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A versatile synthesis of triarylantimony difluorides by fluorination of triarylstibanes with nitrosyl tetrafluoroborate and their antitumor activity

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ABSTRACT

Triarylantimony difluorides were synthesized in moderate to excellent yields by oxidative fluorination of triarylstibanes with nitrosyl tetrafluoroborate ($NOBF_4$) under aerobic conditions. This reaction is the first example of fluorination of trivalent organoantimony compounds using $NOBF_4$ as a fluorinating agent. The triarylantimony difluorides exhibited good anti-proliferation activity against tumor cell lines. In particular, the IC_{50} of *p*-Tol_3SbF_2 (**2c**) was the lowest in each cell lines.

1. Introduction

Organoantimony compounds have attracted much interest because of their use as important reagents in organic synthesis and their potential biological activities [1–4]. Among these, triarylantimony difluorides are used as precursors of pentavalent organoantimony compounds in main-group element chemistry [5–7]. These triarylantimony difluorides have been typically synthesized by fluorination of organoantimony compounds [5,7–19]. Oxidative fluorination of triarylstibanes is a straightforward strategy and has been widely conducted using fluorinating reagents such as HF/*t*BuOOH [15], IF_5 [16], F_2 [17], Et_2NSF_3 [7], methyl 3-azidotetrafluoropropionate ($N_3CF_2CF_2CO_2Me$) [18], and triphenylbismuth difluoride (Ph_3BiF_2) [19]. However, most of these fluorinating reagents are difficult to handle and can cause glass corrosion. In 2012 Fuchigami et al. reported a single example of electrochemical fluorination of triphenylstibane (0.1 mmol scale) using KF as an inexpensive and less glass-corrosive reagent in the presence of poly(ethylene glycol) [14]. However, substrate scope and scalability of this reaction remain unclear. On the other hand, tetrafluoroborates (e.g., $HBF_4{\cdot}OEt_2$, $NOBF_4$, and Bu_4NBF_4) and boron trifluoride (e.g., $BF_3{\cdot}OEt_2$) act as nucleophilic fluorinating reagents that are easy to handle and do not cause glass corrosion [20]. For example, they are used in the fluorination of aliphatic cyanoazides [21,22], and α-diazo-β-keto esters [23,24] and in the ring-opening fluorination of epoxides [25]. To the best of our knowledge, the synthesis of triarylantimony difluorides by the reaction of triarylstibanes with tetrafluoroborate has not hitherto been reported.

We have recently reported the synthesis and biological activity of organoantimony compounds [26–30]. Among these, 1-[(2-di-*p*-tolylstibanophenyl)diazenyl]pyrrolidine [28] and 2-(di-*p*-tolylstibano)-*N*-*p*-tolylbenzamide [29] showed potent anti-proliferative activity against human tumor cell lines such as NB_4, HeLa, L1210, Mm1, and DLD-1. Moreover, tris(pentafluorophenyl)stibane induced gene expression of metallothionein (MT)-1A and -2A, which are the subisoforms of MT in bovine aortic endothelial cells [30]. This knowledge shows that organoantimony compounds with fluorine atoms possibly show potent biological activity. As a continuation of our previous studies, we now report a versatile synthesis of triarylantimony difluorides by the fluorination of triarylstibanes with nitrosyl tetrafluoroborate ($NOBF_4$) and their antitumor activity.

2. Results and discussion

2.1. Synthesis of triarylantimony difluorides

We initially determined the optimum conditions for the fluorination of triphenylstibane (**1a**) with fluorine reagents such as tetrafluoroborate and boron trifluoride. The results of the search for active agents and the optimum amount of fluorine reagents for the reaction are summarized in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC), and the reaction time was determined when **1a** disappeared on TLC. First, we performed the reaction of

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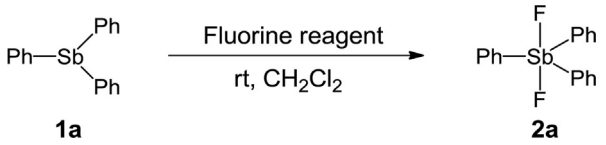
Table 1
Reaction of triphenylstibane **1a** with fluorine reagents.[a]



1a **2a**

Entry	Reagent (eq)	Time (h)	Yield (%)[b]	
			2a	Recovery
1	$HBF_4{\cdot}Et_2O$ (2)	24	4	92
2	$Bu_4N{\cdot}BF_4$ (2)	24	0	96
3	$NOBF_4$ (2)	3	84	0
4	NO_2BF_4 (2)	4	67	0
5	IPy_2BF_4 (2)	24	60	0
6	Cp_2FeBF_4 (2)	24	2	91
7	$NaBF_4$ (2)	24	0	98
8	NH_4BF_4 (2)	24	0	97
9	Et_3OBF_4 (2)	24	0	97
10	Et_2OBF_3 (2)	24	2	95
11	TBAF (2)	24	0	98
12	$NOBF_4$ (0.5)	24	22	69
13	$NOBF_4$ (1.0)	24	49	39
14	$NOBF_4$ (3)	3	50	0
15[c]	$NOBF_4$ (2)	4	88	0

[a] Conditions: **1a** (0.5 mmol), CH_2Cl_2 (3 mL), rt, under air.
[b] Isolated yield.
[c] **1a** (10 mmol), CH_2Cl_2 (60 mL).

1a with a variety of fluorine agents (2 eq) to compare their reactivity in CH_2Cl_2 at room temperature under aerobic conditions (entries 1–11). Among these reagents, $NOBF_4$, NO_2BF_4, and IPy_2BF_4 afforded the expected triphenylantimony difluoride (**2a**) in good to high yields (entries 3–5). $NOBF_4$ appeared to be the best reagent for this reaction in terms of the yield (84%) of the fluorinated product (**2a**) and reaction time (3 h) (entry 3). Next, the optimum amount of fluorine reagent was determined by the reaction of **1a** with $NOBF_4$ (entries 3, 12–14). The best result was observed in the reaction of **1a** with $NOBF_4$ in the ratio 1:2 (entry 3). It seems that one of the four fluorine atoms on the B atom in $NOBF_4$ was involved in the antimony–fluorine bond formation. Moreover, an excess amount of $NOBF_4$ seems to injure the product (entry 14). Screening of solvent showed that the reaction proceeded effectively in CH_2Cl_2 (84%), toluene (71%), and CH_3CN (59%). Other solvents such as tetrahydrofuran and MeOH could not be used because of the poor solubility and low stability of $NOBF_4$. Consequently, the best result was obtained when **1a** was treated with $NOBF_4$ (2 eq) in CH_2Cl_2 at room temperature. This reaction could also be scaled up to 10 mmol and the desired product **2a** was obtained in excellent yields of up to 88%, i. e., 3.44 g of the product could be generated (entry 15).

To demonstrate the efficiency and generality of the abovementioned protocol, the reactions of various Ar_3Sb (**1b–m**) and $NOBF_4$ were investigated under the optimized conditions. The results are shown in Table 2. The yields of Ar_3SbF_2 were sensitive to the electronic nature of the substituents on the phenyl rings. The Ar_3Sb with electron-withdrawing groups (**1d–i**) were fluorinated smoothly in good to excellent yields, whereas those without an electron-attracting group (**1b** and **1c**) gave **2b** and **2c** in moderate yields (entries 2–9). The reaction of **1b**, which has a methoxy group on the phenyl ring, with $NOBF_4$ at room temperature gave the expected **2b** in 25% yield and 4-nitrosoanisole as a side product in 24% yield (entry 1). It was assumed that 4-nitrosoanisole was formed by the nitroso-induced *ipso*-deantimonation of **1b** with $NOBF_4$. Therefore, the reaction of **1b** and $NOBF_4$ was performed at low temperature (−20 °C), and **2b** was obtained in 45% yield without any side product (entry 2). Comparison of methyl-substituted antimony substrates (**1c**, **1j**, and **1k**) showed remarkable influence of the steric hindrance (entries 3, 10, and 11). The most bulky mesityl derivative **1k** was totally unreactive (entry 11). Fluorination of **1l** and **1m** with $NOBF_4$ gave a complex mixture (entries 12 and 13).

At present, the mechanism of the fluorination of organoantimony compounds is unclear. We consider a similar reaction mechanism proposed by Olah and Prakash et al. for the desulfurative fluorination of sulfides and fluorination of arylacetylenes using $NOBF_4$ [31,32]. Fig. 1 shows a possible mechanism for the synthesis of triarylantimony difluorides from Ar_3Sb and $NOBF_4$. The first step of the reaction involves the generation of stibonium ion **A** from Ar_3Sb (**1a–j**) with NO^+. Intermediate **B** is obtained through nucleophilic attack by F^- from BF_4^-. The reaction of **B** with NO^+ affords stibonium ion **D** and $H_2N_2O_2$ (**E**) *via* intermediate **C**. **E** decomposes to N_2O and H_2O [33]. Intermediate **D** is converted to triarylantimony difluorides (**2a–j**) by the nucleophilic attack of F^-. This mechanism is in line with the fact that the present fluorination protocol requires 2 equivalents of $NOBF_4$ (Table 1, entries 3, 12, and 13).

2.2. Antitumor activity

The biological activity of the synthesized triarylantimony difluorides (**2a–j**) was evaluated in terms of the antitumor effect in mouse and human cultured tumor cell lines. The tested compounds presented good anti-proliferation activity against all the cell lines (Table 3). This series of compounds exhibited antitumor activity against not only the mouse and human leukemia cell lines but also human solid tumor cell lines such as colon and breast tumors. In particular, the IC_{50} of *p*-Tol_3SbF_2 (**2c**) with the *p*-tolyl functional group was the lowest values (2.43–3.97 μM) in each cell lines, indicating that this compound exhibited the best antitumor activity among those studied. In our previous paper [29], we reported the anti-proliferative activity of cisplatin (CDDP, 1.0–6.2 μM against 6 tumor cell lines), a famous platinum-based antitumor drug. Interestingly, the antitumor activity of *o*-Tol_3SbF_2 (**2j**), a regioisomer of **2c**, was significantly lower (IC_{50} = 5.13–15.2 μM). It seems that the difference in the position of the methyl functional group caused a conformational change and a