AROMATIC FLUORINATION WITH N.C.A. F-18 FLUORIDE: A COMPARATIVE STUDY

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SUMMARY

Fluorination of aromatic rings with no carrier added (n.c.a.) ^{18}F-fluoride was investigated using aryl triazenes and aryl iodides as substrates. Aryl triazenes give low yields of labeled product under all conditions, and evidence was obtained to indicate that an inert solvent was unnecessary for the reaction. Nucleophilic substitution of aromatic iodides in DMSO was found to be a superior method of fluorination yielding up to 70% incorporation of label. The scope and limitations of this new labeling reaction are reported.

Key words: ^{18}F-fluoride, fluoroaromatics, nucleophilic substitution, triazenes

INTRODUCTION

The satisfactory incorporation of high specific activity fluorine-18[1-5] onto aromatic rings has been an elusive goal. In spite of considerable effort no completely satisfactory method has yet been found. The Balz-Schiemann reaction[3] suffers from poor chemical yields and low specific activity. The other common approach, reaction of fluoride with decomposing aryl triazenes[1,5-7] gives a high specific activity product with very low chemical yields and many labeled and unlabeled by-products.

The molecules that are the goal of much of this work are the butyrophenone dopamine receptor ligands spiroperidol[1,2] and haloperidol.[3-5] Since these compounds are mildly activated towards nucleophilic substitution and since nucleophilic exchange of ^{18}F fluoride for aromatic fluorine has been reported[8] one might expect nucleophilic substitution to be a possible alternative for high

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specific activity labeling. One problem that may be expected in attempting high specific activity fluorination by nucleophilic aromatic substitution is that the very good leaving properties of fluoride would tend to reduce the labeling yield. Another problem is that the required degree of activation of the aromatic ring may be greater than that of a given substrate.

This study was initiated as an investigation of aromatic fluorination using triazene precursors. The results obtained, which we briefly report here, led us to investigate nucleophilic aromatic substitution. Nitrate and halides were investigated as leaving groups. Iodide was chosen as the leaving group for its ease of synthesis and because the physical difference from fluoride aids in purification of the labeled product. We found that this method gives good yields in a short time and appears suitable for use in labeling radiopharmaceuticals.

EXPERIMENTAL

$H^{18}F$ Production

Fluorine-18 fluoride was produced by bombardment of a neon recirculating target with ^{3}He particles as described previously[9]. It was dissolved directly in the required solvents.

[^{18}F]-p-Fluorobenzonitrile by Triazene Reaction

The ^{18}F-fluoride was typically reacted in a closed teflon vessel with 2-N-piperidinyl-p-diazobenzonitrile[7] (30mg, 0.14mmol) in 0.5ml benzene with 54mg (0.56mmol) methanesulfonic acid at 130°C for 30 min. The mixture was then cooled, washed with three 1ml portions of water and both phases were analyzed by thin layer chromatography.

[^{18}F]-p-fluorobenzonitrile by F-for-I exchange reaction

In the optimum labeling reaction ^{18}F-fluoride in dimethylsulfoxide (DMSO, 0.2ml) was added to a mixture of 10mg (70µmol) potassium carbonate and 10mg (45µmol) p-iodobenzonitrile in a glass vessel and heated in an oil bath at 180°C for 15 min. with stirring. After cooling 10ml water and 10ml benzene were

added, the mixture was shaken, separated, and the benzene washed twice more with water. The washes were combined and both layers were analyzed by thin layer chromatography.

Chromatography Systems

Thin layer chromatography (TLC) was found to be the most reliable system for evaluating purity and yield because unreacted fluoride is not totally extracted by water and is not completely eluted on HPLC. Therefore TLC gave the only reliable measure of yield when done with precautions against product evaporation. It was performed with Merck 0.25mm silica gel $60F_254$ plates eluted with 20% ethyl acetate 80% hexane. On this system fluoride ion was retained on the origin and p-fluorobenzonitrile showed an R_f of 0.43.

The identity of the labeled product was also confirmed with high performance liquid chromatography using a Waters C_{18}-μ-bondapak column eluted with an acetronitrile/water gradient at 6ml/min. The solvent composition was changed linearly from 0 to 60% acetonitrile over 5 minutes. Retention times were: p-fluorobenzonitrile-10.5 min, fluoride-2 min.

Precursor syntheses

p-Cyanobenzenediazonium methanesulfonate was prepared by adding p-aminobenzonitrile (3g) to 7.5g methanesulfonic acid in 60ml water and stirring 3 hrs. The mixture was then cooled in an ice bath and 1.75g $NaNO_2$ in 5ml water added dropwise. The mixture was stirred 2 hrs in ice, and the diazonium salt was used as below.

2-N-Piperidinyl-p-diazobenzonitrile was prepared by adding piperidine (8.5g in 50ml water) dropwise to the ice-cooled diazonium salt solution, allowing the mixture to stand overnight and extracting with methylene chloride. Two recrystallizations from hexane gave 3.5g (64%) of product, mp 85-86°C (hot stage).

p-Iodobenzonitrile was prepared by adding a solution of 6g KI in 25ml water dropwise to the ice-cooled diazonium salt and allowing the mixture to stand

overnight at room temperature. Sodium bisulfite (2g) in 20ml water was added and the solution was extracted with ether, dried and evaporated. The residue was taken up in 60ml hot chloroform, filtered and evaporated. The light pink solid was then purified on a silica gel column eluted with chloroform:methylene chloride 100:12. The white product was crystallized from ethanol (50ml) to afford 2.5g (43%) white needles mp 126-127°C. (lit. 126.5,[10] 128-129[11]).

RESULTS

Fluorinations of 2-N-piperidinyl-p-diazobenzonitrile

The reaction of this triazene in bromobenzene and in benzene afforded yields of 5-10% based on fluoride. Other organic solvents gave no desired product. Observations of dependance on other factors (reactant concentrations, acid, temperature) agreed with previous reports.[12] Protonation of the triazene solution by several methods which either eliminated the acid phase or isolated the organic phase gave no detectable fluorinated products. However, washing the activity from the collection tube with 0.1ml of methanesulfonic acid containing triazene and performing the reaction with no added solvent gave a yield of 12% after 5 min. This represents a small improvement over the standard method.

Nucleophilic Aromatic Substitution of Iodide by ^{18}F-fluoride

Initial experiments indicated that DMSO was clearly the solvent of choice for the displacement. Yields in all other solvents used (DMF, DMA, HMPA, alcohols, hydrocarbons, etc.) were either zero or less than half that obtained in DMSO. As with other displacement reactions, an added base was necessary to provide a cation for the fluoride. Cesium carbonate was initially chosen and the reaction course was studied at various temperatures (Table 1). The reaction rate rose markedly as temperature increased.

Subsequent examination of various cations revealed that potassium carbonate gave the best results (Table 2). Examination of the effect of substrate concentration (Table 3) was therefore performed using potassium carbonate.

Table 1: Yield of the exchange of n.c.a. $^{18}F^-$ with p-iodobenzonitrile as a function of time and temperature (0.5ml DMSO + Cs_2CO_3; 180°C)

T(°C)	5 min	15 min	45 min
190	60	66	70
170	20	24	44
150	9	25	38
130	3	5	10

Table 2: Yield of n.c.a. fluoride exchange using carbonates of various cations as the base. Reaction at 180° in DMSO 10 min.

Salt	Yield (%)
Na_2CO_3	2
K_2CO_3	56
Rb_2CO_3	29
Cs_2CO_3	33

Product yield increased with substrate concentration to 0.2M and did not substantially increase at higher concentrations. Neither small amounts of water (1%) nor silver oxide[13] (20 mg) had any noticeable positive or negative effects on the product yields. Addition of tetra-alkyl ammonium chlorides produced no measurable product at any temperature, but this could have been due to decomposition of the ammonium salt in hot DMSO.

The effect of other substituents on the aromatic ring was briefly examined and results are presented in Table 4.

Discussion

p-Fluorobenzonitrile was originally chosen as a suitable model compound for investigation because in previous work with the triazene reaction[7] it was shown to give low yields similar to those of the compounds of interest. For

Table 3: Yield of n.c.a. ^{18}F exchange as a function of temperature and substrate concentration. Reaction for 10 min in each of 0.5ml, 1ml, 2ml DMSO

T(°C)	Concentration (M)		
	0.05	0.1	0.2
180	32	56	74
160	-	39	57
140	-	26	42
120	-	7	6

Table 4: Yields of n.c.a. ^{18}F exchange with halogen or nitrate. 0.2M substrate, 10 min, 180°C, DMSO

Substrate	Exchange yield(%)
p-Iodobenzonitrile	74%
p-Nitrobenzonitrile	75%
Iodobenzene	20%
Bromobenzene	20%
p-Bromoanilin	8%

purposes of comparison we have continued to use this model compound in our displacement experiments.

During the triazene reaction the reactants, triazene and fluoride, are present in two separate phases. Since the majority (95%) of the fluoride is found in the separate acid phase and the triazene can be recovered nearly quantitatively from the organic phase, one might expect an improved yield from a single phase reaction. We therefore attempted several approaches to achieve a single phase reaction. Use of soluble organic acids or single-phase solutions of pre-protonated triazene did not yield fluorinated product. This indicated either that an excess of a sulfonic acid was necessary or that the "inert" solvent was interfering in the reaction. We were then led to attempt fluorination in methanesulfonic acid with no other solvent. The slight improvement in yield (12%) over the standard method combined with the previous negative results indicated that the majority of the labeling must normally occur in the acid phase in contrast to the natural assumption that the organic solvent plays an important role. This is consistent with the decreased concentration of triazene that could be used in the acid. The fact that the yield remained low indicates that factors other than phase separation and inhibition by solvent are limiting the yield.

Nucleophilic substitution now appears to be the method of choice for utilization of high specific activity ^{18}F fluoride. Although nucleophilic aromatic substitution is generally difficult, a ring activated with an electron withdrawing substituent does undergo substitution under appropriate conditions. On the no-carrier-added scale the equilibrium position of the exchange tends to favor a high degree of labeling[14], even though fluoride is a comparatively easily displaced leaving group. The choice of iodide as the leaving group was made for ease of synthesis and purification. The necessary iodides are formed in high yield from the same diazonium salts used to make triazenes, and the physical difference between fluoride and iodide allows easy chromatographic separation. Iodobenzonitrile was chosen as the model substrate to allow a

direct comparison with the triazene results. Incorporation of 70% of ^{18}F activity was obtained at 180°C using potassium carbonate to provide the necessary cation. Above 190°C solvent decomposition became a problem.

The effect of substituent groups on the ring is not very large. The yields from activated and deactivated iodides were within one order of magnitude. Moderately activated substrates gave useful yields, while a deactivated ring performed no better than a typical triazene. This lack of large activation effects could be explained if the rate limiting step for the more activated rings is not aromatic substitution, but is, for example, desolvation of fluoride. As would be expected, bromide and iodide were equal in reactivity. This indicates that bromides, which are more readily available commercially, might also be of significant utility. If purification of the product is difficult iodides are obviously to be preferred.

After the report of our initial results[15] two reports of a similar method using nitro group displacement have appeared.[16,17] We have duplicated these experiments and found that on the no-carrier-added scale the labeling yields of the two methods are indistinguishable. We have also done these displacements with excess stable fluoride. With fluoride in stoichiometric ratio to the substrate, iodobenzonitrile gave incorporation of 2% of the fluoride while p-nitrobenzonitrile gave yields of 40%. The incorporation yield is therefore dependent on specific activity, with the yields given by each leaving group increasing to similar values at high specific activity. The yields are less than the 100% predicted by theory.[14] This may be due to side reactions, presence of an alternate and less reactive form of ^{18}F, or to the finite specific activity. It is most likely not due to insufficient reaction rate because the yield at 180°C (Table 1) clearly tends toward a limit below 100%.

While the high specific activity yield appears to be independent of the leaving group used, published data[16,17] indicates that a nitro group may allow use of slightly lower temperatures. This may be useful for sensitive substrates although one would expect both methods to be difficult in such cases. The

general method does appear very promising for labeling substrates which are stable in hot DMSO.

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