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Convenient preparation of (4-iodophenyl)aryliodonium salts

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ABSTRACT

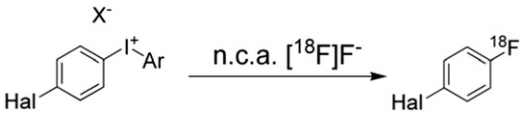
The (4-iodophenyl)aryliodonium salts bis(4-iodophenyl)iodonium, (4-iodophenyl)(4-methoxy-phenyl) iodonium and (4-iodophenyl)(2-thienyl)iodonium, each with three different anions, were prepared using 4-iodo-1-[hydroxy(tosyloxy)iodo]benzene. These are suitable precursor molecules for electrophilic radiofluorination and other 4-iodophenylation reactions, whose products can subsequently serve as reagents for transition metal catalysed cross coupling and other metal organic reactions.

1. Introduction

Diaryliodonium salts are known for over a century. Besides their function as cationic photo initiators and several applications as biologically active molecules, they can serve as powerful arylating agents. They can react with a variety of nucleophiles, including the fluoride ion.[1] This enables an elegant pathway for no-carrier-added (n.c.a.) labelling with fluorine-18,[2,3] an important radionuclide for in vivo molecular imaging with positron emission tomography (PET).[3,4] The properties of these diaryliodonium salts, amongst other hypervalent iodine species, have been extensively reviewed.[5–9]

Today, many iodonium salts are easily accessible via a broad range of reaction sequences including a variety of modern one-pot procedures.[9] However, several of these compounds, especially those with functional groups sensitive to oxidative conditions and strong acids and/or those exhibiting a complex substitution pattern, require more sophisticated synthetic strategies.

(4-Halophenyl)aryliodonium salts are of special interest since nucleophilic substitution reactions with [^{18}F]fluoride on these compounds deliver *p*-[^{18}F]fluorohalobenzenes as products (Scheme 1), which can be used as excellent precursors for following metal organic and cross coupling reactions. This has been demonstrated for n.c.a. 4-[^{18}F]fluorobromobenzene, transferred to lithium- and Grignard-derivatives, and 4-[^{18}F]fluoroiodobenzene coupled by Sonogashira, Stille, Suzuki and N-arylation reactions, yielding complex ^{18}F-labelled molecules.[10–15]



Scheme 1. Synthesis of 1-halo-4-[^{18}F]fluorobenzene from a diaryliodonium precursor (Hal=Br, I; X$^-$=TsO$^-$, TfO$^-$, Br$^-$, Cl$^-$).

A salt of the bis(4-iodophenyl)iodonium cation **1** (Fig. 1) first appeared in the literature in 1958, however, without an anion or synthetic conditions specified.[16] The first detailed report on the synthesis of these iodonium salts was given by Wüst et al. in 2003 describing two procedures.[11] The first one makes use of iodyl sulfate, which is not stable and whose synthesis involves several hazardous materials. The second route is the oxidation of 1,4-diiodobenzene with peracetic acid to 4-(diacetoxyiodo)-1-iodobenzene and subsequent coupling with iodobenzene by Kitamura's procedure.[17] Recently, Wagner and Sanford reported the synthesis of bis(4-iodophenyl)iodonium tetrafluoroborate[18] making use of a one-pot procedure earlier described by Bielawski et al.[19]

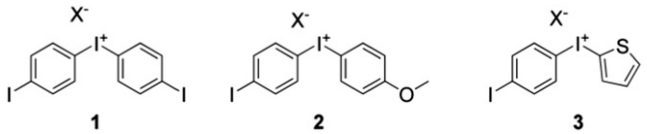


Fig. 1. Target structures, X$^-$=TsO$^-$ (a); TfO$^-$ (b); Br$^-$ (c).

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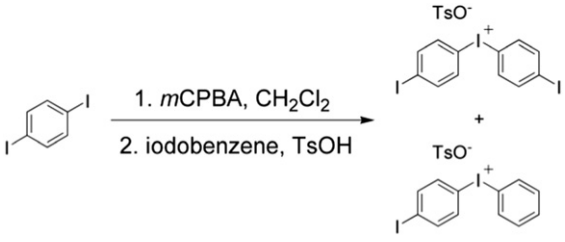
Although this procedure generally proves to be very effective, it is not applicable for n.c.a. radiofluorination since the use of tetrafluoroborate could principally cause isotopic dilution of the n.c.a. [^{18}F]fluoride.[20] Therefore, and also for reasons of general interest in alternative methods, another reaction was developed here, making use of 4-iodo-1-[hydroxy(tosyloxy)iodo]benzene (*p*I-HTIB), a derivative of Koser's reagent ([hydroxy(tosyloxy)iodo]benzene, HTIB). This reagent was directly coupled with iodobenzene in presence of an excess of triflic acid to yield compound **1b**.

In the reaction between iodonium salts and nucleophiles the latter will preferably be bound to the more electron deficient ring.[21] Thus, salts of the (4-iodophenyl)(4-methoxyphenyl)iodonium cation **2** and the (4-iodophenyl)(2-thienyl)iodonium cation **3** are also suitable precursor molecules for the synthesis of 4-[^{18}F]fluoroiodobenzene. Additionally, this reaction is influenced by the nature of the counterion and the optimal one differs in various reactions.[11,21,22] For ^{18}F-fluorination reactions tosylate (a), triflate (b) and bromide (c) are commonly used.[2,11,22] Since it was not possible to predict, which of the salts would deliver the best reaction yields in given case, each of the possible salts was prepared.

2. Results

In a first attempt to synthesize bis(4-iodophenyl)iodonium tosylate, 1,4-diiodobenzene was reacted with iodobenzene in presence of *para*-toluenesulfonic acid monohydrate (TsOH) and *meta*-chloroperbenzoic acid (*m*CPBA) in a two-step one-pot procedure as described by Olofsson's group (Scheme 2).[23,24] For this purpose, 1,4-diiodobenzene was oxidized with *m*CPBA and then iodobenzene and TsOH were added to carry out the coupling step. This sequential procedure was chosen in order to avoid an oxidation of the iodobenzene that would result in the formation of (4-iodophenyl)phenyliodonium tosylate. In spite of this precaution, however, it was still not possible to isolate the desired compound without this by-product (cf. Scheme 2). There are two possible explanations for this fact. Either the oxidation of the 1,4-diiodobenzene is incomplete and iodobenzene is oxidized by residual *m*CPBA, or a ligand transfer occurs between the oxidized 1,4-diiodobenzene and iodobenzene, which would also result in an oxidation of the latter. Since this side reaction could not be eliminated by several attempts, including an elevated temperature for the oxidation step, cooling for the coupling step, prolonged reaction times for both steps and the choice of triflic acid instead of TsOH, this concept was considered not suitable.



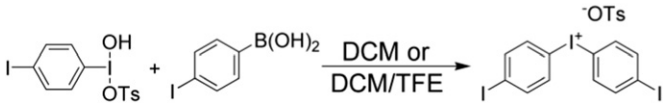
Scheme 2. Preparation of **I** as tosylate salt by a one-pot procedure.

Thus, a selective mono oxidation of 1,4-diiodobenzene seemed rather to be the method of choice. An attempt to synthesize 4-iodo-1-(diacetoxyiodo)benzene (*p*I-DIB) by an oxidation with peracetic acid delivered the product accompanied with an unidentified by-product. An NMR-spectrum could not be recorded due to the insolubility of the solid product in common NMR solvents. However, it melted under decomposition at about 220 °C and combustion analyses delivered a higher amount of oxygen (21.33±0.04%) than calculated (14.29%) for the target compound, meaning that the oxidation of both iodine groups is predominating. When Willgerodt tried to obtain *p*I-DIB by treatment of 4-iodo-1-(dichloroiodo)-benzene with boiling acetic acid he obtained a similar result.[25] He assumed that the product was a mixture of 1,4-bis(diacetoxyiodo)-benzene and 4-iodo-1-iodoxybenzene, what is also consistent with our analytical data.

An alternative oxidation procedure is offered by Koser and Wettach in an early reference, describing the synthesis of *p*I-HTIB amongst others by a ligand transfer reaction.[26] This reaction can simply be performed by stirring the appropriate iodoaryl together with Koser's reagent in dichloromethane (DCM). The major drawback of this reaction is the insolubility of Koser's reagent in DCM, which makes the workup somewhat difficult since the product is also insoluble. Later, Carman and Koser made use of 2-[hydroxy(tosyloxy)iodo]toluene, which is soluble in DCM.[27] This reagent proved to be superior to HTIB, since the product can be collected by simple filtration followed by washing with DCM and diethyl ether. Using this reagent *p*I-HTIB could be produced in almost quantitative yields (Scheme 3), however, containing residual traces of 2-[hydroxy(tosyloxy)iodo]toluene. This can also react with boronic acids forming iodonium compounds, why it was removed by recrystallisation from acetonitrile/methanol 80:20, yielding ca. 68% pure *p*I-HTIB. Although the mother liquor was still containing much of the desired product, the crystallization step was not further optimised since purity was the main objective.

Scheme 3. Preparation of *p*I-HTIB by ligand exchange.

Following the method as depicted in Scheme 3, *p*I-HTIB was reacted with 4-iodophenylboronic acid in DCM (Scheme 4) according to a procedure offered by Carroll et al.[28] Although the product was formed by this reaction, a maximum achieved yield of about 30% was considered rather low. Alternatively, reactions of *p*I-HTIB with 4-methoxyphenylboronic acid or 2-thienylboronic acid delivered the corresponding iodonium salts **2a** and **3a** (cf. Fig. 1) in yields of 57% and 72%, respectively.



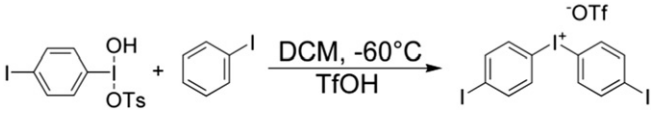
Scheme 4. Preparation of bis(4-iodophenyl)iodonium tosylate by reaction of *p*I-HTIB with 4-iodophenylboronic acid.

According to Dohi et al. the reactivity of iodine-III species can be promoted by the addition of 2,2,2-trifluoroethanol (TFE).[29] Thus, the latter reaction (Scheme 4) was also run in a mixture of TFE and DCM (50:50).[23] This solvent proved to be superior for the direct reaction of *p*I-HTIB with anisole and thiophene, yielding the iodonium salts **2a** (coloured beige[30]) and **3a** in yields of 89% and 90%, respectively. In case of the reaction with iodobenzene, however, no improvement was observed even if the boronic acid was used for further promotion of reactivity. Therefore, the reaction was alternatively run in pure TFE. Surprisingly, this resulted not only in an enhancement of the reaction yield, but also in the formation of a by-product, which is proposed to be (4-iodophenyl)(4-phenylboronic acid)iodonium tosylate due to its *m*/*z* value of 450.90 in mass analysis (corresponding to the iodonium cation).

According to Ito et al., derivatives of Koser's reagent can oxidize aromatic compounds in fluoroalcoholic media by a single electron

transfer (SET) process.[31] Since this by-product was only observed in reactions containing 4-iodophenylboronic acid, it is supposed that the SET process takes place on this reagent. In order to test for this, 4-iodophenylboronic acid was reacted with HTIB in pure TFE. Indeed the by-product was formed, while (4-iodophenyl)phenyliodonium tosylate (m/z=407.00) was still found as the main product. Alternatively, a biphenylic structure containing two iodine substituents and one boronic acid moiety could possibly have been formed. This is, however, not very likely due to the fact that the product crystallizes along with the desired product and has a high polarity (found on TLC). No steps were conducted to isolate the by-product in a pure form.

Since TFE did improve the reactivity of *p*I-HTIB in an undesired way it was tried to convert this reagent in a more specific reaction. In fact, by reacting *p*I-HTIB directly with iodobenzene in presence of triflic acid in DCM **1b** could be produced with up to 85% yield (Scheme 5). The reaction required an excess of triflic acid of 5–10 equiv.. The product can be purified by extraction with chloroform and subsequent precipitation with diethyl ether.



Scheme 5. Preparation of bis(4-iodophenyl)iodonium triflate by direct reaction of *p*I-HTIB with TfOH and iodobenzene.

The triflate salts **2b** and **3b** were prepared by an anion metathesis starting from the corresponding tosylates **2a** and **3a** analogously to the in situ anion exchange reported by Zhu et al..[23] The bromide salts of **1**–**3** were prepared by dissolving the tosylates **2a**, **3a** and the triflate **1b** in a water/methanol mixture (50:50) and subsequent precipitation of the iodonium bromide by addition of a solution of the potassium bromide in the same solvent.[32]

3. Conclusions

Using *p*I-HTIB, a derivative of Koser's reagent, it was possible to synthesize bis(4-iodophenyl)iodonium (**1**) as triflate salt in high yields of about 90%. Furthermore, a series of unsymmetrical iodonium salts of particular interest for ^{18}F-radiochemistry could be synthesized starting from the same reagent. Those included salts of the (4-iodophenyl)(2-thienyl)iodonium cation **3**, another versatile precursor for 4-iodo-[^{18}F]fluorobenzene, and further on three different salts of the so far not described (4-iodophenyl)(4-methoxyphenyl)iodonium cation **2**.

4. Experimental

4.1. General

All chemicals were purchased from Sigma–Aldrich® except for triflic acid, which was acquired from Merck KGaA. 2-[Hydroxy(tosyloxy)iodo]toluene was prepared according to Carman and Koser.[27] All reactions were run under exclusion of light.

NMR spectra were recorded on a Varian-Inova 400 spectrometer. The chemical shifts are given in parts per million relative to the solvent signal. Mass spectra were recorded by a Finnigan MAT 95 spectrometer and the elemental analyses were performed on a Vario El Cube. Melting points were determined on a Büchi B-540 melting point analyser.

4.2. Synthesis of 4-iodo-1-[hydroxy(tosyloxy)iodo]benzene (pI-HTIB)

2-[Hydroxy(tosyloxy)iodo]toluene (4.88 g, 12 mmol) and 1,4-diiodobenzene (3.96 g, 12 mmol) were dissolved in 30 mL of DCM. It took several minutes until the components completely dissolved. A white precipitate formed slowly. After stirring at ambient temperature for 7 days the white solid was collected by filtration, washed with dichloromethane and diethyl ether and dried at the air (6.1 g, 98%). The crude product was recrystallised from acetonitrile/methanol 80:20 (4.9 g white solid, 69%).

Mp 124–125 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73 (bs, 1H), 7.89 (4H), 7.41 (d, 2H, J 8.8 Hz), 7.06 (d, 2H, J 6.8 Hz), 2.23 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 145.6, 140.2, 139.7*, 138.3, 136.4, 128.6, 125.9, 123.2, 100.9, 94.6*, 21.2 (*traces of unreacted 1,4-diiodobenzene). HRMS (FTMS+ESI), m/z calcd for $C_6H_5I_2O^+$ ([M–TsO$^-$]$^+$), 346.84243; found, 346.84248. The substance is poorly ionisable. The sample should be dissolved immediately before analysis. Anal. calcd for $C_{13}H_{12}I_2O_4S$: C, 30.24; H, 2.33; S, 6.19. Found: C, 30.23; H, 2.36; S, 6.23.

4.3. General procedure for the synthesis of iodonium tosylates from boronic acids and pI-HTIB

To a stirred suspension of *p*I-HTIB in DCM (10 mL/mmol) the corresponding boronic acid (1 equiv) was added in one portion. After stirring for 4 h the solvent was reduced to half of its initial volume and the product precipitated by the addition of diethyl ether (20 mL/mmol). The solids were collected by filtration, washed with diethyl ether and dried at the air.

*4.3.1. Bis(4-iodophenyl)iodonium tosylate (**1a**).* White solid (27%). Mp 190 °C (dec) (Lit.[11]: 152–154 °C). The NMR-data were consistent with literature.[11]

*4.3.2. (4-Iodophenyl)(4-methoxyphenyl)iodonium tosylate (**2a**).* White solid (57%). Mp 175–178 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.11 (d, 2H, J=9.2 Hz), 7.89 (d, 2H, J=8.4 Hz), 7.81 (d, 2H, J=8.4 Hz), 7.42 (d, 2H, J=8.0 Hz), 7.06 (d, 2H, J=8.0 Hz), 7.01 (d, 2H J=9.2 Hz), 3.74 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 162.4, 146.1, 140.6, 138.0, 137.7, 136.9, 128.5, 125.9, 117.9, 116.8, 106.0, 100.3, 56.1, 21.2. HRMS (FTMS+p ESI), m/z calcd for $C_{13}H_{11}I_2O^+$ ([M–TsO$^-$]$^+$), 436.88938; found, 436.88927. HRMS (FTMS–p ESI), m/z calcd for $C_7H_7O_3S^-$, 171.01214; found, 171.01206. Anal. calcd for $C_{20}H_{18}I_2O_4S$: C, 39.49; H, 2.98; S, 5.27. Found: C, 39.16; H, 2.85; S, 5.33.

*4.3.3. (4-Iodophenyl)(2-thienyl)iodonium tosylate (**3a**).* White solid (72%). Mp 150 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.02 (d, 1H, J=2.4 Hz), 7.96–7.93 (m, 3H), 7.84 (d, 2H, J=8.4 Hz), 7.43 (d, 2H, J=8.0 Hz), 7.13 (t, 1H, J=4.8 Hz), 7.07 (d, 2H, J=7.6 Hz), 2.24 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 146.1, 141.0, 140.7, 138.0, 137.9, 136.7, 130.1, 128.5, 125.9, 119.2, 101.3, 100.6, 21.2. HRMS (FTMS+p ESI), m/z calcd for $C_{10}H_7I_2S^+$ ([M–TsO$^-$]$^+$), 412.83578; found, 412.83518. HRMS (FTMS–p ESI), m/z calcd for $C_7H_7O_3S^-$, 171.01214; found, 171.01205. Anal. calcd for $C_{17}H_{14}I_2O_3S_2$: C, 34.95; H, 2.42; S, 10.98. Found: C, 34.91; H, 2.41; S, 10.90.

4.4. General procedure for the synthesis of iodonium tosylates from arenes and pI-HTIB

To a stirred suspension of *p*I-HTIB and 1 equiv. of the arene in DCM the desired amount of TFE was added (V(DCM)+V(TFE)= 10 mL/mmol). After stirring for 4 h the solvent was reduced to half of its volume under reduced pressure and the product was precipitated by the addition of diethyl ether (20 mL/mmol). The product was filtered, washed with diethyl ether and dried at the air.

*4.4.1. (4-Iodophenyl)(4-methoxyphenyl)iodonium tosylate (**2a**).* In DCM/TFE 50:50: Beige solid (90%).

In DCM/TFE 97:3: White solid (68%).

*4.4.2. (4-Iodophenyl)(2-thienyl)iodonium tosylate (**3a**).* In DCM/TFE 60:40: White solid (89%).

4.5. Synthesis of bis(4-iodophenyl)iodonium triflate (1b)

A mixture of *p*I-HTIB (1.04 g, 2 mmol) and iodobenzene (0.41 g, 2 mmol) in 40 mL DCM was cooled to −78 °C. Subsequently triflic acid[33] (1.76 mL, 20 mmol) was added slowly and the reaction mixture was allowed to reach ambient temperature by stirring over night without refreshing the cooling bath. Upon addition of the triflic acid the reaction mixture turned to a dark blue colour (iodine-III intermediate), which changed to red upon completion. The product mixture was diluted with chloroform and water and the organic components three times extracted with chloroform. The unified organic phase was dried over $MgSO_4$, the solvent was largely removed under reduced pressure and the product was precipitated as white solid by addition of diethyl ether. This was separated by filtration, washed with diethyl ether and dried at the air. The material could be used for labelling reactions without further purification. 1.12 g Beige solid, (85%). Mp 142–145 °C (dec) (Lit.:[11] 185–187 °C). The NMR-data were consistent with the literature.[11]

4.6. General procedure for the anion metathesis to iodonium triflates

To a stirred solution of the iodonium tosylate in methanol (2 mL/mmol) a solution of 2 equiv of triflic acid in DCM (5 mL/mmol) was added. After stirring for 10 min the solution was washed with water, dried over $MgSO_4$ and the solvent reduced to half of its initial volume. The product was precipitated by the addition of diethyl ether (50 mL/mmol iodonium compound), collected by filtration, washed with diethyl ether and dried at the air.

*4.6.1. (4-Iodophenyl)(4-methoxyphenyl)iodonium triflate (**2b**).* Beige solid (75%). Mp 240–242 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.12 (d, 2H, J=8.8 Hz), 7.90 (d, 2H, J=8.4 Hz), 7.84 (d, 2H, J=8.4 Hz), 7.03 (d, 2H, J=8.8 Hz), 3.75 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 162.5, 140.7, 137.7, 136.8, 121.1 (quartet, J=1.28 kHz), 117.9, 116.8, 105.9, 100.4, 56.1. ^{19}F NMR (400 MHz, DMSO-d_6) δ: −77.8. HRMS (FTMS+p ESI), m/z calcd for $C_{13}H_{11}I_2O^+$ ([M−TfO$^-$]$^+$), 436.88938; found, 436.88924. HRMS (FTMS−p ESI), m/z calcd for CF_3O_3S: 148.95257; found: 148.95250. Anal. calcd for $C_{14}H_{13}F_3I_2O_4S$: C, 28.69; H, 1.89; S, 5.47. Found: C, 29.49; H, 1.98; S, 5.50.

*4.6.2. (4-Iodophenyl)(2-thienyl)iodonium triflate (**3b**).* White solid (69%). Mp 147–148 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.03–8.02 (m, 1H), 7.97–7.93 (m, 3H), 7.87–7.85 (m, 2H), 7.15–7.13 (m, 1H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 141.0, 140.7, 138.0, 139.6, 130.1, 121.1 (quartet, J=1.28 kHz), 119.1, 101.2, 100.7. ^{19}F NMR (400 MHz, DMSO-d_6) δ: −77.8. HRMS (FTMS+p ESI), m/z calcd for $C_{10}H_7I_2S^+$ ([M−TfO$^-$]$^+$), 583.84737; found, 583.84737. HRMS (FTMS−p ESI), m/z calcd for CF_3O_3S: 148.95257; found: 148.95254. Anal. calcd for $C_{11}H_7F_3I_2O_3S_2$: C, 23.50; H, 1.26; S, 11.41. Found: C, 23.58; H, 1.23; S, 11.76.

4.7. General procedure for the anion metathesis to iodonium bromides

A solution containing 20% of potassium bromide in a hot methanol–water mixture (50:50) was prepared. The appropriate iodonium tosylate was dissolved under heating in a minimum quantity of the same solvent. To this the potassium bromide solution was added and the iodonium bromide immediately started precipitating. Due to the temperature sensitivity of iodonium compounds, this process should be performed fast. It is advisable to cool the mixture below 50° after addition of potassium bromide.

*4.7.1. Bis(4-iodophenyl)iodonium bromide (**1c**).* White solid (75%). Mp 195–197 °C. NMR: Due to low solubility in DMSO-d_6 no clear NMR-spectrum could be recorded. HRMS (FTMS+p ESI), m/z calcd for $C_{12}H_8I_3$ ([M−Br$^-$]$^+$), 532.77549; found, 532.77512. HRMS (FTMS−p ESI), m/z calcd for Br$^-$, 80.91629; found, 80.91675. Anal. calcd for $C_{12}H_8BrI_3$: C, 23.52; H, 1.32. Found: C, 24.25; H, 1.46.

*4.7.2. (4-Iodophenyl)(4-methoxyphenyl)iodonium bromide (**2c**).* White solid (82%). Mp 195–196 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.06 (d, 2H, J=8.8 Hz), 7.86 (d, 2H, J=8.4 Hz), 7.79 (d, 2H, J=8.4 Hz), 6.98 (d, 2H, J=8.8 Hz), 3.73 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 162.1, 140.4, 137.4, 136.7, 118.9, 117.7, 108.1, 99.8, 56.1. HRMS (FTMS+p ESI), m/z calcd for $C_{13}H_{11}I_2O^+$ ([M−Br$^-$]$^+$), 436.88938; found, 436.88894. HRMS (FTMS−p ESI), m/z calcd for Br$^-$, 80.91629; found, 80.91676. Anal. calcd for $C_{13}H_{11}BrI_2O$: C, 30.20; H, 2.14. Found: C, 29.46; H, 2.07.

*4.7.3. (4-Iodophenyl)(2-thienyl)iodonium bromide (**3c**).* White crystals (96%). Mp 186–187 (dec) (Lit.[22]: 162 °C). The NMR-data were consistent with literature.[22]

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33. Caution: triflic acid is a highly corrosive liquid, which also destroys silicon septa.