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COPPER-CATALYSED FLUORINATION OF THE PREPARED SYMMETRICAL DIARYLIODONIUM SALTS

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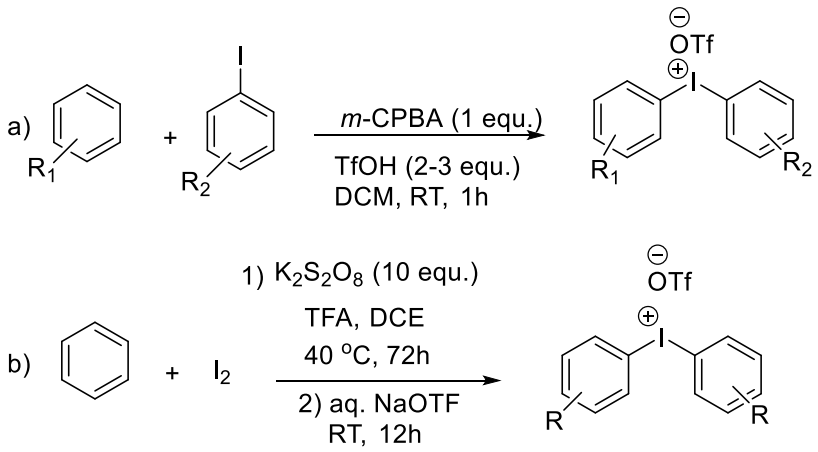
Abstract
A series of symmetrical diaryliodonium salts were prepared successfully in high yields following the Olofsson procedure. These salts were stirred with aqueous solution of NaBF4 to exchange the OTf- anion to BF4-. Different conditions were investigated to fluorinate these salts, including fluorinating reagents, solvents, reaction time, and solvents. Only p-fluoroarenes without any isomers were obtained in high yields during the fluorination of these salts.

Keywords: Symmetrical, Diaryliodonium salts, fluorination, fluoro arenes.

Introduction

Diaryliodonium salts Ar_2I^+ have attracted considerable attention since they are mild and effective reagents that can be involved in many reactions, such as arylation and fluorination. (Abudken et. al., 2024) These non-toxic, air- and moisture-stable iodine (III) compounds are commercially available and can be easily prepared. (Rakshanda et.al, 2023) One-pot procedures are the most straightforward approach to obtaining diaryliodonium salts among the various current ways of preparation which entail using meta-chloroperoxybenzoic acid (mCPBA) (**Scheme 1-a**) (Olofsson et.al, 2007) or potassium peroxodisulfate ($K_2S_2O_8$) (**Scheme 1-b**) (Hossain et.al, 2006) with the existence of arene and a strong acid for oxidising iodine or an Ar-I.



Scheme 1: Different protocols for the synthesis of Diaryliodonium salts

Organic compounds that have undergone fluorination are widely recognised for their distinct stability, reactivity, and biological characteristics. As a result, C-F bonds, especially aryl

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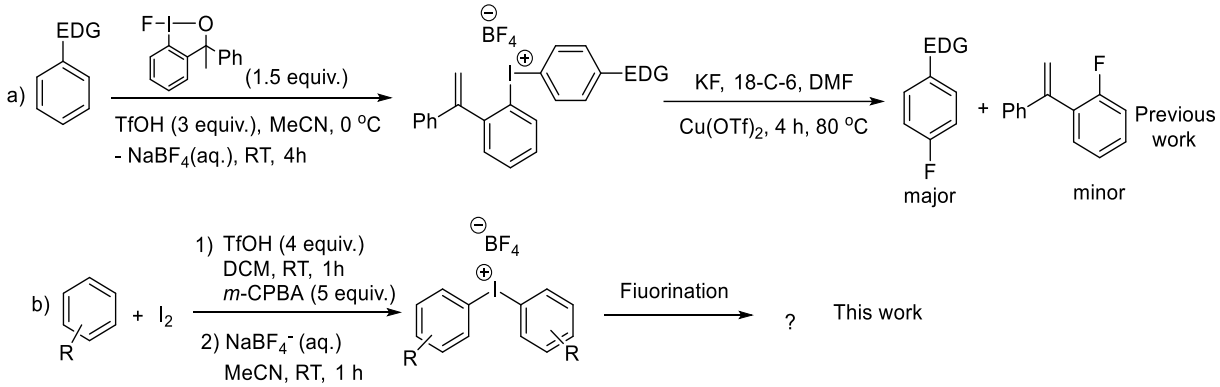
fluorides, are more common in medicines, imaging agents (PET), and agrochemicals. (Dong et.al, 2021) The fact that 20–30% of medications contain at least one F atom indicates the significance of fluorine to the pharmaceutical industry. The development of synthetic techniques for Ar-F bond synthesis is still poor despite the rising need for organofluorine compounds. One of the biggest challenges is developing mild and effective methods for delivering fluorine to electron-rich aromatic rings utilizing cheap nucleophilic fluoride sources like KF and CeF. (Ichiishi et.al, 2013) Two of the most used nucleophilic fluorination techniques in the laboratory are halide exchange between Ar-Cl and metal fluorides (Sharninghausen et.al, 2020) and reactions of diaryliodonium salts Ar_2I^+X with MF. (Adams et.al, 1999) The need for high temperatures and the low reactivity of electron-rich substrates often limit both of these processes. Pike first reported the fluorination of Ar_2I^+X salts in 1995 (Pike et.al., 1995), and it has now become a widely accepted technique for delivering [18F] fluoride to aromatic compounds. Recently, we reported fluorination of Ar_2I^+X using $Cu(OTf)_2$ to produce Ar-F in high yield. However, a miner fluorinated amount of the other ring moiety was obtained by using unsymmetrical diaryliodonium salts (Scheme **2-a**). (Abudken et.al., 2020) To overcome this problem, we introduce a simple and efficient pathway to the synthesis of symmetrical diaryliodonium salt using a modified protocol of Olofsson and co-worker (Olofsson et al., 2007) and fluorination of these salts using Cu catalyst (Scheme **2-b**).



Scheme 2: Fluorination of aryliodonium salt

Experimental

Analytical Techniques

Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400. ASAP (Atmospheric Solids Analysis probe) mass spectra were recorded on a Xevo QT mass spectrometry. GC analysis was conducted on a PERKIN ELMER AUTOSYSTEM XL using a Restek XTI-5 (30 m, 0.25 mm ID, 0.25 µm) column and He as the carrier gas. The hold oven temperature 40 ºC hold 5 min, ramp 15 ºC/min to 250 ºC, and hold for 5 min.

Materials

The chemicals, reagents, and solvents utilised in this study were all obtained from Sigma-Aldrich and used without further purification.

Methods

1. General procedure for preparation of $Ar_2I^+BF_4$

25 mL flask was charged with Iodine (I_2) (1 equvi.), mCPBA (5 equiv.) and DCM (5 mL). This mixture was cooled to 0°C before TfOH (4 equiv.) was added dropwise. Then, it was warmed to RT before substrate (4 equiv.) was added. The reaction was left to react for 1 h at RT. After that, the crude product was stirred with saturated solution of $NaBF_4$ for another 1 h. The organic layer was separated via separating fennel and the aqueous layer was extract with DCM (3 x 5 mL). The organic layer was combined, dried over $MgSO_4$ and concentrated via vacuum. This crude was stirred with diethyl ether for 15 min. to obtain the final product as a white solid. The pure product was analysed via ^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR.

General procedure for fluorination of symmetrical salt

In a glovebox $Ar_2I^+BF_4$ (0.1 mmol, 1 equvi.), $Cu(OTf)_2$ (0.02 mmol, 0.2 equiv.), CeF (0.11 mmol, 1.1 equvi.) and 18-C-6 (0.04 mmol, 0.4 equiv.) was placed in 10 mL Schlenk flask and dissolved in DMSO (3 mL). This solution was left to react for 1 h at 80 °C. After cooling to RT, the final crude solution was filtered and determined via GC and analysed by mass spectroscopy.

Plotting calibration curves to determine the fluorinated products by GC

A stock solutions (0.2 mmol in 10 mL DMSO) were prepared from each fluorinated products (**2a-2f**). From these stock solutions, a series of diluted solutions of each component were prepared by gradual dilution to obtain a series of concentrations ranged from 0.1 to 0.00025 mmol. Each component was analysed by GC. The graphs for each fluorinated products were plotted by drawing the number of equivalents (1 equivalent = 0.02 mmol) against the area for each concentration.

Results and Discussions

Synthesis of Ar_2I^+ BF_4^-

A series of symmetrical aryliodonium salts were prepared based on Olofsson and co-worker procedure. This procedure includes oxidation of iodine (I_2) to iodine (III) using m- CPBA before adding arene with electron donating group and triflic acid (TfOH). High yields of $Ar_2I^+OTf^-$ were obtained in only one hour at RT. Anion exchange step was required to replace OTf^- with BF_4^- due to higher reactivity and solubility of Ar_2I^+ BF_4^-. This could be achieved by stirring aryliodonium triflate salt with saturated solution of $NaBF_4^-$ for 1 hour at RT. ^{19}F-NMR (δ_F) spectra shows the absence of CF_3 peak between -78 to -80 corresponding to OTf^- anion and appear a peak between -148 to -150 corresponding to BF_4^- anion (Figure 1). All Ar_2I^+ BF_4^- were confirmed by ^{1}H-NMR and ^{13}C-NMR spectrum. Scheme 3 shown the prepared compounds

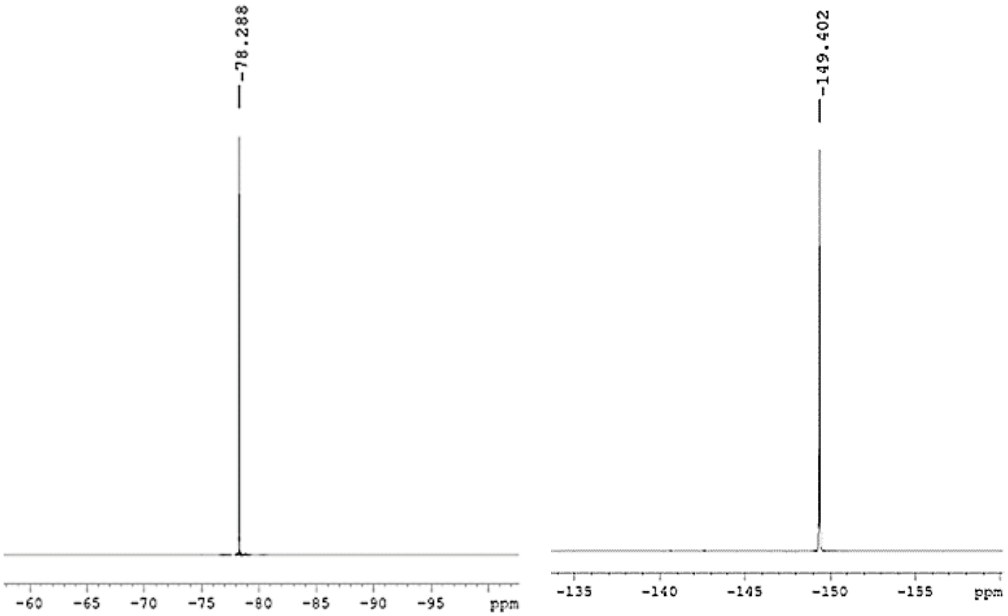
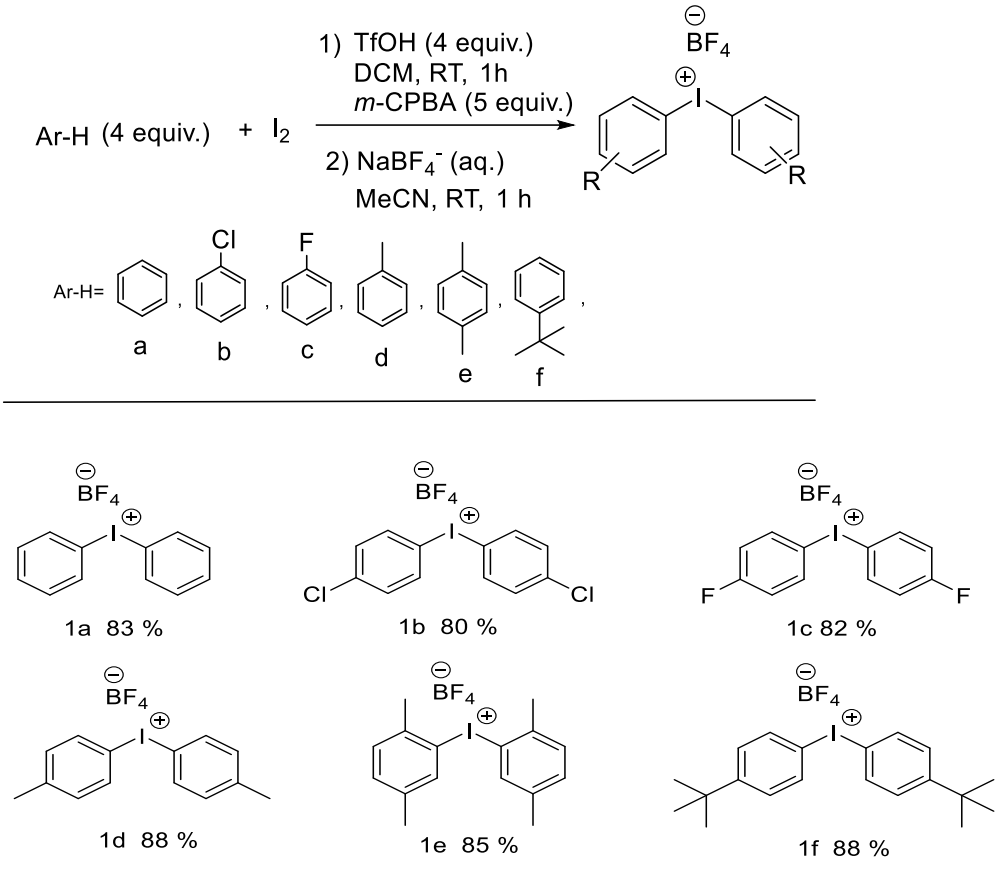


Fig.1: ^{19}F-NMR spectra of OTf^- (-78.2 ppm) and BF_4^-(-149.4 ppm)

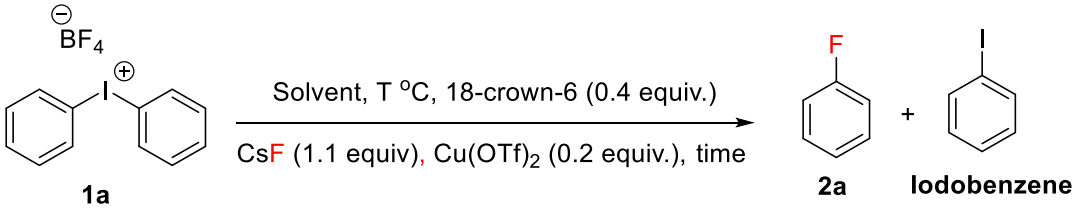


Scheme 3: Synthesis of Ar_2I^+ BF_4 from arenes and I_2

Fluorination of salts

In order to fluorinate the prepared salts, diphenyliodonium tetrafluoroborate **1a** was firstly investigated using different conditions such as, fluorinating reagent, solvents, reaction time and temperature in the presence of $Cu(OTf)_2$ (0.2 equiv.) and 18-crow-6 (0.4 equiv.) and the crude products were analysed using GC and mass spectroscopy. (Sanford et.al, 2013) In the beginning, diphenyliodonium tetrafluoroborate **1a** was reacted with different fluorinating reagent (Table 1, entry 1-4) using DMA as a solvent at RT for 24 h. No results was obtained when AgF and Me_4NF were used as a fluorinating reagents (entry 1 and 2). A small amount of fluorobenzene **2a** was detected by GC (7 %) with potassium fluoride (entry 3). The amount of fluorinating product was increased slightly when CsF was used (10 %) as seen in entry 4. The fluorination of **1a** was also investigated by screening different solvents with CsF as a fluorinating reagent at RT for 24 h (entry 5-8). The yield of fluorobenzene was increased slightly from 10 to 12 % when MeCN was used as a solvent (entry 5). This value was raised to 22 % after using DMF (entry 6). However, the yield of **2a** reduced to 13 % when THF was used (entry 7). Again, the fluorinating product **1a** was increased dramatically to 34 % with DMSO (entry 8). In entry 9, the reaction temperature was increased to 40 ^oC with reducing the time of the reaction to 6 h rather than 24 h. The fluorobenzene was obtained in 39 %. Raising the temperature of the reaction to 60 ^oC for 6 h leads to improve the yield of **2a** to 70 % (entry 10). Reducing the reaction time 6 h to 2 h with the same temperature (60 ^oC) (entry 11) gave only 53 % of **2a** and a peak at 280.89 m/z was observed in Mass spectra corresponding to the starting material salt **1a**. Raising the temperature to 80 ^oC for 2 h (entry 12), high yield of **1a** was produced (83 %). The same amount of products was obtained when the reaction time was reduced to 1 h (entry 13). After that, when the temperature was increased to 100 ^oC for 1 h (entry 14), the yield was reduced to 71 % and a small peak at 154.08 m/z was observed. It was believed that the 1,1'-biphenyl was formed due to coupling of fluorobenzene and iodobenzene molecules and this coupling could be happened at high temperature in the presence of $Cu(OTf)_2$ (Ullmann reaction). (Lewis et.al, 2017). When the reaction time was decreased to 0.5 h in entry 15, only 44 % of product was obtained. 1,1'-biphenyl and **1a** were also observed as a small peaks in Mass spectrum.

Table 1: Optimization conditions for the fluorination of **1a**

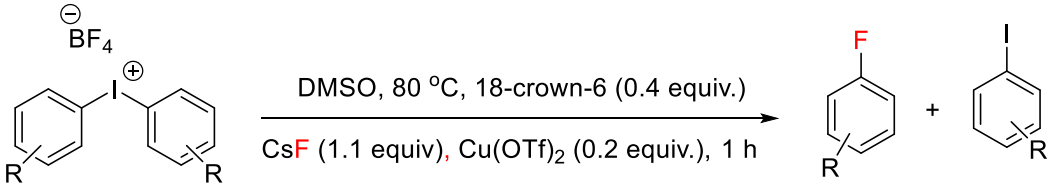


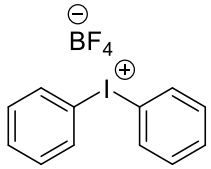
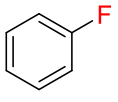
Entry	Flourine resource	solvent	T (°C)	Time (h)	Yield (%)
1	AgF	DMA	RT	24	-

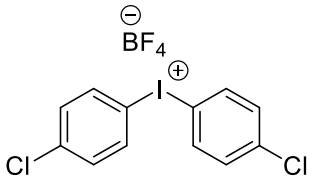
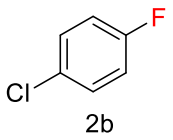
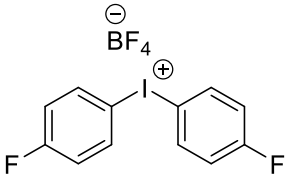
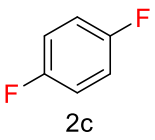
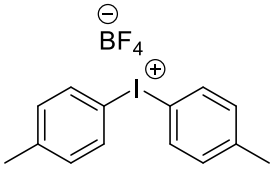
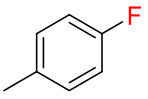
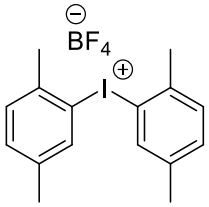
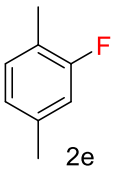
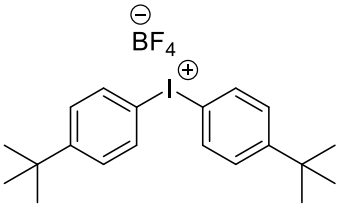
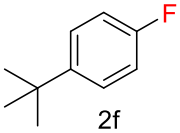
2	Me_4NF	DMA	RT	24	-
3	KF	DMA	RT	24	7
4	CsF	DMA	RT	24	10
5	CsF	MeCN	RT	24	12
6	CsF	DMF	RT	24	22
7	CsF	THF	RT	24	13
8	CsF	DMSO	RT	24	34
9	CsF	DMSO	40	6	39
10	CsF	DMSO	60	6	70
11	CsF	DMSO	60	2	53
12	CsF	DMSO	80	2	83
13	CsF	DMSO	80	1	83
14	CsF	DMSO	100	1	71
15	CsF	DMSO	100	0.5	44

Once optimum conditions have been achieved, each of the symmetrical prepared salts **1a** to **1f** were fluorinated using CsF and 0.2 equiv. $Cu(OTf)_2$ in DMSO at 80 °C for only 1 h (Table 2). High yields of fluorinated products was obtained and determined via GC and analysed by mass spectroscopy.

Table 2: Fluorination of symmetrical iodonium salts



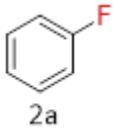
Entry	Substrate	Fluorinated products	Yield %
1		 2a	83

2		 2b	77
3		 2c	76
4		 2d	88
5		 2e	81
6		 2f	90

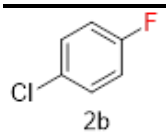
Conclusions

Six symmetrical diaryliodonium salts were prepared from the reaction of arenes with I_2 in the presence of m-CPBA to oxidized I_2 from I(I) to I(III). High yield of products were produced after exchanging of the counter-anion to BF_4. These salts were confirmed by ^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR spectroscopy. Before the fluorination process, the optimum conditions were investigated. It was found that the best conditions were used DMSO as a solvent in the presence of CeF as a fluorinating reagent for 1 h at 80 ^{o}C. The final crude products was determined via Gas Chromatography and analyzed via Mass Spectroscopy. High yields (76-90) of para fluorinated products was produced under the optimum conditions.

Analysing data for the fluorinated products

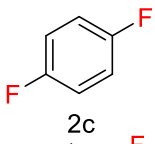

2a

The general procedure for the fluorination of symmetrical salt was followed. **2a** was obtained in 83 % yield. The flourobenzene peak on GC was shown at 3.22 min. Mass spectroscopy (ASAP) m/z (M, C_6H_5F, 96.04).



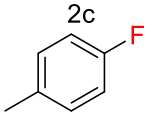
2b

The general procedure for the fluorination of symmetrical salt was followed. **2b** was obtained in 77 % yield. The **2b** peak on GC was shown at 8.12 min. Mass spectroscopy (ASAP) m/z (M, $C_6H^{35}ClF$, 130), (M, $C_6H^{37}ClF$, 132).



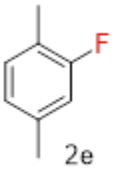
2c

The general procedure for the fluorination of symmetrical salt was followed. **2c** was obtained in 76 % yield. The **2c** peak on GC was shown at 3.97 min. Mass spectroscopy (ASAP) m/z (M, $C_6H_4F_2$, 114.03).



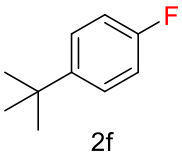
2d

The general procedure for the fluorination of symmetrical salt was followed. **2d** was obtained in 88 % yield. The **2d** peak on GC was shown at 6.23 min. Mass spectroscopy (ASAP) m/z (M, C_7H_7F, 110.05).



2e

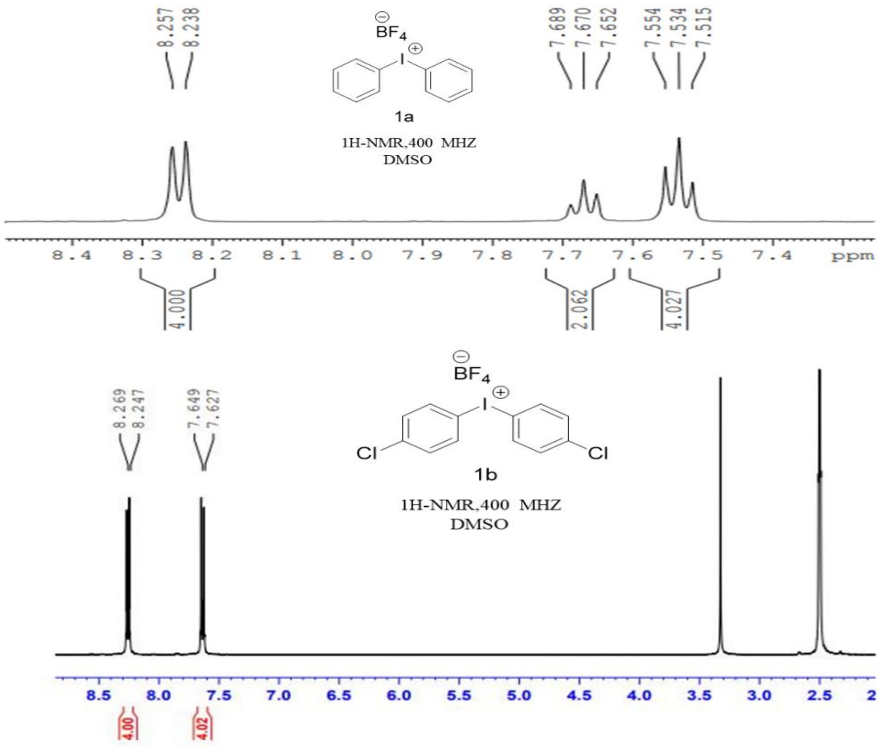
The general procedure for the fluorination of symmetrical salt was followed. **2e** was obtained in 81 % yield. The **2e** peak on GC was shown at 8.31 min. Mass spectroscopy (ASAP) m/z (M, C_8H_9F, 124.06).

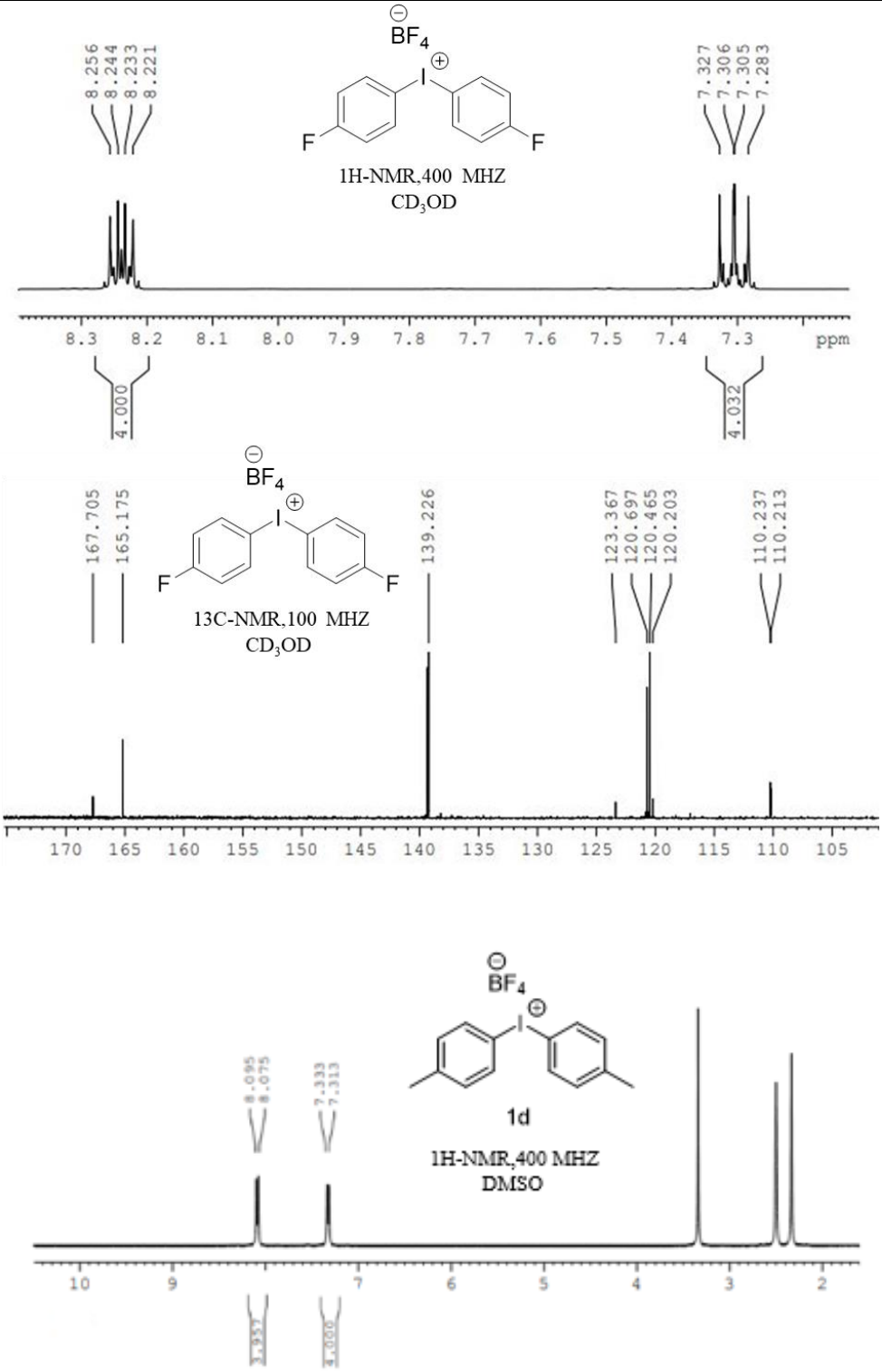


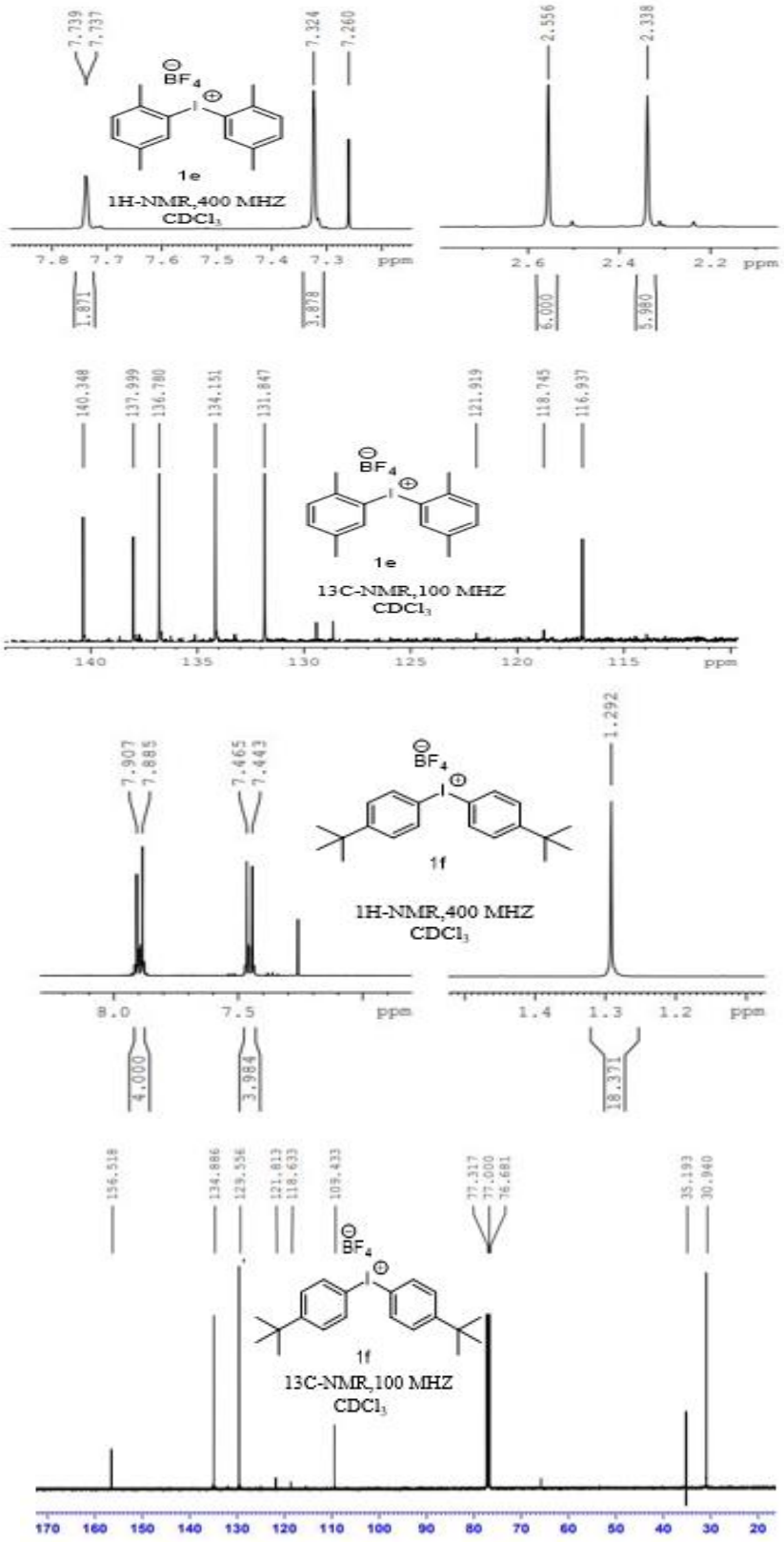
2f

The general procedure for the fluorination of symmetrical salt was followed. **2f** was obtained in 90 % yield. The **2f** peak on GC was shown at 10.61 min. Mass spectroscopy (ASAP) m/z (M, $C_{10}H_{13}F$, 152.13).

NMR spectrum of the symmetrical diaryliodonium salt







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