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On the reaction of 4-substituted trimethyltin aromatics with perchlorylfluoride

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Abstract

To evaluate the suitability of [^{18}F]perchorylfluoride [^{18}F]$FClO_3$ as an electrophilic fluorination agent for the preparation of radiopharmaceuticals, the reactivity non-radioactive $FClO_3$ towards 4-substituted trimethyltin aromatic compounds was studied. Contrary to the expectation, an electrophilic fluorination of the aromatic nucleus did not occur. The reaction of perchlorylfluoride with aromatic trimethylstannyl compounds resulted in the formation of trimethyltin fluoride and the respective destannylated aromatics in variable yields.

Keywords: Aryl stannanes; Perchlorylfluoride; Fluorination; Electrophilic substitution

1. Introduction

Trialkyltin substituted aromatic compounds are versatile precursors for a variety of electrophilic substitution reactions in particular for radiochemical syntheses. The destannylation procedure has been used as a routine method for many years to label specific molecules with radioactive nuclides such as $^{123/131}$I, very recently summarized in [1], ^{18}F [2] and ^{211}At [3]. Numerous precursors are commercially available as trimethyltin or tributyltin aromatics for such applications. Due to their high regioselectivity, (radio)fluorodemetallation reactions are a very efficient method to obtain fluorinated substances and ^{18}F labelled radioligands in good (radiochemical) yields [4], for instance to synthesize 6-[^{18}F]fluoro-L-DOPA [5].

Tracer compounds radiolabelled with the positron emitter fluorine-18 play a pivotal role in functional molecular imaging with positron emission tomography (PET) and thus, ^{18}F labelled compounds are important for non invasive medical diagnostics and biomedical research with PET. Radiolabelling methods starting with [^{18}F]F_2 and the derived electrophilic fluorinating agents (EFAs) have two major disadvantages: (1) The radiochemical yield is ab initio limited to 50%. (2) The radiotracer is diluted by high amounts of isotopic carrier compound ^{19}F (carrier added, c.a.). The importance of n.c.a. (no carrier added) ^{18}F-labelled EFAs is based on the need for radiolabelling nucleophilic moieties of molecules.

Perchlorylfluoride ($FClO_3$) is a mild and selective gaseous EFA [6,7], which has been previously applied for fluorination of various organic substances [8,9]. It was later replaced by more reactive and more easily to handle EFAs such as acetyl hypofluorite (AcOF) and Selectfluor™ [10]. For the synthesis of radiofluorinated EFAs, [^{18}F]$FClO_3$ was identified as the only substance within the scope of our search, which can be generated in principle on an n.c.a. level starting from [^{18}F]fluoride [11]. [^{18}F]fluoride is produced in a cyclotron by proton irradiation of ^{18}O-enriched water and is obtained as aqueous solution with high specific activity.

Ehrenkaufer and MacGregor [12] reported the synthesis of ^{18}F labelled aryl fluorides by the reaction of substituted aryl lithiums with [^{18}F]$FClO_3$, the latter obtained however from [^{18}F]F_2 with $KClO_3$. First experiments in our laboratory to synthesize [^{18}F]$FClO_3$ starting from n.c.a. [^{18}F]fluoride were successful. [^{18}F]$FClO_3$ therefore should be a potential candidate for an n.c.a. [^{18}F]EFA. Coenen and

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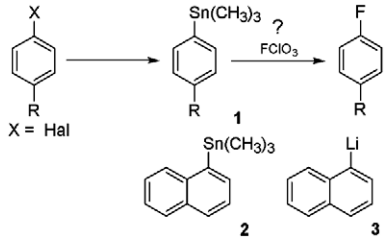
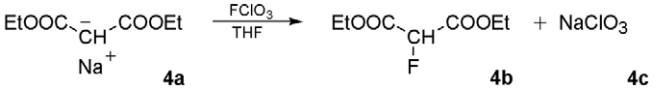
Moerlein [2] investigated the reactions of ^{18}F labelled fluorine and acetyl hypofluorite based on $[^{18}F]F_2$ (see above) with a series of 4-substituted trimethyltin aromatics and found this approach to be a promising preparative radiolabelling method. This encouraged us to study the reactivity of non-radioactive $FClO_3$ on 4-substituted aromatic trimethyltin compounds (**1**) for possible radiochemical applications to prepare n.c.a. ^{18}F labelled radiotracers. Compounds **1**, which comprise both electron deficient and electron rich aromatic systems (see Table 1) were used as model substrates expecting an $SnMe_3$ for F exchange (Scheme 1) and an increasing sensitivity to an electrophilic attack in this direction. For comparison, trimethyl-naphthalen-1-yl-stannane (**2**), naphthalen-1-yl-lithium (**3**), and sodium diethyl malonate (**4a**, see Scheme 2) were included in this study.



Scheme 1.



Scheme 2.

2. Results and discussion

All experiments were performed in micro scale with the main goal to identify fluorinated products.

2.1. Preparation of aromatic trimethyltin compounds

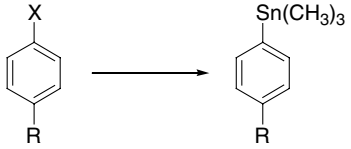
The precursor compounds were prepared as shown in Table 1 mainly referring to procedures reported in the literature. The reaction of an aromatic iodine compound with hexamethyl-distannane (Sn_2Me_6) in the presence of tetrakis(triphenylphosphine)palladium(0) $[Pd(PPh_3)_4]$ as catalyst proved to be the best synthetic approach for the trimethyltin precursors in most cases. Compound **1b** is cited without detailed description [13b]. Both the reaction of (4-bromo-phenyl)-carbamic acid *tert*-butyl ester with *n*-BuLi in THF and trimethyltin chloride and the Pd-catalyzed reaction of the corresponding iodine derivative with hexamethyltin afforded **1b** in good yields.

All trimethyltin aromatic compounds were characterized by ^1H NMR spectra.

2.2. Reactions with perchlorylfluoride

$FClO_3$ was obtained by the reaction of $KClO_4$ with fluorosulfonic acid at elevated temperature [9]. Two methods for the reaction of the trimethyltin compound with $FClO_3$ were used. Method A: addition of $FClO_3$ at about −60 °C followed by gradual warming to 60 °C in a closed vial ("closed system"), method B: introduction of $FClO_3$ at about 0 °C, further reaction at room temperature and at about 60 °C in an open vessel ("open conditions"). The reactions were monitored at various temperatures by

Table 1
Synthesis scheme of 4-substituted aromatic trimethyltin compounds and trimethyl-naphthalen-1-yl-stannane (**2**)



Entry	Starting compound		Method	Separation/purification	Yield (%)	Reference
	X	R				
1a	Iodo	NO_2	A	Recryst., CC PE/EtOAc 3:1	70	[13a]
1b	Bromo	NHBoc	C	CC PE/EtOAc 10:1	81	–
	Iodo		B	CC PE/DEE 5:1	81	–
1c	Bromo	OCH_3	C	CC PE/DEE 3:1	70	[13c, modified]
	Iodo		B	CC PE/EtOAc 10:1	85	[13d]
1d	Bromo	NH_2	B	CC PE/EtOAc 4:1	46[a]	[13e, modified]
1e	Bromo	$N(CH_3)_2$	D	CC PE/EtOAc 10:1	42[a]	[13f]
2	Bromo	Naphthyl	C	Crude product	88[b]	[13g, modified]; [14]

Method. A: Sn_2Me_6; π-allyl $PdCl_2$; B: Sn_2Me_6, $[Pd(PPh_3)_4]$; C: *n*-BuLi, Me_3SnCl; D: Li, Me_3SnCl CC: column chromatography silica gel 60; PE: petroleum ether; EtOAc: ethyl acetate; DEE: diethyl ether.

[a] Tends to decompose (destannylate) upon column chromatography complicating the separation of pure product.

[b] Contains ~8% naphthalene judged by ^1H NMR analysis, TLC: not distinguishable.