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HALOFLUORINATION OF OLEFINS: ELUCIDATION OF REACTION CHARACTERISTICS AND APPLICATIONS IN LABELING WITH THE POSITRON-EMITTING RADIONUCLIDE FLUORINE-18

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SUMMARY

Olefin halofluorination involves the *in situ* generation of a halogen-fluoride reagent and subsequent addition to an olefin. The characteristics of this reaction were investigated with three model olefins (allylbenzene, 1-hexene and propene) in order to assess its potential for labeling molecules with the positron-emitting radionuclide fluorine-18 at the no-carrier-added level. The most favorable conditions for bromofluorination utilized 1,3-dibromo-5,5-dimethyl-hydantoin, with dichloromethane as solvent. Halofluorination proceeds rapidly and efficiently using either equivalent or substoichiometric quantities of fluoride ion; HF/pyridine or metal fluorides with acid can be used, and up to three equivalents of water can be present. By this reaction, allylbenzene was labeled with fluorine-18 in 32% yield, under either carrier-added or no-carrier-added conditions. Thus, we anticipate that this reaction will prove very useful in the labeling of other molecules with fluorine-18.

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INTRODUCTION

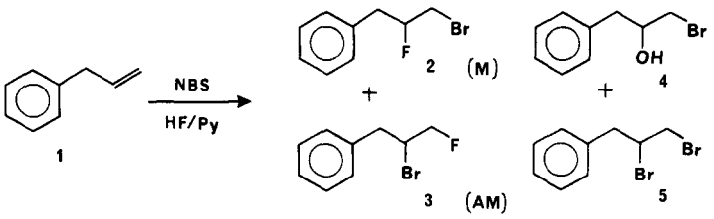
Positron-emitting radiopharmaceuticals labeled with fluorine-18 ($t_{1/2}$ = 110 min) are being increasingly used in basic physiological studies as well as in clinical diagnosis [1]. However, despite their promise, there are few chemical processes suitable for introducing fluorine-18 into these agents. Many methods utilize long reaction times and a large excess of the fluorinating agent [2]. In contrast, an adequate method for labeling a molecule with fluorine-18 requires a reaction that is rapid, convenient, efficient when the fluorinating species is the limiting reagent, effective without addition of carrier fluorine-19 (to produce products with high specific activity for receptor binding studies) and capable of utilizing available sources of fluorine-18 [3]. Several publications have described an effective approach, involving the use of [^{18}F]fluoride ion to displace good leaving groups at aliphatic [4-7] or aromatic [8-11] positions. Still, there is a great need for other novel methods for fluoride-18 labeling.

Olefin halofluorination involves the in situ generation of ClF, BrF, or IF by treatment of a solution of fluoride ion in acid medium with a source of the electrophilic halogen, and subsequent addition of the elements of halogen-fluoride to an olefin [12-14]. Although this reaction has been applied in many synthetic circumstances, the key characteristics of importance in terms of its potential for fluorine-18 labeling (i.e., rate, yield, and efficiency when fluoride is limiting) have not been studied explicitly. In this report, we describe an investigation of the olefin halofluorination reaction in terms of these reaction characteristics, and we assess its applicability to the labeling molecules with fluorine-18. We find that under appropriate conditions, halofluorination is a reaction very well suited to labeling molecules with fluorine-18, both under carrier-added and no-carrier-added conditions.

RESULTS

Results of a Typical Bromofluorination Reaction. Source of Electrophilic Halogen

The products from a typical halofluorination of allylbenzene, utilizing an excess of N-bromosuccinimide as the electrophilic halogen source and HF/pyridine as the source of fluoride, are shown in the Scheme 1. The Markovnikov **2** and the anti-Markovnikov **3** products are found in a 7 to 1 ratio, together with smaller amounts of the halohydrin **4** and the halogen

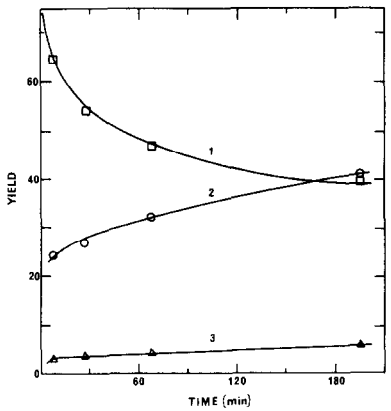


Scheme 1

addition product **5**. In general, we have found that the halohydrin **4** is formed only when excess halogenating agent and water are both present; the halogenation product **5** forms slowly, and only when the source of the electrophilic halogen is present in excess over fluoride.

The time course of a typical reaction of allylbenzene with one equivalent of N-bromosuccinimide and 0.9 equivalents of HF/pyridine in dichloromethane is shown in Figure 1. The consumption of the olefin and formation of the halofluorination products proceed rapidly under these conditions.

The results shown in Figure 2 illustrate the time course of allylbenzene halofluorination with N-iodosuccinimide (NIS),



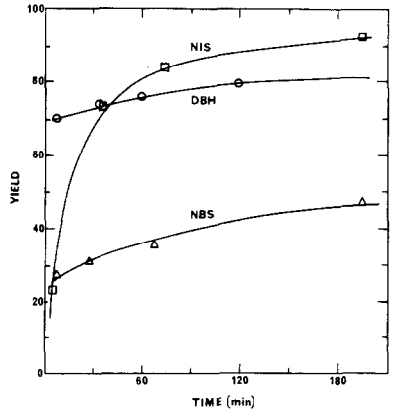


Fig. 1. (left) The time course of a typical halofluorination reaction of allylbenzene (1.0 eq.) with NBS (1.0 eq.) and HF/pyridine (0.9 eq.) in CH_2Cl_2. The yields of the products (**2** and **3**) are based on fluoride, the limiting reagent.

Fig. 2. A comparison of the halogen sources of NBS, DBH, NIS (1.0 eq.) in the reactions with allylbenzene (2.0 eq.) and HF/pyridine (0.9 eq.) in CH_2Cl_2. The combined yields of the Markovnikov and anti-Markovnikov products (**2** and **3** or the iodo analogs) are shown, and the yields are based on fluoride, the limiting reagent.

N-bromosuccinimide (NBS), and 1,3-dibromo-5,5-dimethylhydantoin (DBH) as the source of the electrophilic halogen. Halofluorination proceeds more rapidly with NIS than NBS, but the most rapid reaction was with the DBH; this reagent is also considerably more soluble.

Effect of Temperature and Solvent

Halofluorination is rapid; using an excess of HF/pyridine and DBH, we find the reaction with allylbenzene is essentially complete as fast as we can measure it at room temperature and within about 5 minutes at -23°C (Table 1). Halofluorination can also be performed in various solvents: the reaction in dichloromethane is more rapid than in carbon tetrachloride. In

acetonitrile, the reaction does not go to completion, and in tetrahydrofuran at room temperature no desired product is found, although allylbenzene is consumed (21% by 90 min).

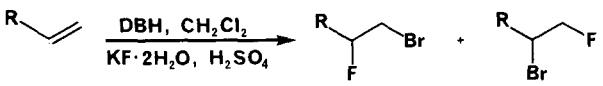
TABLE 1

Rate of Halofluorination of Allylbenzene (**1**) at 0°C and -23°C[a]

Time (min)	Yields (%) of indicated compound[b]					
	1		**2**		**3**	
	RT	-23°C	RT	-23°C	RT	-23°C
5	3.0%	19.8%	54.1%	45.1%	5.7%	4.1%
15	--	11.6	53.0	48.6	5.9	4.5
30	--	9.0	54.6	51.4	6.1	4.5

[a]Allylbenzene (1.0 eq.) was added to HF/pyridine (2.0 eq.) and NBS (1.2 eq.) in CH_2Cl_2. The reaction at -23°C was run in a CCl_4/CO_2 bath. (For further details, see Experimental Section.)
[b]The yields are based on allylbenzene.

A more complete solvent study was done using 1-hexene (**6**) (Scheme 2). Halofluorination is much more efficient in solvents



6, R = $(CH_2)_3CH_3$ **7**, R = $(CH_2)_3CH_3$ **8**, R = $(CH_2)_3CH_3$

9, R = CH_3 **10**, R = CH_3 **11**, R = CH_3

Scheme 2

that lack non-bonded electrons (aliphatic and aromatic hydrocarbon and chlorinated methane solvents), and within this class, the rates appear to correlate nicely with the solvent dielectric constant (Table 2). This is consistent with the development of charge in the transition state. Although starting material was consumed, no

halofluorination products were found in the reaction in tetrahydrofuran. Tetrahydrofuran has been used successfully in other examples of halofluorination [14].

TABLE 2

Bromofluorination of 1-Hexene (**6**) in Different Solvents

Solvent	Dielectric Constant	Yield of **7** and **8**[a]		
		3 min	10 min	60 min
Cyclohexane	2.20	0%	0%	9.9%
Carbon Tetrachloride	2.24	2.6	6.8	22.1
Benzene	2.27	24.7	47.7	60.0
Chloroform	4.81	46.6	70.6	79.9
Dichloromethane	8.93	84.7	86.2	86.5
Tetrahydrofuran	7.58	0	0	0
Acetonitrile	37.5	0	0	0

[a]The ratio of **7** to **8** is 9:1.

Fluoride Source, Acid, and Fluoride Stoichiometry

HF/pyridine is a convenient source of fluoride ion for halofluorinations conducted on macroscopic scales [13], since it is soluble, anhydrous and furnishes the highly acidic medium needed for interhalogen generation. Large quantities of high specific activity (ca. 50,000 Ci/mmol) fluorine-18 can be produced by charged particle bombardment of water targets (protons on O-18 enriched water, or helium-3 on normal water) [15], but the fluorine-18 thus produced is in the form of a dilute aqueous solution containing a variety of metal ions derived from the target, so that it must be dehydrated and an external source of acid provided before use in the halofluorination reaction.

Different metal fluoride salt/acid combinations can be used in halofluorination. With DBH and sulfuric acid, halofluorination proceeded rapidly and efficiently with either

potassium or cesium fluoride (both as the dihydrates); with silver fluoride, reaction was considerably slower. In contrast with the homogeneous reactions with HF/pyridine, these metal fluoride/acid reactions are heterogeneous in dichloromethane: the salt and acid form a separate, denser phase, that contains, presumably, HF and salts in a concentrated aqueous solution, and reaction rates are somewhat slower. The reaction is quite tolerant to water, proceeding equally well with KF-dihydrate or KF-dihydrate to which a third equivalent of water has been added.

The concentration of the acid catalyst also affects the rate of the reaction. With one equivalent of methanesulfonic or sulfuric acids relative to fluoride ion, the reaction of $KF \cdot 2H_2O$ and DBH with allylbenzene proceeds relatively slowly and does not go to completion, but with two equivalents, reaction is relatively rapid; higher concentrations of acid result in rapid consumption of olefin, but low yield of halofluorination products. The type of acid used is also important: Methanesulfonic acid is quite effective, but the stronger acids, sulfuric and trifluoromethanesulfonic acid, give more rapid reactions; the weaker acids, tetrabutylammonium bisulfate and p-toluenesulfonic and 10-camphorsulfonic acids are ineffective.

The effect of fluoride ion stoichiometry was studied: when 1 equivalent of allylbenzene and DBH are treated with one equivalent of $KF \cdot 2H_2O$ (and 2 equivalents of methanesulfonic acid), halofluorination proceeds to ca. 35% completion, whereas if only 0.1 and 0.2 equivalents of fluoride and acid, respectively, are used, the efficiency in terms of fluoride utilization rises to over 65%. This suggests that the halofluorination will be well suited for reactions with [^{18}F]fluoride ion, when only tracer levels of fluoride ion will be present.

Fluorine-18 Labeling of Allylbenzenes, 1-Hexene, and Propene

Allylbenzene, 1-hexene and propene have been labeled with fluorine-18 by halofluorination (Table 3). Reasonably good yields of bromo[^{18}F]fluorination of allylbenzene (**1**) are obtained, both with and without carrier-addition; the addition of

various hydroxide bases reduced the yield. The results with 1-hexene (**6**) and propene (**9**) (Table 3) indicate that bromofluorination can also be extended to the tracer level with these substrates. In a comparison of iodo[^{18}F]fluorination of 1-hexene (using NIS) with bromo[^{18}F]fluorination, the average yield with NIS at room temperature for 15 min is 15.2 ± 7.8% (n=5), compared to 21.2 ± 7.1% for bromo[^{18}F]fluorination.

TABLE 3

Bromo[^{18}F]fluorination of Allylbenzene (**1**), 1-Hexene (**6**) or Propene (**9**)[a]

Olefin	Carrier or Base (μmol)	Time (min)	Yield ± SD (%)	(n)[b]
1	KF (2)	9-12	31.8 ± 14.4	(6)
1	--	10-12	32.0 ± 8.8	(3)
1	KOH (2)	12	9.0	
1	n-Bu_4NOH (2)	9	10.8	
1	Cs_2CO_3 (2)	8	4.4	
1	RbOH (2)	10	8.2	
6	KF (2-5)	10	26.7 ± 12.8	(3)
6	KF (0.5-3.5)	20	21.2 ± 7.1	(8)
6	--	10	18.0 ± 5.7	(4)
9	KF (1)	20	21.2 ± 2.8	(3)

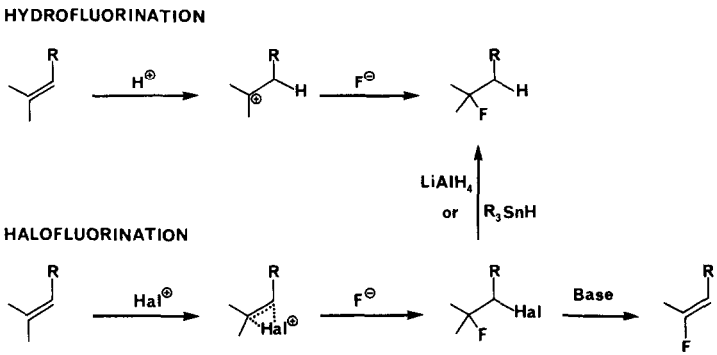
[a]Reactions were conducted with 0.03-2.5 mCi of [^{18}F]fluoride activity as described in the Experimental Section.
[b]Yields are based on initial F-18 activity (decay corrected) are given for individual reactions or as average yields are given for multiple reactions.

DISCUSSION

Halofluorination of olefins is a reaction with many characteristics that make it promising as an approach to labeling molecules with fluorine-18. It proceeds rapidly at room temperature and below in several solvents, and with different

sources of electrophilic halogen; fluoride can be furnished either as HF or as various metal fluorides with acid catalysts, and the reaction is remarkably tolerant of water - In fact, halofluorination proceeds in certain circumstances as a two-phase system, which indicates that BrF can form and then be extracted from an aqueous phase into the dichloromethane layer, where it reacts with the olefin. However, what is most significant is that the reaction remains efficient in fluoride ion even when the fluoride is present at substoichiometric levels (tracer quantities). Thus, halofluorination can be used under no-carrier conditions to produce compounds labeled with fluorine-18 at high specific activities, as is needed for receptor binding studies.

The availability of the olefin halofluorination reaction as a method for labeling molecules with fluorine-18 opens up a number of possibilities (Scheme 3), since the halofluorination product can be reduced (tin or aluminum hydride reagents) to give



Scheme 3

the fluoride product that would result from the Markovnikov addition of HF. However, the net HF addition by halofluorination-reduction can be done under much milder

conditions than direct hydrofluorination itself (see below). In addition, the halofluorination products can undergo elimination to vinyl fluorides, and they can be used as alkylating agents (D. Y. Chi and J. A. Katzenellenbogen, unpublished).

An interesting question is why halofluorination proceeds under much milder conditions than hydrofluorination [14]. Consideration of the relative hard-soft acid-base characteristics of the interacting species provides a possible explanation: In the halofluorination reaction, the olefin (a soft base) is being activated by a large halogen cation (a soft acid) towards reaction with fluoride ion (a hard base); this is a favorable situation for the desired reaction. In the hydrofluorination reaction, however, the activating species, the proton (a hard acid) prefers to interact with fluoride ion (a hard base) rather than with the olefin. Thus, the hydrofluorination reaction is impeded by the non-productive hard acid-hard base (proton-fluoride ion) interaction, whereas by substituting a soft acid (halogen) for the proton, this unfavorable interaction is avoided in halofluorination.

We anticipate that halofluorination will prove to be useful in labeling a wide variety of molecules with fluorine-18.

EXPERIMENTAL

Methods. Analytical gas-liquid chromatography was performed in a Hewlett-Packard 5750B Gas-Liquid Chromatograph equipped with a flame ionization detector using hydrogen as carrier gas and fused silica capillary columns: 1) 12.5 meter x 0.25 mm, 2) 30 meter x 0.25 mm, coated with cross-linked methyl silicone. The chromatograms were recorded with Hewlett-Packard 3390A integrator and were quantitated with appropriate hydrocarbons as internal standards. Column chromatography was done by flash chromatography with Woelm 32-63 micron silica gel [16]. High-performance liquid chromatography (HPLC) was performed on a 30 cm x 4 mm C18 column (Varian MCH-10 Micro Pak).

^1H NMR spectra were obtained on Varian EM-390, Varian XL-200, and Nicolet NT-360 spectrometers and are reported in parts per million downfield from internal tetramethylsilane. ^{19}F NMR spectra were obtained on Varian EM-390 spectrometer at 84.6 MHz and Nicolet NT-360 at 338 MHz and are reported in parts per million from internal $CFCl_3$. Mass spectra were obtained on Finnigan MAT CH5 and MAT 731 spectrometers for low and high resolution spectra. Elemental analyses were performed by the Microanalytical Service, School of Chemical Sciences, University of Illinois. Radioactivity was determined in a sodium iodide well counter or in a dose calibrator.

General Procedures for Halofluorination

Method A. A polyethylene container was charged with an N-halocompound and solvent. HF/pyridine was added with a polyethylene autopipette. After addition of the olefin and n-dodecane as an internal standard, timed aliquots were analyzed by GLC. To purify the products, the reaction was quenched with a saturated $NaHCO_3$ solution, and then extracted with ether. The organic phase was washed with 1 M $CuSO_4$ and brine, and then dried (Na_2SO_4). The solvent was removed *in vacuo*; the residue was further purified by chromatography and/or distillation.

Method B. A polyethylene container was charged with N-halocompound, metal fluoride, and acid in CH_2Cl_2. Then, the olefin and n-dodecane were added into the reactor. The other procedures are the same as in Method A.

1-Bromo-2-fluoro-3-phenylpropane (**2**) and 2-Bromo-1-fluoro-3-phenylpropane (**3**). Using Method A, allylbenzene **1** (1.0 g, 8.46 mmol) was converted to the products **2** and **3**. HF/pyridine was used in ca. thirty five-fold excess. The products were obtained as a colorless oil by bulb-to-bulb distillation (1.35 g, 74%) and characterized as the mixture except by GCMS. The ratio of **2** to **3** was 7:1 by GLC: NMR (90 MHz, $CDCl_3$) **2**: δ 3.03 (dd, 2, J = 20, 6 Hz, CH_2), 3.38 (dd, 2, J = 20, 5 Hz, CH_2Br), 4.78 (dquin, 1, J = 46, 6 Hz, CHF), 7.23 (s, 5, aromatic); ^{19}F NMR (84.6 MHz, CCl_4) **2**: ϕ -171.9 (dtt, J = 45, 20 , 18 Hz); IR (neat) 2900 (CH), 1620

cm^{-1}; GCMS (70 eV), m/z (rel intensity) **2**: 218 (11, M^+), 216 (11, M^+), 115 (9), 91 (100). **3**: 218 (44, M^+), 216 (45, M^+), 137 (27), 115 (23), 91 (100). Anal. Calcd for $C_9H_{10}BrF$: C, 49.80; H, 4.64; F, 8.75. Found: C, 49.67; H, 4.69; F, 8.79.

1-Bromo-2-fluorohexane (**7**) and 2-Bromo-1-fluorohexane (**8**). Using Method A, 1-hexene (1.79 g, 21.2 mmol) was converted to the products **7** and **8**. A quantity of HF/pyridine equivalent to 1-hexene was used. The products were obtained as a colorless oil by bulb-to-bulb distillation (1.72 g, 44.3%). The ratio of **7** to **8** was 9:1 by GLC; NMR (90 MHz, $CDCl_3$) **7**: δ 0.90 (br t, 3, J = 5 Hz, CH_3), 1.2-1.7 (m, 4, C_4H and C_5H), 1.7-2.2 (m, 2, C_3H), 3.40 (dd, 2, J = 19.5, 5 Hz, CH_2Br), 4.56 (dquin, 1, J = 47, 5 Hz, CHF); mass spectrum (70 eV), m/z (rel intensity) 184 (4.08, M^+), 182 (4.03, M^+), 155 (100), 153 (100). Anal. Calcd for $C_6H_{12}BrF$: C, 39.37; H, 6.61; Br, 43.65. Found: C, 39.62; H, 6.66; Br, 43.43.

1-Bromo-2-fluoropropane (**10**). Because of its volatility the separation of the pure product **10** even from a solvent as volatile as CH_2Cl_2 is very difficult. We have overcome this problem by using excess propene (bp -48°C) as solvent. To a 100 mL 2-necked round-bottom flask with a dry ice reflux condenser and gas inlet was added 1,3-dibromo-5,5-dimethylhydantoin (DBH, 10 g, 35 mmol). The flask was cooled to -78°C, and a steady stream of propene (**9**) was fed into the flask until about 20 mL of liquid had condensed. HF/pyridine (2.5 mL, 70 mmol) was added at -78°C, and the mixture was kept at this temperature for 10 min and then allowed to warm to room temperature by removal of the cooling bath. Removal of excess propene left a residue which was distillated *in vacuo* to provide a colorless liquid **10** (4.2 g, 29.8 mmol, 42.4% (based on fluoride)) in a -78°C trap; NMR (200 MHz, $CDCl_3$) δ 1.45 (dd, 3, J = 23.6, 6 Hz, CH_3), 3.45 (dd, 2, J = 18.4, 5.5 Hz, CH_2), 4.82 (dsextet, 1, J = 47.6, 6 Hz, CHF); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ -170.89 (dtq, 1, J = 47.1, 18.6, 23.7 Hz); mass spectrum (70 eV), m/z (rel intensity) 142 (17.48, M^+), 140 (19.44, M^+), 127 (3.77), 125 (4.01), 61 (100), 47 (77.73). Anal. (exact mass, HR-EIMS) Calcd for C_3H_6BrF: 139.9636688. Found: 139.9636688.

Preparation of [^{18}F]Fluoride. Fluorine-18 was prepared from [^{18}O]H_2O by the [$^{18}O(p,n)^{18}F$] reaction in a metal target [15]. The indicated quantity of radioactivity thus produced was combined with or without carrier KF or base and then taken to dryness under a stream of dry nitrogen at 70°C in a polyethylene vial. The residue was further dried by azeotropic distillation using 200 µL of CH_3CN. The entire procedure takes about 10 min, and approximately 90-95% of the dried activity remains in the vessel.

General Procedure for Bromo[^{18}F]fluorination. [^{18}F]Fluoride activity (0.03-2.5 mCi) in water (50-200 µL) in a polyethylene reaction tube was evaporated to dryness at 70°C under a gentle stream of nitrogen (after the addition of the indicated quantity of carrier or base). DBH (25-50 µmol), 200-500 µL CH_2Cl_2, 10 µmol H_2SO_4 were added followed by 50-100 µmol of olefin. (Propene was added in two different ways; 1) bubbling propene through the solution at room temperature for 1 min, 2) trapping propene at -78°C, then removal of cooling bath.) After the reactions were stirred for the indicated times at room temperature, products were isolated in two ways: (a) Extraction - the reaction was quenched by the addition of 1-2 mL water, and the halofluorination products were extracted into two of 1 mL ether, which was dried by passage through a column of Na_2SO_4, (b) Column chromatography - the reaction mixture was transferred to a column of silica gel (3.0 x 0.4 cm) which was washed with an additional 1-2 mL of CH_2Cl_2 to elute the halofluorination products.

1-Bromo-2-[^{18}F]fluoro-3-phenylpropane ([^{18}F]**2**). [^{18}F]Fluoride (0.03-2.5 mCi) DBH (14.3 mg, 50 µmol), CH_2Cl_2 (200 µL), H_2SO_4 (0.53 µL, 10 µmol; in 2 µL of CH_3CN or neat), and allylbenzene (13 µL, 100 µmol) were allowed to react for 8-23 min. Yields are given in Table 3. One radioactive peak was obtained by HPLC (Varian MCH-10, 45:55 CH_3CN:H_2O(0.05% Et_2NH), 1 mL/min, t_R = 11.5 min).

1-Bromo-2-[^{18}F]fluorohexane ([^{18}F]**7**). [^{18}F]Fluoride (0.15-2.5 mCi) with 0.5-5 μmol KF or without carrier, DBH (7 mg, 25 μmol), CH_2Cl_2 (500 μL), H_2SO_4 (0.53 μL, 10 μmol, neat), and 1-hexene (7 μL, 50 μmol), were allowed to react for 10-20 min. Yields are given in Table 3. One radioactive peak was obtained by HPLC (Varian MCH-10, 45:55 CH_3CN:H_2O (0.05% Et_2NH), 1 mL/min, t_R = 13 min).

1-Bromo-2-[^{18}F]fluoropropane ([^{18}F]**10**). [^{18}F]Fluoride (0.3-0.8 mCi with 1 μmol KF), DBH (7 mg, 25 μmol), CH_2Cl_2 (500 μL), H_2SO_4 (0.53 μL, 10 μmol, neat), and propene (added by either bubbling through the solution at room temperature for 1 min or by trapping at -78°C for 1 min then removal of cooling bath), were allowed to react for 20 min. Yields are given in Table 3. One radioactive peak was obtained by HPLC (Varian MCH-10, 45:55 CH_3CN:H_2O(0.05% Et_2NH), 1 mL/min, t_R = 5.7 min).

1-Iodo-2-[^{18}F]fluorohexane. [^{18}F]Fluoride (0.3-54 mCi with 0.05 μmol KF), NIS (10 mg, 44 μmol), CH_2Cl_2 (400 μL), H_2SO_4 (0.53 μL, 10 μmol, neat), and 1-hexene (7 μL, 50 μmol) were allowed to react for 15 min. The average incorporation yield of five reactions, determined by column chromatography, was 15.2 ± 7.8%.

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