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FLUORINATION OF AROMATIC COMPOUNDS WITH F_2 AND ACETYL HYPOFLUORITE: SYNTHESIS OF ^{18}F-ARYL FLUORIDES BY CLEAVAGE OF ARYL-TIN BONDS [1]

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SUMMARY

Elemental fluorine and acetyl hypofluorite, labeled with ^{18}F, were added to eight simple aryl-tin derivatives. Both reagents gave good radiochemical yields of labeled aryl fluorides. Overall, acetyl hypofluorite gave more consistent yields (~70%), while F_2 gave more variable yields (54% - >95%).

INTRODUCTION

The labeling of aromatic compounds with radioactive ^{18}F ($T_{1/2}$ = 110 min), for use in positron emission tomography (PET) [2], places several stringent requirements on the chemistry. The reaction must be rapid, it must use a form of fluorine which can be labeled with ^{18}F, and it must be efficient in its use of that radioactive fluorine.

Several methods exist for the synthesis of ^{18}F-labeled aryl-fluorides. These include the Balz Schiemann reaction [3], the triazene decomposition method [4], the direct fluorination with xenon difluoride [5], and the nucleophilic displacement of a fluorine or nitro group by fluoride ions [6,7]. Although some of these methods are quite successful in certain applications they all have serious limitations. Hence, the continued development of aromatic fluorination methods is needed.

There is ample precedent in the literature for cleavage of aryl-tin bonds by electrophilic reagents such as halogens (Cl_2, Br_2, and I_2) [8].

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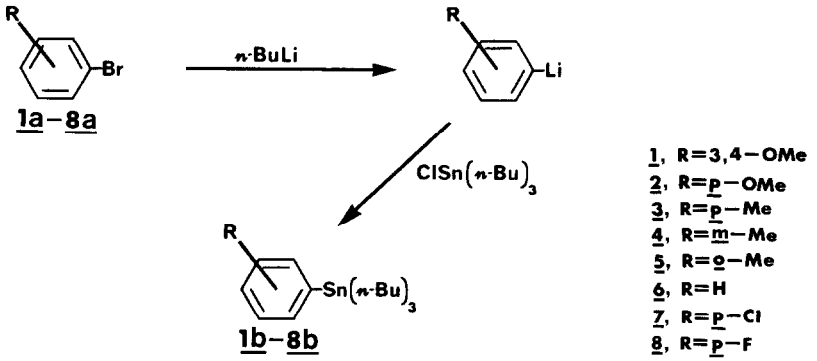
However, prior to our own work [1,9], there were no reports of the cleavage of these bonds with elemental fluorine or other electrophilic fluorinating agents.

Acetyl hypofluorite is a recently developed electrophilic fluorinating agent [10,11]. Its potential utility comes from its mild chemical nature, in comparison to F_2. We therefore thought it might be interesting to compare these two agents for the fluorination of aromatic compounds via carbon-tin bond cleavage. It has been shown that acetyl hypofluorite is conveniently labeled with ^{18}F starting from $^{18}F\text{-}F_2$ [12].

RESULTS AND DISCUSSION

Simple addition of elemental fluorine to aromatic nuclei is rare because the reaction is usually accompanied by unselective, partial or total replacement of hydrogen [13,14]. On the other hand, direct fluorination with acetyl hypofluorite is more successful. However, acetyl hypofluorite only fluorinates activated ring systems and also produces mixtures of isomers [11]. By attaching the tri-n-butyltin moiety to one position on the ring, via a transmetallation reaction, one can achieve an enhanced reactivity, and site selectivity towards electrophilic fluorination, even on deactivated systems. Thus, eight substituted aromatic compounds (1a-8a) were metallated (scheme 1), via lithium halogen exchange with n-BuLi and were subsequently transmetallated using tri-n-butyltin chloride to form the stannylated compounds 1b-8b.



Scheme 1

TABLE 1

Synthesis of aryl-tin compounds 1b-8b

Compounds	M.W.	m/e ^{118}Sn, ^{120}Sn †	GLC* r.t.(min)	Yield %**	Elem. Anal (calc.) found	Ref.+
1b	427.19	426, 428	25.41	67	(C 56.28, H 8.49) C55.34, H 8.49	
2b	397.17	396, 398	14.78	55	(C 57.46, H 8.62) C 57.81, H 9.14	15
3b	381.17	380, 382	8.37	62	(C 59.87, H 8.99) C 59.20, H 9.10	15
4b	381.17	380, 382	7.84	65	(C 59.87, H 8.99) C 59.75, H 9.16	
5b	381.17	380, 382	8.41	50	(C 59.87, H 8.99) C 59.27, H 9.22	15
6b	367.09	366, 368	5.92	69	(C 58.88, H 8.78) C 59.27, H 9.22	17
7b	401.56	$^{118}Sn^{35}Cl$ 400 $^{118}Sn^{37}Cl$ 402 $^{120}SN^{35}Cl$ 402 $^{120}Sn^{37}Cl$ 404	12.50	61	(C 53.84, H 7.78) C 53.57, H 7.73	15,16
8b	385.13	384, 386	5.93	43	(C 56.14, H 8.11) C 56.42, H 8.09	16

†Only the most abundant isotopes of tin (^{118}Sn, ^{120}Sn) are included. Mass peaks corresponding to the other natural isotopes of tin were also seen in the proper intensity ratios.

*See experimental for column type and conditions.

**Yields are not optimised and are for first time preparations only.

+For a general review of organotin compounds see ref. [8].

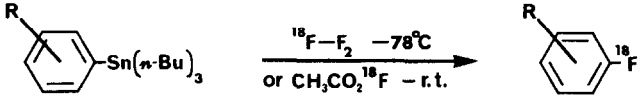
Most of these aromatic tin compounds have been reported before [15-18]. However, for convenience, we have included the analytical and spectroscopic data for compounds 1b-8b in Table 1 and a general procedure for their preparation in the experimental section. Good elemental analysis was difficult to obtain for some of these compounds (1b, 3b and 5b). Additional distillations did not improve their analysis. However, mass spectral and nmr data were consistent with the expected structures.

TABLE 2

Cleavage of compounds 1b-8b with $^{18}F\text{-}F_2$ *or* $CH_3COO^{18}F$

Product	r.c. yields %	
	F_2	CH_3COOF
1c	56	68
2c	72	78
3c	82	72
4c	58	71
5c	54	57
6c	72	72
7c	>95	68
8c	>95	73

Compounds 1b-8b were treated with $^{18}F\text{-}F_2$ at -78°C and $CH_3COO^{18}F$ at room temperature (Scheme 2). The radiochemical yields shown in Table 2 were, in each case, based on the total electrophilic ^{18}F activity and are decay corrected. The conversion efficiency of F_2 to CH_3COOF is about 80%. In both cases only 50% of the original $^{18}F\text{-}F_2$ is available for the reactions since one of the F_2 fluorine atoms is either lost as tri-n-butyltin fluoride when using F_2, or as ammonium fluoride when using the hypofluorite.



Scheme 2

Fluorinated products 1c-8c were identified by physical methods (GC/HPLC) by comparison to authentic samples.

Typical radio-HPLC chromatograms of crude reaction mixtures resulting from the treatment of one of these tin substrates (8c), with both $^{18}F\text{-}F_2$ and $CH_3COO^{18}F$, are shown in figure 1. In most cases, (2c,3c,6c,7c,8c) the F_2 reactions resulted in a cleaner product. However, for compounds 1c, and 4c, F_2 gave a poorer radiochemical purity than did acetyl hypofluorite. The major impurities (unidentified), in both the F_2 and hypofluorite reactions, elute just before the product. The ortho-toluene product (5c) is produced in the lowest yield regardless of which fluorinating agent is used.

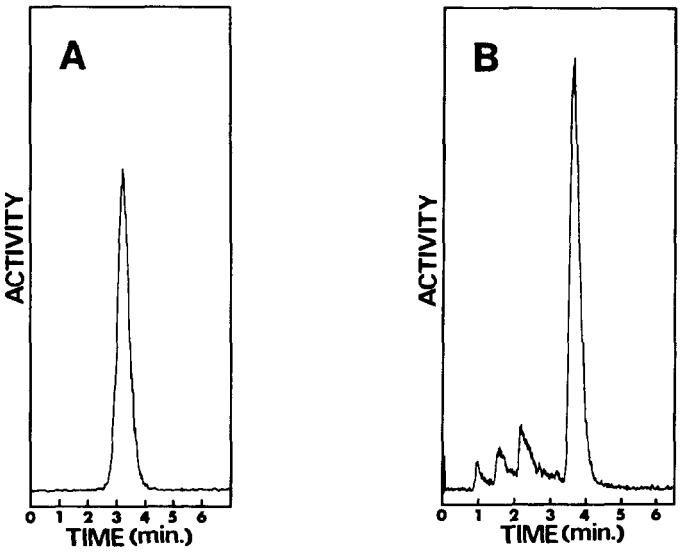


Fig. 1. Radio-HPLC chromatograms of crude reaction mixtures for compound 8c. A: reaction of $^{18}F\text{-}F_2$ with 8b; B: reaction of $CH_3COO^{18}F$ with 8b.

Overall, acetyl hypofluorite gives more consistent yields (~70%), while F_2 gives a wider range of product yields (54%->95%). At this time, we are uncertain as to what factors are influencing the yields in these reactions. Although F_2 is an excellent fluorinating agent with some of these substrates (3b,7b,8b), its high reactivity may adversely affect reactions with aryl-tin compounds containing more complex functionalities. In these cases acetyl hypofluorite may be the preferred fluorinating reagent.

In the present study, we have found acetyl hypofluorite to be more convenient than elemental fluorine since it can be produced readily from F_2 at room temperature and may be added to either the neat substrate or to a solution of the substrate dissolved in a variety of solvents. Hence, its stoichiometry is more easily controlled. In comparison, when F_2 is used, the substrate must be dissolved in the solvent that the fluorine passes through and generally these reactions must be performed at low temperatures. Only a few solvents such as Freon-11 ($CFCl_3$) are stable to treatment with F_2.

EXPERIMENTAL

General remarks

Fluorine gas (1% in research grade neon) and Freon-11 ($CFCl_3$) were purchased from Matheson Co., (Edmonton, Alberta) and were used without further treatment. Glacial acetic acid and ammonium acetate were purchased from Fisher Scientific Ltd. (Vancouver, B.C.) and were used as received. HPLC solvents were purchased from Fisher Scientific Ltd.

Radio-HPLC analyses were achieved with a Waters system (Waters Associates, Inc., Milford, MA) using a C-18 Radial-PAK column with a THF/H_2O (60:40) eluant and UV detection at 254 nm. Gamma radiation was detected using a NaI (Tl) scintillation detector system.

Fluorine gas must be handled with care [18]. For this reason we constructed a stainless steel manifold as shown in ref. [9]. Only stainless steel, teflon and glass components were used in the fluorination system.

The gas target system for the preparation of ^{18}F-F_2 will be described in detail elsewhere. Briefly, the target is essentially a nickel, gas tight cylinder which is bombarded with a 42 MeV proton beam from a CP-42 cyclotron (The Cyclotron Corp. CA) at TRIUMF.

Gas chromatographic analyses were carried out with a Hewlett-Packard 5840A gas chromatograph, equipped with an FID detector using 6'x 1/8" stainless steel columns packed with either 10% SP-1000 on 80-100 mesh Supelcoport (Supelco-Inc., Bellefonte, PA), for the aryl fluoride products, or 5% OV-101 on 100-120 mesh Chromasorb-(W)HP (Western Chromatography, Vancouver, B.C.), for the aromatic tin compounds.

Preparation of aryl-tin substrates 1b-8b (general procedure)

The starting bromo aromatic compounds or iodo in the case of the anisole derivative (5g), were dissolved in dry ether and added dropwise to a stirred equimolar solution of n-BuLi in ether (25 ml) at -78°C. A milky suspension usually resulted after addition. After 30 min, an equimolor amount of n-butyltin chloride dissolved in ether (20 ml) was added and the mixture was allowed to warm to room temperature for 1-2h. The mixture was washed with water and the ether extract was mixed with KF (1g in 10ml of ethanol) and stirred for a few minutes to remove any of the remaining $ClSn(Bu)_3$. The mixture was washed with water and the ether layer dried over $MgSO_4$. After filtration the solution was evaporated and the product distilled on a Kuglerohr distillation apparatus (110-145°C, at 0.1 torr).

Flucrination of aryl-tin substrates with $^{18}F\text{-}F_2$ (general procedure)

Each of the tin compounds 1b-8b(100μmol) was dissolved in Freon-11 ($CFCl_3$) (20ml) and cooled to -78°C in a long narrow glass reaction vessel (1cm x 20cm). During the initial cooling, helium gas is passed through the mixture. Approximately 60μmol of $^{18}F\text{-}F_2$ gas (1-5mCi) was passed into the solution through a 1/16" O.D. teflon tube at a flow rate of ~50 ml/min. After the addition was complete, helium gas was passed through the solution to remove any unreacted F_2 gas. The contents were emptied into a receiver flask for radioactive assay. An overflow-exhaust trap of KI/H_2O was also

measured to determine the amount of $^{18}F\text{-}F_2$ that was not absorbed in the reaction. A small quantity of the reaction mixture was then analysed by HPLC and the activity distribution determined. The product peak was collected, measured for radioactivity and the result compared to that for the original sample activity. The radiochemical yields were calculated by determining the amount of activity in the product fraction as a percentage of the total available, initial ^{18}F activity. Less than 0.1% of the total activity was found in the KI exhaust traps.

Fluorination of aryl-tin substrates with $CH_3COO^{18}F$ (general procedure)

Acetyl hypofluorite was prepared by a modification of the procedure developed for small scale ^{18}F work by Shiue et. al.[12].

^{18}F-F_2(0.1% in Ne, 60 μmol) gas was bubbled through a solution of glacial acetic acid (15 ml) and NH_4OAc (35 mg) in a long narrow glass vessel. The gas was passed from the bottom through a specially designed teflon frit to provide good mixing. After the addition of F_2 was complete the hypofluorite was transferred, via a 1/16" teflon tube, into a vial containing the tin substrate (100 μmol) (1b-8b) dissolved in Freon-11 (1 ml). The reaction mixtures were subject to radioassay and an aliquot was removed for analysis by HPLC. The injected samples were treated in the same manner as described for the reactions with F_2.

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