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Short communication

Cascade iodination–fluorination synthesis of 2-fluorothiophene and 5-fluoro-2-thienyliodonium salts

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ABSTRACT

The first synthesis of fluorine-containing 2-thienyliodonium salts was accomplished using cascade iodination–fluorination. According to this methodology, thiophene is first converted to bis(2-thienyl)iodonium hexafluorophosphate using an electrophilic iodination reaction. Upon heating with potassium fluoride, this salt undergoes regioselective fluorination producing 2-fluorothiophene. 2-Fluorothiophene is then iodinated again to yield fluorothienyliodonium salts.

1. Introduction

Diaryliodonium salts react easily with a variety of nucleophiles to form substitution products [1]. Due to this reactivity pattern, they can be used as selective arylation reagents [1]. Using the reaction of diaryliodonium salts with the fluoride anion for the preparation of aryl fluorides has been explored only in the last three decades [2–8]. The methodology has been used successfully for the synthesis of radiolabeled ^{18}F drugs [4,5]. Despite some limitations, the approach has potential advantages over other fluorination methods and in some cases provides satisfactory results when other methods fail [2]. However, use of iodonium salts for the preparation of heterocyclic fluorides has received less attention due to obvious potential problems. Martin-Santamaria et al. demonstrated that nucleophilic substitution reactions of a series of arylheteroaryliodonium salts with fluoride ion tend to produce aryl rather than heteroaryl fluorides [8]. For example, treatment of phenyl(2-thienyl)iodonium tosylate with cesium fluoride in CH_3CN at 80 °C yields fluorobenzene exclusively [8]. Fluorothiopenes and the corresponding fluorinated iodonium salts are valuable but difficult-to-make compounds (e.g., a direct Balz-Schiemann reaction cannot be used due to chemical instability of aminothiophenes [9]). An alternative approach entails the use of so-called cascade iodination–fluorination synthesis, where starting thiophenes are used to prepare fluorothiophenes and their iodonium salts via a repetitive cycle of electrophilic iodination–nucleophilic fluorination reactions.

2. Results and discussion

Here we report that cascade iodination–fluorination synthesis can be successfully used for the synthesis of biologically promising 2-fluorothiophenes and corresponding iodonium salts from thiophenes. Initially, 5-R-substituted thiophene iodonium salts were prepared by interaction of 2-R-substituted thiophenes **1** with tris(trifluoroaceoxy)-λ^3-iodane **2** (Scheme 1). The presence of electron-withdrawing groups on the thiophene ring decelerates this reaction. Thus, the reaction proceeds readily with R = H, Cl (σ_p 0.227 [10]), whereas thiophenes with strong electron-withdrawing groups (R = COOMe, CN, NO_2, σ_p 0.39, 0.66, and 0.78, respectively [10]) do not form iodonium salts under the same conditions. At the same time, compounds **1d**,**e**, in which electron-accepting groups (COOMe, CN) and the thiophene ring are separated by the CH_2 bridge, react easily to yield substituted iodonium salts **3d**,**e**. 2-Iodothiophene (**1f**), in contrast to its chloro analog **1c**, reacts with **2** under similar conditions to produce a (~1:1) mixture of symmetrical (**3f**) and unsymmetrical iodonium salts (**4**). Bis(2-thiophene)iodonium salts with non-nucleophilic trifluoroacetate (**5a–c**) or hexafluorophosphate counterions (**6a**,**b**) were prepared using a similar procedure (Scheme 1).

Subsequent treatment of the hexafluorophosphate **6a** with potassium fluoride (as a mechanical mixture) at 172–175 °C for 2 h yields 2-fluorothiophene **1g** (R = F) and thiophene **1a** (~20%), which can be easily separated from 2-iodothiophene **1f** (another

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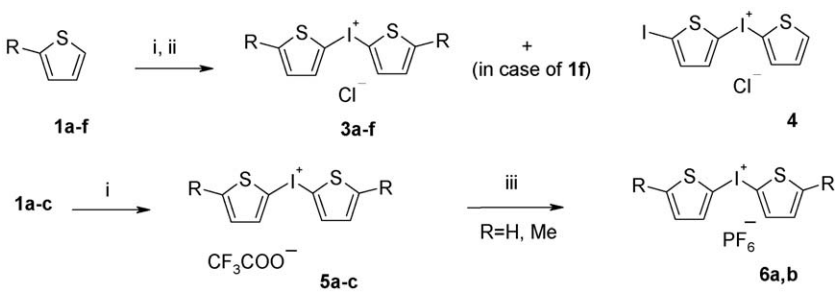
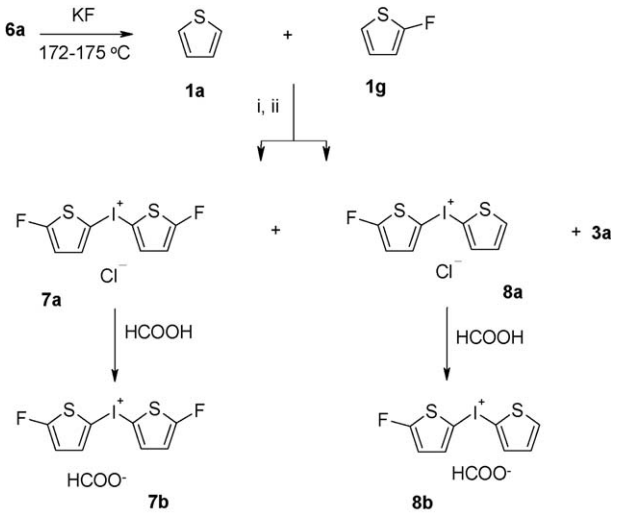


i) $I(OCOCF_3)_3$ (**2**), Ac_2O-TFAA, −15 °C→ r.t.; ii) NH_4Cl, H_2O; iii) MPF_6, H_2O

1a,3a,5a,6a	R = H	**1d,3d**	R = CH_2COOMe
1b,3b,5b,6b	R = Me	**1e,3e**	R = CH_2CN
1c,3c,5c	R = Cl	**1f,3f**	R = I

Scheme 1.



Scheme 2. (i) $I(OCOCF_3)_3$ (**2**), Ac_2O-TFAA, −15 °C → r.t.; (ii) NH_4Cl, H_2O.

product of the reaction) by distillation. Iodination of the mixture of **1g** and **1a** leads to the mixture of symmetrical and unsymmetrical iodonium salts **7a** (δ_F −122.0 ppm), **8a** (δ_F −122.1 ppm) and **3a** (2:1:0.14). Salts **7a** and **8a** were isolated in pure form as formates by preparative chromatography (Scheme 2).

It should be noted that heating trifluoroacetates **5a** or **5b** with KF in DMF yields only trace amounts (2–3%) of 2-fluorothiophene or 2-fluoro-5-methylthiophene. Chloride **3e**, upon heating with an excess of potassium fluoride in the absence of solvent, yields iodinated and chlorinated 2-cyanomethylthiophenes **9**, **10**, and **1e** in ~1:2.5:2.5 ratio, according to ^{1}H NMR spectra (Scheme 3). It is clear that, unlike hexafluorophosphate, more nucleophilic trifluoroacetate and chloride anions interfere with nucleophilic fluorination of these iodonium salts.

The proper choice of the counterion and reaction conditions is essential for successful fluorination. The best results were obtained when the salt with the complex fluorinated anion (PF_6^-) was heated with KF as a mechanical mixture in the absence of solvent.

3. Conclusions

In summary, we have demonstrated that cascade iodination–fluorination can be successfully used for the preparation of 2-fluorothiophene and corresponding iodonium salts. The best results were achieved using thermolysis of hexafluorophosphates in the presence of KF. Iodonium salts with more nucleophilic anions, such as trifluoroacetate, yielded only trace amounts of the desired fluorinated heterocyclic compounds. Finally, chlorination instead of fluorination was observed in the case of chlorides. An effort is currently underway to extend this methodology further for the synthesis of difluothiophenes and their iodonium salts.

4. Experimental

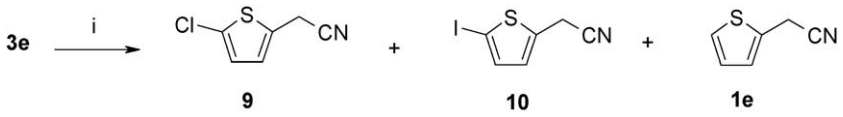
4.1. General experimental procedures

^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer operating at 299.95 MHz; ^{19}F NMR spectra on a Gemini 200 Varian instrument operating at 188.14 MHz; ^{13}C NMR spectra were obtained on a Bruker Avance DRX 500 spectrometer operating at 125.76 MHz. Chemical shifts are reported (ppm) relative to internal TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F) standards. Atmospheric pressure chemical ionization mass spectrometry (APCI MS) spectra were recorded using an Agilent 1100 instrument.

4.2. Bis(5-R-thiophene)iodonium chlorides 3; general procedure [11]

A solution of thiophene **1** (109 mmol) in Ac_2O (60 mL) and TFA (8 mL) was added dropwise with vigorous stirring to the cooled to −15 °C solution of tris(trifluoroacetoxy)-λ^3-iodane **2** [prepared from 3.5 g (13.7 mmol) I_2, 6.5 mL (85 mmol) CF_3COOH, 10 mL (103 mmol) Ac_2O, and 3.7 mL fuming HNO_3] in Ac_2O (25 mL). The reaction mixture was left in a refrigerator overnight and then at room temperature for 24 h. The solvents were evaporated in vacuum; the dark residue was extracted with water (4× 50 mL) and filtered. The saturated aqueous solution of ammonium chloride was added to the filtrate, the precipitated solid chloride **3** was filtered, washed with water, and dried at 50 °C in the dark.

3a, yield 43%, mp 220–221 °C (dec). ^{1}H NMR (DMSO-d_6): δ 7.14 (2H, dd, J 5 Hz, J 3.9 Hz, 4-H, 4′-H), 7.93 (2H, d, J 5 Hz, 5-H, 5′-H),



Scheme 3. (i) KF (10 equiv.), 180–185 °C, 3.5 h.

7.97 (2H, d, *J* 3.9 Hz, 3-H, 3′-H). ^{13}C NMR (DMSO-d_6) δ 110.61 (C-2), 129.34, 135.70, 138.61. MS *m*/*z* (APCI) 292.12 (M-1, 100%). Calc. for $C_8H_6ClIS_2$: C, 29.24; H, 1.84; S, 19.52%. Found: C, 29.03; H, 1.96; S, 19.17%.

3b, yield 73%, mp 233–234 °C. ^{1}H NMR (DMSO-d_6): δ 2.52 (6H, s, Me), 6.79 (2H, d, *J* 3.5 Hz, 4-H, 4′-H), 7.67 (2H, d, *J* 3.5 Hz, 3-H, 3′-H). MS *m*/*z* (APCI) 320.13 (M-1, 100%). Calc. for $C_{10}H_{10}ClIS_2$: C, 33.67; H, 2.83; S, 17.98%. Found: C, 33.92; H, 2.97; S, 17.74%.

3c, yield 38%, mp 189–190 °C. ^{1}H NMR (DMSO-d_6): δ 6.98 (2H, d, *J* 4.2 Hz, 4-H, 4′-H), 7.63 (2H, d, *J* 4.2 Hz, 3-H, 3′-H). MS *m*/*z* (APCI) 361 (M-1, 100%). Calc. for $C_8H_4Cl_3IS_2$: C, 24.17; H, 1.01; S, 16.13%. Found: C, 24.00; H, 0.95; S, 15.85%.

3d, yield 29%, mp 135–136 °C. ^{1}H NMR (DMSO-d_6): δ 3.64 (6H, s, CH_3), 4.09 (4H, s, CH_2), 6.93 (2H, d, *J* 3.6 Hz, 4-H, 4′-H), 7.73 (2H, d, *J* 3.6 Hz, 3-H, 4′-H). ^{13}C NMR (DMSO-d_6): δ 34.28 (CH_2), 52.05 (Me), 125.74, 128.63, 137.71, 144.90 (thiophene ring), 170.21 (CO). MS *m*/*z* (APCI) 436.3 (M-1, 100%). Calc. for $C_{14}H_{14}ClIO_4S_2$: C, 35.57; H, 2.98; S, 13.57%. Found: C, 35.89; H, 3.11; S, 13.28%.

3e, yield 43%, mp 167–168 °C. ^{1}H NMR (DMSO-d_6): δ 4.40 (4H, s, CH_2), 7.04 (2H, d, *J* 3.9 Hz, 4-H, 4′-H), 7.77 (2H, d, *J* 3.9 Hz, 3-H, 3′-H). ^{13}C NMR (DMSO-d_6): δ 17.52, 117.94, 128.77, 138.16, 138.17, 141.52. MS *m*/*z* (APCI) 370.2 (M-1, 100%). Analysis: calc. for $C_{12}H_8ClIN_2S_2$: C, 35.44; H, 1.98; N, 6.89; S, 15.77%. Found: C, 35.12; H, 1.76; N, 6.95; S, 15.49%.

4.2.1. Reaction of 2-iodothiophene 1f with tris(trifluoroacetoxy)-λ^3-iodane 2

A solution of 2-iodothiophene **1f** (2.29 g, 10.9 mmol) in Ac_2O (6 mL) and TFA (0.8 mL) was added dropwise with vigorous stirring to the cooled to −10 °C solution of tris(trifluoroacetoxy)-λ^3-iodane **2** (1.28 g, 2.74 mmol) in Ac_2O (3 mL). The reaction mixture was left at room temperature for 48 h and then evaporated in vacuum to dryness. Water (10 mL) and diethyl ether were added to the black residue and stirred for 8 h; the solid was filtered and stirred with a new portion of water (10 mL) and filtered. The saturated aqueous solution of ammonium chloride was added to the filtrate, and the precipitated solid was filtered, washed with water and diethyl ether, and dried at 40 °C in the dark to yield 0.75 g of the mixture (1:1.06) of **3f** and **4**. The ratio of **3f**:**4** was calculated from ^{1}H NMR spectra and was subsequently confirmed by HPLC-MS data. NMR data for **3f**: ^{1}H NMR (DMSO-d_6): δ 7.32 (2H, d, *J* 3.6 Hz, 4-H, 4′-H), 7.53 (2H, d, *J* 3.6 Hz, 3-H, 3′-H). MS *m*/*z* (APCI) 544 (M-1, 100%). Calculated for $C_8H_4I_3S_2$, *M* = 544.96. NMR data for **4**: ^{1}H NMR (DMSO-d_6): δ 7.10 (1H, dd, *J* 5.1 and 3.6 Hz, 4′-H), 7.33 (1H, m, 4-H), 7.50 (1H, d, *J* 3.6 Hz, 3-H), 7.9 (m, 2H, 3′-H, H-5′-H). MS *m*/*z* (APCI) 418.1 (M-1, 100%). Calculated for $C_8H_5I_2S_2$, *M* = 419.07.

4.2.2. Bis(2-thienyl)iodonium trifluoroacetate (5a)

A solution of thiophene **1a** (0.08 mol) in Ac_2O (35 mL) and TFA (5 mL) was added dropwise with vigorous stirring to the cooled to −15 °C solution of tris(trifluoroacetoxy)-λ^3-iodane **2** (0.02 mol) in Ac_2O (15 mL). The reaction mixture was left in a refrigerator for 20 h. The solvents were evaporated in vacuum, and water (50 mL) was added to the black residue and stirred for 24 h. The solid was filtered and extracted with additional portions of water (4× 50 mL). The combined aqueous extracts were evaporated in vacuum and washed with cold water. Yield 3.9 g (49%). ^{1}H NMR (DMSO-d_6): δ 7.11 (2H, dd, *J* 5.1 Hz, *J* 3.9 Hz, 4-H, 4′-H), 7.90 (2H, d, *J* 5.1 Hz, 5-H, 5′-H), 7.98 (2H, d, *J* 3.9 Hz, 3-H, 3′-H). ^{19}F NMR (DMSO-d_6): δ −73.3. MS *m*/*z* (APCI) 292 (M-1, 100%). Calc. for $C_{10}H_6F_3IO_2S_2$: C, 29.57; H, 1.49; S, 15.79%. Found: C, 29.83; H, 1.64; S, 15.32%.

Bis(*5-methyl-2-thienyl*)*iodonium trifluoroacetate* (**5b**) was synthesized by the same procedure. Yield 17%, mp 91.5–92 °C. ^{1}H NMR (DMSO-d_6): δ 2.55 (6H, s, Me), 6.86 (2H, d, *J* 3.5 Hz, 4-H, 4′-H), 7.83 (2H, d, *J* 3.5 Hz, 3-H, 3′-H). ^{13}C NMR (DMSO-d_6) δ 15.40 (Me), 101.34 (C-2), 117.55, 140.45 (C-3, C-4), 128.26 (q, *J* 300 Hz, CF_3), 151.05 (C-5), 158.60 (q, *J* 31 Hz, CO). ^{19}F NMR (DMSO-d_6): δ −73.0. Calc. for $C_{12}H_{10}F_3IO_2S_2$: I, 29.22; S, 14.77%. Found: I, 29.78; S, 14.73%.

Bis(*5-chloro-2-thienyl*)*iodonium trifluoroacetate* (**5c**) was synthesized by the same procedure. Yield 34%, mp 135–136 °C. ^{1}H NMR (DMSO-d_6): δ 7.25 (2H, d, *J* 4.2 Hz, 4-H, 4′-H), 7.96 (2H, d, *J* 4.2 Hz, 3-H, 3′-H). ^{19}F NMR (DMSO-d_6): δ −73.0. Calc. for $C_{10}H_4Cl_2F_3IO_2S_2$: C, 25.28; H, 0.85; S, 13.50%. Found: C, 24.96; H, 0.83; S, 13.46%.

4.2.3. Bis(2-thienyl)iodonium hexafluorophosphate 6a

A solution of thiophene **1a** (9.45 mL, 0.119 mol) in Ac_2O (40 mL) and TFA (7.5 mL) was added dropwise with vigorous stirring to a cooled to −15 °C solution of tris(trifluoroacetoxy)-λ^3-iodane **2** (0.029 mol) in Ac_2O (20 mL). The reaction mixture was left in a refrigerator overnight. The solvents were evaporated in vacuum, and the dark residue was extracted with water (4× 50 mL) and filtered. To the resulting filtrate 50% aqueous HPF_6 was added dropwise until precipitation ceased. The solid was filtered, washed with water and diethyl ether, and dried. Yield 6.3 g (49%), mp 175–176 °C. ^{1}H NMR (DMSO-d_6): δ 7.14 (2H, m, 4-H, 4′-H), 7.93 (2H, d, *J* 5.1 Hz, 5-H, 5′-H), 8.19 (2H, d, *J* 3.9 Hz, 3-H, 3′-H). ^{19}F NMR (DMSO-d_6): δ −70.3 (d, *J* = 710 Hz). MS *m*/*z* (APCI) 292 (M-1, 100%). Calc. for $C_8H_6F_6IPS_2$: C, 21.93; H, 1.38; P, 7.07. Found: C, 21.69; H, 1.27; P, 6.92%.

Bis(*5-methyl-2-thienyl*)*iodonium hexafluorophosphate* **6b**. A saturated aqueous solution of NH_4PF_6 (2 mL) was added dropwise to the solution of trifluoroacetate **5b** (0.15 g, 0.51 mmol). Precipitated oily product was separated and triturated with ether to yield **6b**. Yield 0.03 g, 19%, mp 190–192 °C. ^{1}H NMR (DMSO-d_6): δ 2.55 (6H, s, Me), 6.86 (2H, d, *J* 3.6 Hz, 4-H, 4′-H), 7.81 (2H, d, *J* = 3.6 Hz, 3-H, 3′-H). ^{19}F NMR (DMSO-d_6): δ −69.6 (d, *J* = 712 Hz). ^{31}P NMR (DMSO-d_6): δ −142.6 (septet, *J* = 712 Hz). MS *m*/*z* (APCI) 292 (M-1, 100%). Calc. for $C_{10}H_{10}F_6IPS_2$: C, 25.76; H, 2.17. Found: C, 25.97; H, 2.35%. Ethereal filtrate, according to ^{1}H NMR spectrum, contained a mixture (1:0.4) of 2-methyl-5-iodothiophene and 5-methyl-2-oxo-2,3-dihydrothiophene identified by comparison with authentic samples.

4.3. 2-Fluorothiophene (1g) and 2-fluorothiophene-based iodonium salts 7,8

A mixture of **6a** (4.6 g, 10.5 mmol) and dry KF (4 g, 68.9 mol) was heated at 172–175 °C for 2 h. The volatile products were distilled at room temperature under reduced pressure (14 mmHg) into a trap cooled with liquid nitrogen yielding 0.4 g (37%) of 2-fluorothiophene **1g** containing ∼20% of **1a**. NMR data for **1g**: ^{1}H NMR ($CDCl_3$): δ 6.47 (1H, m), 6.64 (1H, m), 6.69 (1H, m). ^{19}F NMR ($CDCl_3$): δ −134.44. MS *m*/*z* (APCI) 101 (M-1, 100%). Calc. for C_4H_3FS, *M* = 102.13.

A portion of the above obtained mixture (0.35 g) was dissolved in acetic anhydride (2 mL) and TFA (0.3 mL) and added with vigorous stirring to a cooled to −10 °C solution of iodine tris(trifluoroacetate) **2** (0.5 g, 1.1 mmol) in acetic anhydride (2 mL). The reaction mixture was allowed to stand at room temperature overnight and evaporated to dryness in vacuum. Diethyl ether (10 mL) was added to the residue and extracted with water (3× 5 mL). The combined aqueous extracts were filtered. A saturated solution of ammonium chloride was added to the filtrate until the precipitation ended. The precipitated solid was collected by filtration, washed with water (3× 5 mL), and dried in vacuum at 30–40 °C to give 0.15 g of chlorides **7a**, **8a** and **3a** (2:1:0.14), separated by preparative chromatography as the formates **7b** and **8b**. NMR data for **7a**: ^{1}H NMR (DMSO-d_6): δ 6.81 (2H, m), 7.67 (2H, m). ^{19}F NMR (DMSO-d_6): δ −121.57. MS *m*/*z* (APCI) 328.2 (M-1, 100%). NMR data for **7b**: ^{1}H NMR (DMSO-d_6): δ 6.73 (2H, dd, *J* 4.5

and 2.1 Hz, 4-H, 4′-H), 7.56 (2H, t, *J* 3.6 Hz, 3-H, 3′-H), 8.15 (1H, br s, HCO). ^{19}F NMR (DMSO-d_6): δ −122.66. MS *m*/*z* (APCI) 328.17 (M-1, 100%). Calc. for $C_9H_5F_2IO_2S_2$: C, 28.89; H, 1.35; S, 17.14%. Found: C, 29.00; H, 1.43; S, 16.94%. NMR data for **8b**: ^{1}H NMR (DMSO-d_6): δ 6.79 (1H, m), 7.10 (1H, m), 7.62 (1H, m), 7.89 (2H, m), 8.21 (br s, HCO). ^{19}F NMR (DMSO-d_6): δ −122.35. MS *m*/*z* (APCI) 310.2 (M-1, 100%). Calc for $C_8H_5FIS_2$, *M* = 311.16.

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