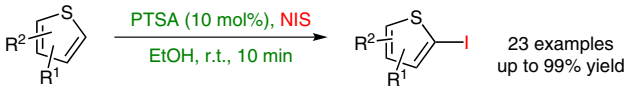
Synthesis J. Grolleau et al. Paper

# Clean and Efficient Iodination of Thiophene Derivatives

**Jérémie Grolleau**
**Pierre Frère**
**Frédéric Gohier***

University of Angers, MOLTECH-Anjou UMR CNRS 6200, SCL group, 2 boulevard Lavoisier, 49045 Angers cedex, France
frederic.gohier@univ-angers.fr




$R^1$ = H, OMe, Oct, Br, CHO, $CH_2CN$, $CH_2OH$
$R^2$ = H, OMe, Br, $CH_2CN$, $CH_2OH$, $SCH_2CH_2CN$, Hex

Received: 26.06.2015
Accepted after revision: 26.08.2015
Published online: 11.09.2015
DOI: 10.1055/s-0035-1560480; Art ID: ss-2015-z0402-op

**Abstract** Iodination of thiophene derivatives is realized using a simple, fast, and efficient methodology. Iodination of thiophene and 2- or 3-substituted or 3,4-disubstituted thiophenes with *N*-iodosuccinimide (NIS) activated with 4-toluenesulfonic acid in ethanol gives pure iodinated products that require no further purification.

**Key words** iodination, thiophene, green methodology, regioselectivity, 4-toluenesulfonic acid, catalysis

Iodinated arenes are valuable intermediates for the promotion of C–C and N–C coupling under mild conditions using the Suzuki–Miyaura,[1] Sonogashira,[2] Heck,[3] or Buchwald reaction.[4] Such methodology is often used in the field of organic semiconductors to produce compounds[5] dedicated to organic solar cells and electroluminescent diodes. Researchers have paid increasing attention to the synthesis of these compounds and particularly syntheses that have reduced environmental impact.[6] For example, the Suzuki reaction is preferred to the Stille reaction[7] for coupling reactions as it avoids the production of tin residues. Thus, iodinated intermediates are attractive if the introduction of iodine is clean and efficient. Generally, bromo and chloro groups are preferred to iodo groups because they are easier to introduce,[8] even though there are numerous methods available in literature for the iodination of arenes. Oxidative reagents, such as sodium periodate,[9] lead tetraacetate,[10] manganese dioxide,[11] periodic acid,[12] and chromium trioxide,[13] used together with iodine or potassium iodide are efficient methods for the synthesis of iodoarenes. An indirect method using a sequence of deprotonation with butyllithium and anion trapping with iodine has also been developed.[14] *N*-Iodosuccinimide alone or activated with a Lewis acid[15] and *N*-chlorosuccinimide/sodium iodide[16] are other conditions that have been developed for the successfully iodination of activated aromatics. However, these routes require chlorinated solvents, toxic reagents, oxidative conditions, or air/moisture sensitive conditions that cannot be considered as part of a clean strategy for the iodination of arenes. More recently, *N*-iodosaccharin has been designed as an alternative iodinative reagent with ionic liquids to promote the clean iodination of electron-enriched, activated arenes.[17] Our interest in the clean and rapid functionalization of thiophene has led to the development of a simple and convenient method for the introduction of iodine using *N*-iodosuccinimide in ethanol, a green solvent, with a catalytic amount of 4-toluenesulfonic acid. *N*-Iodosuccinimide/4-toluenesulfonic acid in various solvents[18] has been previously used for the iodination of thiophene, but these methods have not been developed and optimized. Our method has been tested on various substituted thiophenes and it has been showed to be efficient when the thiophenes are not completely deactivated.

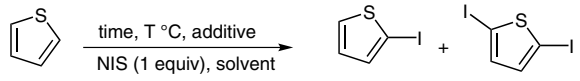
We first studied the iodination of thiophene (**1**) with *N*-iodosuccinimide using varying additives, solvents, temperatures, and times (Table 1); the parameters that have an impact on the progress of the reaction are acidic additives and the solvent. Indeed, without the use of an additive (entries 1 and 2), the reaction takes place very slowly. When 4-toluenesulfonic acid is added to the mixture, the solution became darker and after stirring for 10 minutes the *N*-iodosuccinimide was consumed completely (entry 3), however a mixture of monoiodinated thiophene **2** and diiodinated thiophene **3** is unavoidably obtained. Decreasing the temperature diminished the kinetics of the reaction (entry 4) and increasing the temperature (entry 5) did not favor monoiodination. The solvent has a non-negligible impact on the reaction; water did not solubilize thiophene (**1**) (entry 6), whereas ethanol was an efficient solvent. Other green solvents, such as ethyl acetate or ethyl lactate (entries



Downloaded by: Flinders University of South Australia. Copyrighted material.

7 and 8) did not afford good yields. Indeed, activation of *N*-iodosuccinimide is more efficient in ethanol than in ethyl acetate due to the protic properties of ethanol, and *N*-iodosuccinimide was not soluble in ethyl lactate hence no reaction took place. Other acidic additives were tested. Acetic acid (entry 9) was inefficient whereas sulfuric acid (entry 10) afforded a mixture of **2** and **3**. Iodination was realized successfully with a catalytic amount of 4-toluenesulfonic acid (entry 11) to give predominately 2-iodothiophene (**2**). Finally, 2,5-diiodothiophene (**3**) was obtained pure using 2 equivalents of *N*-iodosuccinimide (entry 12). This methodology was applied to unsymmetrical thiophenes **4**, **6**, **9**, and **12** and the results are gathered in Tables 2–5.

**Table 1** Iodination of Thiophene



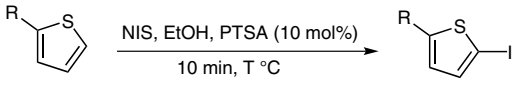

**1** **2** **3**

| Entry | Additive (equiv) | Solvent | Temp (°C) | Time | Conversion[a] **1**/**2**/**3** |
|---|---|---|---|---|---|
| 1 | – | EtOH | 25 | 24 h | 46:36:17 |
| 2 | – | EtOH | 25 | 10 min | 100:0:0 |
| 3 | PTSA (1) | EtOH | 25 | 10 min | 27:57:16 |
| 4 | PTSA (1) | EtOH | 0 | 10 min | 83:16:0 |
| 5 | PTSA (1) | EtOH | 50 | 10 min | 21:62:17 |
| 6 | PTSA (1) | $H_2O$ | 25 | 10 min | 100:0:0 |
| 7 | PTSA (1) | EtOAc | 25 | 10 min | 96:3:0 |
| 8 | PTSA (1) | EtCOCH(OH)Me | 25 | 10 min | 99:0:0 |
| 9 | AcOH (1) | EtOH | 25 | 10 min | 98:0:0 |
| 10 | $H_2SO_4$ (1) | EtOH | 25 | 10 min | 22:62:15 |
| 11 | PTSA (0.1) | EtOH | 25 | 10 min | 18:64:17 |
| 12[b] | PTSA (0.1) | EtOH | 25 | 10 min | 0:0:77[c] |

[a] Conversion based on $^1$H NMR integration of characteristic signals of each compound.
[b] NIS (2 equiv).
[c] Isolated yield.

With these optimized conditions in hand, we decided to investigate the scope of our iodination reaction either at room temperature or at 50 °C. Electrophilic aromatic substitution ($S_EAr$) of 2-substituted thiophenes **4** takes place in position 5 (Table 2). The reaction of electron-donating group substituted thiophenes **4a**,**b** took place at room temperature to give **5a**,**b** (entries 1 and 2), whereas some reactions with electron-withdrawing group substituted thiophenes required slight heating. Thiophene-2-carbaldehyde (**4d**) (entry 4) requires acidic conditions to hydrolyze the intermediate acetal formed in the course of the reaction at the end of the reaction; this reaction worked certainly due to acetal formation. Cyanomethyl-substituted thiophene **4e** (entry 5) requires a reaction temperature of 50 °C, whereas cyano- or ester-substituted thiophenes **4f**,**g** (entries 6 and 7) did not give the products of iodination even at higher temperatures (100 °C, sealed tube); all attempts to obtain the iodinated derivatives under microwave irradiation at 100 °C failed. All compounds **5** were obtained in pure form with only washing of the crude mixture diluted in ethyl acetate with sodium thiosulfate and sodium carbonate solutions required; the products were isolated without column chromatography.

**Table 2** Iodination of 2-Substituted Thiophenes




**4** **5**

| Entry | R | NIS (equiv) | Temp (°C) | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | OMe | 1 | 25 | **5a** | 77 |
| 2 | $(CH_2)_7Me$ | 1.1 | 25 | **5b** | 98 |
| 3 | Br | 1.1 | 50 | **5c** | 94 |
| 4 | CHO | 1.1 | 50 | **5d** | 99 |
| 5 | $CH_2CN$ | 1.1 | 50 | **5e** | 94 |
| 6 | $CO_2Et$ | 1.1 | 100[b] | **5f** | 0 |
| 7 | CN | 1.1 | 100[b] | **5g** | 0 |
| 8 | $CH_2OH$ | 1.1 | 25 | **5h** | 98 |

[a] Isolated yield.
[b] Experiments carried out in a screw-capped glass tube.

We also explored the iodination of the more challenging 3-substituted thiophenes **6** since there are two α-positions that can be functionalized (Table 3). Thiophenes **6a**,**d** substituted by strong electron-enriched groups (S and O) in position 3 cleanly give the products **7a**,**d** of direct monoiodination in position 2 (entries 1 and 6). Thiophenes **6b**,**e**,**f** substituted by poor electron-donating and poor electron-withdrawing groups, such as hexyl, cyanomethyl, and hydroxymethyl, do not afford the products of regiospecific iodination (entries 2, 8, and 10) and mixtures of monoiodinated and diiodinated products and starting material were observed. If monoiodination does not proceed efficiently, diiodination can be realized using 2.2 equivalents of *N*-iodosuccinimide to give **7b**,**c**,**e**,**f** in good yields (entries 3, 5, 9, and 11).

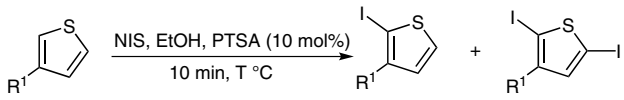
Iodination of unsymmetrical 3,4-disubstituted thiophenes **9a**,**b** (Table 4) takes place cleanly and selectively (entries 1 and 2). Iodination of 3,4-(ethylenedioxy)thiophene (EDOT) **9c** with 2.2 equivalents of *N*-iodosuccinimide gives diiodo product **11c** (entry 4), the use of 1.1 equivalents affords a mixture of starting material and mono- and diiodinated compounds (entry 3).

Other substituted thiophenes have been successfully iodinated (Table 5). Iodination of 4-bromo-2-methylthiophene (**12a**) gives **13a** in 95% yield (entry 1). Monoiodina-



Downloaded by: Flinders University of South Australia. Copyrighted material.

**Table 3** Iodination of 3-Substituted Thiophenes

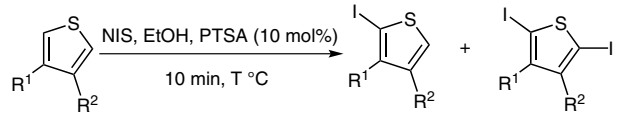



**6** **7** **8**

| Entry | R | NIS (equiv) | Temp (°C) | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | OMe | 1.1 | 25 | **7a** | 80 |
| 2 | $(CH_2)_5Me$ | 1.1 | 25 | **7b** | –[b] |
| 3 | $(CH_2)_5Me$ | 2.2 | 50 | **8b** | 99 |
| 4 | Br | 1.1 | 50 | **7c** | 64 |
| 5 | Br | 2.2 | 50 | **8c** | 61 |
| 6 | $S(CH_2)_2CN$ | 1.1 | 25 | **7d** | 93 |
| 7 | $S(CH_2)_2CN$ | 2.2 | 50[c] | **8d** | 81 |
| 8 | $CH_2CN$ | 1.1 | 25 | **7e** | –[b] |
| 9 | $CH_2CN$ | 2.2 | 50 | **8e** | 93 |
| 10 | $CH_2OH$ | 1.1 | 25 | **7f** | –[b] |
| 11 | $CH_2OH$ | 2.2 | 50[c] | **8f** | 99 |

[a] Isolated yield.
[b] Mixture of compounds obtained and not purified.
[c] Stirring, 30 min.

**Table 4** Iodination of 3,4-Disubstituted Thiophene




**9** **10** **11**

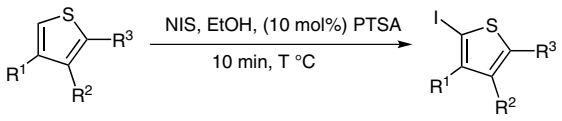
| Entry | $R^1$ | $R^2$ | NIS (equiv) | Temp (°C) | Product | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | OMe | CN | 1.1 | 25 | **10a** | 94 |
| 2 | OMe | Br | 1.1 | 25 | **10b** | 92 |
| 3 | $OCH_2CH_2O$ | | 1.1 | 25 | **10c** | –[b] |
| 4 | $OCH_2CH_2O$ | | 2.2 | 25 | **11c** | 87 |

[a] Isolated yield.
[b] Mixture of compounds.

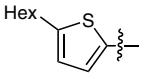
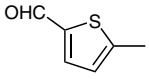
tion takes place regioselectively on 5-hexyl-2,2′-bithiophene (**12b)** and [2,2′-bithiophene]-5-carbaldehyde (**12c**) (entries 2 and 3). Iodination of substituted 3,4-(ethylenedioxy)thiophene (EDOT) **12d** gave iodinated derivative **13d** almost quantitatively. We also explored iodination of 2,2′-bithiophene (**14**); the expected compound **15** was obtained in good yield using 2.1 equivalents of *N*-iodosuccinimide (Scheme 1).

In conclusion, iodination can be realized on substituted thiophenes with *N*-iodosuccinimide and a catalytic amount of 4-toluenesulfonic acid using ethanol, a green solvent.

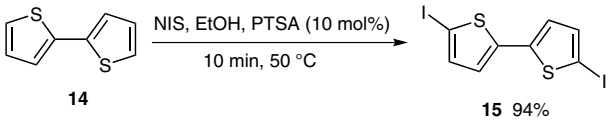
**Table 5** Iodination of Various Thiophenes




**12** **13**

| Entry | $R^1$ | $R^2$ | $R^3$ | NIS (equiv) | Temp (°C) | Product | Yield[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | Br | H | Me | 2.2 | 50 | **13a** | 95 |
| 2 | H | H |  | 1.1 | 25 | **13b** | 95 |
| 3 | H | H |  | 1.1 | 50 | **13c** | 79 |
| 4 | $OCH_2CH_2O$ | | CHO | 1.1 | 25 | **13d** | 98 |

[a] Isolated yield.




**14** **15** 94%

**Scheme 1** Diiodination of 2,2′-bithiophene

The iodinated compounds were obtained in pure form after 10 minutes reaction without using chromatography for separation. Thiophenes substituted by powerful electron-withdrawing group do not react, but the reaction proceeds regioselectively with thiophenes substituted with poor electron-withdrawing groups and electron-donating groups. Diiodinated thiophenes are obtained as simply and as rapidly as monoiodinated thiophenes under the same conditions using 2.2 equivalents of *N*-iodosuccinimide.

Characterization of the isolated products was carried out in $CDCl_3$ or DMSO-$d_6$ at 25 °C. Chemical shifts are reported relative to the solvent residual value: δ = 7.26 ($CDCl_3$), 2.50 (DMSO-$d_6$) for $^1H$ NMR and δ = 77.16 ($CDCl_3$), 39.52 (DMSO-$d_6$) for $^{13}C$ NMR. NMR spectra were recorded on a 300.1 MHz spectrometer for $^1H$ and 75.7 MHz spectrometer for $^{13}C$ at T = 300 K. Spectra were referenced against the internal NMR solvent standard. Mass spectra were recorded under EI mode; the main peaks are described, the peak corresponding to the molecular mass is expressed as ($M^{+\bullet}$). Analytical grade solvents were used.

### Monoiodothiophenes 2, 5, 7, 10, 13; General Procedure

The thiophene derivative (1 mmol, 1 equiv) was dissolved in EtOH (2 mL) at the temperature indicated in Tables 1–5. Then, NIS (1 or 1.1 equiv, see Tables 1–5) was added followed by PTSA (10% mol). The mixture was stirred for 10 min, then sat. $Na_2S_2O_3$ (2 mL) was added. The mixture was diluted with EtOAc (3 mL). After phase separation,

Downloaded by: Flinders University of South Australia. Copyrighted material.

the organic phase was washed with 1 M $Na_2CO_3$ solution, dried ($MgSO_4$), filtered through cotton, and evaporated to give the iodinated thiophene derivative.

**Diiodothiophenes 3, 8, 11, 15; General Procedure**

The thiophene derivative (100 mg, 1 equiv) was dissolved in EtOH (4 mL) at the temperature indicated in Tables 1–5. Then, NIS (2.2 equiv, see Tables 1–5) was added followed by PTSA (10% mol). The mixture was stirred 10 min, then sat. $Na_2S_2O_3$ (2 mL) was added. The mixture was diluted with EtOAc (3 mL). After phase separation, the organic phase was washed with 1 M $Na_2CO_3$ solution, dried ($MgSO_4$), filtered through cotton, and evaporated to give the diiodinated thiophene derivative.

**2,5-Diiodothiophene (3)**[19]

Yellow solid; yield: 307 mg (77%); mp 40–42 °C.

IR (KBr): 3076, 1184, 818, 683 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 6.93 (s, 2 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 138.9, 76.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_4H_2I_2S$: 335.7967; found: 335.7960.

**2-Iodo-5-methoxythiophene (5a)**[20]

Pale yellow oil; yield: 162 mg (77%).

IR (KBr): 1667, 1550, 1403, 1151, 631 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 3.7 Hz, 1 H), 5.92 (d, *J* = 3.7 Hz, 1 H), 3.86 (s, 3 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 169.9, 134.5, 105.7, 60.4, 57.4.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_5H_5IOS$: 239.9106; found: 239.9106.

**2-Iodo-5-octylthiophene (5b)**[21]

Colorless oil; yield: 161 mg (98%).

IR (KBr): 2922, 1463, 938, 789 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 3.6 Hz, 1 H), 6.46 (d, *J* = 3.6 Hz, 1 H), 2.79 (t, *J* = 7.5 Hz, 2 H), 1.60 (m, 2 H), 1.27 (m, 10 H), 0.86 (t, *J* = 6.5 Hz, 3 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 152.5, 136.8, 126.1, 69.7, 32.2, 31.9, 30.6, 29.6, 29.5, 29.3, 23.0, 14.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{19}IS$: 322.0252; found: 322.0241.

**2-Bromo-5-iodothiophene (5c)**[22]

Colorless oil; yield: 167 mg (94%).

IR (KBr): 1684, 1185, 817, 638 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 3.8 Hz, 1 H), 6.75 (d, *J* = 3.8 Hz, 1 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 137.7, 131.9, 115.3, 72.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_4H_2BrIS$: 287.8105; found: 287.8098.

**5-Iodothiophene-2-carbaldehyde (5d)**[23]

Thiophene **4d** (1 mmol, 1 equiv) was dissolved in EtOH (2 mL) at 50 °C. Then, NIS (1.1 equiv) was added followed by PTSA (10 mol%). The mixture was stirred for 10 min, then 1 M HCl solution was added. After phase separation, sat. $Na_2S_2O_3$ (2 mL) was added to the organic phase. The mixture was diluted with EtOAc (3 mL). After phase separation, the organic phase was washed with 1 M $Na_2CO_3$ solution, dried ($MgSO_4$), filtered through cotton, and evaporated to give the iodinated thiophene derivative **5d**.

Pale yellow solid; yield: 211 mg (99%); mp 48–50 °C.

IR (KBr): 1680, 1410, 1220, 1032, 961, 791 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 9.77 (s, 1 H, CHO), 7.39 (m, 2 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 181.2, 149.6, 138.3, 137.2, 88.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_5H_3IOS$: 237.8949; found: 237.8945.

**2-(5-Iodothiophen-2-yl)acetonitrile (5e)**[24]

Pale yellow oil; yield: 190 mg (94%).

IR (KBr): 2251, 1405, 943, 797, 708 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 3.7 Hz, 1 H), 6.74 (dt, *J* = 3.7, 1.0 Hz, 1 H), 3.86 (d, *J* = 1.0 Hz, 2 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 137.2, 136.7, 129.0, 116.4, 73.4, 18.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_6H_4NIS$: 248.9109; found: 248.9104.

**(5-Iodothiophen-2-yl)methanol (5h)**[25]

Pale yellow oil; yield: 206 mg (98%).

IR (KBr): 3500, 1426, 1045, 790 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 3.6 Hz, 1 H), 6.66 (d, *J* = 3.6 Hz, 1 H), 4.76 (s, 2 H), 2.21 (s, 1 H, OH).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 150.3, 136.8, 127.1, 73.5, 59.9.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_6H_5IOS$: 239.9106; found: 239.9107.

**2-Iodo-3-methoxythiophene (7a)**[26]

Colorless oil; yield: 168 mg (80%).

IR (KBr): 1168, 799, 706 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 6.8 Hz, 1 H), 6.69 (d, *J* = 6.8 Hz, 1 H), 3.89 (s, 3 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 159.8, 130.0, 115.8, 59.2, 53.5.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_5H_5IOS$: 239.9106; found: 239.9105.

**3-Hexyl-2,5-diiodothiophene (8b)**[27]

Colorless oil; yield: 247 mg (99%).

IR (KBr): 2922, 2853, 1455, 1394, 981, 827 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 6.90 (s, 1 H), 2.49 (t, *J* = 7.9 Hz, 2 H), 1.56 (m, 2 H), 1.33 (m, 6 H), 0.89 (t, *J* = 6.5 Hz, 3 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 149.6, 137.9, 77.2, 76.0, 32.1, 31.7, 30.0, 28.9, 22.7, 14.3.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{14}I_2S$: 419.8906; found: 419.8903.

**3-Bromo-2-iodothiophene (7c)**[28]

Colorless oil; yield: 113 mg (64%).

IR (KBr): 1488, 1335, 1143, 854, 696 $cm^{-1}$.

$^1H$ NMR (300.1 MHz, $CDCl_3$): δ = 7.41 (d, 1 H), 6.90 (d, 1 H).

$^{13}C$ NMR (75.7 MHz, $CDCl_3$): δ = 132.3, 130.5, 120.7, 77.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_4H_2BrIS$: 287.8105; found: 287.8103.

**3-Bromo-2,5-diiodothiophene (8c)**[29]

White solid; yield: 255 mg (61%); mp 55–56 °C.

IR (KBr): 1481, 1133, 956, 818 $cm^{-1}$.

Downloaded by: Flinders University of South Australia. Copyrighted material.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.02 (s, 1 H).

$^{13}$C NMR (75.7 MHz, $CDCl_3$): δ = 139.1, 121.0, 80.3, 77.4.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_4HBrI_2S$: 413.7072; found: 413.7071.

**3-[(2-Iodothiophen-3-yl)thio]propanenitrile (7d)**

Pale yellow oil; yield: 162 mg (93%).

IR (KBr): 2250, 1416, 962, 872, 710 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 4.5 Hz, 1 H), 6.97 (d, *J* = 4.5 Hz, 1 H), 3.03 (t, *J* = 7.3 Hz, 2 H), 2.56 (t, *J* = 7.3 Hz, 2 H).

$^{13}$C NMR (75.7 MHz, $CDCl_3$): δ = 135.5, 132.1, 131.2, 117.9, 85.4, 31.4, 18.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_7H_6INS_2$: 294.8986; found: 294.8983.

**3-[(2,5-Diiodothiophen-3-yl)thio]propanenitrile (8d)**

Brown powder; yield: 202 mg (81%); mp 92–93 °C.

IR (KBr): 2245, 1410, 1277, 962, 828 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.11 (s, 1 H), 3.02 (t, *J* = 7.3 Hz, 2 H), 2.52 (t, *J* = 7.3 Hz, 2 H).

$^{13}$C NMR (75.7 MHz, $CDCl_3$): δ = 140.0, 137.5, 117.8, 88.5, 77.8, 31.6, 18.6.

Anal. Calcd for $C_7H_5I_2NS_2$: C, 19.97; H, 1.20; N, 3.33. Found: C, 20.09; H, 1.10; N, 3.50.

**2-(2,5-Diiodothiophen-3-yl)acetonitrile (8e)**

Pale brown powder; yield: 283 mg (93%); mp 63–64 °C.

IR (KBr): 2247, 1399, 966, 813 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.14 (s, 1 H), 3.61 (s, 2 H).

$^{13}$C NMR (75.7 MHz, $CDCl_3$): δ = 137.4, 136.6, 116.5, 79.7, 77.7, 21.0.

Anal. Calcd for $C_6H_3I_2NS$: C, 19.22; H, 0.81; N, 3.74. Found: C, 19.24; H, 0.79; N, 4.01.

**2-(2,5-Diiodothiophen-3-yl)methanol (8f)**

Brown powder; yield: 266 mg (81%); mp 93–94 °C.

IR (KBr): 3187, 1020, 988, 830 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.13 (s, 1 H), 4.54 (s, 2 H).

$^{13}$C NMR (75.7 MHz, DMSO-$d_6$): δ = 149.3, 137.9, 79.1, 78.8, 60.0.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_5H_4I_2OS$: 365.8072; found: 365.8067.

**5-Iodo-4-methoxythiophene-3-carbonitrile (10a)**

White solid; yield: 191 mg (94%); mp 82–83 °C.

IR (KBr): 3187, 1020, 988, 830 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 4.02 (s, 3 H).

$^{13}$C NMR (75.6 MHz, $CDCl_3$): δ = 159.5, 139.5, 112.6, 105.1, 61.9, 61.5.

Anal. Calcd for $C_6H_4INOS$: C, 27.19; H, 1.52. Found: C, 27.12; H, 1.46.

**4-Bromo-2-iodo-3-methoxythiophene (10b)**

Pale yellow oil; yield: 152 mg (92%).

IR (KBr): 1521, 1334, 990, 732 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.38 (s, 1 H), 3.88 (s, 3 H).

$^{13}$C NMR (75.7 MHz, $CDCl_3$): δ = 156.9, 127.3, 105.4, 61.7, 61.6.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_5H_4BrIOS$: 317.8211; found: 317.8207.

**5,7-Diiodo-2,3-dihydrothieno[3,4-*b*][1,4]dioxin (11c)**[30]

White solid; yield: 313 mg (87%); mp 181–183 °C.

IR (KBr): 1483, 1358, 1075, 889 cm$^{-1}$.

$^1$H NMR (300.1 MHz, DMSO-$d_6$): δ = 4.21 (s, 4 H).

$^{13}$C NMR (75.6 MHz, DMSO-$d_6$): δ = 143.9, 64.8, 54.1.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_6H_4I_2O_2S$: 393.8021; found: 393.8021.

**3-Bromo-2-iodo-5-methylthiophene (13a)**[31]

Yellow oil; yield: 164 mg (95%).

IR (KBr): 1530, 1168, 959, 818 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 6.60–6.57 (m, 1 H), 2.45 (d, 3 H).

$^{13}$C NMR (75.6 MHz, $CDCl_3$): δ = 146.5, 128.5, 119.6, 73.0, 15.8.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_5H_4BrIS$: 301.8262; found: 301.8254.

**5-Hexyl-5′-iodo-2,2′-bithiophene (13b)**[32]

Yellow oil; yield: 143 mg (95%).

IR (KBr): 1374, 1128, 1065, 1091 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 3.7 Hz, 1 H), 6.93 (d, *J* = 3.6 Hz, 1 H), 6.77 (d, *J* = 3.7 Hz, 1 H), 6.67 (d, *J* = 3.6 Hz, 1 H), 2.80 (t, *J* = 7.5 Hz, 2 H), 1.70 (m, 2 H), 1.35 (m, 6 H), 0.93 (t, *J* = 6.8 Hz, 3 H).

$^{13}$C NMR (75.6 MHz, $CDCl_3$): δ = 146.0, 144.0, 137.6, 133.7, 124.9, 124.4, 123.9, 71.1, 31.7 (2 C), 30.2, 28.9, 22.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{17}IS_2$: 375.9816; found: 375.9808.

**5′-Iodo-[2,2′-bithiophene]-5-carbaldehyde (13c)**[33]

White solid; yield 140 mg (79%); mp 179–180 °C.

IR (KBr): 1638, 1227, 1050, 786 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 9.87 (s, 1 H, CHO), 7.65 (d, *J* = 3.9 Hz, 1 H), 7.23 (d, *J* = 3.8 Hz, 1 H), 7.20 (d, *J* = 3.9 Hz, 1 H), 7.01 (d, *J* = 3.8 Hz, 1 H).

$^{13}$C NMR (75.6 MHz, DMSO-$d_6$): δ = 1834.9, 144.1, 141.5, 140.8, 139.1, 138.4, 128.5, 125.6, 79.2.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_9H_5IOS_2$: 379.8826; found: 319.8823.

**7-Iodo-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-carbaldehyde (13d)**[34]

White solid; yield: 170 mg (98%); mp 155–157 °C.

IR (KBr): 1631, 1485, 1434, 1357, 1075, 955 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 9.77 (s, 1 H), 4.35 (s, 4 H).

$^{13}$C NMR (75.6 MHz, $CDCl_3$): δ = 178.8, 147.0, 144.4, 123.4, 65.9, 65.4, 65.1.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_7H_5IO_3S$: 295.9004; found: 295.8995.

**5,5′-Diiodo-2,2′-bithiophene (15)**[35]

Pale yellow solid; yield: 237 mg (94%); mp 143–145 °C.

IR (KBr): 1409, 864, 785 cm$^{-1}$.

$^1$H NMR (300.1 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 3.8 Hz, 2 H), 6.78 (d, *J* = 3.8 Hz, 2 H).

$^{13}$C NMR (75.6 MHz, $CDCl_3$): δ = 142.2, 137.8, 125.7, 72.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_8H_4I_2S_2$: 417.7844; found: 417.7847.

Downloaded by: Flinders University of South Australia. Copyrighted material.

## Acknowledgment

We thank Angers Loire Metropole for the fellowship accorded for the Ph.D. of C. Moussallem and Region Pays de la Loire for financial support accorded to the Green-SCO project.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560480.

## Primary Data

Primary data for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084 and can be cited using the following DOI: 10.4125/pd0071th.

## References

(1) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(2) Bakherad, M. *Appl. Organomet. Chem.* **2013**, *27*, 125.
(3) Strappaveccia, G.; Ismalaj, E.; Petrucci, C.; Lanar, D.; Marrocchi, A.; Drees, M.; Facchetti, A.; Vaccaro, L. *Green Chem.* **2015**, *17*, 365.
(4) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.
(5) (a) Heinrich, A. C. J.; Thiedemann, B.; Gates, P. J.; Staubitz, A. *Org. Lett.* **2013**, *15*, 4666. (b) Fin, A.; Jentzsch, A. V.; Sakai, N.; Matile, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 12736.
(6) Marzano, G.; Ciasca, C. V.; Babudri, F.; Bianchi, G.; Pellegrino, A.; Po, R.; Farinola, G. M. *Eur. J. Org. Chem.* **2014**, 6583.
(7) Burke, D. J.; Lipomi, D. J. *Energy Environ. Sci.* **2013**, *6*, 2053.
(8) (a) Arsenyan, P.; Paegle, E.; Belyakov, S. *Tetrahedron Lett.* **2010**, *51*, 205. (b) Goldberg, Y.; Alper, H. *J. Mol. Catal.* **1994**, *88*, 377.
(9) Kraszkiewicz, L.; Sosnowski, M.; Skulski, L. *Synthesis* **2006**, 1195.
(10) Krassowska-Swiebocka, B.; Lulinski, P.; Skulski, L. *Synthesis* **1995**, 926.
(11) Lulinski, P.; Krassowska-Swiebocka, B.; Skulski, L. *Molecules* **2004**, *9*, 595; http://www.mdpi.com/journal/molecules.
(12) Sosnowski, M.; Skulski, L. *Molecules* **2005**, *10*, 401; http://www.mdpi.com/journal/molecules.
(13) Lulinski, P.; Skulski, L. *Bull. J. Chem. Soc. Jpn.* **1997**, *70*, 1665.
(14) L'Helgoual'ch, J. M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177.
(15) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.
(16) Yamamoto, T.; Toyota, K.; Morita, N. *Tetrahedron Lett.* **2010**, *51*, 1364.
(17) Bailey, L.; Handy, S. T. *Tetrahedron Lett.* **2011**, *52*, 2413.
(18) (a) Fisyuk, A. S.; Bogza, Y. P.; Belyaeva, L. V.; Belyaev, V. B. *Chem. Heterocycl. Compd.* **2012**, *48*, 1078. (b) Jacobson, K. A.; Shi, D.; Gallo-Rodriguez, C.; Manning, M. Jr.; Müller, C.; Daly, J. W.; Neumeyer, J. L.; Kiriasis, L.; Pfleiderer, W. *J. Med. Chem.* **1993**, *36*, 2639. (c) Ryabova, V.; Ignatovich, L. *Thiophenes*, In *Topics in Heterocyclic Chemistry*; Vol. 39; Joule, J. A., Ed.; Springer: Heidelberg, **2014**, 74.
(19) Cardolaccia, T.; Funston, A. M.; Kose, M. E.; Keller, J. M.; Miller, J. R.; Schanze, K. S. *J. Phys. Chem. B* **2007**, *111*, 10871.
(20) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Trecourt, F.; Queguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron* **2005**, *61*, 4779.
(21) Ashizawa, M.; Niimura, T.; Yu, Y.; Tsuboi, K.; Matsumoto, H.; Yamada, R.; Kawauchi, S.; Tanioka, A.; Mori, T. *Tetrahedron* **2012**, *68*, 2790.
(22) Notaras, E. G. A.; Lucas, N. T.; Humphrey, M. G.; Willis, A. C.; Rae, A. D. *Organometallics* **2003**, *22*, 3659.
(23) Guilard, R.; Fournari, P.; Person, M. *Bull. Soc. Chim. Fr.* **1967**, *11*, 4121.
(24) Onys'ko, P. P.; Kim, T. V.; Kiseleva, O. I.; Rassukana, Y. V.; Gakh, A. A. *J. Fluorine Chem.* **2009**, *130*, 501.
(25) Muehlhausen, U.; Schirrmacher, R.; Piel, M.; Lecher, B.; Briefert, M.; Piee-Staffa, A.; Kaina, B.; Roesch, F. *J. Med. Chem.* **2006**, *49*, 263.
(26) Miller, L. L.; Yu, Y. *J. Org. Chem.* **1995**, *60*, 6813.
(27) Tam, I. W.; Yan, J.; Breslow, R. *Org. Lett.* **2006**, *8*, 183.
(28) Ishii, A.; Kobayashi, S.; Aoki, Y.; Annaka, T.; Nakata, N. *Heteroat. Chem.* **2014**, *25*, 658.
(29) Wonneberger, H.; Ma, C. Q.; Gatys, M. A.; Li, C.; Bauerle, P.; Mullen, K. *J. Phys. Chem. B* **2010**, *114*, 14343.
(30) L'Helgoual'ch, J. M.; Bentabed-Ababsa, G.; Chevallier, F.; Yonehara, M.; Uchiyama, M.; Derdour, A.; Mongin, F. *Chem. Commun.* **2008**, 5375.
(31) Karlsson, J. O.; Svensson, A.; Gronowitz, S. *J. Org. Chem.* **1984**, *49*, 2018.
(32) Meng, Q.; Gao, J. H.; Li, R. J.; Jiang, L.; Wang, C. L.; Zhao, H. P.; Liu, C. M.; Li, H. X.; Hu, W. P. *J. Mater. Chem.* **2009**, *19*, 1477.
(33) Gupta, A.; Ali, A.; Bilic, A.; Gao, M.; Hegedus, K.; Singh, B.; Watkins, S. E.; Wilson, G. J.; Bach, U.; Evans, R. A. *Chem. Commun.* **2012**, *48*, 1889.
(34) Jessing, M.; Brandt, M.; Jensen, K. J.; Christensen, J. B.; Boas, U. *J. Org. Chem.* **2006**, *71*, 6734.
(35) Li, Z. H.; Wong, M. S.; Fukutani, H.; Tao, Y. *Chem. Mater.* **2005**, *17*, 5032.

Downloaded by: Flinders University of South Australia. Copyrighted material.