COMMUNICATION

Synthesis of functionalised unsymmetrical diaryliodonium salts

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A generalised synthesis of unsymmetrical functionalised diaryliodonium salts has been developed through the direct reaction of bis(acetoxy)iodoarenes with arenes in a trifluoromethanesulfonic or trifluoroacetic acid medium.

Diaryliodonium salts are used in organic synthesis as arylating agents for organic and inorganic bases,[1–6] including the fluoride anion.[7] They also have practical application due to their antimicrobial activity and photochemical properties[8] and have been suggested as efficient catalysts for radiation-initiated polymerisation.[9] There is a lack of efficient or convenient methods for the synthesis of functionalised unsymmetrical diaryliodonium salts and therefore much interest in developing new methodology for the synthesis of these useful compounds.

Several methods for the preparation of diaryliodonium salts are known. The most common procedures depend on the prior synthesis of pure iodyl- or iodosyl-arenes or their diacetates from starting iodoarenes, followed by acidic or alkaline coupling with arenes (Scheme 1).[1–3,8] Beringer and co-workers[5,6]

$$ArI \longrightarrow Ar(OAc)_2 \longrightarrow ArIO \longrightarrow Ar_2I^+X^-$$

Scheme 1

developed a convenient short-cut by oxidising the iodo compounds to the corresponding iodine(III) hydrosulfates *in situ* using barium peroxide or potassium persulfate, followed by coupling with an arene in strongly acidic solution (Scheme 2).

$$ArI \xrightarrow{[O]} ArIO \xrightarrow[H_2SO_4]{Ar'H} ArI^+Ar'\,HSO_4^- + H_2O$$

Scheme 2

More recently Kazmierczak[10] developed a similar procedure involving *in situ* oxidation of iodoarenes with a CrO_3–AcOH–H_2SO_4 liquid system to give the iodine(III) hydrosulfates, followed by acidic coupling with various arenes. A problem with these approaches is that only a limited number of aromatic substrates are available; also, the strongly acidic work-up procedures make crystallisation of solid products difficult and yields are generally moderate to low.

A different approach was developed by Zefirov *et al.*[11] involving the prior synthesis of iodosyl fluorosulfate ($O{=}IOSO_2F$) from fluoromethanesulfonic acid and anhydroiodic acid (HI_3O_8) under stringently dry conditions. A major drawback of this method is that $O{=}IOSO_2F$ is unstable as well as being difficult to synthesize. Kitamura *et al.*[12] developed a much more convenient synthesis of some 4-substituted diphenyliodonium trifluoromethanesulfonates (triflates) *via* a reactive intermediate prepared from 1:2 molar ratio of bis(acetoxy)iodobenzene and trifluoromethanesulfonic (triflic) acid [$PhI(OAc)_2$–2TfOH]. This reagent was then treated with substituted arenes to give diaryliodonium triflates in good yield (Scheme 3).

A limitation is that the reaction has high *para* selectivity.

$$PhI(OAc)_2 + 2TfOH \longrightarrow [PhI(OAc)_2{-}2TfOH] \longrightarrow PhI^+Ar^-OTf$$

Scheme 3

Table 1 Newly synthesised unsymmetrically substituted diaryliodonium salts **1**

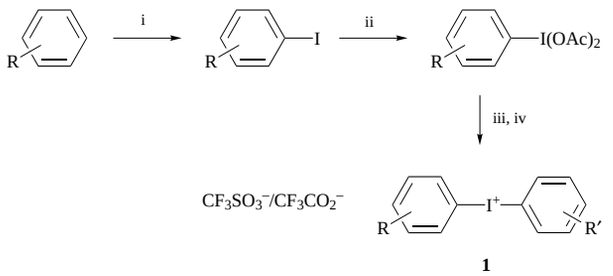
	R	R′	Anion	Yield (%)
1a	2-$CH_3C_6H_4$	4-$Bu^tC_6H_4$	$CF_3SO_3^-$	60
1b	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	$CF_3SO_3^-$	70
1c	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	$CF_3CO_2^-$	50
1d	2-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	$CF_3CO_2^-$	30
1e	3-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	$CF_3SO_3^-$	65
1f	3-$CH_3C_6H_4$	2,4,6-$(CH_3)_3C_6H_2$	$CF_3SO_3^-$	85
1g	2,4,6-$(CH_3)_2C_6H_2$	2,4,6-$(CH_3)_3C_6H_2$	$CF_3SO_3^-$	73
1h	2,4,6-$(CH_3)_2C_6H_2$	4-$CH_3OC_6H_4$	$CF_3CO_2^-$	60
1i	3,5-$(CH_3)_2C_6H_3$	4-$CH_3OC_6H_4$	$CF_3SO_3^-$	60
1j	3-$CH_3OC_6H_4$	4-$C(CH_3)_3CH_2C_6H_4$	$CF_3SO_3^-$	82

Furthermore, as with nearly all methods for the synthesis of unsymmetrical diaryliodonium salts, one aryl group is nearly always a simple phenyl. Therefore there is an urgent need for the development of a general new methodology which would allow the synthesis of mixed diaryliodonium salts.

We previously reported reactions of cyclotron-produced [^{18}F]fluoride ($t_{1/2}$ 109.6 min) with diaryliodonium salts **1** as a novel single-step procedure for the synthesis of simple no-carrier-added [^{18}F]fluoroarenes,[13,14] which may have useful application in the preparation of radiopharmaceuticals for clinical research with the imaging technique, Positron Emission Tomography.[15] As a continuation of this work, we report here a newly devised procedure for the synthesis of a wider range of unsymmetrically functionalised diaryliodonium salts (Table 1), as a basis for future investigations of substituent effects on [^{18}F]fluoride incorporation and to help in the elucidation of reaction mechanisms.

Our procedure draws on Kitamura's synthesis of simple 4-substituted diphenyliodonium triflates,[12] but by combining a generalised bis(acetoxy)iodoarene synthesis with a simple coupling procedure, it leads to unsymmetrical diaryliodonium salts in which either or both aryl rings can be functionalised. The new route is more general than previous methods and leads to a wider range of unsymmetrically substituted diaryliodonium salts in good yields (Scheme 4).

Iodoarenes were obtained commercially or were synthesised from starting arenes by treatment with silver(II) trifluoroacetate and iodine.[16] These were then oxidised to known bis(acetoxy)-iodoarenes by treating with peracetic acid.[17] Reaction with 2 equiv. of triflic or trifluoroacetic acid gave an intermediate complex, [$ArI(OAc)_2$–$2CF_3SO_3H$] or [$ArI(OAc)_2$–$2CF_3CO_2H$]. These activated complexes were not isolated but were treated *in situ* with substituted benzene at low temperature (−30 to 0 °C) (Table 1). In general, the reactions took between 30 min and 1 h. The new diaryliodonium salts **1** were obtained by crystallisation from diethyl ether as creamy coloured or



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Scheme 4 Reagents and conditions: i, I_2, AgO_2CCF_3, CH_2Cl_2; ii, 40% peracetic acid in acetic acid; iii, $2CF_3SO_3H$ or $2CF_3CO_2H$, CH_2Cl_2, −30 to 0 °C, 1 h; iv, substituted arene, CH_2Cl_2, −30 to 0 °C, 1–3 h

white solids and were all unambiguously characterised (see Experimental).

The key signals in their ^{13}C NMR spectra (observed in the range δ 122–103) were due to the two carbons directly attached to the iodine of the iodonium ions and were assigned by use of the HETCOR technique. In addition, for example in the case of (2-methylphenyl)(4′-methoxyphenyl)iodonium trifluoroacetate, the aryl carbon attached to the methoxy group was similarly identified at δ 161.52 and that attached to the methyl group at δ 142.19, with the methoxy and methyl carbons at δ 57.14 and 22.27 respectively. The signals for the trifluoromethyl groups of both counter ions and the carbonyl of the trifluoroacetate anion were not intense enough to be seen in the ^{13}C NMR spectra.

Reactions of the new diaryliodonium salts with caesium fluoride and with [^{18}F]fluoride are currently under investigation.

Experimental

Substituted aromatic iodides that were not commercially available were synthesised from the starting arenes according to the literature;[16] all other reagents were used as supplied. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard. ^{1}H and ^{13}C NMR spectra were recorded in CD_3CN on a Bruker DRX 300 spectrometer (300 MHz ^{1}H and 75 MHz ^{13}C). Mass spectra were recorded on VG Micromass 7070E and Autospec-Q instruments.

Substituted diaryliodonium triflates: general procedure

Peracetic acid (0.025 mol, 40% solution) in acetic acid was added dropwise over 30 min with stirring to a chilled (ice) solution of starting iodoarene (0.01 mmol) in diethyl ether (5 ml). The mixture was stirred below 10 °C for 1 h and then for a further 2 h at room temperature. The solvent was removed under reduced pressure and the crystals formed were washed with diethyl ether and dried overnight *in vacuo* over P_2O_5. The identities of the bis(acetoxy)iodoarenes were confirmed by comparison of their mp, mass spectrum and ^{1}H and ^{13}C NMR spectra with literature values.

To a stirred suspension of bis(acetoxy)iodoarene (2 mmol) in CH_2Cl_2 (10 ml) was added dropwise either trifluoromethanesulfonic acid (0.36 ml, 4 mmol) or trifluoroacetic acid (0.31 ml, 4 mmol) at −30 °C (CO_2, acetone) under N_2. The mixture was stirred for 15–20 min keeping the temperature at −30 °C and then at 0 °C for a further 15 min before being stirred at room temperature for 1 h. The mixture changed in appearance to a clear brown solution (triflates) or a clear yellow solution (trifluoroacetates).

The reagent solution was cooled to −30 °C and the aromatic compound (4 mmol) was added dropwise *via* syringe. The mixture, cooled in ice, was stirred for 30 min and allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure and the residue was crystallised from Et_2O. The solid product was filtered and washed with Et_2O before being dried *in vacuo*. The triflates were obtained as creamy coloured solids and the trifluoroacetates were obtained as white solids. All new compounds were unambiguously characterised by mass spectroscopy, accurate mass and ^{1}H and ^{13}C NMR spectroscopy as set out below.

(2-Methylphenyl)(4′-*tert*-butylphenyl)iodonium triflate 1a
δ_H 7.93–7.25 (m, ArH), 7.21–6.94 (m, ArH), 2.20 (s, 3H, CH_3), 0.91 [s, 9H, $C(CH_3)_3$]; δ_C 141.31 (CCH_3), 138.25, 134.95, 134.21, 133.10, 132.05, 131.22, 117.31 (CI), 117.01, 110.31 (CI), 34.43 [$C(CH_3)_3$], 24.51 [3C, $C(CH_3)_3$], 21.31 (CH_3); *m*/*z* (FAB) 351 (M^+, 100%), 91 (23) {Found: 351.2701 [M^+]. $C_{17}H_{20}I$ requires: 351.2701}.

(2-Methylphenyl)(4′-methylphenyl)iodonium triflate 1b
δ_H 8.13–7.97 (m, ArH), 7.90–7.41 (m, ArH), 2.35 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); δ_C 143.39 (CCH_3), 141.38 (CCH_3), 137.88, 135.94, 133.68, 133.34, 132.30, 130.17, 122.44 (CI), 113.12 (CI), 25.90, 21.76; *m*/*z* (FAB) 309 (M^+, 100%), 154 (23), 91 (16) {Found: 309.0158 [M^+]. Calc. for $C_{14}H_{14}I$: 309.0158}.

(2-Methylphenyl)(4′-methylphenyl)iodonium trifluoroacetate 1c
δ_H 8.21–7.92 (m, ArH), 7.83–7.31 (m, ArH), 2.45 (s, 3H, CH_3), 2.33 (s, 3H, CH_3); δ_C 144.92 (CCH_3), 143.31 (CCH_3), 138.93, 134.79, 133.66, 133.51, 131.31, 130.18, 121.95 (CI), 113.17 (CI), 24.94 (CH_3), 22.01 (CH_3); *m*/*z* (FAB) 309 (M^+, 100%), 91 (20) {Found: 309.0166 [M^+]. $C_{14}H_{14}I$ requires: 309.0166}.

(2-Methylphenyl)(4′-methoxyphenyl)iodonium trifluoroacetate 1d
δ_H 8.33–7.84 (m, ArH), 7.47–7.01 (m, ArH), 3.62 (s, 3H, CH_3O), 2.21 (s, 3H, CH_3); δ_C 161.52 ($COCH_3$), 143.01 (CCH_3), 138.62, 135.93, 134.01, 132.33, 131.81, 117.83, 117.03 (CI), 106.61 (CI), 57.14 (CH_3O), 22.27 (CH_3); *m*/*z* (FAB) 325 (M^+, 100%), 91 (20) {Found: 325.0099 [M^+]. Calc. for $C_{14}H_{14}IO$: 325.0099}.

(3-Methylphenyl)(4′-methoxyphenyl)iodonium triflate 1e
δ_H 8.16–7.97 (m, ArH), 7.44–7.04 (m, ArH), 3.79 (s, 3H, CH_3O), 2.33 (s, 3H, CH_3); δ_C 162.47 ($COCH_3$), 142.19 (CCH_3), 137.66, 135.44, 133.10, 132.33, 131.80, 117.92, 117.11 (CI), 105.58 (CI), 56.14 (CH_3O), 21.18 (CH_3); *m*/*z* (FAB) 325 (M^+, 100%), 91 (12) {Found: 325.0103 [M^+]. $C_{14}H_{14}IO$ requires: 325.0103}.

(3-Methylphenyl)(2′,4′,6′-trimethylphenyl)iodonium triflate 1f
δ_H 7.53–7.50 (m, ArH), 7.42–7.01 (m, ArH), 2.56 (s, 3H, CH_3), 2.42 (s, 6H, $2CH_3$), 2.05 (s, 3H, CH_3); δ_C 146.01, 144.93, 139.52, 138.31, 130.01, 124.39, 123.01, 117.52 (CI), 117.21, 103.10 (CI), 27.01 ($2CH_3$), 21.31 (CH_3), 20.31 (CH_3); *m*/*z* (FAB) 337 (M^+, 100%), 119 (21) {Found: 337.0499 [M^+]. $C_{16}H_{18}I$ requires: 337.0499}.

(2,4,6-Trimethylphenyl)(2′,4′,6′-trimethylphenyl)iodonium triflate 1g
δ_H 7.22–7.01 (m, ArH), 2.32 (s, 12H, $4CH_3$), 2.22 (s, 6H, $2CH_3$); δ_C 139.25, 135.21, 126.21, 103.13 (2CI), 26.31 ($4CH_3$), 21.32 ($2CH_3$); *m*/*z* (FAB) 365 (M^+, 100%), 119 (30) {Found: 365.3001 [M^+]. $C_{18}H_{22}I$ requires: 365.3001}.

(2,4,6-Trimethylphenyl)(4′-methoxyphenyl)iodonium trifluoroacetate 1h
δ_H 7.79–7.76 (m, ArH), 7.76–6.93 (m, ArH), 3.78 (s, 3H, OCH_3), 2.62 (s, 6H, $2CH_3$), 2.30 (s, 3H, CH_3); δ_C 162.41 ($COCH_3$), 144.30, 141.88, 129.82, 123.44, 117.49 (CI), 117.26, 102.70 (CI), 55.53 (OCH_3), 26.10 ($2CH_3$), 20.32 (CH_3); *m*/*z* (FAB) 353 (M^+, 100%), 119 (24) {Found: 353.0437 [M^+]. $C_{16}H_{18}IO$ requires: 353.0437}.

(3,5-Dimethylphenyl)(4′-methoxyphenyl)iodonium triflate 1i
δ_H 8.05–7.77 (m, ArH), 7.45–6.85 (m, ArH), 3.25 (s, 3H, OCH_3), 2.24 (s, 6H, $2CH_3$); δ_C 160.93 ($COCH_3$), 144.03, 137.21, 136.35,

130.25, 117.10, 117.01 (CI), 110.25 (CI), 56.35 (OCH_3), 24.31 ($2CH_3$); *m*/*z* (FAB) 339 (M^+, 55%), 105 (21), 89 (50), 77 (100), 55 (50) {Found: 339.0287 [M^+]. $C_{15}H_{16}IO$ requires: 339.0287}.

(3-Methoxyphenyl)[4′-(2,2-dimethylpropyl)phenyl]iodonium triflate 1j

δ_H 8.28–8.03 (m, ArH), 7.98–7.03 (m, ArH), 3.99 (s, 3H, OCH_3), 2.93 (br s, 2H, CH_2), 0.88 [s, 9H, $C(CH_3)_3$]; δ_C 161.39 ($COCH_3$), 142.12, 135.99, 135.41, 133.09, 132.83, 131.80, 117.92, 117.25 (CI), 106.10 (CI), 57.15 (OCH_3), 35.31 [$C(CH_3)_3$], 25.01 [3C, $C(CH_3)_3$], 24.05 (CH_2); *m*/*z* (FAB) 381 (M^+, 65%), 81 (49), 69 (100), 55 (91) {Found: 381.0751 [M^+]. $C_{18}H_{22}IO$ requires: 381.0751}.

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