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Synthesis of [^{18}F]Perchloryl Fluoride and its Reactions with Functionalized Aryl Lithiums

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[^{18}F]Perchloryl fluoride ($^{18}FClO_3$) has been synthesized by the reaction of [^{18}F]F_2 with $KClO_3$ and its synthetic utility demonstrated by the successful syntheses of [^{18}F] labeled 2-fluoroaniline, 2-fluoroanisole, 2-fluorobenzaldehyde and 3-fluoroveratrole by reaction with their respective ortho-lithiated aromatic precursors in 24, 34, 3 and 21% yields, respectively.

Introduction

CURRENT investigations have demonstrated the need for continued development of methods for aromatic fluorination which are adaptable to radiopharmaceutical applications.[1–5] Previous studies have shown that $FClO_3$ would react with unfunctionalized aryllithiums (such as phenyllithium) to produce moderate yields of aryl fluorides (i.e. fluorobenzene).[6–8] However, its ^{18}F-synthesis and use in the labeling of functionalized aryl fluorides has not been reported. The goal of this work therefore, was to synthesize [^{18}F]$FClO_3$ from a readily accessible ^{18}F precursor and demonstrate its usefulness in the fluorination of aryl lithiums containing pharmacologically interesting functional groups.

Materials and Methods

Aryl precursors

Anisole and veratrole were distilled and dried over molecular sieve prior to use. The blocked aniline [*N*-(t-Boc)-aniline] and the appropriate blocked benzaldehyde (1,3-dimethyl-2-phenylimidazolidine) were prepared by the method of MUCHOWSKI[9] and the method of HARRIS,[10] respectively.

Lithiations were carried out in ether, ether–hexane or tetrahydrofuran solutions using n-butyllithium or t-butyllithium according to literature procedures (see Table 1).

^{18}F production

[^{18}F]F_2 was prepared by deuteron irradiation of F_2/Ne (0.1% up to 1.0% F_2) by the ^{20}Ne (d, α) ^{18}F nuclear reaction.[11] Irradiations were carried out on the 60 in. (1.5 m) Brookhaven National Laboratory Cyclotron.

WARNING: Perchloryl fluoride ($FClO_3$) is a moderately toxic gas stable under many conditions. However it poses a serious threat of explosion due to the fact that it is a strongly oxidizing compound and must be handled with care and proper shielding against potential detonation.*

$^{18}FClO_3$ synthesis

The synthesis of $^{18}FClO_3$ was carried out by the reaction of [^{18}F]F_2 with $KClO_3$.[12] After irradiation of the F_2/Ne target gas mixture the ^{18}F–F_2/Ne was purged rapidly (200 ml/min) from the target through a column of granular $KClO_3$ at 90°C yielding $^{18}FClO_3$. Rapid on-line purification of the $^{18}FClO_3$ was accomplished by passing the resulting gas stream effluent from the $KClO_3$ reactor through a series of two solid-phase scrubbers containing crushed NaOH pellets and granular $Na_2S_2O_3$ respectively. These effectively removed any unreacted F_2 and potential chlorine oxides that may have formed in the $KClO_3$ reactor. The effluent gas was then passed through a trap at liquid nitrogen temperature to isolate the $^{18}FClO_3$ (b.p.—47°C; m.p.—148°C). Under these conditions $^{18}FClO_3$ was rapidly prepared (less than 10 min). The $^{18}FClO_3$ was analyzed gas chromatographically both on a halocarbon/Kel-F column and an Porapak-Q using a heated-effluent proportional gas counter.[13] The GC conditions were the following: (1) 5% Kel-F no. 10 on teflon, 5.5 m × 3.2 mm o.d., carrier gas flow was 10 ml/min at an ambient temperature of 30°C. Under these conditions $FClO_3$ had a retention time of 1.7 min; (2) Porapak-Q, 1.8 m × 3.2 mm o.d., helium flow was 20 ml/min, at an ambient temperature of 30°C, $FClO_3$ had a retention time of 4.2 min.

* Perchloryl fluoride was purchased from the Ozark Mahoning Company in Tulsa, Oklahoma through whom safety literature can be obtained.

TABLE 1. [^{18}F] Yields of the aryl fluorides

Starting compound	Product	% Yield (^{18}F)†	Lithiation references
Anisole*	2-fluoroanisole	34	9
Veratrole*	3-fluoroveratrole	21	9
N-(t-Boc) aniline	2-fluoroaniline	24	8
	N-methyl-2-fluoroaniline‡	2	
1,3-dimethyl-2-phenyl-imidazolidine	2-fluorobenzaldehyde	3	7

* Anisole and veratrole are methoxybenzene and 1,2-dimethoxybenzene (or dimethyl catechol), respectively.

† Yields were based on $^{18}FClO_3$ radioactivity and determined by radiogaschromatography. These do not represent optimized yields. Except in the case of the aniline derivative no other volatile ^{18}F labeled peaks were observed. The remaining ^{18}F-activity was usually accounted for in the aqueous extraction phase.

‡ Since the dianion of t-Boc-aniline is formed by reaction with t-butyllithium, sequential reaction with $^{18}FClO_3$ followed by CH_3I is expected to yield this product.[8] Identity was confirmed by GC/MS analysis (M/e 125).

Reaction of $^{18}FClO_3$ with aryl lithiums

The $^{18}FClO_3$ was transferred into a reaction vessel (−78°C) containing an excess of the desired aryl lithium (300 μmol) by flushing the $^{18}FClO_3$ trap (containing 10 to 100 μmol $FClO_3$) at room temperature with an inert-dry carrier gas (N_2, neon). The reactions were conveniently carried out in the solvents in which the aryl lithiums were initially formed (Et_2O, THF, hexane, etc.) and were complete in 5–10 min. Workup consisted of an initial quenching of unreacted anion with CH_3I followed by aqueous extraction of the organic phase containing the aryl fluoride (as in the case of anisole and veratrole). With benzaldehyde (which was protected as the 1,3-dimethyl-imidazolidine)[10] and aniline protected as the *N*-t-Boc derivative)[9] acidic workup at this point rapidly yielded the unblocked labeled aryl fluorides which were analyzed by radiogas chromatography (RCG).

Results and Discussion

Using this method $^{18}FClO_3$ was prepared, purified and trapped in less than 10 min in yields averaging 23%. These yields were essentially independent of the F_2 concentrations which ranged from 0.1 to 1.0% (20–200 μmol F_2), target purge gas flow rate (30–300 ml/min) or temperature (90°, 120° and 150°C). It should be noted that a maximum yield of 50% based on [^{18}F]F_2 is possible since 50% in the activity is consumed as $K^{18}F$ as shown below.

$$[^{18}F]F_2 + KClO_3 \rightarrow {}^{18}FClO_3 + K^{18}F$$

$^{18}FClO_3$ thus produced, was shown to have a purity which ranged from 91 to >99% (by RGC). The only radiochemical impurities present were determined to be ^{18}F-labeled CF_4 and NF_3, inert gases which are known to be formed during [^{18}F]F_2 production within the target from impurities in the target gas mixture.[14]

Results from the reactions of $^{18}FClO_3$ with the various aryl lithiums are shown in Table 1. As indicated in the table, yields of aryl fluorides, based on $^{18}FClO_3$ ranged from 3 to 34%. Since the average yield of $^{18}FClO_3$ was 23% (based on starting ^{18}F–F_2) all over yields of ^{18}F-aryl fluorides ranged from approximately 1–8%. Although the yields for these reactions have not yet been optimized, products resulting in the formation of ^{18}F-orthofluoro-aryls were observed in low to moderate yields in all cases studied.

These model systems were chosen due to their high regioselectivity for the metallation reaction (nearly complete ortho lithiation has been reported for the cases studied) as well as for their potential pharmacologic interest and synthetic utility.[15–17] The ortho regioselectivity was further confirmed by chromatographic analysis (HPLC or GLC) under conditions where all three mono fluoro isomers could be separated (except for 3-fluoro-veratrole whose identity was confirmed by NMR and GC/MS analyses).[18]

Furthermore all product mixtures were analyzed by GC/MS to confirm the presence of the desired fluoroaryl.

Similar reactions of aryl lithiums with [^{18}F]F_2 were also carried out. These reactions resulted in very poor yields of desired product and complex mixtures of other unidentified ^{18}F labeled peaks in the RGC which may be attributable to reaction with solvent.

Conclusion

With the ease of $^{18}FClO_3$ synthesis and the wide availability of organolithium precursors this synthetic approach should provide ready access to a wide variety of fluorinated pharmaceuticals and ^{18}F radiopharmaceuticals.

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