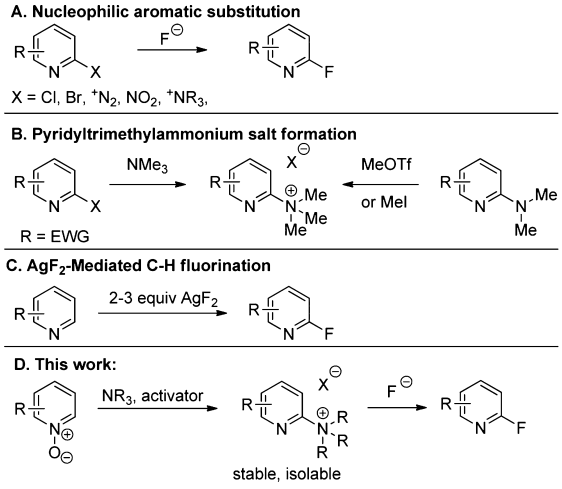


Figure 1. Selected PET tracers containing 2-[^{18}F]fluoropyridines.

Moreover, nonradioactive fluorinated heterocycles have shown broad applicability in medicinal chemistry as both target compounds and synthetic intermediates.[3,4b] Traditionally, 2-fluoropyridines have been synthesized by nucleophilic displacement of a suitable leaving group at the 2 position by fluoride (Scheme 1, A). The displacement of 2-chloro- and 2-bromopyridines with fluoride either requires elevated temperatures or the use of anhydrous TBAF,[5a] and the Balz–Schiemann reaction to synthesize fluoropyridines from aminopyridines features potentially explosive diazonium salt intermediates.[5b] 2-Nitro- and 2-trialkylammonium pyridines have been shown to be effective precursors to 2-fluoropyridines,[5c,6] though their general use has been limited due to synthetic inaccessibility using established methods (Scheme 1, B).[7] In a recent example of 2-fluoropyridine synthesis using a Chichibabin reaction-inspired approach, Hartwig and coworkers reported the direct C–H fluorination of pyridines employing AgF_2 (Scheme 1, C).[4] Their method was shown to

Scheme 1. Synthetic Approaches to 2-Fluoropyridines



be quite tolerant of functional groups, and it provided rapid access to a wide variety of 2-fluoropyridines that in some cases greatly improved synthetic access to clinically relevant compounds. Robust synthetic methods that allow for rapid, late-stage, site-specific installation of fluorine into pyridine rings will continue to be of considerable value to both the drug discovery and radiochemistry communities. Moreover, a general synthetic method that provides access to both

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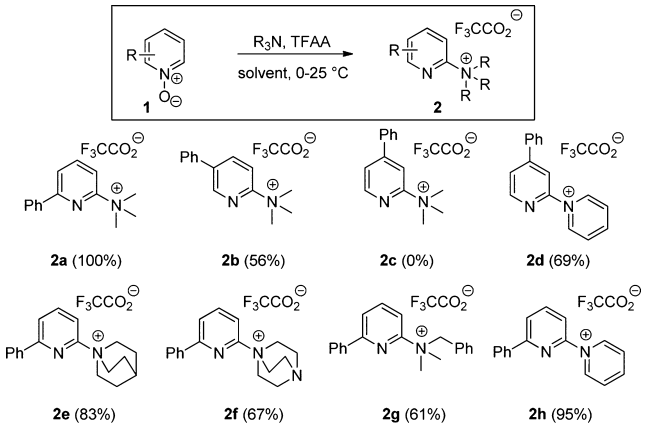
nonradioactive fluoropyridines and ^{18}F radioligands through a common intermediate is desirable.

It has been demonstrated that a range of 2-substituted pyridines can be prepared upon activation of pyridine *N*-oxides in the presence of a wide variety of nucleophiles (Cl, Br, CN, amine, etc.).[8,9] There are a few reported examples of preparing 2-pyridyltrimethylammonium salts from activated pyridine *N*-oxides,[10] though to our knowledge, a comprehensive study regarding the scope and use of these ammonium salts has not been published. We hypothesized that suitable activation of a pyridine *N*-oxide in the presence of a tertiary amine would furnish a trialkylammonium salt that would be reactive toward a fluoride nucleophile, thereby allowing for a method to achieve the delivery of fluoride to pyridine (Scheme 1, D).

Using 2-phenylpyridine *N*-oxide **1a** as a model substrate, we found that direct addition of fluoride (1 M tetrabutylammonium fluoride [TBAF] in THF) to the reaction mixture of **2a**, formed *in situ* from the activation of **1a** in the presence of trimethylamine, resulted in the formation of (dimethylamino)-pyridine instead of the desired fluoropyridine.[11] It was discovered that isolation of crude **2a** by trituration from Et_2O/CH_2Cl_2 and exposure to fluoride resulted in the formation of 2-fluoropyridine **3a**. Further optimization revealed that the fluorination reaction proceeded smoothly in polar aprotic solvents (DMF and CH_3CN), and 1 M TBAF in THF was found to be an effective fluoride source (see the Supporting Information).

Encouraged by the successful formation of **3a** via **2a**, we identified preferred conditions for trimethylammonium salt formation by screening a variety of reaction conditions including activating electrophile and reaction solvent using **1a** as a model substrate (3.0 equiv of trifluoroacetic anhydride [TFAA] or *p*-toluenesulfonic anhydride [Ts_2O] and 6.0 equiv of NMe_3 in CH_2Cl_2 [0.1 M], 0 °C - rt). For complete details, see the Supporting Information. As shown in Scheme 2, we

Scheme 2. Preparation of Trialkylammonium and Pyridinium Salts



explored the ammonium salt formation of phenyl-substituted pyridine *N*-oxides using a variety of amine nucleophiles. Both 2- and 3-phenylpyridine *N*-oxides reacted smoothly to give trimethylammonium salts **2a** and **2b** in good yields and as single regioisomers. We believe that the observed regioselectivity could be explained by stereoelectronic (2- vs 4-position) and steric (2- vs 6-position) effects as well as the relatively mild reaction conditions.

Surprisingly, activation of 4-phenylpyridine *N*-oxide in the presence of trimethylamine failed to produce isolable salt **2c**. Instead, a mixture of 4-phenylpyridin-2(1*H*)-one and 2-chloro-4-phenylpyridine was observed in less than 30 min, presumably derived from nucleophilic addition of trifluoroacetate and chloride[12] to **2c** generated *in situ*, respectively. In contrast, activation of 4-phenylpyridine *N*-oxide in the presence of excess pyridine over 48 h resulted in the formation of pyridinium salt **2d** in 69% isolated yield with only trace amounts of chlorinated and hydrolyzed byproducts. Failure to isolate **2c** could be attributed to its relatively high reactivity.

Alternative amine nucleophiles were selected on the basis of either the lack of a β-proton (*N*,*N*-dimethylbenzylamine and pyridine) or a conformational restriction to deprotonation (quinuclidine and 1,4-diazabicyclo[2.2.2]octane [DABCO]) that would otherwise lead to rapid elimination and formation of a neutral 2-(dialkylamino)pyridine. As expected, salts **2e**–**h** (Scheme 2) were isolated in good yields following either silica gel or reversed-phase column chromatography.

Having demonstrated the synthesis and isolation of a small number of pyridyltrialkylammonium salts, this approach was applied to the synthesis of a variety of fluoropyridines from their corresponding pyridine *N*-oxides assembled via an assortment of synthetic transformations (e.g., Buchwald–Hartwig, Suzuki, Sonogashira, and Pd-mediated *N*-oxide couplings,[13] aromatic substitution, and *m*-CPBA oxidation; see the Supporting Information). A set of 2-substituted pyridine *N*-oxides were converted into their corresponding fluoropyridines **3a**–**e** (Scheme 3) in good yields (37–87%), with the exception of the electron-deficient ethyl picolinate *N*-oxide **1f** (25%). Notably, Lewis basic hetereocycles and amines were tolerated in the reaction sequence.

The conversion of 3-substituted pyridine *N*-oxides proved to be highly regioselective. In all cases, ammonium salt formation and subsequent fluorination occurred exclusively *para* to the existing substituent (i.e., 2-fluoro-5-phenylpyridine **3g** was isolated in 84% yield, and 2-fluoro-3-phenylpyridine was not detected). The observed site selectivity is noted to be complementary to Hartwig's AgF_2-mediated C–H fluorination process.[4] Aryl and heteroaryl groups were all well tolerated, producing the corresponding fluoropyridines **3g**–**j** in moderate to excellent yields (61–99%). 3-Morpholinyl- and *N*-Boc-amino-substituted pyridine *N*-oxides were converted to compounds **3k** and **3l**, albeit in lower yields. 5-Azetidin-3-yl-2-fluoropyridine **3m** was also prepared in 57% yield, and the alkyne-containing dipyridyl derivative **3n** was isolated in 72% yield.

Although conversions of various 4-monosubstituted pyridine *N*-oxides were not successful (see the Supporting Information), 2,4- and 3,4-disubstituted pyridine *N*-oxides afforded trisubstituted pyridines **3o** and **3p** in good yields (51 and 74%). 2,5-Disubstituted pyridine *N*-oxides afforded **3q** and **3r** in 68% and 23% yields, respectively. The yield of **3r** was improved to 50% when quinuclidine was used in place of trimethylamine. Fused hetereocyclic *N*-oxides also participated in the process, providing quinoline **3s**, isoquinoline **3t**, and oxazolopyridine **3u**. When both 2- and 2′-positions were substituted, we observed addition of trimethylamine and subsequent fluorination at the 4-position to furnish 4-fluoro-2,6-diphenypyridine (**3v**) in 76% yield.

Nonradioactive analogues of several PET tracers were prepared from their parent *N*-oxides. AV-1451[14] (**3w**) was

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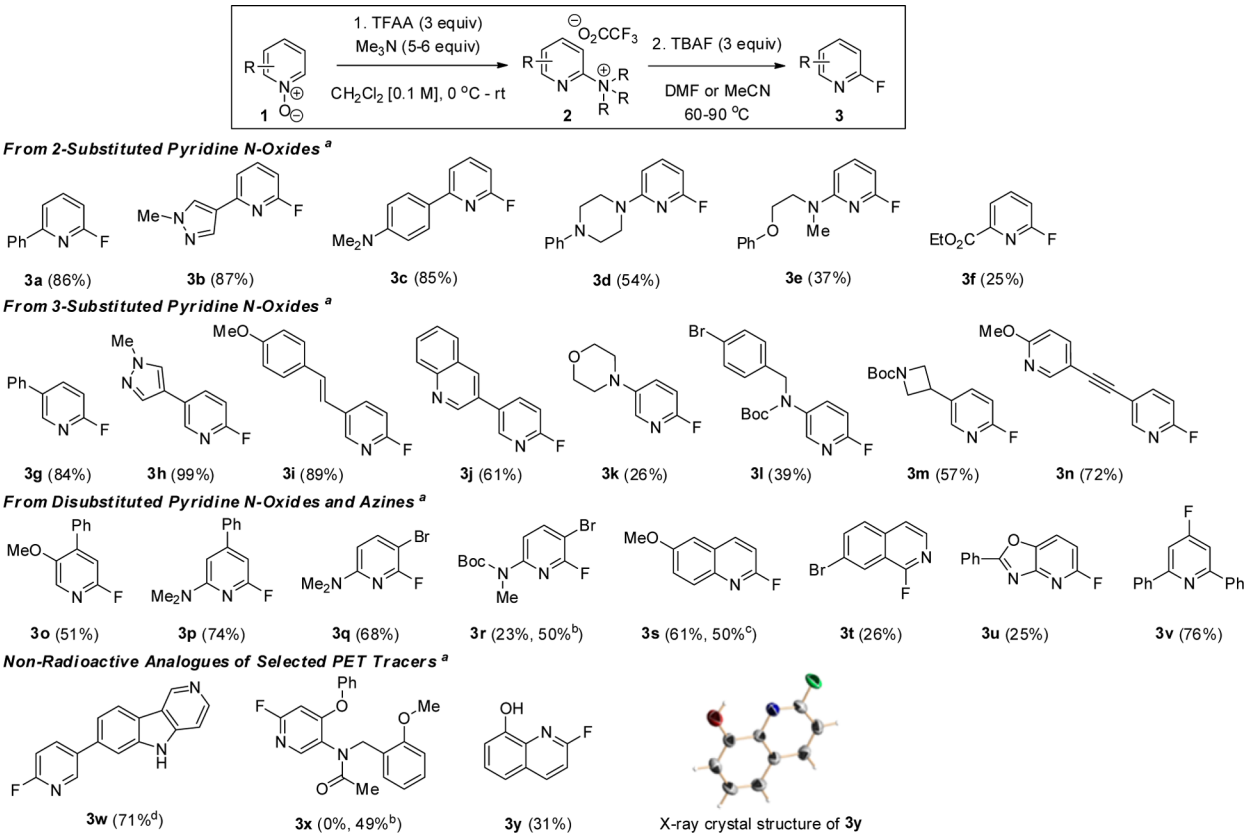
Scheme 3. Synthesis of 2-Fluoropyridines

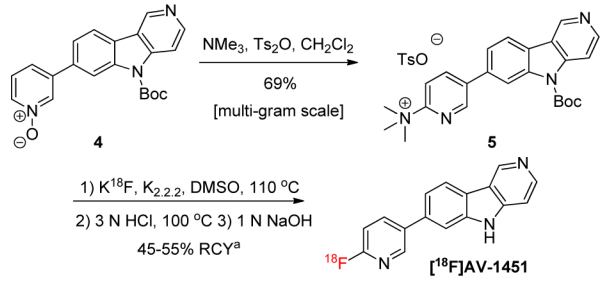


[a]Isolated yields in parentheses. All compounds were obtained as single regioisomers. [b]Using quinuclidine in step 1. [c]Using DABCO in step 1. [d]Following purification and subsequent *N*-Boc removal (TFA, CH_2Cl_2).

prepared in 71% overall yield following *N*-Boc deprotection of the carboline scaffold. 6-Fluoro-PBR28[15] (**3x**) was obtained in 49% yield using quinuclidine as the amine nucleophile, as trimethylamine was not effective. Lastly, the synthesis of 2-fluoroquinolin-8-ol[16] (CABS13, **3y**) was achieved from commercially available 8-hydroxyquinoline *N*-oxide in 31% yield, without any protecting group manipulations. It is noteworthy that this metal-free process provided **3y** as a colorless crystalline solid, which was suitable for X-ray crystallography and confirmed the site of fluorination. These examples illustrate the strategic use of pyridine *N*-oxides to achieve the site-specific, late-stage introduction of fluorine into complex, biologically relevant molecules.[17]

The 2-pyridyltrialkylammonium approach toward 2-fluoropyridine synthesis was also successfully extended to the preparation of [^{18}F]AV-1451 (Scheme 4).[18] The activation of pyridine *N*-oxide **4** with Ts_2O in the presence of trimethylamine cleanly afforded trimethylammonium **5** in 69% yield on multigram scale.[19] To achieve the radiosynthesis of [^{18}F]AV-1451, **5** was treated with K^{18}F in the presence of Kryptofix 2.2.2 in DMSO at 110 °C for 5 min, followed by acidic removal of the *N*-Boc group, neutralization, and semi-preparative HPLC purification. [^{18}F]AV-1451 was consistently and reproducibly obtained in decay-corrected 45−55% radiochemical yields (n > 50; yields were calculated using initial ^{18}F activity in ^{18}O-enriched water and isolated [^{18}F]AV-1451 activity). The total synthesis time was 45 min. It is noteworthy that [^{18}F]AV-1451 is chromatographically well separated from all other impurities as well as the precursor, leading to a rapid and facile purification. This automated process has been successfully implemented at multiple sites to supply doses of [^{18}F]AV-1451 in ongoing clinical trials.

Scheme 4. Radiosynthesis of [^{18}F]AV-1451 from Precursor 5



[a]Decay-corrected radiochemical yield.

In summary, we explored the scope and limitations of an efficient, metal-free synthesis of 2-fluoropyridines using inexpensive reagents. Pyridine *N*-oxide starting materials can be easily converted into 2-pyridyltrialkylammonium salt intermediates in a site-specific manner with broad functional group compatibility. Subsequently, the trialkylammonium salts can be used as common synthetic precursors for both ^{19}F and ^{18}F fluoropyridine analogues. Finally, this method was shown to be applicable to ^{18}F-labeling by the preparation of [^{18}F]AV-1451. Because of the broad availability of pyridine *N*-oxides and the extensive application potential of fluoropyridines in

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drug/PET tracer discovery, we believe that this fluorination method can be applied broadly.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures and spectroscopic data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01703.

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Notes

The authors declare the following competing financial interest(s): The authors are current employees of Avid Radiopharmaceuticals, Inc., a wholly-owned subsidiary of Eli Lilly and Co..

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