

# Regiospecific synthesis of 3,4-disubstituted thiophenes

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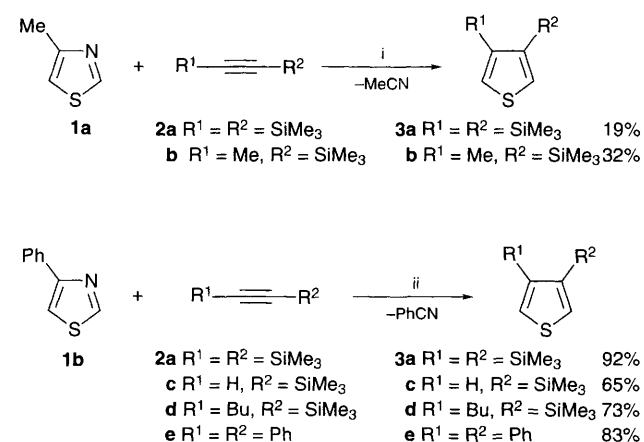
**3,4-Bis(trimethylsilyl)thiophene and several other 3,4-disubstituted thiophenes are synthesised by an unprecedented intermolecular cycloaddition–cycloreversion procedure between disubstituted acetylenes and 4-methyl- or 4-phenyl-thiazole; 3,4-bis(trimethylsilyl)thiophene undergoes consecutive regiospecific mono-*ipso*-iodination and palladium-catalysed reactions to provide unsymmetrically 3,4-disubstituted thiophenes.**

Substituted thiophenes<sup>1</sup> have lately emerged as attractive target molecules because of their potential applications in the food<sup>2</sup> and pharmaceutical<sup>3</sup> industries, in conducting polymer design,<sup>4</sup> as well as in non-linear optical devices.<sup>5</sup> However, the inclination of thiophene to endure both metallation and electrophilic substitution preferentially at the  $\alpha$ -positions<sup>1</sup> has made the synthesis of 3-substituted and 3,4-disubstituted thiophenes an exceedingly arduous assignment. Despite the fact that an urgent need for new materials has inspired an unrelenting search to devise synthetic methods for 3-substituted<sup>6</sup> and 3,4-disubstituted thiophenes,<sup>7</sup> 'genuine' synthetic solutions of these compounds still await investigation. Recently we have reported the conversions of 3,4-bis(trimethylsilyl)furan to 3,4-disubstituted furans,<sup>8</sup> involving the concomitant functions of a silyl group as a protecting group<sup>9</sup> and as an *ipso*-substitution director.<sup>10</sup> In line with this notion, here we report practical syntheses of structurally elaborate 3,4-disubstituted thiophenes.

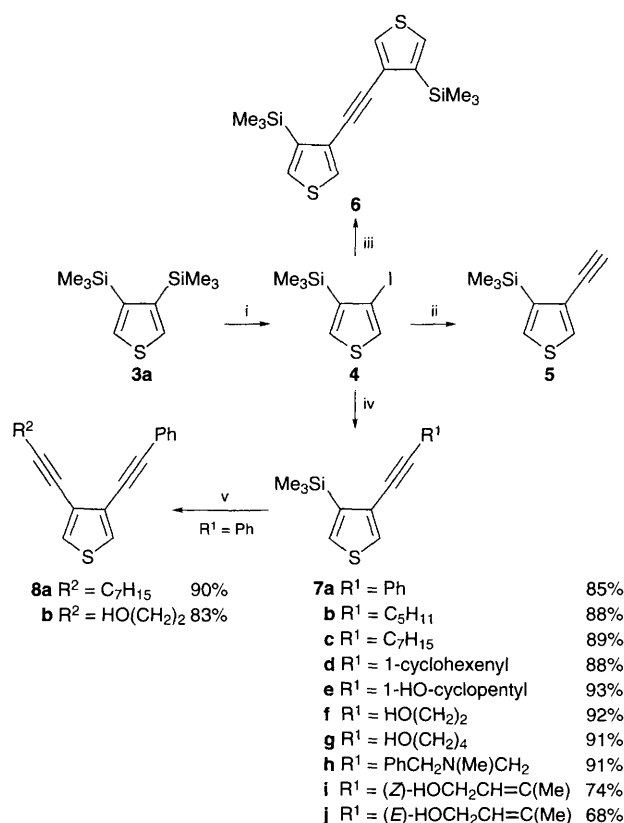
Owing to the low reactivity of thiazoles towards Diels–Alder cycloaddition,<sup>11</sup> only a few examples are known in which thiophene rings were assembled *via* a crucial intramolecular thiazole–alkyne cycloaddition.<sup>12</sup> The intermolecular version of these reactions has hitherto been unexplored. However, after a large amount of experimentation, we eventually found that at 320–360 °C alkynes **2** were able to react with 4-methylthiazole **1a**<sup>13a</sup> and 4-phenylthiazole **1b**,<sup>13b</sup> with the latter giving better yields, providing 3-substituted and 3,4-disubstituted thiophenes **3** after extrusion of acetonitrile or benzonitrile (Scheme 1). In this way, 3,4-bis(trimethylsilyl)thiophene **3a** was obtained in an

inferior yield by treating **1a** with bis(trimethylsilyl)acetylene **2a** in Et<sub>3</sub>N at 360 °C, or in 92% yield from a similar reaction between **1b** and **2a** in DBU at 325 °C. This thermal reaction between **1b** and **2a** is quite amenable to large scale production of **3a**, which was generated routinely in about an 8 g quantity in one single run.<sup>†</sup> A base was somehow needed to play the role as a proton scavenger because **3a** can undergo a facile acid-catalysed rearrangement.<sup>14</sup> Reaction of thiazole **1a** and **2b** in DBU at 340 °C again only gave **3b** in an unsatisfactory yield. Nevertheless, **1b** reacted with **2c** and **2d** in DBU to produce **3c** and **3d** in good yields, respectively. The preparation of **3e** from **1b** and **2e**, on the other hand, did not require a base.

Another preparation of unsymmetrically 3,4-disubstituted thiophenes was by employing **3a** as a building block.<sup>8</sup> As shown in Scheme 2, a regiospecific mono-*ipso*-iodination<sup>8</sup> cleanly converted **3a** to iodide **4**, which was in turn transformed by the Stille reaction to alkynes **5** and **6**, and by the Sonogashira reaction to alkynes **7**. The remaining trimethylsilyl group of **7a** was also replaced by iodine in merely 30% yield under more rigorous conditions,<sup>8,15</sup> presumably due to alkyne interference. Further Sonogashira reaction of the resulting iodide gave bisalkynes **8** in increased yields.



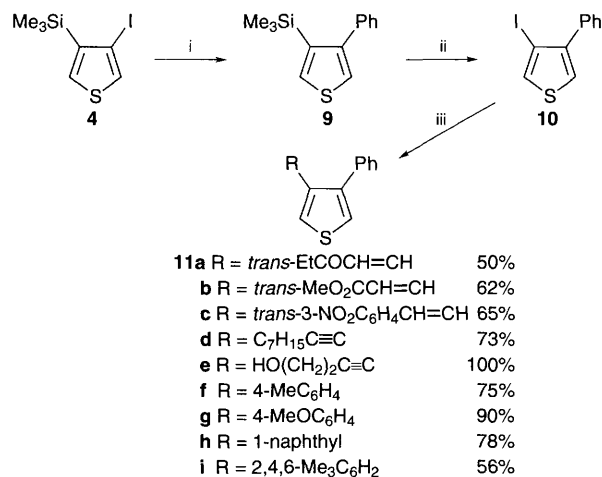
**Scheme 1** Reagents and conditions; i, Sealed tube, 340–360 °C, Et<sub>3</sub>N or DBU; ii, sealed tube, 325–340 °C, DBU



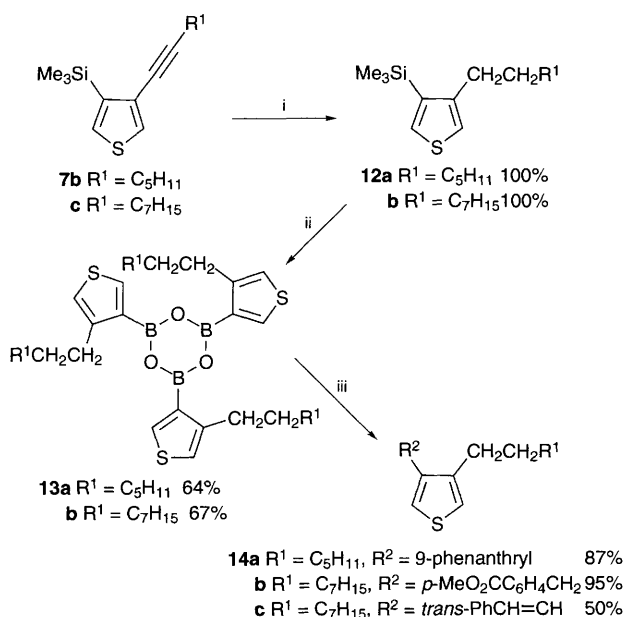
**Scheme 2** Reagents and conditions: i, I<sub>2</sub>, CF<sub>3</sub>CO<sub>2</sub>Ag, THF, -78 °C, 6 h, 96%; ii, Pd(PPh<sub>3</sub>)<sub>4</sub>, Bu<sub>3</sub>SnC≡CH, dioxane, reflux, 1 h, 90%; iii, Pd(PPh<sub>3</sub>)<sub>4</sub>, Bu<sub>3</sub>SnC≡CSnBu<sub>3</sub>, dioxane–Et<sub>3</sub>N, 90 °C, 8 h, 56%; iv, Pd(PPh<sub>3</sub>)<sub>4</sub>, R<sup>1</sup>C≡CH, CuI, Et<sub>3</sub>N, MeCN, reflux; v, (a) I<sub>2</sub>, CF<sub>3</sub>CO<sub>2</sub>Ag, THF–MeOH, 0 °C, 30% (b) Pd(PPh<sub>3</sub>)<sub>4</sub>, R<sup>2</sup>C≡CH, CuI, Et<sub>3</sub>N, MeCN, reflux

To widen the scope of our strategy, iodide **4** was first converted to **9** by the Suzuki reaction. Regiospecific iodination of **9** produced the key intermediate **10** for the preparation of **11**. Compound **11** could thus be formed *via* **10** through the use of various palladium-catalysed processes such as the Heck reaction (**11a**, **11b**, **11c**), the Sonogashira reaction (**11d**, **11e**) and the Suzuki reaction (**11f**, **11g**, **11h**, **11i**) (Scheme 3).

The synthesis of **14a**, **14b** and **14c** (Scheme 4) is a befitting example demonstrating the malleability of our silicon protocol. As can be seen, **7b** and **7c** were hydrogenated to **12a** and **12b** respectively in almost quantitative yields. Conversion of **12a** and **12b** to boroxines **13a** and **13b** was in keeping with our own



**Scheme 3 Reagents and conditions:** i, Pd(PPh<sub>3</sub>)<sub>4</sub>, PhB(OH)<sub>2</sub> 2 mol dm<sup>-3</sup> Na<sub>2</sub>CO<sub>3</sub>, MeOH-PhMe, reflux, 77%; ii, I<sub>2</sub>, CF<sub>3</sub>CO<sub>2</sub>Ag, THF, -78–0 °C, 67%; iii, (a) for **11a** and **11b**, Pd(OAc)<sub>2</sub>, EtCOCH=CH<sub>2</sub> or MeO<sub>2</sub>CCH=CH<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, Bu<sub>4</sub>NI, DMF, 80–90 °C (b) for **11c**, Pd(OAc)<sub>2</sub>, 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CH=CH<sub>2</sub>, PPh<sub>3</sub>, Et<sub>3</sub>N, reflux (c) for **11d** and **11e**, Pd(PPh<sub>3</sub>)<sub>4</sub>, C<sub>7</sub>H<sub>15</sub>C≡CH or HO(CH<sub>2</sub>)<sub>2</sub>C≡CH, CuI, Et<sub>3</sub>N, MeCN, reflux (d) for **11f**, **11g** and **11h**, Pd(PPh<sub>3</sub>)<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, B(OH)<sub>2</sub>, 4-MeO-C<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> or naphthalene-1-B(OH)<sub>2</sub>, 2 mol dm<sup>-3</sup> Na<sub>2</sub>CO<sub>3</sub>, MeOH-PhMe, reflux (e) for **11i**, Pd(PPh<sub>3</sub>)<sub>4</sub>, 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>B(OH)<sub>2</sub>, Bu<sup>t</sup>OK, Bu<sup>t</sup>OH, reflux



**Scheme 4 Reagents and conditions:** i, H<sub>2</sub>, 10% Pd/C, C<sub>6</sub>H<sub>14</sub>-Et<sub>3</sub>N; ii, (a) BCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C (b) 0.5 mol dm<sup>-3</sup> Na<sub>2</sub>CO<sub>3</sub>; iii, Pd(PPh<sub>3</sub>)<sub>4</sub>, R<sup>2</sup>Br, 2 mol dm<sup>-3</sup> Na<sub>2</sub>CO<sub>3</sub>, MeOH-PhMe, reflux

route to 3,4-disubstituted furans.<sup>8,16</sup> Boroxine **13a** as expected delivered the unsymmetrically 3,4-disubstituted thiophene **14a** in good yield *via* the use of a Suzuki-type reaction.<sup>8</sup> Likewise, **13b** was also converted to the 3-alkyl- and 4-benzyl-disubstituted **14b** as well as the 3-alkyl- and 4-*trans*-phenylethenyl-disubstituted **14c**.

In conclusion, we have developed an efficient and stepwise preparation of 3,4-disubstituted thiophenes. Noteworthy is that in order to furnish easy synthetic routes to these potentially useful thiophenes, only readily manageable palladium-catalysed reactions were employed in the conversion of **3a** and **4**.

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## Footnote

†**Experimental Procedure:** For **3a**: A mixture of **1b** (9.7 g, 60 mmol), **2a** (11.1 g, 65 mmol) and DBU (1.5 cm<sup>3</sup>) was placed in a tube (15 × 2.5 cm<sup>2</sup>) which was then attached to a vacuum manifold (0.05 mmHg) and subjected to three freeze-thaw cycles (liquid nitrogen). The tube was then sealed and heated at 325 °C for 6 d. The resulting dark mixture was chromatographed on a silica gel column (230–400 mesh, 250 g, hexanes; then hexanes/EtOAc 10:1 to 5:1) to give **3a** as a colourless oil (8.2 g, 92% based on reacted **1b**) and recovered **1b** (3.4 g). For thiophene **3a**: <sup>1</sup>H NMR (250.132 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 0.34 (s, 18 H) and 7.61 (s, 2 H); <sup>13</sup>C NMR (62.896 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 1.09, 134.73 and 145.43; EI-MS (70 eV): *m/z* 228 (M<sup>+</sup>).

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