Regiospecific synthesis of 3,4-disubstituted thiophenes

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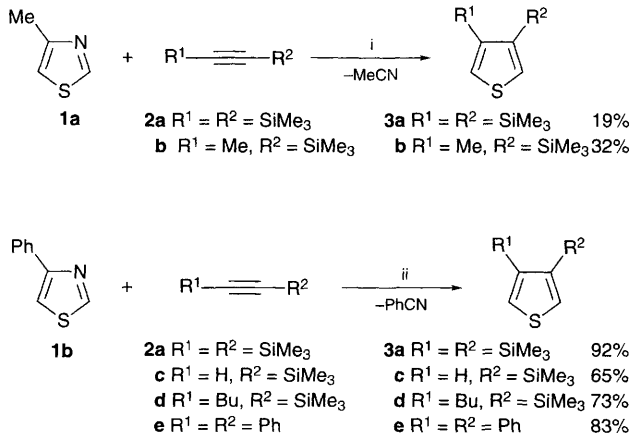
3,4-Bis(trimethylsilyl)thiophene and several other 3,4-disubstituted thiophenes are synthesised by an unprecedented intermolecular cycloaddition–cycloreversion procedure between disubstituted acetylenes and 4-methyl- or 4-phenyl-thiazole; 3,4-bis(trimethylsilyl)thiophene undergoes consecutive regiospecific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

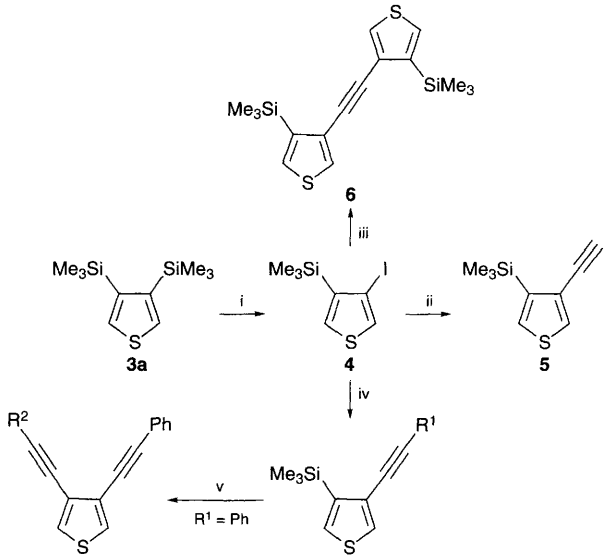
Substituted thiophenes[1] have lately emerged as attractive target molecules because of their potential applications in the food[2] and pharmaceutical[3] industries, in conducting polymer design,[4] as well as in non-linear optical devices.[5] However, the inclination of thiophene to endure both metallation and electrophilic substitution preferentially at the α-positions[1] 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[6] and 3,4-disubstituted thiophenes,[7] '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,[8] involving the concomitant functions of a silyl group as a protecting group[9] and as an *ipso*-substitution director.[10] 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,[11] only a few examples are known in which thiophene rings were assembled *via* a crucial intramolecular thiazole–alkyne cycloaddition.[12] 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**[13a] and 4-phenylthiazole **1b**,[13b] 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_3N 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.† A base was somehow needed to play the role as a proton scavenger because **3a** can undergo a facile acid-catalysed rearrangement.[14] 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.



Scheme 1 *Reagents and conditions*: i, Sealed tube, 340–360 °C, Et_3N or DBU; ii, sealed tube, 325–340 °C, DBU

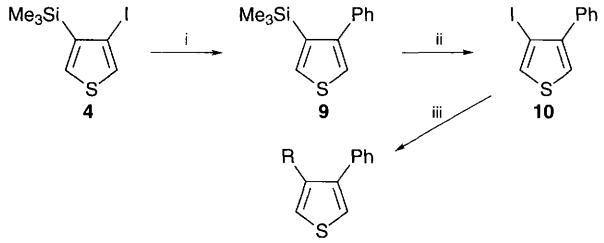
Another preparation of unsymmetrically 3,4-disubstituted thiophenes was by employing **3a** as a building block.[8] As shown in Scheme 2, a regiospecific mono-*ipso*-iodination[8] cleanly converted **3a** to iodide **4**, which was in turn transformed by the Stille reaction to alkynes **5** and **6**, 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,[8,15] presumably due to alkyne interference. Further Sonogashira reaction of the resulting iodide gave bisalkynes **8** in increased yields.



Scheme 2 *Reagents and conditions*: i, I_2, CF_3CO_2Ag, THF, −78 °C, 6 h, 96%; ii, $Pd(PPh_3)_4$, $Bu_3SnC{\equiv}CH$, dioxane, reflux, 1 h, 90%; iii, $Pd(PPh_3)_4$, $Bu_3SnC{\equiv}CSnBu_3$, dioxane–Et_3N, 90 °C, 8 h, 56%; iv, $Pd(PPh_3)_4$, $R^1C{\equiv}CH$, CuI, Et_3N, MeCN, reflux; v, (*a*) I_2, CF_3CO_2Ag, THF–MeOH, 0 °C, 30% (*b*) $Pd(PPh_3)_4$, $R\ ^2C{\equiv}CH$, CuI, Et_3N, MeCN, reflux

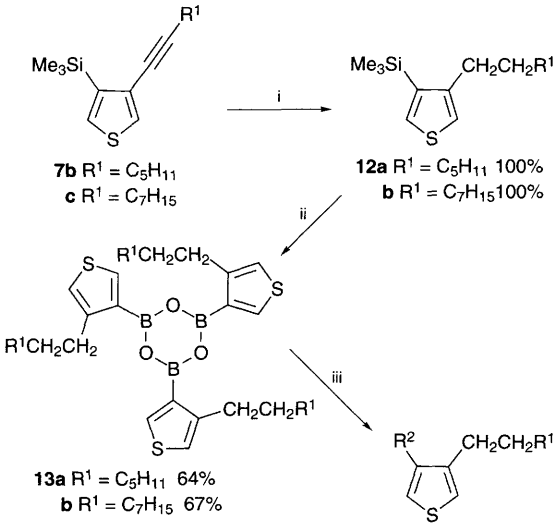
To widen the scope of our strategy, iodide **4** was first converted to **9** by the Suzuki reaction. Regiospecific iodination of **9** produced the key intermediate **10** for the preparation of **11**. Compound **11** could thus be formed *via* **10** through the use of various palladium-catalysed 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 route to 3,4-disubstituted furans.[8,16] Boroxine **13a** as expected delivered the unsymmetrically 3,4-disubstituted thiophene **14a** in good yield *via* the use of a Suzuki-type reaction.[8] 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**.



11a	R = *trans*-EtCOCH=CH	50%
b	R = *trans*-MeO_2CCH=CH	62%
c	R = *trans*-3-$NO_2C_6H_4$CH=CH	65%
d	R = $C_7H_{15}C{\equiv}C$	73%
e	R = $HO(CH_2)_2C{\equiv}C$	100%
f	R = 4-MeC_6H_4	75%
g	R = 4-$MeOC_6H_4$	90%
h	R = 1-naphthyl	78%
i	R = 2,4,6-$Me_3C_6H_2$	56%

Scheme 3 *Reagents and conditions*: i, $Pd(PPh_3)_4$, $PhB(OH)_2$ 2 mol dm^{-3} Na_2CO_3, MeOH–PhMe, reflux, 77%; ii, I_2, CF_3CO_2Ag, THF, −78–0 °C, 67%; iii, (*a*) for **11a** and **11b**, $Pd(OAc)_2$, EtCOCH=CH_2 or $MeO_2CCH{=}CH_2$, K_2CO_3, Bu_4NI, DMF, 80–90 °C (*b*) for **11c**, $Pd(OAc)_2$, 3-$NO_2C_6H_4CH{=}CH_2$, PPh_3, Et_3N, reflux (*c*) for **11d** and **11e**, $Pd(PPh_3)_4$, $C_7H_{15}C{\equiv}CH$ or $HO(CH_2)_2C{\equiv}CH$, CuI, Et_3N, MeCN, reflux (*d*) for **11f**, **11g** and **11h**, $Pd(PPh_3)_4$ 4-MeC_6H_4, $B(OH)_2$, 4-MeO-$C_6H_4B(OH)_2$ or naphthalene-1-$B(OH)_2$, 2 mol dm^{-3} Na_2CO_3, MeOH-PhMe, reflux (*e*) for **11i**, $Pd(PPh_3)_4$, 2,4,6,-$Me_3C_6H_2B(OH)_2$, Bu^tOK, Bu^tOH, reflux



13a R^1 = C_5H_{11} 64%
b R^1 = C_7H_{15} 67%

14a	R^1 = C_5H_{11}, R^2 = 9-phenanthryl	87%
b	R^1 = C_7H_{15}, R^2 = *p*-$MeO_2CC_6H_4CH_2$	95%
c	R^1 = C_7H_{15}, R^2 = *trans*-PhCH=CH	50%

Scheme 4 *Reagents and conditions*: i, H_2, 10% PdC, C_6H_{14}-Et_3N; ii, (*a*) BCl_3, CH_2Cl_2, −78 °C (*b*) 0.5 mol dm^{-3} Na_2CO_3; iii, $Pd(PPh_3)_4$, R^2Br, 2 mol dm^{-3} Na_2CO_3, MeOH–PhMe, reflux

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**.

The financial support by a Research Grants Council (Hong Kong) Earmarked Grant for Research (CU93/7.01) is gratefully acknowledged. X-S. Y. is on study leave from Department of Fundamental Courses, The Agricultural University of Central China, Wuhan, China.

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^3) was placed in a tube (15 × 2.5 cm^2) 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**: ^1H NMR (250.132 MHz, $CDCl_3$): δ_H 0.34 (s, 18 H) and 7.61 (s, 2 H); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C 1.09, 134.73 and 145.43; EI-MS (70 eV): *m/z* 228 (M^+).

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Received, 9th October 1995; Com. 5/06677H