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Research paper

One-pot Synthesis of Unsymmetrical Diaryliodonium Tetrafluoroborate Salts Bearing an Isoxazole Moiety from Aryl Boronic Acids

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Abstract

Hypervalent iodine compounds exhibit attractive features of low cost, mild and selective reagents in organic synthesis. These reagents serve as environmentally benign alternatives to toxic heavy-metal based oxidants and expensive organometallic catalysts. The practical and simple synthesis of unsymmetrical diaryl iodonium tetrafluoroborate salts is described. This synthetic method has allowed the production of isoxazole tetrafluoroborate salts from readily available aryl boronic acids without an extra anion exchange step in acceptable yields of 45% and 50%.

Keywords: *Hypervalent; iodonium; unsymmetrical; isoxazole; tetrafluoroborate*

1. Introduction

The first organic hypervalent iodine compound, (dichloroiodo) benzene was prepared by German chemist Conrad Willgerodt by reacting iodobenzene with ICl_3.[1] This was rapidly followed by the discovery of other important hypervalent iodine compounds such as (diacetoxyiodo) benzene, iodosylbenzene, 2-iodoxybenzoic acid (IBX) and diaryliodonium salts.[2–4] The next major contributor to the field was Beringer and co-workers, with their pioneering work to improve synthetic routes and applications of hypervalent iodine compounds for various organic transformations.[5] The discovery of Dess-Martin periodinane (DMP) as a mild and non-toxic oxidation reagent by Dess and Martin in the 1980s was a major breakthrough in hypervalent iodine chemsistry.[6] Since then, synthetic chemistry related to such compounds has received considerable attention. According to IUPAC nomenclature, hypervalent iodine compounds are generally classified according to the oxidation state of the iodine and are denoted with a lambda notation.[7] Diaryliodonium salts are one of the most important λ^3 hypervalent compounds. For example, they have been widely employed as a precursors in fluorination reactions especially in the field of positron emission tomography.[8,9] The general structure of λ^3-iodane diaryliodonium salts is shown in Figure **1**. It is referred to as a symmetrical salt if $R^1 = R^2$ and unsymmetrical salt if $R^1 \neq R^2$ and can be classified as 8-I-2 cationic species according to the Martin-Arduengo *N-X-L* rule, with two aryl moieties associated with an anion X^-.[10,11]

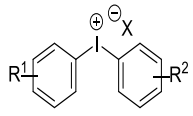

Figure 1: General structure of diaryliodonium salts.

Diaryliodonium salts can be prepared by several different approaches and most of them are carried out under acidic conditions.[5,12] The widely employed strategy for the synthesis of such compound requires two or three steps, with initial oxidation of the aryl iodide to an iodine(III) compound followed by ligand exchange reaction with an arene or organometallic reagent to afford a diaryiodonium salt.[5,13] In many cases, anion exchange is required in order to obtain a suitable anion for further reaction.[14] The one-pot strategy described herein provides access to the preparation of unsymmetrical diaryl iodonium tetrafluoroborate salts in acceptable yields without an extra anion exchange step.

2. Experimental Section

2.1. General experimental procedures

All the chemicals, reagents and solvents for the synthesis of compounds were analytical grade and used without further purification. NMR spectra were acquired on either Bruker Avance 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) equipped with BBFO probe, Bruker Avance III HD 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz, ^{19}F at 470 MHz) equipped with BBFO probe or Bruker Avance III 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) equipped with TCI cryoprobe. The chemical shifts (δ) are reported in parts per million (ppm) and are quoted relative to centre of the residual non-deuterated solvent peak for δ_H ($CDCl_3$: 7.26 ppm; DMSO: 2.50 ppm) and δ_C ($CDCl_3$: 77.16 ppm; DMSO: 39.52 ppm). Chemical shifts δ_F are quoted relative to $CFCl_3$ (δ_F $CFCl_3$:0.00 ppm). ^{13}C NMR spectra were recorded using the DEPT Q or UDEFT pulse sequence with broadband ^{1}H decoupling. ^{19}F{^{1}H} spectra were recorded with inverse-gating, to avoid errors on the integrals. Coupling constants (*J*) are given in

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Hertz (Hz). Signal splitting patterns are described as: br s (broad singlet), d (doublet) or s (singlet). Spectroscopic data were assigned based on the combination of one- and two-dimensional experiments (HSQC and HMBC). IR spectra were recorded using the ATR technique on Shimadzu IR Affinity-1S FTIR spectrometer. High and low resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service, Swansea or at the University of St Andrews on a Waters Micromass LCT time of flight mass spectrometer coupled to a Waters 2975 HPLC system. Values are reported as a ratio of mass to charge (*m/z*).

2.2. X-ray crystallography

All diffraction data were collected by using a Rigaku FR-X Ultrahigh brilliance Microfocus RA generator/confocal optics and Rigaku XtaLAB P200 system, with Mo Kα radiation (λ = 0.71075 Å). Intensity data for all samples were collected using ω steps accumulating area detector images spanning at least a hemisphere of reciprocal space. All data were corrected for Lorentz polarization effects. A multiscan absorption correction was applied by using CrystalClear[15] or CrysAlisPro.[16] Structures were solved by Patterson (PATTY)[17] or direct (SIR2004, SIR2011)[18,19] methods and refined by full-matrix least-squares against F^2 (SHELXL-2013).[20] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the CrystalStructure[21] interface.

2.2. Synthesis of methyl 3-methoxyisoxazole-5-carboxylate (2)[22]

K_2CO_3 (2.9 g, 21.0 mmol, 1.5 eq) and CH_3I (1.3 mL, 21.0 mmol, 1.5 eq) were added to a solution of methyl 3-hydroxyisoxazole-5-carboxylate (**1**) (2.0 g, 13.9 mmol, 1.0 eq) in DMF (10 ml) at 0 °C. After 14 h stirring at rt, the mixture was poured into an ice-cold aqueous solution of HCl (0.5 M, 100 mL) and extracted into Et_2O (5 × 80 mL). The combined organic layers were washed with a saturated aqueous solution of Na_2CO_3 (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a light yellow crystalline solid, which was purified by silica gel column chromatography (petroleum ether/Et_2O, 80:20), affording methyl-3-methoxyisoxazole-5-carboxylate (**2**) (1.45 g, 66%) as colourless crystalline solid: $\mathbf{R_f}$ 0.71 (petroleum ether/Et_2O, 70:30, UV/$KMnO_4$); **mp** 72-73 °C [Lit.[22] 70 °C]; δ_H (500 MHz, $CDCl_3$) 6.53 (1H, s, H-4), 4.02 (3H, s, H-8), 3.94 (3H, s, H-7); δ_C (125 MHz, $CDCl_3$) 172.2 (C-3), 160.5 (C-5), 157.2 (C-6), 100.8 (C-4), 57.6 (C-8), 53.0 (C-7); **HRMS** *m/z* (ESI^+), found: $[M+Na]^+$ 180.0266, $C_6H_7NO_4Na$ requires $[M+Na]^+$ 180.0273. These data are in accordance with the literature.[22]

2.3. Synthesis of 5-hydroxymethyl-3-methoxyisoxazole (3)[23]

$NaBH_4$ (1.51 g, 40.0 mmol, 2.5 eq) was added to a solution of methyl 3-methoxyisoxazole-5-carboxylate (**2**) (2.50 g, 16.0 mmol, 1.0 eq) in MeOH (50 mL) at 0 °C. The mixture was stirred at rt overnight and quenched with saturated solution NH_4Cl (40 mL). The reaction mixture was partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a pale yellowish oil, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 60:40) to afford 5-hydroxymethyl-3-methoxyisoxazole (**3**) (1.75 g, 85%) as colourless oil: $\mathbf{R_f}$ 0.65 (petroleum ether/EtOAc 50:50, $KMnO_4$); δ_H (500 MHz, $CDCl_3$) 5.88 (1H, s, H-4), 4.65 (2H, d, $^3J_{HH}$ 6.0, H-6), 3.96 (3H, s, H-7), 2.20 (br s, 1H, -OH); δ_C ($CDCl_3$, 125 MHz) 172.5 (C-3), 172.4 (C-5), 93.2 (C-4), 57.1 (C-6), 56.7 (C-7). **HRMS** *m/z* ($APCI^+$), found: $[M+H]^+$ 130.0496, $C_5H_8NO_3$ requires $[M+H]^+$ 130.0496. These data are in accordance with the literature.[23,24]

2.4. Synthesis of 3-methoxy-5-(methoxymethyl)isoxazole (4)[25]

NaH (60% dispersion in mineral oil, 232 mg, 5.80 mmol, 1.1 eq) was added in single portion to a solution of 5-hydroxymethyl-3-methoxyisoxazole (**3**) (680 mg, 5.27 mmol, 1.0 eq) in THF (30 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h, cooled to 0 °C and CH_3I (0.36 mL, 5.80 mmol, 1.1 eq) was added. After 1 h stirring at rt, the reaction was quenched by slow addition of ice-cold water (30 mL). The aqueous layer was extracted into EtOAc (4 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel column chromatography (petroleum ether/Et_2O, 80:20) to afford 3-methoxy-5-(methoxymethyl)isoxazole (**4**) (473 mg, 57%) as a colourless oil: $\mathbf{R_f}$ 0.52 (petroleum ether/Et_2O, 70:30, $KMnO_4$); **FT-IR** (ATR, cm^{-1}) 2949, 1620, 1516, 1454, 1411, 1382, 1098, 1030, 966, 916, 795; δ_H (500 MHz, $CDCl_3$) 5.88 (1H, s, H-4), 4.42 (2H, s, H-6), 3.97 (3H, s, H-8), 3.42 (3H, s, H-7); δ_C ($CDCl_3$, 125 MHz) 172.5 (C-3), 170.3 (C-5), 94.4 (C-4), 65.8 (C-6), 58.9 (C-7), 57.2 (C-8); **HRMS** *m/z* (ESI^+), found: $[M+H]^+$ 144.0651, $C_6H_{10}NO_3$ requires $[M+H]^+$ 144.0661. These data are in accordance with the literature.[25]

2.5. Synthesis of 4-iodo-3-methoxy-5-(methoxymethyl)isoxazole (5)

NIS (997 mg, 4.43 mmol, 1.5 eq) was added to a solution of 3-methoxy-5-(methoxymethyl)isoxazole (**4**) (422 mg, 2.95 mmol, 1.0 eq) in TFA (10 mL). After stirring at rt overnight, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/Et_2O, 90:10), affording 4-iodo-3-methoxy-5-(methoxymethyl)isoxazole (**5**) (696 mg, 88%) as colourless crystalline solid: $\mathbf{R_f}$ 0.50 (petroleum ether/Et_2O, 70:30, UV/$KMnO_4$); **mp** 88-89 °C; **FT-IR** (ATR, cm^{-1}) 2990, 1609, 1526, 1447, 1408, 1371, 1277, 1192, 1105, 1086, 1053, 959, 947, 928, 783, 716, 546; δ_H (500 MHz, $CDCl_3$) 4.47 (2H, s, H-6) 4.03 (3H, s, H-8), 3.40 (3H, s, H-7); δ_C (125 MHz, $CDCl_3$) 171.5 (C-3), 169.8 (C-5), 64.8 (C-6), 59.0 (C-7), 57.8 (C-8), 51.7 (C-4); **HRMS** *m/z* (ESI^+), found: $[M+H]^+$ 269.9619, $C_6H_9NO_3{}^{127}I$ requires $[M+H]^+$ 269.9627.

2.6. Synthesis of (3-methoxy-5-(methoxymethyl)isoxazol-4-yl) (4-methoxyphenyl)iodonium tetrafluoroborate (6)

4-Iodo-3-methoxy-5-(methoxymethyl)isoxazole (**5**) (70 mg, 0.26 mmol, 1.0 eq) and $BF_3{\cdot}Et_2O$ (80 μL, 0.65 mmol, 2.5 eq) were added to a solution of *m*CPBA (70% active oxidant, 83 mg, 0.34 mmol, 1.3 eq) in DCM (1.5 mL) at rt. The resulting yellow solution was stirred at rt for 2 h and cooled to 0 °C, 4-methoxyphenylboronic acid (43 mg, 0.29 mmol, 1.1 eq) was added and the temperature was allowed to warm to rt. After 2 h of stirring, the crude mixture was applied on silica plug (0.8 g) and eluted with DCM (10 mL) to remove unreacted ArI (**5**) and *m*CBA followed by (DCM/MeOH) (20:1 v/v mixture, 42 mL) to elute the product, leaving any boronic acid derivatives on the column. The latter solution was concentrated and Et_2O (1 mL) was added to the residue to induce precipitation. The ether phase was decanted and the solid was washed twice more with Et_2O (2 x 1 mL) and dried in *vacuo* to give (3-methoxy-5-(methoxymethyl)isoxazol-4-yl) (4-methoxyphenyl)iodonium tetrafluoroborate salt (**6**) in (60 mg, 50%) as a pale yellow solid: **mp** 161-163 °C (dec.); **FT-IR** (ATR, cm^{-1}) 2945, 1601, 1497, 1408, 1246, 1088, 1039, 756, 692; δ_H (500 MHz, d_6-DMSO) 8.00 (2H, d, $^3J_{HH}$ 8.9, H-10),

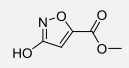
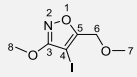
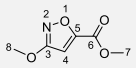
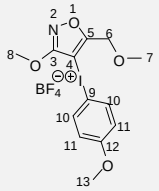
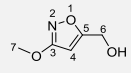
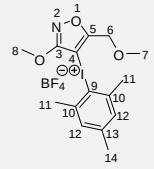
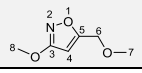
7.08 (2H, d, $^3J_{HH}$ 8.9, H-11), 4.79 (2H, s, H-6), 4.02 (3H, s, H-8), 3.80 (3H, s, H-13), 3.38 (3H, s, H-7); **δ_C** (125 MHz, d_6-DMSO) 174.4 (C-5), 169.6 (C-3), 162.0 (C-12), 136.9 (C-10), 117.6 (C-11), 106.7 (C-9), 78.0 (C-4), 64.6 (C-6), 58.8 (C-7), 58.6 (C-8), 55.8 (C-13); **δ_F** (470 MHz, d_6-DMSO) -148.17, -148.23 (4F, s, BF_4^-); **HRMS** *m/z* (ESI^+), found: $[M\text{-}BF_4]^+$ 376.0028, $C_{13}H_{15}NO_4{}^{127}I$ requires $[M\text{-}BF_4]^+$ 376.0040].

2.7. Synthesis of mesityl(3-methoxy-5-(methoxymethyl)isoxazol-4-yl)iodonium tetrafluoroborate (7)

4-Iodo-3-methoxy-5-(methoxymethyl)isoxazole (**5**) (70 mg, 0.26 mmol, 1.0 eq) and $BF_3{\cdot}Et_2O$ (80 µL, 0.65 mmol, 2.5 eq) were added to a solution of *m*CPBA (70% active oxidant, 83 mg, 0.34 mmol, 1.3 eq) in DCM (1.5 mL) at rt. The resulting yellow solution was stirred at rt for 2 h and cooled to 0 °C, 2,4,6-trimethylphenylboronic acid (48 mg, 0.29 mmol, 1.1 eq) was added and the temperature was allowed to warm to rt. After 2 h of stirring, the crude mixture was applied on silica plug (0.8 g) and eluted with DCM (10 mL) to remove unreacted ArI (**5**) and *m*CBA followed by (DCM/MeOH) (20:1 v/v mixture, 42 mL) to elute the product, leaving any boronic acid derivatives on the column. The latter solution was concentrated, and Et_2O (1 mL) was added to the residue to induce precipitation. The ether phase was decanted and the solid was washed twice more with Et_2O (2 x 1 mL) and dried in *vacuo* to give mesityl(3-methoxy-5-(methoxymethyl)isoxazol-4-yl)iodonium tetrafluoroborate salt (**7**) in (55 mg, 45%) as a pale yellow solid: ; **mp** 157-160 °C (dec.); **FT-IR** (ATR, cm^{-1}) 2916, 1607, 1470, 1377, 1032, 1003, 962, 835, 687; **δ_H** (500 MHz, d_6-DMSO) 7.20 (2H, s, H-12), 4.72 (2H, s, H-6), 3.96 (3H, s, H-8), 3.37 (3H, s, H-7), 2.63 (6H, s, H-11), 2.29 (3H, s, H-14); **δ_C** (125 MHz, d_6-DMSO) 174.3 (C-5), 169.9 (C-3), 143.0 (C-13), 141.5 (C-10), 129.6 (C-12), 123.9 (C-9), 75.9 (C-4), 64.7 (C-6), 58.9 (C-7), 58.5 (C-8), 26.0 (C-11), 20.5 (C-14); **δ_F** (470 MHz, d_6-DMSO) -148.16, -148.21 (4F, s, BF_4^-); **HRMS** *m/z* (ESI^+), found: $[M\text{-}BF_4]^+$ 388.0392, $C_{15}H_{19}NO_3{}^{127}I$ requires $[M\text{-}BF_4]^+$ 388.0404.

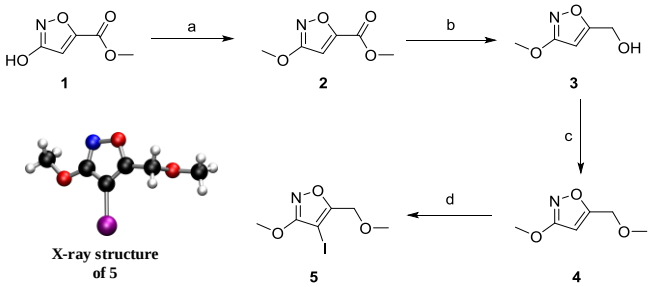
The chemical structures and numbering of the synthesized compounds are shown in Table **1**.

Table 1: Structures assigned to synthesized compounds

Compound	Structure	Compound	Structure
1		5	
2		6	
3		7	
4			

3.1. Result and discussion

The synthesis of iodoisoxazole (**5**) is illustrated in Scheme **1**. Ester (**2**) was synthesized from the commercially available isoxazole (**1**). Protection of (**1**) as a methyl ether afforded methyl ester (**2**). Reduction of (**2**) with $NaBH_4$ in MeOH afforded alcohol (**3**) in good yield and then conversion of (**3**) to its methyl-ether derivative (**4**) was carried out with methyl iodide and sodium hydride. This reaction afforded (**4**) in acceptable yield (57%). Iodination of methyl ether (**4**) was carried out with NIS in TFA. The desired product (**5**) was isolated in good yield (88%) and its structure was confirmed by X-ray crystallography (ball-and-stick representation) (Scheme **1**). The summary of crystal data and structure refinement parameters for iodoisoxazole (**5**) are shown in Table **2**.



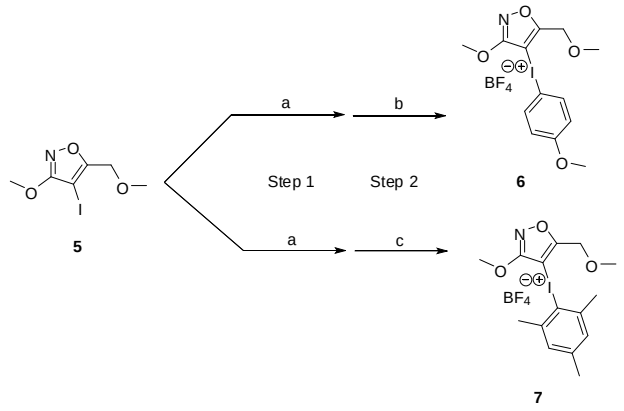
Scheme 1: Synthesis of iodoisoxazole (**5**). Reagents and conditions: a) MeI, K_2CO_3, DMF, 14 h, 66%; b) $NaBH_4$, MeOH rt, overnight, 85%; c) NaH (60% dispersion oil), MeI, THF, 0 °C→rt, 1 h, 57%; d) NIS, TFA, rt, overnight, 88%.

Table 2: Crystal data and structure refinement parameters for iodoisoxazole (**5**)

Crystal parameters	**5**
Formula	$C_6H_6INO_4$
Molecular weight	283.02
Crystal description	Colourless platelet
Crystal dimensions (mm)	0.21×0.12×0.02
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	4.1252(13)
b (Å)	15.712(4)
c (Å)	13.231(4)
α (°)	
β (°)	95.941(9)
γ (°)	
Volume ($Å^3$)	853.0(4)
Z	4
Calculated density (g cm^{-3})	2.204
Temperature (K)	173
µ (mm^{-1})	3.731
F(000)	536
Reflections collected	9717
Unique reflections (R_{int})	1549 (0.1853)
Max./min. transmission	0.928, 0.181
R_1, wR_2 [$I>2\sigma(I)$]	0.0964, 0.2438
R_1, wR_2 (all data)	0.1131, 0.2514
Goodness of fit	0.985
Data/restraints/parameters	1549/0/112
Max. difference peak/hole (e A^{-3})	3.89, -1.97

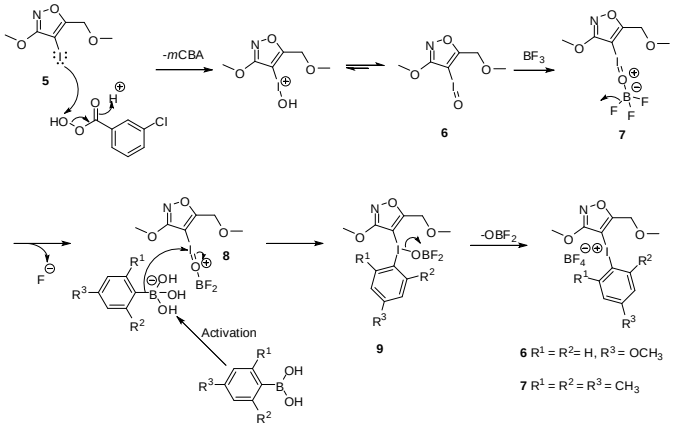
3.1. One-pot synthesis of diaryliodonium tetrafluoroborate salts (6) and (7)

A one-pot synthesis of the tetrafluoroborate iodonium salt was investigated. Such a protocol has been shown to be efficient in generating such salts without anion-exchange step.[26] Accordingly, a solution of *m*CPBA (1.3 eq) in DCM was treated with iodoisoxazole (**5**) (1.0 eq) and boronic acid precursors (1.1 eq) in the presence of boron trifluoride (2.5 eq) at room temperature. Diaryliodonium tetrafluoroborate salts (**6**) and (**7**) were obtained in acceptable yields upon precipitation with diethyl ether (Scheme **2**).



Scheme 2: One-pot synthesis of iodonium tetrafluoroborate salts (**6**) and (**7**). Reagents and conditions: a) *m*CPBA, $BF_3{\cdot}OEt_2$, rt, 2 h; b) 4-OMePh-$B(OH)_2$, rt, 2 h, 50%; c) 2,4,6-TriMePh-$B(OH)_2$, rt, 2 h, 45%.

Despite a wide level of interest over many years in the one-pot synthesis of diaryliodonium salts, the exact mechanism remains unclear. A possible mechanism, shown in Scheme **3**, starts with nucleophilic attack of iodoisoxazole (**5**) on *m*CPBA to generate iodo oxide (**6**). Further activation of (**6**) by Lewis acid BF_3 followed by loss of fluoride of (**7**), leads to intermediate (**8**). The free fluoride can then attack BF_3 to generate BF_4^-. Intermediate (**8**) then undergoes nucleophilic addition at the electrophilic iodine centre to give (**9**) which then collapses to afford the desired iodonium tetrafluoroborate salts.



Scheme 3: Putative mechanism for one-pot synthesis of diaryliodonium tetrafluoroborate salts (**6**) and (**7**).

4. Conclusion

The synthesis and putative mechanism for the formation of unsymmetrical diaryl iodonium tetrafluoroborate salts have been described. This method is operationally simple and proceeded through the reaction of iodo isoxazole with a commercially available oxidant (*m*CPBA) in the presence of aryl boronic acids and boron trifluoride. The protocol can be extended to the synthesis of symmetrical and unsymmetrical 3,5-disubstituted isoxazole iodonium salts directly from their iodinated precursors and various aryl boronic acid derivatives.

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