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ELECTROPHILIC RADIOFLUORINATION OF ARYLTRIMETHYLSILANES AS A GENERAL ROUTE TO ^{18}F-LABELED ARYL FLUORIDES

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SUMMARY

The reactions of a variety of aryltrimethylsilanes with elemental fluorine and acetyl hypofluorite have been studied with the aim of developing a general method for labeling aromatic compounds with fluorine-18. Extensive ^{18}F incorporation into the aromatic ring of the selected aryltrimethylsilanes was invariably observed, leading to the ipso (^{18}F-for-Si) electrophilic substitution products together with variable yields of other (^{18}F-for-H) electrophilic substitution products. The relative extent of the ^{18}F substitution processes [$(C\text{-}Si/C\text{-}H)_{subst.}$] is found to depend largely upon the substituent group on the aromatic ring of the substrate, the leaving moiety, and the radiofluorination procedure used. The utility of aryltrimethylsilyl derivatives as precursors for the rapid synthesis of high specific activity of ^{18}F-labeled radiopharmaceuticals is discussed.

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INTRODUCTION

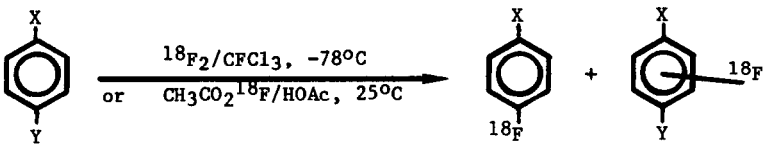
The need for efficient methods for incorporation of ^{18}F ($t_{1/2}$ = 110 min; 97% β^+) into radiotracers for metabolic studies using positron emission tomography (PET) [1] has stimulated a growing armamentarium of synthetic methods for rapid incorporation of the radionuclide into organic molecules of potential biomedical interest [2]. The synthetic methods adopted must comply with several stringent requisites, namely that they should be rapid, efficient, and compatible with the accessible chemical forms of ^{18}F. In many instances, the ^{18}F incorporation step of the synthetic sequence must give reasonable yields of the radioactive derivative with appropriate specific activity, and with the label being introduced into desired positions regio- and steroespecifically. In particular, in most aromatic compounds, the most desirable radiofluorination site or the most convenient one is on the aromatic ring (e.g., ^{18}F-spiroperidol) [3].

Until recently, the preparation of ^{18}F-labeled aryl fluorides has relied principally on two different classes of reactions, these being based on the incorporation of ^{18}F either via a nucleophilic or an electrophilic substitution process. Among the first type of reactions, the classical Balz-Schiemann reaction is characterized by low radiochemical yields and by unavoidable isotopic dilution [4]. The latter drawback has been overcome by a recent modification, exploiting the decomposition of aryl triazenes in the presence of $H^{18}F$ or $Cs^{18}F$ to give ^{18}F-labeled aryl fluorides at no-carrier-added (NCA) levels although in very low and often poorly reproducible yields [5]. More recently, the nucleophilic displacement of chloro, nitro, and trimethylammonium groups in activated aromatic rings by [^{18}F]fluoride has been developed into an effective radiofluorination technique for the syntheses of NCA ^{18}F-labeled aryl fluorides [6-8]. Despite its restriction to aromatic systems with strong electron-withdrawing groups (e.g., NO_2, CN, etc.), this method represents the most convenient source of NCA ^{18}F-labeled aryl fluorides.

On the other hand, only few examples of direct electrophilic radiofluorination of aromatic compounds have been reported so far. In the reactions which have been studied, it is apparent that strong electron-donating groups are required in the aromatic ring when mild electrophilic fluorination reagents such as XeF_2 [9] and CH_3CO_2F [10] are

used. Contrary to this, reactions of F_2 with the aromatic compounds are usually accompanied by nonselective hydrogen substitution and uncontrollable fragmentation and oxidation of the aromatic substrate [11,12]. A recent approach circumventing these obstacles makes use of aromatic precursors containing a carbon-metal bond which is recognized to be highly reactive toward electrophilic species. Accordingly, satisfactory yields of regiospecifically halogenated and radiohalogenated arenes were readily obtained from suitable aryl tin precursors [13], aryl mercury precursors [14] and aryl germanium precursors [15].

Aryltrimethylsilanes have also been shown to react with electrophilic halogens via ipso aromatic substitution to yield the corresponding aryl halides [16]. Application of aryltrimethylsilane intermediates for regiospecifically introducing NCA quantities of radiobromine and radioiodine into aromatic rings has been reported [17]. Now, we have extended the scope of this reaction to the rapid preparation of ^{18}F-labeled aryl fluorides. We report here the results of radiofluorination of a variety of aryltrimethylsilanes using two ^{18}F-labeled reagents, i.e., $[^{18}F]F_2$ and $CH_3COO^{18}F$ to give ^{18}F-for-Si substitution products together with variable yields of other ^{18}F-for-H substitution products (eq. 1). A preliminary report of this study has appeared [18].



(1)

X	Y
H	TMS
CH_3	TMS
OCH_3	TMS
Cl	TMS
Br	TMS
$-\overset{O}{\overset{\|}{C}}-CH_3$	TMS
$O-\overset{O}{\overset{\|}{C}}-CH_3$	TMS
TMS	TMS
H	CH_2TMS

EXPERIMENTAL

Materials Phenyltrimethylsilane and benzyltrimethylsilane were obtained from Aldrich Chemical Co. and PCR Research Chemicals Inc., respectively. Other aryltrimethylsilanes which were not commercially available were synthesized by the literature procedures [19] and their purities were checked by GLC and HPLC. Benzyl fluoride was purchased from Pierce Chemical Co. p-Chlorofluorobenzene and p-difluorobenzene were obtained from ICN Pharmaceuticals Inc., fluorobenzene was obtained from Aldrich Chemical Co., p-fluoroanisole and p-fluorophenyl acetate were obtained from Fairfield Chemical Co., Inc. Commercially available N_2 + 1% F_2 gaseous mixtures (Matheson Co.) were used in the direct fluorination reactions and to prepare acetyl hypofluorite (CH_3COOF). The latter reactant was conveniently generated *in situ* by bubbling F_2 into glacial acetic acid containing 0.1% CH_3COONH_4 [20]. Freon-11 ($CFCl_3$) was purchased from Matheson Co. and used without further purification.

Labeled Reagents Fluorine-18 labeled fluorine was prepared from a Ne - 0.1% F_2 target using the $^{20}Ne(d,\alpha)^{18}F$ reactions [21] at the Brookhaven 60-inch cyclotron. Typically for a 3 minute irradiation at a beam current of 5 μA, the yield of $[^{18}F]F_2$ is ~ 5-6 mCi. Fluorine-18 labeled acetyl hypofluorite was generated *in situ* using $[^{18}F]F_2$ as described previously [20].

Reaction Conditions and Analytical Procedures In the reactions of aryltrimethylsilanes with molecular fluorine, $[^{18}F]F_2$ (5-6 mCi) was allowed to slowly bubble through a solution containing 50-60 μmol of the aryltrimethylsilane in 13 ml of $CFCl_3$ at -78°C. After the addition was complete (~ 10 min), the reaction mixture was extracted with saturated KOH/MeOH solution and H_2O. The activities in both phases were measured (Capintec, Model CRC 453X). The freon-11 phase was then analyzed by radio-GLC (Varian Aerograph Model 920 gas chromatograph equipped with a hot-wire detector and connected to a heated flow proportional counter) [22] and radio-HPLC (Perkin-Elmer Series 3B liquid chromatograph equipped with an UV detector and connected to a Berthold Radioactivity Monitor, Model LB 503

flow scintillation counter). The identities of the labeled products were established by comparison of their retention times with those of authentic, unlabeled samples on at least two columns of GLC, and with at least two different solvent systems in HPLC. As an example, the ^{18}F-labeled toluenes from fluorination of p-tolyltrimethylsilane were identified and analyzed on the following columns: (i) 20% Carbowax 20 M on chromosorb W (3.6 m x 6 mm) column operated at 70°C; (ii) 5% SP-1200/1.75% Bentone 34 on supelcoport (1.8 m x 6 mm) column operated at 75°C; (iii) 10% p,p'-Azoxydiphenetole on chromosorb P AW(3.6 m x 6 mm) column operated at 135°C. The HPLC analysis was performed on a C18 column (4.5 x 250 mm) from IBM Co., using two different solvent systems (MeOH:H_2O, 4:1 and MeOH:0.01 M $(NH_4)_2HPO_4$ 7:3). Static activity analyses were also carried out using a Picker NaI well counter.

In the reactions of aryltrimethylsilanes with acetyl hypofluorite, a solution of ^{18}F-labeled acetyl hypofluorite in glacial CH_3COOH (2 ml, 8-10 μmol) was added to the aryltrimethylsilane (20-30 μmol) dissolved in 0.5 ml of glacial CH_3COOH. After a few minutes (5-10 min), the reaction was stopped by adding 2 ml of water, made basic with 10 N NaOH and extracted with n-hexane. The activities of both fractions were measured by static counting, and the hexane solution was analyzed by radio-GLC and radio-HPLC on the same columns employed in the $[^{18}F]F_2$ experiments.

RESULTS

Fluorinations Initial experiments were carried out to determine the reactivity of aryltrimethylsilanes toward F_2 and CH_3COOF, generated under the reaction conditions in such a way as to approach the radiofluorination conditions. Both fluorinating reagents were reacted with the different aryltrimethylsilanes to compare the yields and the distribution of the products from these two reactions.

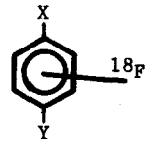
Reactions of molecular fluorine (30 μmol) with aryltrimethylsilanes (20-30 μmol) in $CFCl_3$ at -78°C resulted in reaction mixtures with F-for-Si substitution products accompanied by other F-for-H substitution products. Similar results were obtained from the reactions with acetyl hypofluorite.

The yields of the products from both F_2 and CH_3COOF fluorination procedures, which are based on the F_2 used, were found to vary considerably depending upon the reaction conditions used, such as the substrate concentration and the reaction temperatures.

Radiofluorinations The radiofluorination experiments were carried out with $[^{18}F]F_2$ or $CH_3CO_2{}^{18}F$ under the reaction conditions which had been optimized in the non-radioactive fluorinations. The yields and the product distributions from the radiofluorination of aryltrimethylsilanes by $CH_3CO_2{}^{18}F$ in acetic acid at 25°C are reported in Table 1. The same substrates have also been fluorinated with $[^{18}F]F_2$ in $CFCl_3$ at -78°C and the results are listed in Table 2.

TABLE 1

Radiochemical Yields of ^{18}F-Labeled Aryl Fluorides from the Fluorination of Aryltrimethylsilanes with $CH_3CO_2{}^{18}F$ in CH_3CO_2H at 25°C

Substrate		Radiochemical Yield (%)		$\frac{C\text{-}Si}{C\text{-}H}$ subst.
				
X	Y			
H	TMS	10.0	5.9	1.7
CH_3	TMS	12.6	1.2	10.8
OCH_3	TMS	8.8	9.7	0.9
Cl	TMS	14.9	2.9	5.2
Br	TMS	14.2	1.1	12.9
$-\overset{O}{\overset{\|}{C}}-CH_3$	TMS	5.7	0.8	7.1
$-O-\overset{O}{\overset{\|}{C}}-CH_3$	TMS	6.3	1.3	4.9
TMS	TMS	15.6	3.3	4.7
H	CH_2TMS	2.4*	13.4	0.2

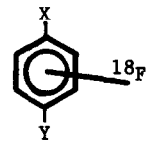
* Benzyl $[^{18}F]$fluoride.

In some experiments, the reaction mixtures from either $[^{18}F]F_2$ or $CH_3COO^{18}F$ were subjected to chemical degradation with the aim of evaluating the site(s) of substitution of the fluorine atom on the aryltrimethylsilanes. For instance, the reaction mixture from $[^{18}F]F_2$ fluorination of phenyltrimethylsilane was treated with a drop of Br_2 at 40°C for 5-15 min. Under these conditions, any alkylsilyl group present in the labeled products are readily replaced by a Br atom [23]. Analysis of the bromination products revealed the formation of a 1:1 mixture of o- and p-$[^{18}F]$fluorobromobenzene from partial degradation of the ^{18}F-labeled phenyltrimethylsilane. Their combined activity fully accounts for the decrease of activity observed for ^{18}F-labeled phenyltrimethylsilane.

An alternative degradation route was followed for the radiofluorination products obtained from p-chlorophenyltrimethylsilane. In this case, the

TABLE 2

Radiochemical Yields of ^{18}F-Labeled Aryl Fluorides from the Fluorination of Aryltrimethylsilanes with $[^{18}F]F_2$ in Freon-11 at -78°C

Substrate		Radiochemical Yield (%)		$(\frac{C\text{-}Si}{C\text{-}H})$ subst.
				
X	Y			
H	TMS	24.5	4.0	6.1
CH_3	TMS	27.9	2.5	11.3
OCH_3	TMS	21.3	18.6	1.2
Cl	TMS	21.5	2.5	8.6
H	CH_2TMS	19.8*	7.0	2.8
TMS	TMS	21.6	trace	---

* Benzyl $[^{18}F]$fluoride.

silyl group in the ^{18}F-labeled p-chlorophenyltrimethylsilane was replaced by a hydrogen atom by treating the fluorination mixture with 2 ml of a MeOH:$HClO_4$ (1:1) solution at 90°C for 2 hr [24]. Apart from p-[^{18}F]fluorochlorobenzene directly formed from ^{18}F-fluorodesilylation of p-chlorophenyltrimethylsilane, analysis of the reaction mixture after acid treatment revealed the formation of o- and m-[^{18}F]fluorochlorobenzene, at activity levels counterbalancing the activity loss of ^{18}F-labeled p-chlorophenyltrimethylsilane.

DISCUSSION

Electrophilic substitution reactions have been used to produce a number of ^{18}F-labeled aryl fluorides in moderate yields using aryltrimethylsilanes as the substrates (see Tables 1 and 2). The reactions were found to be rapid and mild. However, since the electrophilic radiofluorination procedures such as the one we describe here require [^{18}F]F_2 or $CH_3CO_2{}^{18}F$ which is generated from [^{18}F]F_2, the maximum radiochemical yield of the organic products is 50%. In addition the specific activity of [^{18}F]F_2 is only moderately high. For example, for a 2 hr irradiation at a beam current of 12 μA, the yield of [^{18}F]F_2 is ~ 400 mCi. Therefore the specific activity of the radiotracers produced is ~ 10 mCi/μmol.

A more recent report on the radiofluorination of certain arylsilanes with [^{18}F]F_2 to give only the corresponding ^{18}F-labeled aryl fluorides has appeared [25]. However, in contrast to those results, the results shown in Tables 1 and 2 indicated that in addition to the ^{18}F-labeled aryl fluorides which resulted from ^{18}F-for-Si substitution, the radiofluorination of aryltrimethylsilanes using either [^{18}F]F_2 in $CFCl_3$ at -78°C or with $CH_3CO_2{}^{18}F$ in CH_3CO_2H at 25°C also produced ^{18}F-for-H substitution products. The identities of the products were established by comparison of their GLC and HPLC retention times with those of authentic samples, and by degradation experiments. The combined radiochemical yield of the ^{18}F-for-Si and ^{18}F-for-H substitution products (i.e., aryl [^{18}F]fluorides $C_6H_4X{}^{18}F$ and ^{18}F-labeled aryltrimethylsilanes $C_6H_3XY{}^{18}F$) range from 20 to 40% for the reactions with [^{18}F]F_2 and 10-20% for the reactions with $CH_3CO_2{}^{18}F$. The yields as well as the relative distribution of the labeled products appear to depend markedly upon the presence and the nature of the substituent in the position para to the leaving trimethylsilyl group.

Hydrogen substitution ($C_6H_3XY^{18}F$) efficiently competes with silicon substitution ($C_6H_4X^{18}F$) in aryltrimethylsilanes when X is a strong electron-donating group, such as OCH_3, as demonstrated by the low $(C\text{-}Si/C\text{-}H)_{subst.}$ value. The situation is quite different when X is a weak electron-donating group, such as CH_3, or an electron-withdrawing group, such as Cl, Br, $-\overset{O}{\overset{\|}{C}}-CH_3$ wherein the relative extent of silicon substitution exceeds that of the hydrogen substitution as evidence by the high $(C\text{-}Si/C\text{-}H)_{subst.}$ values.

It is interesting to note that fluorination of p-trimethylsilylphenyltrimethylsilane with either $CH_3CO_2{}^{18}F$ in acetic acid or with $[^{18}F]F_2$ in $CFCl_3$ gave only p-[^{18}F]fluorophenyltrimethylsilane without any detectable amount of p-[^{18}F]difluorobenzene.

It is also interesting to note that $CH_3CO_2{}^{18}F$ does not seem to be able to cleave the C-Si bond when the Si atom is bound to an aliphatic carbon such as Y = CH_2TMS and the relative extent of ^{18}F incorporation via ^{18}F-for-Si substitution is invariably lower than those from the $[^{18}F]F_2$ experiments as shown by comparison of the relevant $(C\text{-}Si/C\text{-}H)_{subst.}$ ratio. These results are expected in view of the milder electrophilic character of CH_3CO_2F as compared to the much stronger F_2.

CONCLUSION

Regioselective incorporation of radiofluorine into simple aromatic molecules can be accomplished by fluorinating aryltrimethylsilanes with ^{18}F-labeled reagents such as $[^{18}F]F_2$ or *in situ* generated $CH_3CO_2{}^{18}F$. The reactions can be carried out under very mild conditions in short reaction times, using $CFCl_3$ at -78°C or acetic acid at 25°C. Although complicated by ring fluorination processes, the syntheses of ^{18}F-labeled aryl fluorides using aryltrimethylsilyl derivatives appear superior to other methods previously described in the literature especially on deactivated aromatic substrates. This method thus provides an alternative route to ^{18}F-labeled radiopharmaceuticals which are not required to be NCA and contain an aromatic ring without activating groups. An obvious application of this method would be the syntheses of 6-[^{18}F]fluoro DOPA [26] and p-fluoroamphetamine from the corresponding silanes.

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