Synthesis of Thiophene-Based Building Blocks via Facile α-Monoiodination

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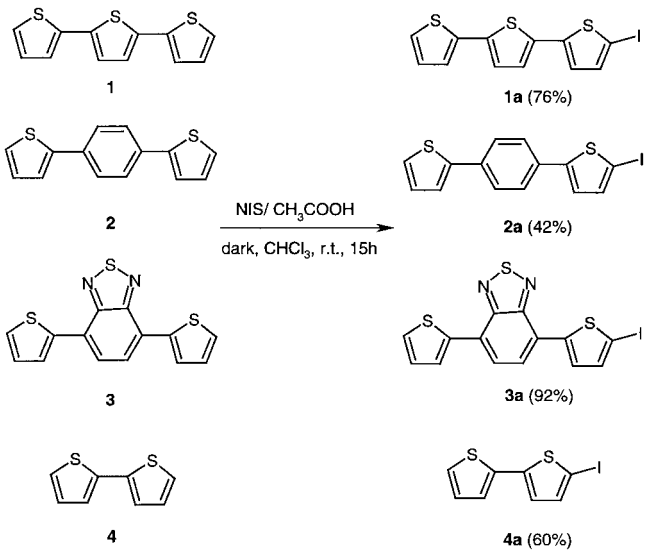
Received 18 January 2001

Abstract: A new procedure to selectively α-monoiodinate symmetrical thiophene-capped segments is described. The monoiodinated derivatives are further modified, giving access to a variety of thiophene-based building blocks, which are useful for e.g. oligomer synthesis via segmental coupling.

Key words: monoiodination, N-iodosuccinimide, oligothiophenes, thiophene-based segments

Monoiodinated oligothiophene segments have received attention in recent years as useful intermediates in the synthesis of conjugated materials,[1,2] self-assembled monolayers[3] and as bioactive reagents in e.g. anti-tumor therapy.[4,5] Despite this, only few methods to selectively α-monoiodinate symmetrical thiophene-based segments are known.[4-10] Monoiodination of symmetrical bi- and terthiophenes utilises mostly either mercurioxide, or mercurichloride followed by subsequent reaction of the oligothienylmercuri compound with elemental iodine.[6,7] An alternative route via the monobromo compound and cuprous iodide gives α-monoiodinated bithiophene in low yield.[8] Since the method employing mercuri compounds is both toxic, cumbersome, and, in the case of terthiophene, only gives a moderate yield[7], we searched for a simpler procedure. Wu et al.[11] used N-bromosuccinimide (NBS) in combination with acetic acid, in an attempt to synthesise 5-bromo-[2,2']bithiophene; however, the product contained starting material and bisbromo compound even after purification. By applying N-iodosuccinimide (NIS) and acetic acid in a procedure analogous to the bromination described by Wu, we found that bithiophene **4** could be monoiodinated with excellent selectivity. Small amounts of bisiodo-bithiophene formed could easily be removed by a filtration of the crude reaction mixture giving 5-iodo-[2,2']bithiophene **4a** in 92-97% purity. Monoiodination of terthiophene **1** showed an even higher selectivity, and monoiodinated terthiophene **1a** was obtained in 76% yield, after simple workup.[12] Our findings prompted us to apply this procedure to various thiophene containing segments **1**-**4**, as shown in Scheme 1.

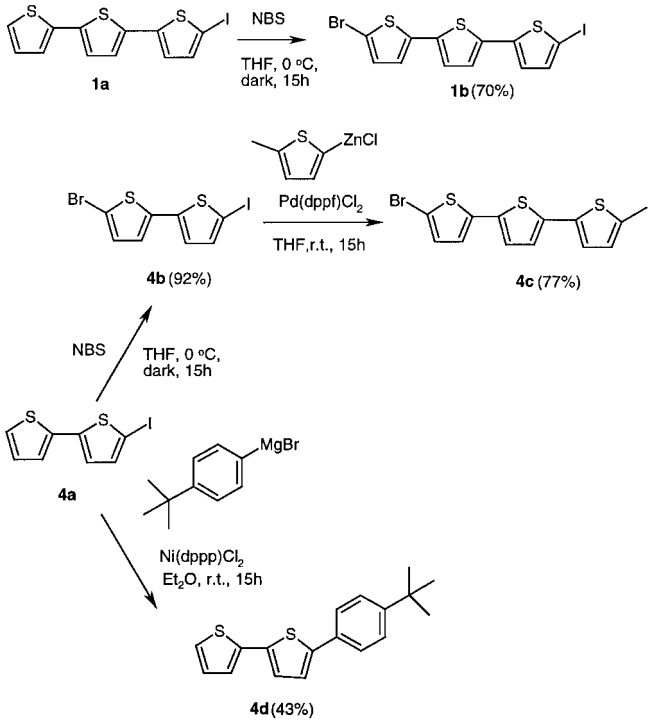


Scheme 1

Monoiodo-terthiophene **1a** and monoiodo-bithiophene **4a**[13] segments are easily made by this procedure, however, in the case of compound **2a**[13] a lower selectivity was observed under the reaction conditions employed, creating a larger amount of bisiodo compound (27% by GC-MS). The latter could, however, be removed by filtration through a short silicagel column. Upon introduction of a biphenyl unit between the terminal thiophenes, attempts to synthesise the monoiodinated compound failed, due to low solubility of the starting material. In the case of **3a**,[13] 1.3 equivalents of NIS were needed in order to minimise the amount of starting material in the crude mixture, and, also here, the bisiodinated compound could easily be removed by a column filtration; the monoiodinated segment **3a** was obtained in good yield and 95% purity (GC-MS).

The monoiodo ter- and bithiophene compounds **1a**, **4a** were subsequently modified by bromination to yield new mixed halogenated ter- and bithiophene **1b**, **4b** in good yields (70% and 92%, respectively).[14] Negishi coupling under mild conditions gave chemoselective derivatisation of the iodo position on **4b**, obtaining 5-bromo-5''methylterthiophene **4c** in 77% yield (Scheme 2).[15] Nickel-catalysed coupling between monoiodo bithiophene **4a** and 4-*tert*-butylphenyl-magnesiumbromide gave 5-*tert*-butyl phenyl-[2,2']bithiophene **4d** in acceptable yield.[16]

In summary, some useful building blocks for e.g. segment coupling have been synthesised using an easy monoiodination procedure. The introduced monoiodination procedure has shown to be a useful alternative to previous described methods. The monoiodinated building blocks have been further derivatised in good yields, giving access to a variety of asymmetrical thiophene segments.



Scheme 2

Acknowledgement

The University of Copenhagen is gratefully thanked for financial support. The Authors gratefully thank Xianwen Lou for performing MALDI-TOF analysis.

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(12) Monoiodination, typical procedure, 5-iodo-[2, 2', 5', 2''']terthiophene (**1a**): **1** (2.0 g, 8.1 mmol) and NIS (2.1 g, 9.26 mmol) were dissolved in a mixture of dry $CHCl_3$ (30 ml) and glacial AcOH (20 ml). The mixture was shielded from light and stirred overnight at r.t. Solvents were removed by evaporation using an oil pump. Residual succinimide and bisiodo terthiophene were removed on a short silicagel column (Et_2O-hexane 1:1). Yield: 2.6 g (76%); mp: 142-143 °C (lit. 138-139 °C);[7] ^{1}H NMR (300 MHz, d_6-acetone): δ 7.06 (d, *J* 3.8 Hz, 1H), 7.12 (dd, ^3J 4.9 Hz, ^4J 1.4 Hz, 1H), 7.24 (d+d, *J* 3.8 Hz, *J* 3.8 Hz, 2H), 7.34 (d+dd, *J* 3.6 Hz, ^3J 3.6 Hz, ^4J 1.1 Hz, 2H), 7.48 (dd, ^3J 4.9 Hz, ^4J 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.0, 124.0, 124.4, 124.8, 125.1, 128.0, 135.0, 136.8, 136.9, 137.8, 143.1; LRMS, calcd. ($C_{12}H_7IS_3$): 374.27. Found: 374.0; GC: 99% purity
(13) 2-(4-(thiophen-2'-yl)-phenyl)-5-iodo-thiophene (**2a**): **2**[17] (0.50 g, 2.10 mmol) and NIS (0.54 g, 2.40 mmol) in $CHCl_3$ (12 ml) and AcOH (7 ml) was treated as above. Purification on short silicagel column, (1. hexane, 2. EtOAc-hexane 1:1). Yield: 0.32 g (42%); mp: 198 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, *J* 3.9 Hz, 1H), 7.12 (dd, ^3J 5.2 Hz, ^4J 1.6 Hz, 1H), 7.25 (d, *J* 3.9 Hz, 1H), 7.33 (dd, ^3J 4.9 Hz, ^4J 1.1 Hz, 1H), 7.36 (dd, ^3J 3.6 Hz, ^4J 1.1 Hz, 1H), 7.53-7.56 (m, 2H), 7.63-7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.5, 123.3, 124.6, 125.2, 126.2-126.4, 128.2, 132.6, 134.0, 138.1, 143.8, 150.0; LRMS calcd. ($C_{14}H_9IS_2$): 368.25. Found: 368.0; GC: 97% purity; 4-(5-iodo-thiophen-2-yl)-7-(thiophen-2'-yl)-benzo[2.1.3]thiadiazole (**3a**):
3[17](0.50 g, 1.70 mmol) and NIS (0.50 g, 2.2 mmol) in $CHCl_3$ (10 ml) and AcOH (5 ml) was treated as above. Purification on short silicagel column (Et_2O-hexane 1:1). Yield: 0.67 g (92%); mp: 124-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (dd, ^3J 3.6 Hz, ^4J 1.4 Hz, 1H), 7.37 (d, *J* 4.1 Hz, 1H), 7.49 (dd, ^3J 5.2 Hz, ^4J 1.1 Hz, 1H), 7.73 (d, *J* 3.8 Hz, 1H), 7.83 (d, *J* 8.0 Hz, 1H), 7.89 (d, *J* 7.7 Hz, 1H), 8.15 (dd, ^3J 3.9 Hz, ^4J 1.1 Hz, 1H); ^{13}C NMR (75 MHz, d_8-THF): 82.7, 130.4, 130.7, 130.8, 131.0, 131.9, 132.8, 133.4, 133.9, 143.3, 144.9, 150.9, 157.9, 158.0; MS (MALDI-TOF), calcd. ($C_{14}H_7IN_2S_3$): 426.31 Found: 426.62; 5-Iodo-[2,2']bithiophene (**4a**): **4** (2.0 g, 12.0 mmol) and NIS (3.2 g, 14.4 mmol) in $CHCl_3$ (24 ml) and AcOH (24 ml), was stirred overnight and the reaction mixture was filtered to remove bisiodinated bithiophene. Solvents were removed by evaporation on oil pump. The residue was filtered through a short silicagel column (hexane). Yield: 2.1 g (60%); ^{1}H NMR (300 MHz, d_6-acetone): δ 7.00 (dd, ^3J 3.9 Hz, ^4J 0.8 Hz, 1H), 7.09 (m, 1H), 7.26 (d, *J* 3.6 Hz, 1H), 7.29 (dd, ^3J 3.6 Hz, ^4J 0.8 Hz, 1H), 7.44 (d, *J* 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.2, 124.4, 124.6, 125.0, 128.1, 136.4, 137.8, 143.5; LRMS calcd.($C_8H_5IS_2$): 292.15. Found: 291.9; GC: 95% purity
(14) 5-Bromo-5''-iodo[2.2'.5'.2''']terthiophene (**1b**): **1a** (0.374 g, 1.00 mmol) was dissolved in dry THF (5ml), and the mixture cooled in an ice bath and NBS (0.178 g, 1.00 mmol) was added in the cold. The ice bath was removed, the mixture was shielded from light and stirred overnight at r.t. The solvent was removed by evaporation and the residue was filtered through a short silicagel coloumn (Et_2O). Yield: 0.320 g (70%); mp: 175-177 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (d, *J* 3.4 Hz, 1H), 6.91 (d, *J* 3.4 Hz, 1H), 6.98-7.00 (d+br s, *J* 3.9 Hz, 3H), 7.17 (d, *J* 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.3, 111.4, 124.0, 124.6, 124.8, 125.3, 130.8, 135.5, 135.7, 137.8, 138.4, 142.8.; LRMS calcd. ($C_{12}H_6BrIS_3$): 453.3. Found: 453.8; GC: 96% purity; 5-Bromo-5'-iodo-[2.2']bithiophene (**4b**): **4a** (1.85 g, 6.34 mmol) was reacted with NBS (1.13 g, 6.34 mmol) in dry THF (30ml) as above. Filtration through a short silicagel coloumn (Et_2O-hexane 1:1). Yield: 2.17 g (92%); mp: 148-150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (d, *J* 3.9 Hz, 1H), 6.86 (d, *J* 3.9 Hz, 1H), 6.96 (d, *J* 3.9 Hz, 1H), 7.15 (d, *J* 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.5, 111.7, 124.2, 124.4, 125.5, 130.7, 137.8, 142.3; LRMS calcd. ($C_8H_4BrIS_2$): 371.14. Found: 371.6; GC: 98% purity

(15) 5''-Bromo-5-methyl[2.2'.5'.2'']terthiophene (**4c**): A solution of 2-methyl-thiophene (0.10 g, 1.00 mmol) in dry THF (5ml) was cooled on an ice bath. A 1.6 M solution of n-BuLi (0.70 ml, 1.10 mmol) was added in the cold and the mixture was stirred 30 min. on ice bath. $ZnCl_2$ (0.21 g, 1.50 mmol) was added and the mixture stirred for 1 h at r.t. This solution was added dropwise to **4b** (0.37 g, 1.00 mmol) and Pd (dppf)Cl_2 (cat.) in dry THF (5 ml). The mixture was stirred overnight at r.t. and was poured into water (50 ml). The aqueous layer was extracted with hexane (2 × 20 ml), the combined organic fractions were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. Purification by chromatography (hexane). Yield: 0.264 g (77%); mp: 135-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (s, 3H), 6.67 (br s, 1H), 6.89 (d, *J* 3.9 Hz, 1H), 6.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.5, 110.9, 123.6, 123.9, 124.2, 124.6, 126.1, 130.7, 134.5, 134.6, 137.3, 138.8, 139.7; LRMS calcd. ($C_{13}H_9Br_3$): 341.4. Found: 342.0; GC: 96% purity

(16) 5-(4-*tert*-butyl phenyl)-[2,2']bithiophene (**4d**): 1-Bromo-4-*tert*-butyl-benzene (2.3 ml, 13.3 mmol) was added to magnesium turnings (0.5 g, 20.0 mmol) in dry Et_2O (13 ml). The reaction was initiated by shortly heating in an oil bath. The mixture was refluxed for 30 min, and 1.1 ml (1.1 mmol) of this solution was added to a mixture of **4a** (0.29 g, 1.00 mmol) and Ni(dppp)Cl_2 (5.4 mg, 0.01 mmol) in dry Et_2O (5ml). The mixture was stirred for 2 h at r.t. and refluxed for 30 min. The solvent was removed in vacuo and the residue was purified by chromatography (Et_2O-hexane 1:1). Yield: 0.145 g (43%); mp: 95 °C (dec); ^{1}H NMR (300 MHz, d_6-acetone): δ 1.33 (s, 9H), 7.1 (t, *J* 4.0 Hz, 1H), 7.26 (d, *J* 3.7 Hz, 1H), 7.31 (d, *J* 2.9 Hz, 1H), 7.38 (d, *J* 3.7 Hz, 1H), 7.43 (d, *J* 5.1 Hz, 1H), 7.47 (d, *J* 8.4 Hz, 2H), 7.61 (d, *J* 8.4 Hz, 2H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.4, 34.7, 114.8, 123.4, 123.6, 124.3, 124.7, 125.5, 126.0, 126.5, 127.9, 131.4, 136.3, 137.7, 143.4, 150.9; LRMS calcd. ($C_{18}H_{18}S_2$): 298.5. Found: 298.0; GC: 97% purity

(17) Compounds **2** and **3** were prepared by Stille reaction between 2-(tributyl-stannyl)-thiophene and 1.4-dibromo-benzene or 4.7-dibromo-benzo[2.1.3]thiadiazole, respectively, according to: Dhanabalan, A.; Boas, U.; van Duren, J. K. J.; Janssen, R. A. J.: To be published.

Article Identifier:
1437-2096,E;2001,0,05,0634,0636,ftx,en;G01001ST.pdf