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Nucleophilic ^{18}F-Fluorination of Heteroaromatic Iodonium Salts with No-Carrier-Added [^{18}F]Fluoride

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Abstract: Diaryliodonium salts containing the 2-thienyl group as an example of an electron-rich heteroaromatic moiety proved to be very potent precursors for the nucleophilic, regioselective no-carrier-added (nca) radiofluorination of various arenes. It even allowed the nucleophilic introduction of nca [^{18}F]fluoride into electron-rich arene compounds in one step. The influences of the substitution pattern, of counteranions, and of different reaction conditions were studied. Effects of counterions could be explained by the influence of solvent on ion pair separation of precursor salts. Different aryl(2-thienyl)iodonium salts were used as precursors, where the homoaromatic group systematically varied from bearing electron-deficient to electron-rich substituents. Relative rates of exchange kinetics correlated linearly with Hammett constants of the appropriate substituents confirming a nucleophilic aromatic substitution reaction of high reactivity and low selectivity.

1. Introduction

Radiopharmaceuticals labeled with short-lived positron emitters play an important role for *in vivo* studies using positron emission tomography (PET).[1,2] This molecular imaging method allows the quantitative determination of the biodistribution of those radiotracers and hence that of physiological parameters. Because of its suitable decay properties ($t_{1/2}$ = 109.7 min, β^+-energy = 635 keV) fluorine-18 is an ideal radionuclide for PET. However, no-carrier-added (nca) procedures available for introducing fluorine-18 into organic molecule systems, especially needed when high molar activities are demanded in order to avoid pharmacological or toxicological effects of the labeled compound, are limited to nucleophilic methods. In contrast to electrophilic fluorination agents like [^{18}F]F_2 or [^{18}F]acetylhypofluorite, only [^{18}F]fluoride is available with sufficient high molar activity (>75 TBq/mmol). Therefore, the labeling reactions of aromatic target molecules with nca [^{18}F]fluoride so far are generally limited to substitution on electron-deficient arenes. Accessory activating groups, which decrease the electron density in arenes, enlarge the scope of the nucleophilic ^{18}F-labeling approach, but the additional groups have to be eliminated or converted after the ^{18}F-intoduction (see for example refs 3−5).

Since diaryliodonium salts have allowed efficient nucleophilic substitution on arenes,[6] they have also been shown to be suitable for a single-step introduction of fluoride into various arenes[7−11] and gain more and more interest for direct radiofluorination of electron-rich arenes. The introduction of nca [^{18}F]fluoride into one aryl substituent of dihomoaryliodonium salts via an S_NAr mechanism accordingly leads to nca [^{18}F]fluoroarenes and the corresponding iodoarenes (cf. Scheme 1).

The nucleophilic attack on the diaryliodonium salt occurs preferably at the more electron-deficient ring. Furthermore, a steric influence of substituents, especially for ortho-substituents, could be observed. This so-called ortho-effect is attributed to a iodine-centered trigonal bipyramidal intermediate with the sterically more demanding ortho-substituted ring in the equatorial position upon attack of a nucleophile which favors its introduction into this moiety.[12,13] This mechanistic model was also used to explain increasing radiofluorination yields with increasing numbers of (electronically deactivating) methyl substituents[9] and also accepted in other studies on nucleophilic ^{18}F-fluorination via iodonium salts.[10,14,15] Hence, both param-

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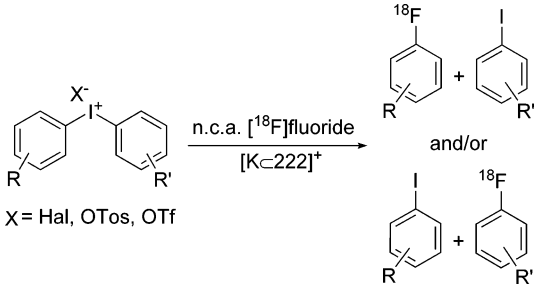
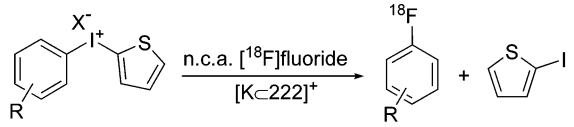
Scheme 1. Reaction of nca [^{18}F]Fluoride with Dihomoaryliodonium Salts



Scheme 2. Aryl(2-thienyl)iodonium Salts Used as Model Precursors for nca Radiofluorination of Homoarenes of Different Electron Densities



X = Br, I, OTs, OTf

R = 2-OCH_3, 3-OCH_3, 4-OCH_3, 4-CH_3, 4-OBn, H, 4-I, 4-Br, 4-Cl

eters, the electron density and the steric structure of a iodonium precursor, determine the orientation of the substitution.

So far, reactions of symmetric and asymmetric diaryliodonium salts with nca [^{18}F]fluoride were studied with homoaryl groups only. However, a more electron-rich aryl substituent like a heteroaromatic moiety in the iodonium salt should allow the direct single-step nucleophilic ^{18}F-labeling of a second aryl group which is lesser but still electron-rich.[13,15] Indeed, various reactions of nonradioactive nucleophiles, including fluoride, with mixed arylheteroaryliodonium salts are described and show a very high regioselectivity up to regiospecificity.[13,15,16]

In this study, the 2-thienyl group was used as a highly electron-rich heteroaromatic group. As a model reaction for optimization studies the formation of the electron-rich target molecule *ortho*-[^{18}F]fluoroanisole was studied using the precursors 2-methoxyphenyl(2-thienyl)iodonium bromide, iodide, tosylate, and triflate. Further, the influence of the steric conformation by comparison with the meta- and para-derivates and the influence of the electronic character were examined. Using different para-substituted aryl(2-thienyl)iodonium bromides (R = 4-CH_3, 4-OBn, H, 4-I, 4-Br, 4-Cl) with systematic variation of the electron density in the homoaromatic moiety, the mechanistic features and the chemoselectivity of the reaction toward ^{18}F-substituted homoarenes were tested (cf. Scheme 2).

2. Results and Discussion

2.1. Synthesis of Precursors. With respect to the principally high reactivity of diaryliodonium salts with nucleophiles, the preparation of these precursors is a crucial step to exploit this concept for radiofluorination of arenes. Several methods are known for the synthesis of diaryliodonium salts. In a classical way, the reaction of a diacetoxyiodoarene with an aromatic compound is catalyzed with concentrated sulfuric acid to yield the iodonium hydrogensulphate. Subsequent addition of aqueous potassium bromide or iodide solution leads to the precipitation of the corresponding diaryliodonium salt.[16,17] This route has the advantage of achieving reliable and good yields with electron-rich molecules. Additionally, it is a comfortable way to get the bromide or iodide salts of iodonium compounds. Other described methods mostly lead to tosylates, triflates, tetrafluoroborates, or further salts with complex counteranions.[18−22] However, these methods imply problems with electron-rich arenes, especially for purification, and only enable moderate yields due to many side products.[21]

All aryl(2-thienyl)iodonium bromides and iodides used for this study are prepared starting from their diacetoxyiodoarenes and thiophene in acetic acid anhydride with sulfuric acid as catalyst. The necessary diacetoxyiodoarenes are synthesized from the appropriate iodoarenes by oxidation with sodium perborate or periodate in acetic acid.[17,23,24] Exceptionally, for 1-iodo-4-(diacetoxyiodo)benzene, equimolar peracetic acid is the oxidant, because it is necessary to oxidize only one iodine of the 1,4-diiodobenzene and to leave the other one unaltered.[25]

The tosylates and triflates of the iodonium precursors for [^{18}F]-fluoroanisoles are suitably obtained from the bromides by an oxidative anion metathesis with hydrogen peroxide and the corresponding organic acid in very high yields.[26] All diacetoxyiodoarenes are prepared in sufficient yields of 42 to 74% as well as the corresponding aryl(2-thienyl)iodonium salts in 30 to 67% yield. The oxidative anion metathesis results in nearly quantitative conversion with yields of 90 to 98%.

2.2. Reaction Conditions of the ^{18}F-Substitution on 2-Methoxyphenyl(2-thienyl)iodonium Bromide. The Kryptofix 2.2.2/K_2CO_3 system was used to activate the nca [^{18}F]fluoride in all labeling reactions.[27] For the optimization of the general conditions the ^{18}F-labeling reactions were carried out with 2-methoxyphenyl(2-thienyl)iodonium bromide as the model precursor. This precursor enables very high radiochemical yields and is an example of an electron-rich molecule.

The radiochemical yields (RCYs) were determined by radio-HPLC or radio-TLC (autoradiographically) and are decay corrected. In case of [^{18}F]fluoroanisoles, 4-[^{18}F]fluorotoluene, and [^{18}F]fluorobenzene, the RCY could not be exactly determined by radio-TLC systems due to their volatility. Thus, the RCY for these compounds were acquired only by radio-HPLC. All ^{18}F-labeled products were identified by comparison with the R_f- or *k*-values of their nonradioactive reference molecules. 2-Fluorothiophene, a possible product of the substitution reaction, was not available as a reference compound. However, given the facts that all fluoroanalogues exhibit a slightly slower retention than their corresponding arenes (*k*-value within 10% higher) and that no radioactivity is coeluted with thiophene which is well separated from all fluoroarenes examined here,

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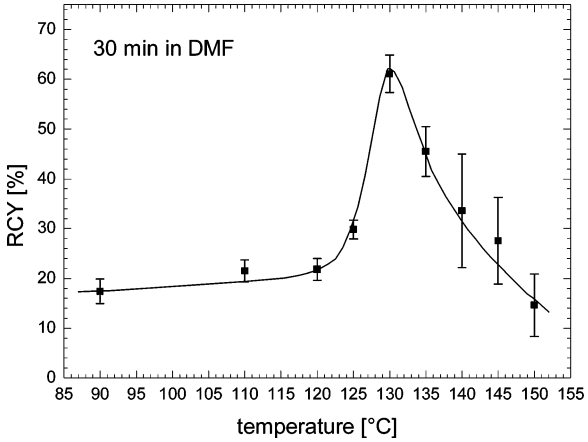

Figure 1. Temperature dependence of the nucleophilic ^{18}F-substitution on 2-methoxyphenyl(2-thienyl)iodonium bromide.

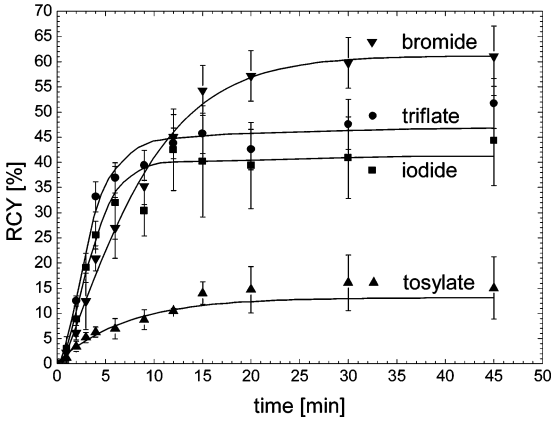

Figure 2. Dependence of RCY of the nucleophilic ^{18}F-substitution on 2-methoxyphenyl(2-thienyl)iodonium salts on the counterion (130 °C in DMF).

formation of 2-[^{18}F]fluorothiophene can be excluded. This is in agreement with reactions on an equimolar scale.[15]

The solvent used for the labeling reaction has a strong influence on the RCY. The S_NAr reaction generally demands aprotic, polar solvents. In the majority of cases, dimethylsulfoxide (DMSO) is the most suitable one and a highly effective medium for nucleophilic ^{18}F-labeling reactions. According to previous studies,[9,11,25] however, it does not work for the reaction type studied here, and with 2-methoxyphenyl(2-thienyl)iodonium bromide as the model compound, it led only to an RCY of 1 to 2%. There are two possible explanations for this outcome. On one hand, the low reduction potential of DMSO presumably causes redox processes between iodine(III) species and DMSO molecules. On the other hand, the S−O bond in DMSO has a semipolar character in favor of a S^+-O^- polarization and shows distinct nucleophilicity and a strong solvation of cations,[28] what would lower or even prevent their reactivity. Furthermore, there is evidence that DMSO affects diaryliodonium cations in a way that the oriented oxygen atom partially neutralizes the positive charge of the iodine(III).[29,30] Likely, a combination of both processes with a preliminary strong solvation and subsequent redox process is assumed for the nonsuitability of DMSO in ^{18}F-labeling reactions with diaryliodonium salts.

Acetonitrile (ACN) and dimethylacetamide (DMAA) give only low RCYs of 5 to 15%. The best results were received by using dimethylformamide (DMF), where RCYs up to 60% could be obtained. These effects of the solvent on the nucleophilic ^{18}F-fluorination of iodonium salts are comparable to findings in other studies.[11,25]

The concentration of the precursor 2-methoxyphenyl(2-thienyl)iodonium bromide was varied in a range from 6 mmol/L to 75 mmol/L DMF. More than 25 mmol/L did not notably improve the RCY of 2-[^{18}F]fluoroanisole, thus a concentration of 25 mmol/L was kept as optimal. Further on, higher concentrations caused problems of solubility and led to suspensions, which however cleared within seconds when the mixture was added to the warm reaction vial.

The same precursor was used to examine the influence of the reaction temperature, which strongly affects the RCYs. The yields increased from 90 to 130 °C as it is graphically depicted in Figure 1. At temperatures higher than 132 °C the rate is still increasing, whereas the radiochemical yields decrease.

The decreasing yields may be a result of the thermal instability of the precursor, and its decomposition competes with the ^{18}F-substitution. At higher temperatures diaryliodonium salts are known to be cleaved by an internal nucleophilic attack of the counteranion, which leads here to 2-bromoanisole and 2-iodothiophene.[13,31] Thus, the highest radiochemical yields of 2-[^{18}F]fluoroanisole could be obtained in a narrow range of 129 to 133 °C, and 130 °C was selected as the most suitable reaction temperature.

Raising the concentration of Kryptofix 2.2.2 (ratio Kryptofix 2.2.2 and K_2CO_3: 2:1) to more than 26 μmol does not affect the RCY or the reaction rate. However, less than 26 μmol considerably reduces the RCY of 2-[^{18}F]fluoroanisole. Very high concentrations of 52 μmol and above surprisingly lead to traces of an unidentified radioactive side product (<5%) with higher polarity than that of 2-fluoroanisole. This, however, originates obviously from labeling of an impurity in Kryptofix as was confirmed by control experiments without the presence of the iodonium precursor.

2.3. Influence of Counteranions on Iodonium Salts. Different counteranions of iodonium salts are known to strongly effect their reaction with nucleophiles. Earlier studies show slightly differing results,[8,11] but all found the highest RCY by using an inorganic counterion. An advantage of the inorganic counterions is the effective ion pair separation of iodonium salts in polar solvents,[31,32] but there are also indications for partially dimeric and trimeric structures of the iodonium salt with inorganic counterions, even in polar solvents.[33,34] On one side, the nucleophilic attack of [^{18}F]fluoride is favored by a dissociated iodonium salt and hence a "naked" iodonium cation. On the other side, anions with a high nucleophilicity compete with [^{18}F]fluoride for the substitution reaction. Considering their low nucleophilicity, organic counterions appear attractive under this aspect. Otherwise their bond to the iodine exhibits a more pronounced covalent character which causes a steric and electronic hindrance. Hence an additional step becomes neces-

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Table 1. Proton Shifts δ (ppm) of 2-Methoxyphenyl(2-thienyl)iodonium Cations in d_6-DMF

	δ [ppm]							
	2-methoxyphenyl ring					thienyl ring		
counterion	OCH_3	H3	H4	H5	H6	H3	H4	H5
bromide (nondissociated, 92%)	4.166	7.437	7.736	7.169	8.432	7.973[a]	7.209	7.973[a]
bromide (dissociated, 8%)	4.014	*b*	7.522	6.901	*b*	*b*	*b*	7.939
iodide (nondissociated, 87%)	4.104	7.451	7.770	7.198	8.466	8.036[a]	7.242	8.036[a]
iodide (dissociated, 13%)	4.016	7.280	7.525	6.903	*b*	7.829	7.039	7.939
tosylate	4.199	7.521	7.820	7.242[c]	8.513	8.142	7.313	8.184
triflate	4.223	7.549	7.846	7.267	8.531	8.172	7.342	8.214

[a] Signals are overlaid and show a multiplet. [b] Signals are too small or overlaid completely. [c] Signals show a multiplet with tosylates' H2 + H6.

sary in which [^{18}F]fluoride must replace the organic counteranion before it can form the trigonal-bipyramial transition complex via which aromatic substitution proceeds as generally accepted.[33,34] In this study the effects of different counterions were examined in DMF at 130 °C with 2-methoxyphenyl(2-thienyl)iodonium bromide, iodide, tosylate, and triflate. The following order of increasing RCY was obtained: tosylates < iodides < triflates < bromides (cf. Figure 2).

Here, the bromides prove the aforementioned assumptions for inorganic counteranions just as the tosylates do for the organic counteranions. Only the triflates stand out and show a slightly higher RCY than that of iodides, which may be caused by their very high reactivity as leaving group. Nevertheless, the sequence is in agreement with previous studies of nucleophilic ^{18}F-fluorination of diaryliodonium salts.[8]

In terms of kinetics, the triflates and iodides exhibit the highest reaction rates and a different series was attained for the increasing reaction rates: tosylates < bromides < iodides < triflates (cf. Figure 2). The tosylates show the lowest rates as well as the lowest yields, this may be attributed to the fact that their rather covalent bond combines with a major steric demand. However, the triflates give the fastest rates, which correlates with their high quality and reactivity as a leaving group. The iodide shows a slightly higher rate than the bromide, although bromide is the better leaving group considering the highest RCY obtainable.[35,36]

The strong influence of the character of counteranions argues for incomplete dissociated diaryliodonium salts, even with iodides and bromides. Evidence for the grade of dissociation can be received from NMR spectra of these solutions. Although the ^{18}F-fluorination was examined in DMF at 130 °C, the proton shifts in NMR spectra of *ortho*-methoxyphenyl substituted iodonium salts, measured in d_6-DMF at room temperature, diverge (cf. Table 1). In the case of fully dissociated iodonium salts, the proton shifts of the cations would be identical, regardless of the nature of the anions.[37,38]

The clear differences between the proton shifts disprove the presence of fully dissociated iodonium salts. Between the bromide and tosylate, the deviations are very notable. Especially for the bromide and the iodide, the spectra show both proton shifts of nondissociated salt and proton shifts of the free aryl(2-thienyl)iodonium cations. The signals of the latter are identical with signals obtained from spectra in d_6-DMSO (cf. analytical data in the Experimental Section). Although the signals of the dissociated salts are very small and largely overlaid, they are significant for the free iodonium cation and similar for both counteranions as expected.

The tosylate and the triflate present more similarities of their proton shifts. This is likely not a result of dissociated ion pairs but rather the fact that both counteranions are sulfonic acids, and consequently the immediate vicinity of the iodine(III) is the same. Consequently, their inductive effects on the proton shifts are nearly the same. The grade of dissociation for the bromide and iodide was determined by integration of the peak areas; the results are given in Table 1. The variations in both the proton shifts and the outcome of the nucleophilic ^{18}F-fluorination reactions are in favor of nonfully dissociated aryl(2-thienyl)iodonium salts with all anions examined. In the case of the iodide and the bromide, a disagreement in RCYs and reaction rates occurs. Presumably, this is an effect of the aforementioned thermal instability and tendency of the precursors to decompose. As a result, the iodide is more reactive to both the ^{18}F-introduction and the decomposition, which causes a faster initial reactivity but also loss of reactive precursor and in the net result leads to a lower RCY.

2.4. Influence of the Substitution Pattern of Methoxyphenyl(2-thienyl)iodonium Bromide. In general, the influence of the substitution pattern in the S_NAr reaction is very predictable for common arenes. Making a rough estimate for the reactivity, the effects of ortho- and para-position are approximately comparable and differ from those of the meta-position. This is explainable by the character of the S_NAr mechanism and the corresponding resonance structures. In the nucleophilic attack on the ipso-carbon, a so-called Meisenheimer complex with a negative charge is formed as an intermediate. Those negatively charged intermediates can be stabilized by electron-accepting groups in the ortho- and para-position by resonance. Such resonance stabilization cannot occur in the meta-position.

The nucleophilic attack on diaryliodonium salts is strongly affected by the substitution pattern. Especially a huge difference between ortho- and para-substituted rings is not explainable by the regular character of the S_NAr mechanism and is due to the influence of the ortho-effect mentioned above.

Ortho-, meta-, and para-methoxyphenyl(2-thienyl)iodonium bromides were labeled under the optimized conditions, viz 130 °C in DMF (cf. Figure 3). The results correspond to the expectations, and indeed a strong ortho-effect could be observed. The para-derivative shows moderate RCYs of 25−30%, and the meta-derivative only reaches RCYs of ~20%.

The ortho-derivative gave a 2-fold higher RCY of ~60% than the para-derivative after a reaction time of 35 min. Obviously, this rise results from the ortho-effect alone. Considering kinetics,

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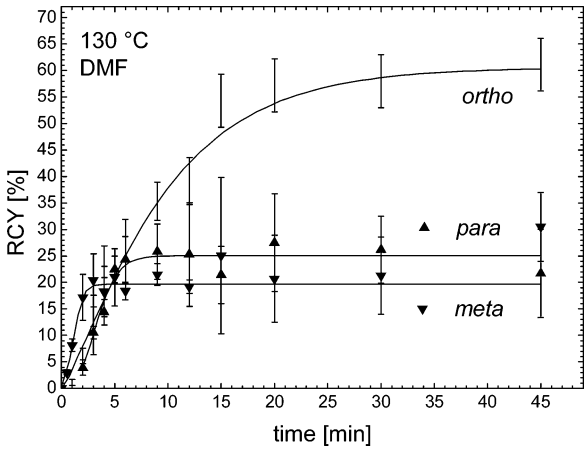


Figure 3. Dependence of the RCY on the substitution pattern of methoxyphenyl(2-thienyl)iodonium bromide (130 °C in DMF).

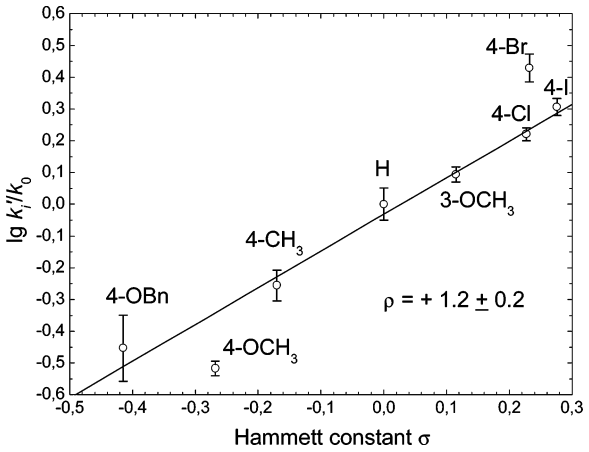


Figure 4. Hammett diagram for the ^{18}F-substitution on substituted aryl-(2-thienyl)iodonium bromides (130 °C in DMF).

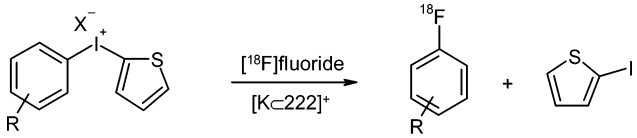
all precursors show relatively fast rates. The meta-derivative shows even a slightly higher initial reaction rate than the ortho- and para-derivative but ends in a lower RCY.

The methoxy group is obviously not able to stabilize a negatively charged transition state due to its electron-donating character. However, the aryl(2-thienyl)iodonium cation represents a positively charged initial state and can be stabilized by conjugation with ortho- and para-methoxy substituents. As a result, both positions show slower initial reaction rates but also a smaller tendency for decomposition. In contrast, the meta-derivative is more activated for the radiofluorination as well as for the decomposition by an ipso-attack of the counteranion, which reduces the amount of the precursor and results in low RCYs.

2.5. Influence of the Phenyl Substituents. The attack of the nca [^{18}F]fluoride on the diaryliodonium salt depends on the electronic character of the aromatic rings. If differences in electron density are present, the outcome will generally be a product ratio with a preference for the electron-poor group.[7−11] In this study the 2-thienyl group represents a highly electron-rich group, which directs the nucleophilic attack to the second, less electron-rich ring in the iodonium salt. A detailed insight in the influence of the electronic character on the nucleophilic ^{18}F-fluorination should be obtained by comparison of aryl(2-thienyl)iodonium bromides with substituted phenyl rings of systematically differing electron densities.

All aryl(2-thienyl)iodonium bromides were labeled under the above-mentioned optimal conditions. Expectedly, the RCY generally increases with a decrease of the electron density, with the ortho-methoxy derivative being an exception, which reaches an RCY of 61% (Table 2). This is probably due to the strong ortho-effect as discussed above. Based on the RCY the following series of substituents was obtained: 4-Br > H > 4-Cl > 2-OCH_3 > 4-I > 4-OBn > 4-CH_3 > 4-OCH_3 > 3-OCH_3. The differences of the substituents' effect on the reaction are more visible from a kinetic approach. A quantitative treatment of the total electronic effects (resonance and field) of a substituent is represented by the Hammett constant σ, a characteristic parameter for each substituent when attached to a benzene ring.[39−41]

Table 2. RCY and the First-Order Reaction Rates of Nucleophilic ^{18}F-Fluorination of Aryl(2-thienyl)iodonium Bromides in Dependence on Substituents (R) and Their Hammett Constants



R	σ[41]	RCY [%]	k_i [min^{-1}]
4-OBn	−0.42	36 ± 3	0.0305 ± 0.004
4-OMe	−0.28	29 ± 3	0.0263 ± 0.001
4-Me	−0.17	32 ± 2	0.0480 ± 0.004
H	0.00	64 ± 4	0.0860 ± 0.001
3-OMe	0.12	20 ± 3	0.1072 ± 0.006
4-Cl	0.23	62 ± 4	0.1437 ± 0.017
4-Br	0.23	70 ± 5	0.2325 ± 0.045
4-I	0.27	60 ± 8	0.1750 ± 0.020
2-OMe	-	61 ± 5	0.0518 ± 0.002

The Hammett constant is part of the Hammett equation, which is a *linear free-energy relationship*.

$$\log \frac{k_i}{k_0} = \sigma\rho \text{ (Hammett equation)}$$

k_0 is the rate constant or equilibrium constant for R = H, k_i is the constant for the substituent R, ρ is a constant for a given reaction under a given set of conditions (reaction parameter), and σ is the Hammett constant for the substituent R. The application of the Hammett treatment generally fails for the ortho-position because no steric aspects can be taken into account.

Therefore the reaction rate k_i values of the ^{18}F-fluorinations of the aryl(2-thienyl)iodonium bromides were determined by linear regression of the diagram $\ln(A_0/A_0 - A_t)$ versus time, where A_0 is the starting activity of the nca [^{18}F]fluoride and A_t is the activity of the [^{18}F]fluoroarene product at time t. The corresponding log k'/k_0 values were plotted against the Hammett substituent constants (cf. Figure 4).

The relationship in the Hammett diagram shows a reasonable good linear fit, which corresponds to the implication of the expected S_NAr mechanism of the ^{18}F-substitution on aryl(2-thienyl)iodonium salts. Furthermore, since ρ is larger than unity, the reaction is positively influenced by electron-withdrawing groups. Thus, the reaction parameter (slope) with $\rho = +1.2 \pm$

(39) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96−102.
(40) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191−261.
(41) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

0.2 confirms the nucleophilic mechanism over the range of the investigated substituents, even for electron-donating groups. The low absolute value of ρ implies a high reactivity, which causes a relatively low sensitivity with respect to substituent effects.[42] The high reactivity can be understood due to the high energetic level of the iodonium reaction center and is crucial for this reaction type. Consequently, the influence of substituents in the para-position has only a relatively marginal effect.

Besides the 4-methoxy group, the 4-bromo substituent gives the widest deviations. For the former this is presumably caused by its strong resonance stabilization of the initial state. The deviation of the 4-bromo derivative cannot completely be understood.

3. Summary

In a systematic approach 18 aryl(2-thienyl)iodonium salts were prepared and used as model precursors for nucleophilic nca ^{18}F-labeling of arenes. For the first time the highly electron-rich heteroaromatic 2-thienyl group was used in iodonium precursors for nca ^{18}F-fluorination reactions.

The 2-thienyl group offers the possibility of one-step ^{18}F-introduction into electron-rich arenes, e.g., [^{18}F]fluoroanisoles. It proved that the 2-thienyl group directs the nca [^{18}F]fluoride to a regiospecific attack of the *ipso*-carbon of the arylgroup, and consequently only the desired [^{18}F]fluoroarenes without any other radioactive side product were formed.

Optimization of the general reaction conditions shows a strong dependence on reaction parameters. In the case of different solvents, especially for DMSO the nonsuitability of this reaction type is explained with an electronic and a steric deactivation of the iodonium cation. For the ^{18}F-labeling via aryl(2-thienyl)-iodonium salts the following conditions are suggested: DMF, 25 mmol/L concentration of precursor, 130 °C. The necessary reaction time depends on the precursor molecule and ranges from 5 to 20 min.

The influence of counteranions was determined with bromides, iodides, tosylates, and triflates. The strong dependence on the counteranions indicated that the iodonium salts are not fully dissociated in the reaction mixture. At this point, the grade of dissociation was determined for the inorganic anions in d_6-DMF by NMR investigations. The bromides showed the highest dissociation and hence gave the best labeling results.

Investigations of the effect of the substitution pattern of the target arenes were made. Expectedly, ortho-substituted molecules showed a strong ortho-effect, which considerably enhanced the RCY even for these electron-rich molecules. In terms of kinetics, the meta-derivatives showed a faster initial reaction rate than the ortho- and para-derivative with almost similar rates. With regard to the ortho-effect and the S_NAr mechanism, *ortho*-substituted arenes appeared as ideal target molecules for this reaction type.

In terms of kinetics, the initial reaction rates of the ^{18}F-labeling reaction for all precursor bromide salts were quantified and correlated in a Hammett relationship. The Hammett diagram exhibited a linear relationship and a reaction parameter $\rho = +1.2 \pm 0.2$, which confirmed an expected nucleophilic aromatic substitution mechanism. Due to the activated ipso-aryl carbon, the high reactivity of this reaction type with aryl(2-thienyl)-iodonium salts led to a relatively low sensitivity to substituent effects.

In the case of electron-rich [^{18}F]fluoroarenes the 2-methoxyphenyl(2-thienyl)iodonium bromide gave the best result with 60% RCYs within 20−30 min. Based on the comparison of all precursors examined, the 4-bromophenyl(2-thienyl)iodonium bromide enabled the highest RCY of ∼70% forming 4-bromo-[^{18}F]fluorobenzene within 5−10 min.

4. Experimental Section

4.1. General. Unless otherwise noted all reagents and anhydrous solvents were purchased from Aldrich (Steinheim, Germany), Fluka (Buchs, Switzerland), or Merck (Darmstadt, Germany). They were used without further purification. Oxygen-18 enriched water (>95% enriched) was purchased from Chemotrade (Leipzig, Germany).

The syntheses of 4-benzyloxy-1-fluorobenzene,[43] 2-(diacetoxyiodo)-anisole,[24] 3-(diacetoxyiodo)anisole,[24] 4-(diacetoxyiodo)anisole,[24] 4-(diacetoxyiodo)toluene,[24] 4-iodo-1-(diacetoxyiodo)benzene,[25] 4-bromo-1-(diacetoxyiodo)benzene,[24] 4-chloro-1-(diacetoxyiodo)benzene,[24] 4-methoxyphenyl(2-thienyl)iodonium bromide,[16] 4-methoxyphenyl(2-thienyl)iodonium iodide,[16] 4-methylphenyl(2-thienyl)-iodonium bromide,[16] phenyl(2-thienyl)iodonium bromide,[16] and 4-chlorophenyl(2-thienyl)iodonium bromide[16] were performed as described in the literature, and the identity was confirmed by comparison of NMR data and/or melting points.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-200. The chemical shifts δ are in ppm relative to the solvents. Mass spectra were obtained on an Automass Multi III mass spectrometer. Melting points are uncorrected and were determined on a Mettler FP-61 and a Büchi Melting Point B-540, respectively. Elemental analyses (EA, microanalyses) were performed on a Leco CHNS-932 CHNS analyzer (Zentralabteilung für chemische Analysen, Forschungszentrum Jülich).

4.2. Syntheses. 4.2.1. 4-Benzyloxy-1-(diacetoxyiodo)benzene. The 4-benzyloxy-1-(diacetoxyiodo)benzene was synthesized by an oxidation of 4-benzyloxy-1-iodobenzene with sodium periodate.[24]

Yield: 2.83 g (66%). Melting point: 113 °C. ^{1}H NMR ($CDCl_3$): δ = 2.03 (s, 6H, CH_3), 5.15 (s, 2H, CH_2), 7.07 (d, 2H, H2 + H6), 7.39 − 7.47 (m, 5H, CH_{Ph}, H9 − H13), 8.03 (d, 2H, H3 + H5). ^{13}C NMR ($CDCl_3$): δ = 20.8 (2C, CH_3), 70.8 (CH_2), 112.3 (C, C1), 117.9 (2C, CH, C3 + C5), 127.9 (2C, CH, C9 + C13), 128.9 (CH, C11), 129.2 (2C, CH, C10 + C12), 136.2 (C, C8), 137.6 (2C, CH, C2 + C6), 161.8 (C, C4), 176.8 (2C, CO). MS: *m*/*z* 369 [M^+, 100]. $C_{17}H_{17}IO_5$ calculated: C, 47.7; H, 4.00. Found: C, 45.6; H, 3.71.

4.2.2. Aryl-2-thienyliodonium Bromides and Iodides. (Diacetoxyiodo)arene (2 mmol) and thiophene (6 mmol) were stirred in 10 mL of acetic acid anhydride at −30 °C. Concentrated sulfuric acid (0.5 mL) was added dropwise over 1 h. The mixture was allowed to warm up to 5 °C and further stirred at this temperature for 3 h.

The dark solution was poured into 15 mL of ice water. The organic compounds were extracted with ether and discarded. The aqueous layers were treated with activated coal for 10 min at 40 °C to become a clear solution.

To the filtered, clear solution 10 mL of a potassium bromide or a potassium iodide solution (25%) were added. After 1 h of storage in the refrigerator precipitates were collected and washed with acetone (small portion) and ether. The product was dried and stored in an exsiccator. The so stored precursors could be used for the ^{18}F-labeling without any further purification. For a recrystallization the compounds were dissolved in hot methanol and precipitated with ether.[12,17]

4.2.3. 2-Methoxyphenyl(2-thienyl)iodonium Bromide. Yield: 0.31 g (39%). Melting point: 174 °C. ^{1}H NMR (DMSO-d_6): δ = 3.91 (s,

(42) Exner, O. In *Advances in Linear Free Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1972; Chapter 1.

(43) Jones, B. *J. Chem. Soc.* **1938**, 1414−1417.

3H, OCH_3), 6.99 (t, 1H, 5-ar), 7.03 (t, 1H, 4-th), 7.23 (d, 1H, 3-ar), 7.55 (t, 1H, 4-ar), 7.78 (d, 1H, 5-th), 7.80 (d, 1H, 3-th), 8.21 (d, 1H, 6-ar). ^{13}C NMR (DMSO-d_6): δ = 57.3 (OCH_3), 104.9 (2-th), 112.3 (1-ar), 113.2 (3-ar), 123.6 (5-ar), 129.4 (4-th), 134.8 (4-ar), 136.0 (3-th), 137.2 (6-ar), 139.1 (5-th), 156.1 (2-ar). MS 317 [M^+, 100]. $C_{11}H_{10}$BrIOS, calculated: C, 33.3; H, 2.54. Found: C, 32.9; H, 2.46.

4.2.4. 2-Methoxyphenyl(2-thienyl)iodonium Iodide. Yield: 0.51 g (58%). Melting point: 183 °C. ^{1}H NMR (DMSO-d_6): δ = 3.93 (s, 3H, OCH_3), 7.01 (t, 1H, 5-ar), 7.06 (t, 1H, 4-th), 7.25 (d, 1H, 3-ar), 7.58 (t, 1H, 4-ar), 7.84 (d, 1H, 3-th), 7.84 (d, 1H, 5-th), 8.24 (d, 1H, 6-ar). ^{13}C NMR (DMSO-d_6): δ = 57.4 (OCH_3), 102.6 (2-th), 111.1 (1-ar), 113.3 (3-ar), 123.7 (5-ar), 129.6 (4-th), 135.1 (4-ar), 136.5 (3-th), 137.2 (6-ar), 139.7 (5-th), 156.2 (2-ar). MS 317 [M^+, 100]. $C_{11}H_{10}I_2$OS, calculated: C, 29.8; H, 2.27. Found: C, 29.5; H, 2.21.

4.2.5. 3-Methoxyphenyl(2-thienyl)iodonium Bromide. Yield: 0.54 g (67%). Melting point: 161 °C. ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3H, OCH_3), 7.11 (t, 1H, 4-th), 7.16 (d, 1H, 4-ar), 7.39 (t, 1H, 5-ar), 7.74 (d, 1H, 2-ar), 7.88 (d, 1H, 5-th), 7.89 (d, 1H, 3-th), 7.96 (d, 1H, 6-ar). ^{13}C NMR (DMSO-d_6): δ = 56.7 (OCH_3), 107.7 (2-th), 117.8 (1-ar), 121.0 (4-ar), 123.2 (2-ar), 127.3 (5-ar), 130.0 (4-th), 132.8 (6-ar), 136.6 (3-th), 139.7 (5-th), 160.9 (3-ar). MS 317 [M^+, 100]. $C_{11}H_{10}$BrIOS, calculated: C, 33.3; H, 2.54. Found: C, 33.6; H, 2.47.

4.2.6. 3-Methoxyphenyl(2-thienyl)iodonium Iodide. Yield: 0.32 g (36%). Melting point: 155 °C. ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3H, OCH_3), 7.11 (t, 1H, 4-th), 7.17 (d, 1H, 4-ar), 7.39 (t, 1H, 5-ar), 7.74 (d, 1H, 2-ar), 7.87 (d, 1H, 5-th), 7.89 (d, 1H, 3-th), 7.96 (d, 1H, 6-ar). ^{13}C NMR (DMSO-d_6): δ = 56.7 (OCH_3), 107.6 (2-th), 117.8 (1-ar), 121.0 (4-ar), 123.2 (2-ar), 127.3 (5-ar), 129.4 (4-th), 132.2 (6-ar), 136.6 (3-th), 139.7 (5-th), 160.9 (3-ar). MS 317 [M^+, 100]. $C_{11}H_{10}I_2$OS, calculated: C, 29.8; H, 2.27. Found: C, 30.2; H, 2.56.

4.2.7. 4-Benzyloxyphenyl(2-thienyl)iodonium Bromide. Yield: 0.52 g (55%). Melting point: 202 °C. ^{1}H NMR (DMSO-d_6): δ = 5.08 (s, 2H, CH_2), 7.05 (2H, 3-ar), 7.06 (1H, 4-th), 7.25−7.40 (m, 5H, phenyl), 7.83 (d, 1H, 3-th), 7.89 (d, 1H, 5-th), 8.01 (d, 2H, 2-ar). ^{13}C NMR (DMSO-d_6): δ = 70.07 (CH_2), 104.6 (2-th), 110.4 (1-ar), 118.3 (2C, 3-ar), 128.3 (2C, 9-ar), 128.6 (11-ar), 128.9 (2C, 10-ar), 129.7 (4-th), 136.5 (8-ar), 136.7 (3-th), 137.0 (3-th), 139.6 (5-th), 161.1 (4-ar). MS 393 [M^+, 100]. $C_{17}H_{14}$BrIOS, calculated: C, 43.2; H, 2.98. Found: C, 43.2; H, 2.93.

4.2.8. 4-Iodophenyl(2-thienyl)iodonium Bromide. Yield: 0.17 g (18%). Melting point: 162 °C. ^{1}H NMR (DMSO-d_6): δ = 7.04 (t, 1H, $H4_{Th}$), 7.56 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.81 (d, 1H, $H3_{Th}$), 7.88 (d, 1H, $H5_{Th}$), 8.14 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$). ^{13}C NMR (DMSO-d_6): δ = 97.1 (C, $C4_{ar}$), 106.3 (C, $C2_{Th}$), 120.8 (C, $C1_{ar}$), 129.7 (CH, $C4_{Th}$), 136.0 (2C, CH, $C3_{ar}$ + $C5_{ar}$), 136.4 (CH, $C3_{th}$), 137.2 (2C, CH, $C2_{ar}$ + $C6_{ar}$), 139.6 (CH, $C5_{th}$). MS 413 [M^+, 100]. $C_{10}H_7BrI_2S$, calculated: C, 24.4; H, 1.43. Found: C, 23.8; H, 1.39.

4.2.9. 4-Bromophenyl(2-thienyl)iodonium Bromide. Yield: 0.33 g (36%). Melting point: 162 °C. ^{1}H NMR (DMSO-d_6): δ = 7.05 (t, 1H, 4-th), 7.61 (d, 2H, 3-ar), 7.81 (d, 1H, 3-th), 7.88 (d, 1H, 5-th), 8.06 (d, 2H, 2-ar). ^{13}C NMR (DMSO-d_6): δ = 106.3 (2-th), 120.9 (1-ar), 125.9 (4-ar), 129.7 (4-th), 134.6 (2C, 3-ar), 136.6 (3-th), 136.9 (2C, 2-ar), 139.6 (5-th). MS 366 [M^+, 100], 365 (97). $C_{10}H_7Br_2IS$ calculated: C, 26.9; H, 1.58. Found: C, 26.7; H, 1.65.

4.2.10. Aryl-2-thienyliodonium Tosylates and Triflates. An appropriate aryl-2-thienyliodonium bromide (2.5 mmol) and *cyclo*-hexene (2.5 mmol) were suspended in 8 mL in pure methanol. *p*-Toluenesulfonic acid monohydrate (3 mmol) or trifluoromethane sulfonic acid (3 mmol) was added while the mixture stirred. Finally, 30% aqueous hydrogen peroxide solution (3.4 mmol) was added. The mixture was heated to reflux until complete dissolution. The reflux was continued for 15 min further.

Under reduced pressure the solvent and most of the water were removed. The crude product was dissolved in methanol at 60 °C, and the solution quickly cooled down. The product was precipitated with addition of ether and *n*-hexane.[26]

4.2.11. 2-Methoxyphenyl(2-thienyl)iodonium Tosylate. Yield: 0.9 g (76%). Melting point: 140 °C. ^{1}H NMR (DMSO-d_6): δ = 2.24 (s, 3H, CH_3-Ots), 3.94 (s, 3H, OCH_3), 7.03 (t, 1H, 5-ar), 7.10 (2H, 2-Ots), 7.11 (1H, 4-th), 7.28 (d, 1H, 3-ar), 7.44 (d, 2H, 3-Ots), 7.60 (t, 1H, 4-ar), 7.89 (d, 1H, 3-th), 7.90 (d, 1H, 5-th), 8.27 (d, 1H, 6-ar). ^{13}C NMR (DMSO-d_6): δ = 21.2 (CH_3-Ots), 57.5 (OCH_3), 100.5 (2-th), 109.7 (1-ar), 113.4 (3-ar), 123.8 (5-ar), 125.9 (2C, 2-Ots), 128.6 (2C, 3-Ots), 129.8 (4-th), 135.5 (4-ar), 137.2 (6-ar), 137.3 (3-th), 138.3 (4-Ots), 140.5 (5-th), 145.8 (1-Ots), 156.3 (2-ar). MS 317 [M^+, 100]. $C_{18}H_{17}IO_4S_2$, calculated: C, 44.3; H, 3.51. Found: C, 43.6; H, 3.39.

4.2.12. 2-Methoxyphenyl(2-thienyl)iodonium Triflate. Yield: 2.03 g (98%). Melting point: 170−175 °C. ^{1}H NMR (DMSO-d_6): δ = 3.95 (s, 3H, OCH_3), 7.04 (t, 1H, 5-ar), 7.10 (1H, 4-th), 7.28 (d, 1H, 3-ar), 7.61 (t, 1H, 4-ar), 7.89 (d, 1H, 3-th), 7.90 (d, 1H, 5-th). ^{13}C NMR (DMSO-d_6): δ = 57.4 (OCH_3), 100.4 (2-th), 109.6 (1-ar), 113.4 (3-ar), 121.1 (CF_3), 123.8 (5-ar), 129.8 (4-th), 135.5 (4-ar), 137.17 (6-ar), 137.23 (3-th), 140.5 (5-th), 156.3 (2-ar). MS 317 [M^+, 100]. $C_{12}H_{10}F_3IO_4S_2$, calculated: C, 30.9; H, 2.16. Found: C, 30.7; H, 2.13.

4.2.13. 3-Methoxyphenyl(2-thienyl)iodonium Tosylate. Yield: 1.1 g (93%). Melting point: 161 °C. ^{1}H NMR (DMSO-d_6): δ = 2.07 (s, 3H, CH_3-Ots), 3.57 (s, 3H, OCH_3), 7.01 (d, 2H, 3-Ots), 7.06 (t, 1H, 4-th), 7.09 (t, 1H, 4-ar), 7.33 (t, 1H, 5-ar), 7.38 (d, 2H, 2-Ots), 7.68 (d, 1H, 6-ar), 7.81 (s, 1H, 2-ar), 7.85 (d, 1H, 3-th), 7.96 (d, 1H, 5-th). ^{13}C NMR (DMSO-d_6): δ = 20.7 (CH_3-OTs), 55.8 (OCH_3), 100.7 (2-th), 117.7 (4-ar), 119.2 (1-ar), 120.0 (2-ar), 125.4 (2C, 2-Ots), 126.5 (6-ar), 128.1 (2C, 3-Ots), 129.5 (4-th), 132.3 (5-ar), 137.1 (3-th), 137.8 (4-Ots), 140.3 (5-th), 145.1 (1-Ots), 160.2 (3-ar). MS 317 [M^+, 100]. $C_{18}H_{17}IO_4S_2$, calculated: C, 44.3; H, 3.51. Found: C, 44.6, H, 3.61.

4.2.14. 3-Methoxyphenyl(2-thienyl)iodonium Triflate. Yield: 0.94 g (81%). Melting point: 88 °C. ^{1}H NMR (DMSO-d_6): δ = 3.73 (s, 3H, OCH_3), 7.11 (t, 1H, 4-th), 7.14 (t, 1H, 4-ar), 7.38 (t, 1H, 5-ar), 7.72 (d, 1H, 6-ar), 7.85 (s, 1H, 2-ar), 7.89 (d, 1H, 3-th), 7.99 (d, 1H, 5-th). ^{13}C NMR (DMSO-d_6): δ = 56.3 (OCH_3), 101.1 (2-th), 118.3 (4-ar), 119.5 (1-ar), 120.5 (CF_3), 126.9 (6-ar), 130.0 (4-th), 132.8 (5-ar), 137.7 (3-th), 140.8 (5-th), 160.7 (3-ar). MS 317 [M^+, 100]. $C_{12}H_{10}F_3IO_4S_2$, calculated: C, 30.9; H, 2.16. Found: C, 30.6; H, 2.21.

4.2.15. 4-Methoxyphenyl(2-thienyl)iodonium Tosylate. Yield: 1.01 g (93%). Melting point: 185 °C. ^{1}H NMR (DMSO-d_6): δ = 2.21 (s, 3H, CH_3-Ots), 3.72 (s, 3H, OCH_3), 6.98 (d, 2H, 3-ar), 7.04 (d, 2H, 3-Ots), 7.08 (t, 1H, 4-th), 7.41 (d, 2H, 2-Ots), 7.87 (d, 1H, 3-th), 7.94 (d, 1H, 5-th), 8.10 (d, 2H, 2-ar). ^{13}C NMR (DMSO-d_6): δ = 21.2 (CH_3-Ots), 56.1 (OCH_3), 101.8 (2-th), 108.7 (1-ar), 117.7 (2C, 3-ar), 125.9 (2C, 2-Ots), 128.5 (2C, 3-Ots), 129.9 (4-th), 137.2 (2C, 2-ar), 137.3 (3-th), 138.1 (4-Ots), 140.2 (5-th), 145.1 (1-Ots), 162.3 (4-ar). MS 317 [M^+, 100]. $C_{18}H_{17}IO_4S_2$, calculated: C, 44.3; H, 3.51. Found: C, 43.8; H, 3.50.

4.2.16. 4-Methoxyphenyl(2-thienyl)iodonium Triflate. Yield: 0.44 g (37%). Melting point: 93 °C. ^{1}H NMR (DMSO-d_6): δ = 3.72 (s, 3H, OCH_3), 7.00 (d, 2H, 3-ar), 7.10 (t, 1H, 4-th), 7.86 (d, 1H, 3-th), 7.93 (d, 1H, 5-th), 8.10 (d, 2H, 2-ar). ^{13}C NMR (DMSO-d_6): δ = 56.1 (OCH_3), 101.6 (2-th), 108.6 (1-ar), 117.8 (2C, 3-ar), 121.0 (CF_3), 129.9 (4-th), 137.2 (2C, 2-ar), 137.3 (3-th), 140.2 (5-th), 162.4 (4-ar). MS 317.2 [M^+, 100]. $C_{12}H_{10}F_3IO_4S_2$, calculated: C, 30.9; H, 2.16. Found: C, 31.1; H, 2.26.

4.3. Radioactive Synthesis. For all radioactive experiments no-carrier-added [^{18}F]fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction via bombardment of an isotopically enriched [^{18}O]water target (1.3 mL) with a 17 MeV proton beam at the JSW BC 1710 cyclotron (Forschungszentrum Jülich). Nca [^{18}F]fluoride (30−50 MBq) in 10−50 μL of water, 10 mg (26.5 μmol) of Kryptofix 2.2.2, and 13.25 μL of a 1 M aqueous K_2CO_3 solution in a 5-mL Wheaton glass vial were dried three times by azeotropic evaporation with 0.8 mL anhydrous acetonitrile at 80 °C and 800 mbar under a constant argon flow.

4.4. General ^{18}F-Labeling Procedure. The appropriate precursor (25 μmol) was dissolved in 1.0 mL anhydrous DMF. This solution was added by a syringe through a silicone septum into a closed vial

Table 3. R_f-Values and Solvent Systems (given as v/v Ratios) of the Relevant Reference Compounds for Radio-TLC on Silica Gel Plates

compound	solvent system (v/v)	R_f
4-benzyloxy-1-fluorobenzene	*n*-hexane/ether (2:1)	0.79
	n-hexane/ethyl acetate (3:1)	0.91
1-chloro-4-fluorobenzene	*n*-hexane	0.52
1-bromo-4-fluorobenzene	*n*-hexane/ether (1:1)	0.85
1-fluoro-4-iodobenzene	*n*-hexane/ether (1:1)	0.78

Table 4. *k*-Values, Solvent Systems (in v/v Ratios), and Flow Rates of the Relevant Reference Compounds for Radio-HPLC

compound	solvent system (v/v); flow [ml/min]	*k'*
2-fluoroanisole	acetonitrile/water (40:60); 0.7	2.44
3-fluoroanisole	acetonitrile/water (40:60); 0.7	3.82
4-fluoroanisole	acetonitrile/water (40:60); 0.7	3.32
4-benzyloxy-1-fluorobenzene	acetonitrile/water (60:40); 1.0	3.39
4-methyl-1-fluorobenzene	acetonitrile/water (40:60); 0.7	4.81
fluorobenzene	acetonitrile/water (40:60); 0.7	3.00
1-chloro-4-fluorobenzene	acetonitrile/water (40:60); 0.7	5.30
1-bromo-4-fluorobenzene	acetonitrile/water (40:60); 0.7	6.65
4-iodo-1-fluorobenzene	acetonitrile/water (40:60); 0.7	8.84

containing the dry nca [^{18}F]fluoride and stirred at 130 °C under 1100 mbar of argon. The light overpressure was necessary to avoid losses of volatile products (e.g., [^{18}F]fluoroanisoles). At the appropriate times aliquots (10 μL) of the reaction mixture were taken by syringe and quenched with 50 μL of cold HPLC-eluent. The aliquots were analyzed by reversed-phase radio-HPLC using a Phenomenex Luna 5μ C18 column (3 mm × 250 mm) and acetonitrile/water (40/60) as eluent. RCYs of nonvolatile products were also determined by radio-TLC.

All ^{18}F-labeled products were identified by their nonradioactive reference compounds via comparison of their UV signals with the radioactive signals. Since [^{18}F]fluoroanisoles, 4-[^{18}F]fluorotoluene, and [^{18}F]fluorobenzene are volatile and their RCYs are not determinable by radio-TLC, these products were only analyzed by radio-HPLC.

Analytical radio-HPLC was performed on a system consisting of a Knauer WellChrom Mini-Star K-500 HPLC pump connected with a Rheodyne-Injector block 7125 and a Merck/Hitachi UV/vis photometer L4000. Radioactivity was measured by an NaI(Tl) well-type scintillation detector (EG&G ACE Mate) connected to the outlet of the UV detector. Radio-TLC was carried out on Merck silica gel TLC sheets with the solvent mixture of *n*-hexane/diethylether in various v/v ratios. The radio-TL-chromatograms were measured on an Instant Imager (Packard, USA). The *k*- and R_f-values of the appropriate fluoro compounds are listed in Tables 3 and 4 .

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