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Complete List of Authors:	Sasaki, Ichiro; QST, Department of Radiation-Applied Biology Tada, Masatoshi; Tokyo Institute of Technology - Ookayama Campus Liu, Ziyun; Tokyo Kogyo Daigaku - Ookayama Campus, Chemical Science and Engineering; The University of Tokyo, Graduate School of Pharmaceutical Science Tatsuta, Maho; Tokyo Institute of Technology Okura, Takeru; Tokyo Institute of Technology - Ookayama Campus Aoki, Miho; Fukushima Medical University Takahashi, Kazuhiro; Fukushima Medical University, Advanced Clinical Research Center Ishioka, Noriko; QST, Department of Radiation-Applied Biology Watanabe, Shigeki; QST, Department of Applied Biology Tanaka, Hiroshi; Tokyo Kogyo Daigaku - Ookayama Campus, Chemical Science and Engineering

1-(*N*,*N*-Dialkylcarbamoyl)-1,1-difluoromethanesulfonyl ester as a stable and effective precursor for neopentyl labeling group with astatine-211

Ichiro Sasaki,[b] Masatoshi Tada,[a] Ziyun Liu,[a] Maho Tatsuta,[a] Takeru Okura,[a] Miho Aoki,[c] Kazuhiro Takahashi,[c] Noriko S. Ishioka,[b] Shigeki Watanabe,[b] and Hiroshi Tanaka*,[a]

[a]Department of Chemical Science and Engineering, Tokyo Institute of Technology
Address 12-12-1-H101 Ookayama, Meguro, Tokyo, 152-8552, Japan
E-mail: thiroshi@cap.mac.titech.ac.jp

[b]Department of Quantum-Applied Biosciences, Takasaki Institute for Advanced Quantum Science National Institutes for Quantum Science and Technology
1233 Watanuki-machi, Takasaki, Gunma 370-1292, Japan

[c]Advanced Clinical Research Center, Fukushima Global Medical Science Center, Fukushima Medical University
1 Hikariga-oka, Fukushima, Fukushima 960-1295, Japan

Abstract:

Radiohalogens with a short half-life are useful radioisotopes for radiotheranostics. Astatine-211 is an α-emitting radiohalogen and is expected to be applicable to targeted α therapy. A neopentyl labeling group is an effective hydrophilic labeling unit for various radiohalogens, which includes ^{211}At. In this study, a 1-(*N*,*N*-dialkylcarbamoyl)-1,1-difluoromethanesulfonyl (CDf) ester was developed as a stable precursor for labeling with ^{211}At as well as ^{77}Br and ^{125}I through a neopentyl labeling group. The CDf ester

remained stable in an acetonitrile solution at room temperature and enabled the successful syntheses of ^{211}At-labeled compounds in a highly radiochemical conversion in the presence of K_2CO_3. ^{77}Br- and ^{125}I-labeled compounds can be prepared from the CDf ester without a base. The utility of the CDf ester was demonstrated in the synthesis of a benzylguanidine with a neopentyl ^{211}At-labeling group. The developed method returned a 32% radiochemical yield of ^{211}At-labeled benzylguanidine. However, a partial deastatination was observed under acidic conditions during the removal of an *N*-Boc protecting group. Deprotecting these groups under milder acidic conditions may improve the radiochemical yield. In conclusion, the CDf ester facilitates the syntheses of ^{211}At, ^{125}I and ^{77}Br-labeled compounds that use a neopentyl labeling group for radiotheranostic applications. Further optimization of protecting groups and reaction conditions should enhance the total radiochemical yield of the ^{211}At-labeled compounds.

Introduction

Radiotheranostics is an innovative approach to cancer treatment. This strategy combines internal radiation therapy with diagnostics based on molecular imaging and provides a potent yet non-invasive method for cancer therapy.[1] At the heart of this technique is the 'theranostic pair'—two distinct radiopharmaceuticals that can be used for either diagnosis and therapy. This pair of ligands selectively accumulate in cancer cells, and each is labeled with an appropriate diagnostic or therapeutic radioisotope.

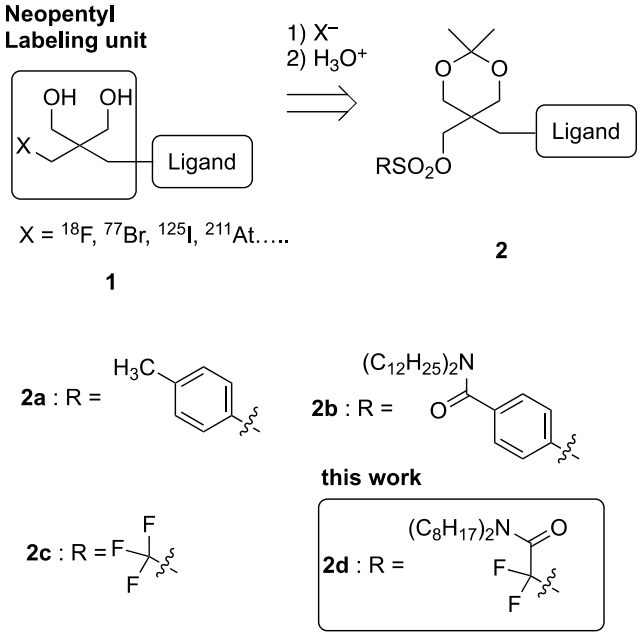
Radiohalogens with a short half-life have been used as radioisotopes for radiopharmaceuticals.[2] For instance, fluorine-18 and iodine-123, as positron and single-

photon emitters, respectively, allow for external visualization, thereby proving indispensable for diagnostic applications. By contrast, astatine-211, iodine-131, and bromine-77, which are as alpha, beta, and Auger electron emitters, respectively, tend to damage surrounding cells, but could potentially be utilized for therapeutic purposes.

In addition, iodine-125 as a low-energy gamma emitter with a longer half-life (60 days) can support biological research to develop these radiopharmaceuticals. Furthermore, owing to the ability of halogens to form direct covalent bonds with organic compounds, alterations in the pharmacokinetics of the labeled compounds are minimal when the type of radioactive halogen is changed. This inherent property makes them particularly appropriate for the synthesis of radiopharmaceutical pairs designed for theranostic applications. However, the chemical properties of halogens can vary significantly according to their placement in the periodic table. For example, compounds labeled with ^{211}At through an ^{211}At-carbon bond more readily undergo dehalogenation *in vivo* than those labeled with iodine.[3] The release of ^{211}At from labeled compounds not only reduces the accumulation rate of astatine in targeted cancer cells, but also contributes to the nonspecific accumulation of ^{211}At in the stomach and thyroid.

The neopentyl labeling group present in **1** has recently been identified as an effective hydrophilic labeling unit for various radiohalogens, which includes both ^{18}F and ^{211}At (Scheme 1).[4-6] The carbon-halogen bond in the labeling group exhibits high *in vivo* stability and significantly resists dehalogenation even in ^{211}At-labeled compounds. Moreover, the hydrophilicity offered by the two primary alcohols enhances their clearance from the blood. The process of preparing radiohalogen-labeled compound **1** via a neopentyl labeling group involves a nucleophilic substitution of the sulfonyl ester **2** with radiohalides, which is followed by hydrolysis of the acetal. For ^{18}F-fluorination, the tosyl

ester **2a** and the 4-(*N*,*N*-dialkylcarbamoyl)benzenesulfonyl ester **2b** were used as precursors and heated with [^{18}F]fluoride and phase-transfer catalysts at 100 ^{o}C or higher. The dialkylcarbamoyl group serves as a lipophilic phase-tag, facilitating the removal of tagged compounds from the reaction mixture via reverse-phase solid-phase extraction.[7] By contrast, for ^{211}At-astatination and ^{125}I-iodination, triflate **2c** was treated as a precursor with [^{211}At]astatide and [^{125}I]iodide under mild heating conditions.[6] Nevertheless, despite the high reactivity that makes triflate **2c** an exceptional precursor, careful handling is necessary due to its instability. In addition, triflate **2c** must be stored under cool and dark conditions in an appropriate solvent, or synthesized immediately prior to use. To streamline the development of radiopharmaceuticals using a neopentyl ^{211}At- and ^{125}I-labeling group, it is necessary to develop precursors that can be stably stored in the solvent that is used for radiohalogenation, and these precursors should be optimally reacted with radiohalogens in this solvent. Herein, we report the substituted difluoromethanesulfonyl ester **2d** as a stable precursor for synthesizing neopentyl ^{211}At-, ^{77}Br- and ^{125}I-labeling groups.



Scheme 1. Different sulfonated ester precursors **2** for radiohalogenated neopentyl synthesis.

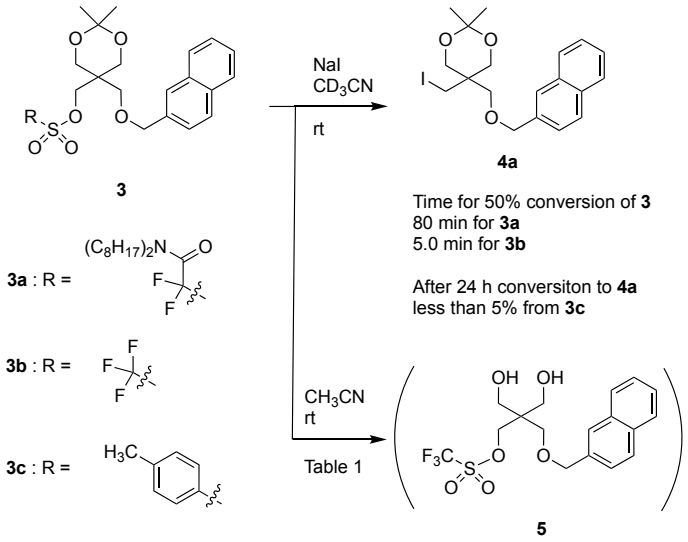
Results and Discussion

We designed the CDf ester **2d** as a precursor for radiohalogenation (Scheme 1). The CDf ester **2d** has a structure in which one fluorine atom of trifluoromethanesufonyl ester is replaced with an *N*,*N*-dialkylcarbamoyl group. The carbamoyl group is expected to enhance the chemical stability of the sulfonyl ester due to its weaker electron-withdrawing effect compared with that of fluorine, although it may reduce the reactivity of the sulfonyl ester towards nucleophilic substitution. Additionally, the *N*-alkyl groups could act as a phase-tag facilitating the removal of tagged compounds, such as a precursor, via a solid-phase extraction.

We initially compared the reactivity of the neopentyl sulfonates **3a**, **3b**, and **3c** possessing a naphthyl group towards nucleophilic iodination with sodium iodide in acetonitrile-d3 (Scheme 2). The naphthyl group acts as a strong chromophore to ease detection of the attached compound. The 8.9 mmol/L acetonitrile-d3 solutions of the neopentyl sulfonates **3a**, **3b**, and **3c** were reacted with 10 equivalents of sodium iodide at room temperature. The conversion rate of **3** into the iodinated compound **4a** was estimated via real-time ^{1}H NMR analysis of the reaction mixture employing dimethyl sulfone as an internal standard. Under these reaction conditions, triflate **3b** smoothly underwent nucleophilic iodination, achieving 50% conversion to iodide **4a** within 5.0 min. By contrast, the CDf ester **3a** required a significantly greater amount of time — more than 80 min — to reach the same conversion point. When tosyl ester **3c** was used, after 24

hours, most of the the tosyl ester **3c** was unaffected and the conversion to the iodinated compound **4a** remained at less than 5%. This result also indicates that the tosyl ester **3c** is very stable. Overall, these results indicated that the CDf ester **3a** was less reactive than triflate **3b**, however, much more reactive than tosyl ester **3c**.

Next, we compared the stability of sulfonyl esters **3a** and **3b** in acetonitrile-d3 (Scheme 2 and Table 1). Acetonitrile is a solvent that is suitable for nucleophilic substitution. A solution of the sulfonyl esters **3a** and **3b** in acetonitrile can be used directly for nucleophilic radiohalogenation. The remaining neopentyl sulfonate in the solution was quantitatively analyzed using ^{1}H NMR spectroscopy with dimethyl sulfone serving as an internal standard. After 24 hours, more than 99% of the CDf ester **3a** remained. Moreover, no significant degradation of sulfonate **3a** was observed after 30 days. By contrast, the triflate **3b** was completely decomposed after 24 h. TLC analysis of the mixture indicated that triflate **3b** was converted to a compound of higher polarity. ^{1}H NMR analysis of the resultant mixture showed that the majority of the sulfonyl esters had not been hydrolyzed. These findings suggest that the partial hydrolysis of triflate **3b** with acetonitrile resulted in the release of triflic acid, which then might promote the hydrolysis of acetal **3b** to diol **5**.



Scheme 2. The reactivity and stability of neopentyl sulfonyl esters **3**.

Table 1. Survival rates of sulfonyl esters **3a** and **3b** in acetonitrile-d3 at room temperature

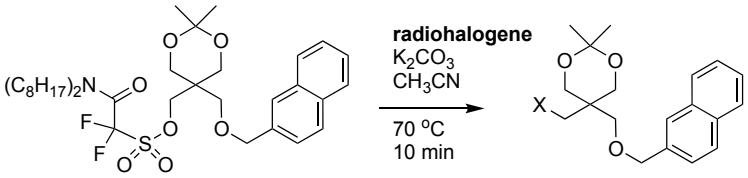
Entry[a]	Sulfonyl esters	Time	Survival rate of **3** (%)
1	**3a**	24 h	>99
2	**3b**	30 day	>99
3	**3b**	24 h	<1

We evaluated the ^{125}I-iodination, ^{77}Br-bromination, and ^{211}At-astatination of CDf ester **3a** (Table 2). A 0.05 M NaOH aqueous solution of [^{125}I]NaI[8] was concentrated by evaporation. The resultant residue, which contained [^{125}I]NaI was reacted with CDf ester **3a** (2.5 μmol) in acetonitrile (35 μL) at 70 ^{o}C for 10 min. The radiochemical conversion (RCC) value from the CDf ester **3a** to the ^{125}I- neopentyl iodide **4b** was 83%. Next, we examined the ^{77}Br-bromination of CDf ester **3a**. Initially, we prepared an aqueous solution containing [^{77}Br]bromide via a dry-distillation method from an irradiated $Cu_2{}^{nat}Se$ target.[9] The aqueous solution of [^{77}Br]bromide was then purified and

concentrated using anion exchange column chromatography. The resultant residue contained [^{77}Br]bromide was reacted with CDf ester **3a** under conditions similar to those of the initial experiment. The RCC value of ^{77}Br-neopentyl bromide **4c** was 80%. On the other hand, a residue containing ^{211}At, was prepared via dry-distillation from an irradiated ^{209}Bi target using helium as a carrier gas and water as an elution solvent.[10] The elution was concentrated under heating conditions. The residue was then reacted with CDf ester **3a** under the same reaction conditions. This reaction provided only a trace amount of ^{211}At-neopentyl astatide **4d**. Considering the influence that the periodic trends exerted on the nucleophilicity of the halide ions, astatide was expected to exhibit higher reactivity than that of either bromide or iodide. We postulated that the significant decrease in the RCC value during ^{211}At-Astatination of **3a** under these conditions could have been because astatine obtained by dry distillation forms a neutral chemical species. Therefore, we hypothesized that a base might improve the nucleophilicity of the astatine-containing chemical species. Therefore, we investigated labeling in the presence of K_2CO_3, which has a proven track record in the synthesis of ^{18}F-labeled compounds. As a result, the RCC value of neopentyl [^{211}At]astatide **4d** in the reaction with residue containing ^{211}At with CDf ester **3A** (2.5 μmol) and K_2CO_3 (0.5 mg) in acetonitrile (35 μL) at 70 ^{o}C for 10 min was 95%. K_2CO_3 is a basic salt that has no significant oxidizing or reducing activity. Therefore, we believe that potassium carbonate simply increases the nucleophilicity of the astatine species when isolated by dry distillation.[11] Astatine from dry distillation, however, is known to contain a variety of oxidated astatines[12] and requires a reducing agent prior to use in nucleophilic substitution.[13] Based on the reaction mechanism of DMSO oxidation of alkyl halides to aldehydes, it seemed logical that a precursor of highly reactive neopentyl sulfonyl ester might reduce the oxidated astatine species to astatine

under basic conditions. However, no results are available that could prove this. In total, the CDf ester **3A** is sufficiently stable as stock for acetonitrile and possesses sufficient reactivity to synthesize ^{77}Br-, ^{125}I-, and ^{211}At-labeled compounds using a neopentyl labeling group under these mild heating conditions.

Table 2. Radiochemical conversion (RCC) values during the radiohalogenation of sulfonyl ester **3a**.



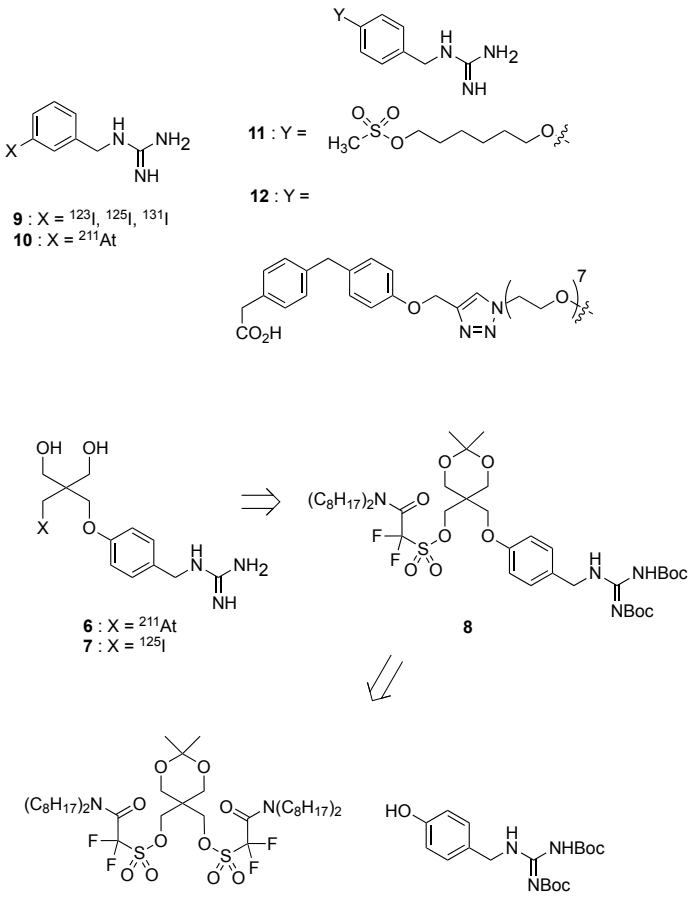
3a

4b : X = ^{125}I
4c : X = ^{77}Br
4d : X = ^{211}At

Entry	X	Product **4**	K_2CO_3	RCC to **4** (%)
1	Na[^{125}I]I	**4b**	–	83
2	^{77}Br	**4c**	–	80
3	^{211}At	**4d**	–	9
4	^{211}At	**4d**	O	95 and 90

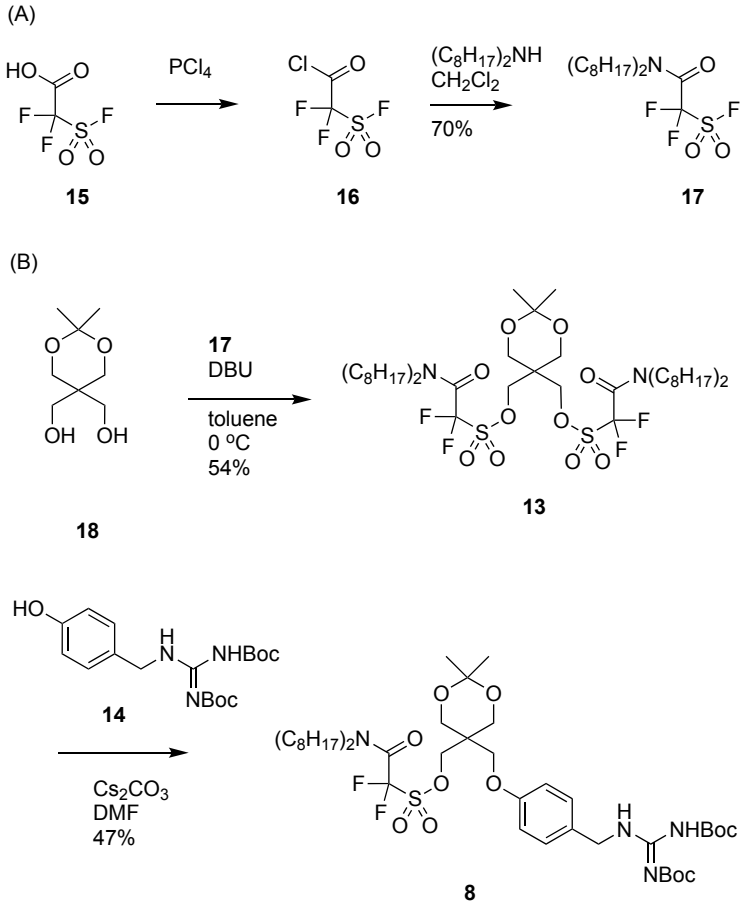
To demonstrate the efficacy of our method, we utilized CDf ester **8** as a common precursor (Scheme 3) to synthesize benzylguanidines (NP-BG) **6** and **7** labeled with ^{211}At and ^{125}I via a neopentyl labeling group. Benzylguanidines **9** labeled with radioiodines have been identified as crucial components in the development of ligands intended for targeted therapy and imaging of cancers expressing the norepinephrine transporter (NET).[14] For many years, [^{131}I]*m*-iodobenzylguanidine has been employed for targeted

therapy and imaging of NET-expressing tumors.[15] More recently, *m*-[^{211}At]astatobenzylguanidine **10** has been synthesized for targeted alpha therapy[16] and has demonstrated a reduction in tumor size in a mouse model of pheochromocytoma without triggering weight loss.[17] Based on these findings, a clinical trial using [^{211}At]MABG has started. We hypothesized that the use of a neopentyl labeling group in the ^{211}At-astatination of benzylguanidines could enhance the in vivo stability of the labeled products. This approach could also facilitate their clearance from non-target tissues, thereby promoting a more efficient anticancer action with fewer side effects. Following the structural patterns of the previously reported bioactive benzylguanidine hybrid molecules **11**[18] and **12**[19], we positioned the neopentyl labeling group at the *p*-position of benzylguanidine. The synthesis of neopentyl ^{211}At- and ^{125}I-NP-BG **6** and **7** involved a nucleophilic substitution of sulfonyl ester **8** possessing an *N,N'*-di(*tert*-butylcarbonyl(Boc))guanidino group. This was achieved using [^{211}At] astatide and [^{125}I] iodide, which was followed by the hydrolysis of acetal *N,N'*-diBoc-guanidine. The highly reactive CDf ester facilitated efficient and selective ^{211}At-astatination and ^{125}I-iodination in the presence of an *N,N*-diBoc guanidino group, which is known for its weak nucleophilicity. CDf ester **8** was prepared via O-alkylation of phenol **14** with diCDf ester **13**, while diCDf ester **13** allowed a one-step transformation of various ligands possessing a phenolic hydroxyl group to serve as precursors for radiohalogenation.



Scheme 3. Synthetic plan for the ^{211}At- and ^{125}I-NP-BG and **6** and **7**

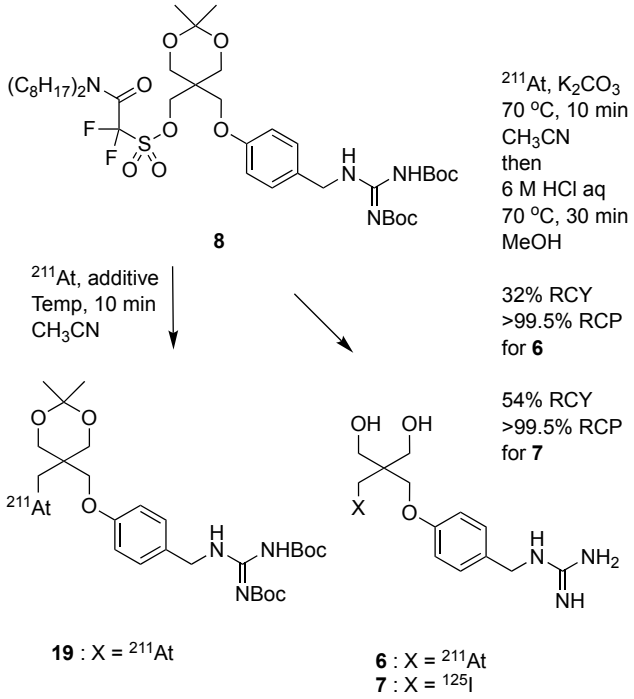
The preparation of precursor **8** is outlined in Scheme 4. Carboxylic acid **15** was converted to acid chloride **16** according to a reported method.[20] Subsequent amidation of the acid chloride **16** with dioctylamine provided sulfonyl fluoride **17** in a 70% yield in 2 steps. Diol **18** was treated with 2.2 equivalents of sulfonyl fluoride **17** to provide disulfonyl ester **13** in a 54% yield. Finally, O-alkylation of the phenolic alcohol **14**[21] possessing an *N*,*N*'-diBoc-guanidinyl group with the disulfonyl ester **13** provided CDf ester **8** as a precursor in 47% yield.



Scheme 4. The preparation of CDf ester **8**

The synthesis of ^{211}At-NP-BG **6** from CDf ester **8** was examined (Scheme 5). To begin, the ^{211}At-astatination of sulfonyl ester **8** to yield the ^{211}At-labeled diBoc guanidine **19** was examined (Table 1). The residue containing ^{211}At was reacted with CDf ester **8** in the presence of K_2CO_3 at 70 °C for 10 minutes. The RCC value was 87% for the ^{211}At-labeling of CDf ester **8** and conversion to ^{211}At-labeled diBoc guanidine **19** (entry 1). Conducting the ^{211}At-astatination at room temperature resulted in a lower RCC value of 66% (entry 2), although the reaction was found to proceed sufficiently even under these reaction conditions. Without the addition of K_2CO_3, the RCC values were decreased (entries 3 and 4). Following these findings, a one-pot synthesis of ^{211}At-NP-BG [^{211}At]**8**

was pursued. The residue containing ^{211}At was reacted with CDf ester **8** (0.5 mg) in the presence of K_2CO_3 (0.5 mg) in acetonitrile (150 μL) under the conditions to provide the ^{211}At-labeled diBoc guanidine **19**. Afterward, the addition of 6.0 M HCl aq. (80 μL) and MeOH (20 μL) to the reaction mixture, followed by heating at 70 ^{o}C for 30 min, enabled hydrolysis of the acetal and complete removal of the *N*-Boc groups. Post-neutralization with NaOH aq during radio-HPLC purification furnished ^{211}At-NP-BG **6** in a 32% radiochemical yield (RCY) with >99.5% radiochemical purity (RCP). Radio-HPLC analysis of the reaction mixture after deprotection under acidic conditions revealed a significant amount of released ^{211}At. By contrast, utilizing a similar labeling procedure for the synthesis of ^{125}I-NP-BG **7** resulted in a 54% RCY with >99.5 RCP, and no detectable release of ^{125}I. These results suggest that neopentyl astatide ^{211}At-NP-BG **6** is more prone to instability under acidic conditions compared with that of ^{125}I-NP-BG **7**. Direct 211At-astatination using a precursor with a free guanidino group is a potential solution to this problem. However, to carry out this study, the corresponding unprotected CDf ester precursor must be prepared with a high purity. Despite these findings, we noted that previous literature has reported no dehalogenation of neopentyl astatide following treatment with TsOH. We predicted that the use of protecting groups that could be deprotected under milder acidic conditions would minimize deastatination, which would potentially enhance the radiochemical yield of the neopentyl astatide.



Scheme 5. Radiosynthesis of ^{211}At-NP-BG **6** and ^{125}I-NP-BG **7**

Table 3. Radiochemical conversion (RCC) in ^{211}At-astatination of **11**

Entry[a]	Temp	base	RCC to **19** (%)
1	70 °C	K_2CO_3	87
2	RT	K_2CO_3	65
3	70 °C	-	45
4	RT	-	23

In conclusion, we investigated the syntheses of ^{77}Br, ^{125}I, and ^{211}At-labeled compounds via a neopentyl labeling group using CDf esters. Compared with triflate, the CDf esters exhibited superior stability compared with that of triflate, and they can be stored in

acetonitrile, which is the labeling solvent. This contributes to reducing the research burden of requiring a radiopharmacist or radiochemist for handling of the precursor. The CDf ester also showed satisfactory reactivity, and in ^{77}Br-bromination and ^{125}I-iodination, high levels of RCC to the corresponding neopentyl halides were achieved without the use of special additives. On the other hand, in ^{211}At-asatatination, the addition of potassium carbonate was important for a high level of RCC. Moreover, we successfully synthesized ^{211}At-labeled benzyl guanidine **6** that possesses a neopentyl labeling group, via a one-pot procedure. Although a released ^{211}At was partially observed during the deprotection step under acidic conditions, and the overall radiochemical yield was acceptable at 32%. By contrast, the synthesis of a ^{125}I-labeled benzylguanidine **7** possessing a neopentyl labeling group using a similar reaction recipe yielded 54% RCY with no released ^{125}I detected. Our findings suggest that compared with neopentyl iodide, neopentyl astatide is more prone to instability under acidic conditions. However, dehalogenation has never been reported when neopentyl astatide is treated with TsOH. This highlights the potential for using protecting groups that can be deprotected under milder acidic conditions, which may improve the radiochemical yield of neopentyl astatide. Overall, our study provides valuable insight into the synthesis of radiohalogen-labeled compounds for radiotheranostic applications, and these results emphasize the importance of balancing stability and reactivity to optimize radiochemical yields, which enhances the potential of these compounds in cancer treatment. Currently, the development of a process for ^{18}F-fluorination of the CDf ester is underway.

Acknowledgments

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funding for operating expenses.

Conflicts of interest

There are no conflicts to declare.

Keywords: astatine-211 • radiotheranostics • neopentyl labeling unit • target alfa therapy •radiohalogens

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