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^{18}F-Radiolabeling of Aromatic Compounds Using Triarylsulfonium Salts

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A new method for the ^{18}F-radiolabeling of aromatic compounds based on the aromatic nucleophilic substitution (S_NAr) reaction using triarylsulfonium salts has been developed. Experiments and DFT calculations indicated that sulfonium ions have the potential to be optimized for labeling nonactivated and deactivated aryl rings that have Hammett σ_P substituent constants greater than –0.170. This method is applicable to a range of halogen-substituted aryl systems including nonactivated and deactivated aryl rings. In particular, the high radiochemical yield of [^{18}F]-4-fluoroiodobenzene from precursor **1a** represents a ready source of compound **1b** for subsequent use in palladium-catalyzed C–H activation/C–C bond-forming reactions.

Introduction

Traditional synthetic methods for the preparation of [^{18}F]-fluoroaromatic compounds are generally limited to aromatic rings functionalized with electron-withdrawing groups.[1] Standard activating/leaving groups used in the S_NAr reaction include trifluoromethyl (CF_3), nitro (NO_2), and trimethylammonium salts.[2] Recently, the use of diaryliodonium salts as precursors in nucleophilic ^{18}F-substitution reactions was developed as an alternative route for the synthesis of nonactivated or electron-rich [^{18}F]-fluoroaromatic compounds.[3] However, the majority of ^{18}F-radiochemical syntheses employing the aforementioned leaving groups often require the use of harsh reaction conditions with high temperatures (ca. >130 °C),[4] which frequently leads to low radiochemical yields, precursor/product decomposition, and the necessity to use complicated isolation methods.

To the best of our knowledge, the published results in the 1980s using the dimethylsulfonium ion as a leaving group for ^{18}F-fluoride nucleophilic substitution was only possible with activated aromatic rings.[5] Here we present a method for the ^{18}F-radiolabeling of aromatic compounds including nonactivated and deactivated aryl rings based on the aromatic nucleophilic substitution (S_NAr) reaction using triarylsulfonium salts as the substrates.

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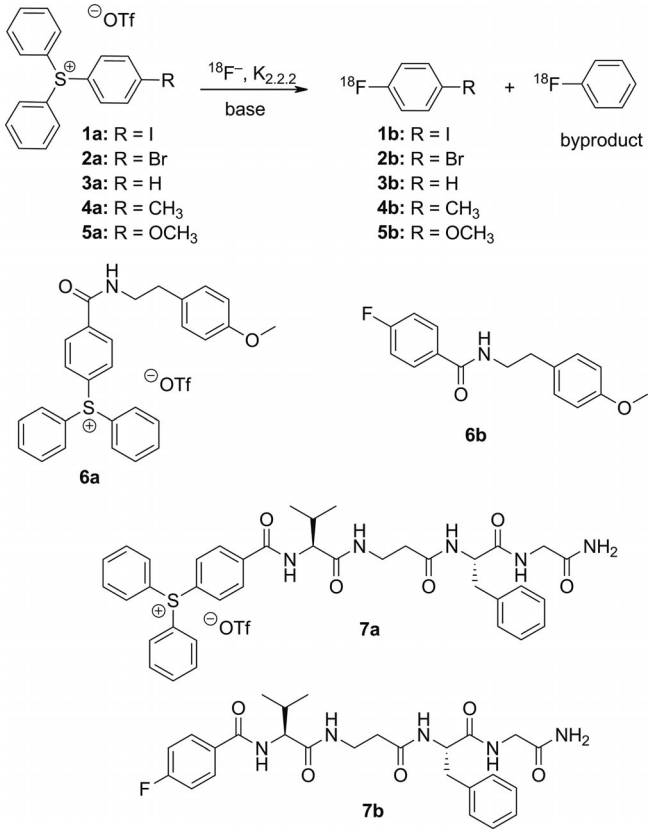
Results and Discussion

Scheme 1 illustrates the general radiochemical reaction employed here in the synthesis of a range of [^{18}F]-*para*-fluoroaryl derivatives **1b**–**7b** from their corresponding triarylsulfonium salts **1a**–**7a**. A variety of synthetic methods for preparing triarylsulfonium salts have been reported.[6] Compounds **1a**–**5a** and their corresponding *para*-fluoroaryl derivatives **1b**–**5b** are commercially available, facilitating their use as model systems in these feasibility studies. Amide derivative precursors **6a** and **7a** and their corresponding products **6b** and **7b** were synthesized by adapting previously reported methods.[7] Full experimental details are presented in the Supporting Information.

^{18}F-Radiolabeling experiments were optimized by using K[^{18}F]F (or Cs[^{18}F]F) and kryptofix as a source of nucleophilic ^{18}F-fluoride (ca. 2–5 GBq), 2 mg of precursor compound **1a**–**7a** dissolved in 200 μL of anhydrous aprotic organic solvent [acetonitrile (MeCN), dimethyl sulfoxide (DMSO), dimethyl formamide (DMF)] in the presence of a base (K_2CO_3 or Cs_2CO_3) and reacted at various temperatures (80–130 °C) for a total time of 15 min. Product conversion yields and radiochemical purity (RCP) were determined from integration analysis of the radio-ultra performance liquid chromatography (radio-UPLC) chromatograms based on the ratio of the radioactivity area of product to the total radioactivity area. In all cases, product identity was confirmed by co-injection of the known reference compound by using UPLC. Results for the radiolabeling reactions are presented in Table 1.

The radiochemical experiments demonstrate that ^{18}F-labeling of aromatic systems by nucleophilic substitution with the use of sulfonium ion precursors is feasible. In MeCN, compound **1a** could be ^{18}F-radiolabeled to give [^{18}F]-4-



Scheme 1. Radiochemical (S_NAr) reaction employed in the synthesis of [^{18}F]-*para*-fluoroaryl derivatives and structures of **6a**, **6b** and **7a**, **7b**.

Table 1. Selected data for optimization of ^{18}F-radiochemical reactions by using sulfonium precursors **1a**–**7a** (n = 2, 3).

Entry	Precursor	Solvent	T [°C]	Conversion [%] Byproduct	Product
1	**1a**	MeCN[a,c]	80	7 ± 1	91 ± 1
2	**1a**	MeCN[a]	90	8 ± 2	90 ± 2
3	**1a**	DMF[a]	80	10 ± 2	81 ± 4
4	**1a**	DMF[a]	90	9 ± 1	88 ± 1
5	**1a**	DMF[a]	130	13 ± 2	76 ± 5
6	**1a**	DMF[b]	130	16 ± 3	62 ± 2
7	**1a**	DMF[b], 10 μL H_2O	130	31 ± 2	42 ± 4
8	**1a**	DMSO[b]	130	6 ± 1	49 ± 3
9	**1a**	DMSO[a]	130	12 ± 2	61 ± 6
10	**1a**	DMSO[a]	90	7 ± 1	48 ± 1
11	**2a**	MeCN[a]	80	6 ± 2	36 ± 1
12	**2a**	DMF[a]	90	10 ± 1	23 ± 2
13	**3a**	MeCN[a]	80	0	48 ± 3
14	**3a**	DMF[a]	90	0	70 ± 7
15	**4a**	MeCN[a]	80	19 ± 4	1 ± 1
16	**4a**	DMF[a]	90	10 ± 3	2 ± 1
17	**5a**	MeCN[a]	80	25 ± 5	0
18	**5a**	DMF[a]	90	71 ± 4	0
19	**6a**	MeCN[a]	80	0	98 ± 1
20	**6a**	DMF[a]	90	0	89 ± 5
21	**7a**	MeCN[a]	80	0	0
22	**7a**	DMF[a]	90	0	0
23	**7a**	DMF[b]	90	0	18 ± 1
24	**7a**	DMF[b]	110	0	68 ± 4
25	**7a**	DMSO[b]	90	0	30 ± 5
26	**7a**	DMSO[b], 10 μL H_2O	90	0	15 ± 7
27	**7a**	DMSO[b]	110	0	63 ± 6

[a] K_2CO_3 was used as the base. [b] Cs_2CO_3 was used as the base. [c] Specific activity was 5 GBq μmol^{-1} with starting activity at 2.3 GBq.

fluoroiodobenzene in excellent yields (91 ± 1%, n = 3) at 80 °C in 15 min (Table 1, Entry 1). High radiochemical yields were also obtained by changing the solvent to DMF. For compounds **1a**, **2a**, **6a**, and **7a**, ^{18}F-fluorination occurred preferentially on the substituted aromatic ring, with minimal [^{18}F]-fluorobenzene observed. In the case of nonactivated aromatic compound **3a** (Hammett σ_P = 0.0) and deactivated compounds **4a** (σ_P = –0.17) and **5a** (σ_P = –0.268), [^{18}F]-fluorobenzene was the favored product, which could be obtained in up to 70% yield (Table 1, Entries 14, 15, and 18) under mild radiolabeling conditions. Purification of compound **3a** in acetonitrile by using a Sep-Pak C18 light cartridge (Waters) resulted in 31 ± 2% (n = 2) isolated radiochemical yield (RCY, decay corrected). The measured difference between the isolated RCY and the conversion yield of 48 ± 3% determined by UPLC (Table 1, Entry 13) is in the normal range observed for fluorine-18 labeled compounds in our laboratory. All the radiolabeling steps were performed in sealed reaction vials, which were cooled to room temperature 5 min prior to taking an aliquot for UPLC analysis. Nevertheless, the loss of radioactive product, and the possibility of erroneously high conversion yields arising from the potential volatility of [^{18}F]-fluorobenzene was investigated. In this regard, we found that no radioactivity was lost during our procedure.

The effect of changing the substituent on the aryl ring was also studied (Scheme 1 and Table 1). In general, bromine derivative **2a** gave lower conversion yields under the same conditions compared to that obtained with iodine derivative **1a**. Notably, the conversion yield for compound **2a** in MeCN at 80 °C was only 36%, whereas for **1a** 91% yield was obtained. The lower yield for **2a** is consistent with the slightly less activating Br (σ_P = 0.232) vs. I (σ_P = 0.276) substituent. Replacing the halogen substituent on the aryl ring with a hydrogen, methyl, or methoxy group (i.e., **3a**–**5a**) favors the formation of [^{18}F]-fluorobenzene. For deactivated compound **4a**, although [^{18}F]-fluorobenzene was the preferred product, a small amount of [^{18}F]-fluorotoluene (1–2%) was also obtained. The fact that conversion into [^{18}F]-fluorobenzene occurred for compounds **3a**, **4a**, and **5a**, as well as the observation of some [^{18}F]-fluorotoluene product **4b**, confirms that the use of sulfonium ions as leaving groups for ^{18}F-substitutions can facilitate (albeit modest) the radiolabeling of nonactivated and even deactivated aryl rings.

To assess the chemical scope and potential applications of sulfonium ions as precursors for ^{18}F-radiolabeling of peptides, the influence of amide bonds in the *para*-position was investigated by using model compound **6a** and tetrapeptide **7a** (NH-Val-βAla-Phe-Gly-OH). For compound **6a**, desired product **6b** was obtained in near quantitative conversion (98%; Table 1, Entry 19) by using the optimized la-

beling conditions derived from compound **1a** (K_2CO_3, MeCN at 80 °C). Encouraged by this positive result, we applied the same conditions to tetrapeptide **7a**, however, no product was observed in either MeCN or DMF. Changing the base to Cs_2CO_3 and increasing the temperature from 90 to 110 °C did provide the product in 18 and 68%, respectively.

To understand further the influence of the substituent effect on radiolabeling efficiency, we used density functional theory (DFT) calculations to map the reaction potential energy surface. As accurate predictions of overall reaction free energies are not accessible due to the difficulty in calculating the energy for the fluoride anion, we explored the nature of the transition state for the S_NAr substitution. For each system, we used the common fluorobenzene byproduct reaction as an internal reference and calculated the vibrational modes, ν, as well as the difference in free energy, $\Delta_{TS}G$, between the transition states for the reaction pathways leading to either the desired product (TS_1) or the fluorobenzene byproduct (TS_2), where $\Delta_{TS}G = G[TS_1] - G[TS_2]$.

A schematic diagram of the DFT calculated reaction coordinate with optimized reactant, transition state, and product structures based on compound **1a** is shown in Figure 1. Calculated energies are presented in Table 2 and full details are given in the Supporting Information.

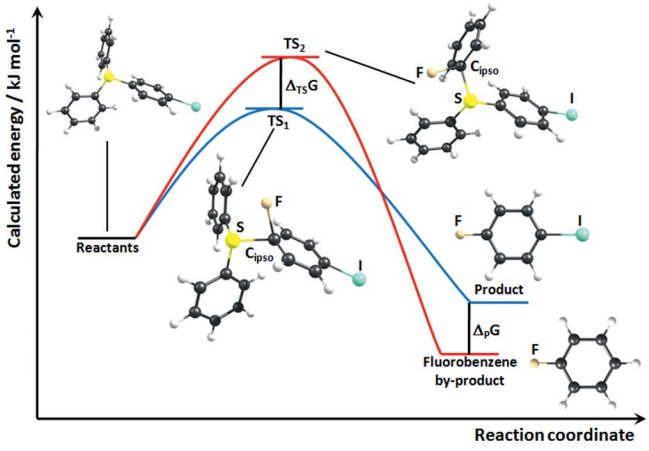


Figure 1. Schematic of the DFT calculated reaction coordinates for the S_NAr substitution reaction between fluoride and sulfonium ion precursor **1a**.

Table 2. DFT calculated energies and vibrational modes.[a]

Compd.	Substituent	$\Delta_{TS}G$ [kJ mol^{-1}]	Δ_PG [kJ mol^{-1}]	ν(TS$_1$) [cm^{-1}]	Hammett constant σ_P
1a	I	–4.3	4.7	–348	0.276
2a	Br	–5.1	4.6	–349	0.232
3a	H	0	0	–364[b]	0.0
4a	Me	5.4	3.1	–378	–0.170
5a	OMe	14.9	3.4	–393	–0.268
8a	Cl	–2.4	3.9	–356	0.227
9a	C(O)NHCH$_3$	–13.5	2.4	–323	–

[a] Negative values of $\Delta_{TS}G$ indicate that the TS for the desired product is favored. Positive values for Δ_PG indicate that the byproducts are lower in energy. [b] Calculated vibrational mode for TS_2 for SPh_3.

Trends calculated by DFT are fully consistent with the observed experimental data on reaction conversion and with the expected reactivities, as predicted from Hammett σ_P substituent constants. Using the calculated free energy of TS_2 (the transition state for the common fluorobenzene byproduct in all reactions) as an internal reference, the data indicate that for halogenated compounds **1a**, **2a**, and **8a** and model amide **9a**, attack of the fluoride at C_{ipso} of the substituted ring is favored by 2–5 kJ mol^{-1} for the halogens and by 13.5 kJ mol^{-1} for the more-activated/electron-poor amide ring system (Table 2). In contrast, S_NAr substitution on the methoxy-substituted aryl group of compound **5a** is strongly disfavored by 14.9 kJ mol^{-1}, which is consistent with the experimental data showing that only the [^{18}F]-fluorobenzene byproduct was formed.

Calculated frequencies for the asymmetric ν_{as} (F–C_{ipso}–S) vibrational stretching modes of the transition states reveal that across all compounds studied, the frequency of the imaginary TS_2 stretch was very similar and in the range from –359 to –369 cm^{-1}. This confirms the validity of using the calculated structure of TS_2 as an internal reference for the energy calculations (control compound **3a**: R = H, SPh_3). The imaginary stretching frequencies for TS_1 leading to the desired product vary substantially (ranging from –323 cm^{-1} for **9a** to –393 cm^{-1} for **5a**). For systems that undergo experimentally facile S_NAr reactions like **1a**, **2a**, and **7a** (here modeled by compound **9a**), the vibrational frequency was lower in energy than that of TS_2, whereas for nonreactive methoxy-substituted compound **5a**, $\nu(TS_1)$ was calculated to be 44 cm^{-1} higher in energy. Changes in the calculated free energy difference between TS_1 leading to the product and TS_2 are also consistent with the experimental data in Table 1. For activated, electron-poor systems, **1a**, **2a**, **8a**, and **9a**, $\Delta_{TS}G < 0$ kJ mol^{-1} indicate that the pathway leading to the desired product is favored. For deactivated precursors **4a** and **5a**, calculated $\Delta_{TS}G$ values >0 kJ mol^{-1} are consistent with the higher observed radioactive conversion to the [^{18}F]-fluorobenzene byproduct. However, it is noteworthy that for methyl-substituted compound **4a**, formation of product **4b** is not as strongly disfavored as for more deactivated methoxy compound **5a**. Collectively, these experimental and computational data also confirm the theory that transition states having high frequency vibrational modes are generally higher in energy and are associated with a less favored reaction pathway.

Conclusions

In conclusion, a new method for the ^{18}F-radiolabeling of nonactivated aromatic compounds using triarylsulfonium salts has been successfully developed. The method is applicable to a range of substituted aryl systems including amides. In particular, the high radiochemical yield of [^{18}F]-4-fluoroiodobenzene from precursor **1a** represents a ready source of compound **1b** for subsequent use in palladium-catalyzed C–H activation/C–C bond-forming reactions.[2,3b,8] These studies also indicate that sulfonium ions

have the potential to be optimized for labeling nonactivated and deactivated aryl rings that have Hammett σ_p substituent constants greater than –0.170. In spite of the encouraging preliminary results for labeling peptide-based model systems, further work is required to fully optimize this method as a potential tool for ^{18}F-labeling of full, biologically relevant peptides.

Experimental Section

The syntheses and chemical characterization of compounds **6a**, **6b**, **7a**, and **7b** have been described in the Supporting Information. No-carrier-added ^{18}F-fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of isotopically enriched ^{18}O-water in a fixed-energy Cyclone 18/9 cyclotron (IBA). Dried ^{18}F-fluoride–cryptate complex was prepared by using a standard separation and azeotropic drying procedure in the presence of Kryptofix 2.2.2 and potassium carbonate.

Supporting Information (see footnote on the first page of this article): All synthetic and radiochemical details, HPLC chromatograms, and full computational methods.

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