SELECTIVE FUNCTIONALIZATION OF 2,2'-BITHIOPHENES

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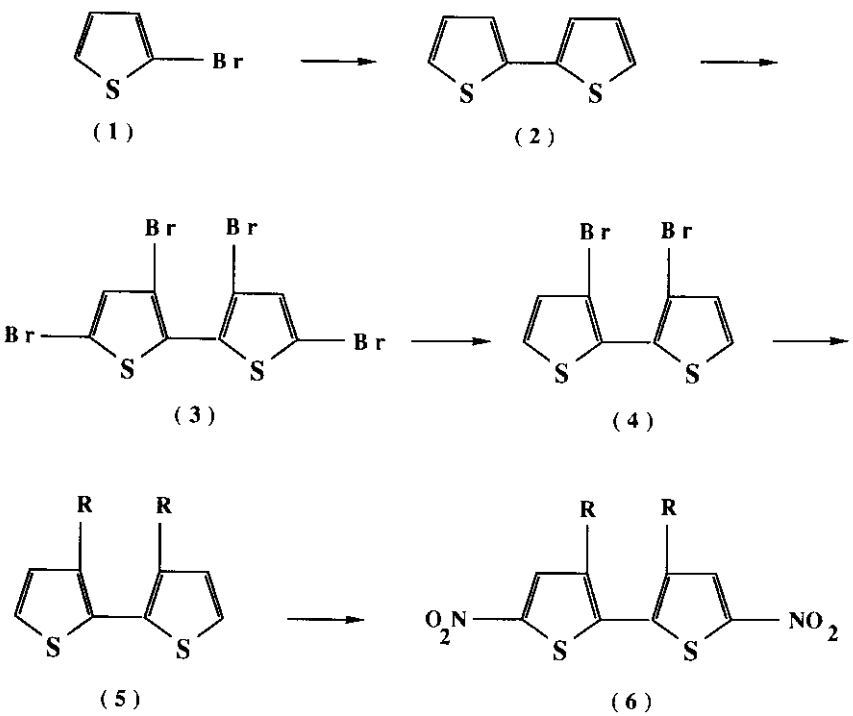
Abstract - The selective functionalization of the 2,2'-bithiophene molecule is described. Selective alkyl substitution at the 3,3' positions was achieved by sequential bromination of the 3,3' and 5,5' positions followed by debromination at the 5,5' positions. The resultant 3,3'-dibromo-2,2'-bithiophene was transformed *via a Grignard reaction to give a series of* 3,3'-dialkyl-2,2'-bithiophenes. Finally, nitration of the active 5,5' positions gave the corresponding 3,3'-dialkyl-5,5'-dinitro-2,2'-bithiophenes.

INTRODUCTION

Since their discovery more than 100 years ago,[1] bithiophenes have been regarded as unimportant by-products of primary thiophene reactions. To date, although the syntheses of thiophene systems with more than one ring are reported,[2] not much of their chemistry has been explored even in the updated and extensive review by Gronowitz.[3] Recent interest in various bi-, tri- and tetra-thiophene systems as models or precursors for polythiophene in conductive polymers research[4] has led us into deriving selective procedures for the functionalization of bithiophene with the aim of exploiting the resultant chemistry for the generation of novel and interesting monomers for polymeric systems. In this submission, we would like to present our work on the selective functionalization of the 3,3' positions of the 2,2'-bithiophene molecule with alkyl groups and the subsequent dinitration at the 5,5' positions on such systems. Alkyl chains attached to the thiophene ring have been shown to enhance the solvent compatibility of polythiophenes[5] while the reduction of dinitro functionality to the corresponding diamine may give rise to good precursors for polyimides, polyamides and polyurethanes. We are seeking to

combine these two characteristics with the 2,2'-bithiophene molecule so as to study the resultant properties of a new class of polymers.

Figure 1



5a, 6a: R = C_4H_9

5b, 6b: R = C_6H_{13}

5c, 6c: R = C_8H_{17}

5d, 6d: R = $C_{10}H_{21}$

5e, 6e: R = $C_{12}H_{25}$

RESULTS AND DISCUSSION

The synthetic scheme is outlined in Figure 1. In each instance, we extended the simple reactions of the thiophene nucleus to 2,2'-bithiophene. There are several methods reported for synthesizing the 2,2'-bithiophene molecule.[6] In our work, we chose the Grignard cross-coupling

of 2-bromothiophene(1) with bis(1,3-diphenylphosphino)propane nickel(II) chloride ($NiCl_2$.dppp) as catalyst in ether to give 2,2'-bithiophene (2) in 90% yield.

It is well documented that the 5,5' positions of the 2,2'-bithiophene nucleus are the most reactive to electrophilic substitution followed by the 3,3' positions.[7] This reactivity was exploited by us in a 4 step synthetic sequence to derive the desired 3,3'-dialkyl-5,5'-dinitro product. Because nitration of the 5,5' positions would deactivate the bithiophene molecule to further substitution at the 3,3' positions, alkylation had to occur prior to nitration. This was accomplished by subjecting the 2,2'-bithiophene molecule to tetrabromination followed by selective debromination of the 5,5'-dibromo functionality. Therefore, reaction of 4 mol equivalent of bromine with 2,2'-bithiophene in glacial acetic acid produced 3,3', 5,5'-tetrabromo-2,2'-bithiophene (3) in 97% yield. Subsequent selective debromination with Zn powder under reflux in a *n*-propanol-acetic acid-water mixture gave 3,3'-dibromo-2,2'-bithiophene (4) in 88% yield. The 3,3'-dibromo-2,2'-bithiophene was then subjected to a Grignard reaction as above using 2 mol equivalent of the Grignard reagent derived from the respective alkyl bromides with 3,3'-dibromo-2,2'-bithiophene to give 3,3'-dialkyl-2,2'-bithiophene (5) in 90-95% yield. These 3,3'-dialkyl-2,2'-bithiophenes can be used as precursors for novel soluble polythiophene systems.[5] The attainment of these compounds demonstrates the possibility of selective functionalization of the 3,3' positions of the 2,2'-bithiophene nucleus, hitherto unexplored.

The vacant 5,5' positions of the 3,3'-dialkyl-2,2'-bithiophenes are still the most reactive sites on the 2,2'-bithiophene nucleus and are easily subjected to nitration. Typically, dinitration is achieved in a one-pot synthetic procedure by first, the attachment of one nitro group on the ring under "mild conditions" using a HNO_3/acetic acid mixture, followed by the more "drastic conditions" of a HNO_3/H_2SO_4 mixture for the second nitro group. The dialkylated 2,2'-bithiophenes were subjected to this treatment, which after separation through a column, gave the corresponding dialkyl-dinitro-2,2'-bithiophenes (6) in 50-60% yield.

The dialkyl-dinitro-2,2'-bithiophenes are interesting compounds with potential nematocidal properties.[8] They may also serve as precursors for possible drug applications and charge transfer complexes.[9] Alternatively, they can be readily reduced to the diamines using Sn and HCl/MeOH. Preliminary reactions in our laboratory show that the diamines are formed but are rather unstable compounds.

In conclusion, we have demonstrated that careful choice of reaction pathways using simple reactions of the thiophene molecule can be extended to functionalize the bithiophene molecule for the generation of new and potentially useful systems.

EXPERIMENTAL

All reagents were obtained from commercial sources and dried using standard procedures before use. All reactions were monitored by tlc for completion. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Mass spectra were obtained using a micromass 7035E mass spectrometer. Nmr spectra were obtained on either a JEOL FX-90Q FT spectrometer or a Bruker AC-F300 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal reference. FTir spectra of samples in the form of KBr disks were obtained on a Perkin-Elmer 1710 Infrared FT spectrophotometer. Elemental analyses were performed by the Department of Chemistry's microanalytical laboratory, NUS and were within 0.5% of the theoretical value.

2,2'-Bithiophene. 2-Bromothiophene (88.92 g, 546 mmol) in dry ether (250 ml) was added to Mg (15.72 g, 655 mmol) activated with iodine in ether (50 ml) in a dry, oxygen free atmosphere at room temperature and refluxed for 1 h. The resultant Grignard reagent was cooled and added to a second portion of 2-bromothiophene (73.53 g, 451 mmol) in ether (200 ml) containing $NiCl_2$.dppp (2.47 g, 4.56 mmol) at 5-10 °C. The mixture was stirred overnight at room temperature; ice-cooled and treated with saturated NH_4Cl solution. The ether layer was collected, dried with $MgSO_4$ and the ether removed to give 71.5 g (96%) of 2-2'-bithiophene: bp 87-88 °C/1.5 mmHg (lit ., bp 144°C/25 mmHg).[6]

3,3', 5,5'-Tetrabromo-2,2'-bithiophene. Bromine (19.74 g, 123 mmol) in chloroform (120 ml) was added over 40 min to an ice-cooled solution of 2,2'-bithiophene (10.00 g, 60.2 mmol) in glacial acetic acid (200 ml) and chloroform (150 ml). To the resultant mixture was added a second portion of bromine solution over 1 h at room temperature. The mixture was stirred overnight at room temperature and refluxed for 24 h. The reaction solution was then cooled and the solvent removed. The crystalline 3,3', 5,5'-tetrabromo-2,2'-bithiophene (28 g, 97%) was

collected by cold filtration, recrystallized with ethanol and dried in vacuo at room temperature: mp 139-140 °C (lit ., mp 139-140°C);[10] ^{1}H nmr 7.05 (2H, s), m/z 482 (M^+:100%).

3,3'-Dibromo-2,2'-bithiophene. Zinc dust (20.8 g, 318 mmol) was added in small portions over 5 h to a refluxing solution of 3,3', 5,5'-tetrabromo-2,2'-bithiophene (27.88 g, 57.8 mmol) in *n*-propanol (700 ml), glacial acetic acid (30 ml) and distilled water (15 ml). When the reaction was completed, the solvent was removed and the product was extracted with ether, washed with deionized water, saturated $NaHCO_3$ solution and brine. After drying with $MgSO_4$, the ether was removed to give 3,3'-dibromo-2,2'-bithiophene (18.7 g, 88%): mp 95-97 °C; ^{1}H nmr 7.41 (2H, d, J = 5.4 Hz,), 7.08 (2H, d, J = 5.6 Hz); m/z 324 (M^+:100%); Anal. Calcd for $C_8H_4Br_2S_2$:C, 29.65, H, 1.24, S, 19.79; Found: C, 29.63, H, 1.10, S, 19.43.

3,3'-Dialkyl-2,2'-bithiophene. 1-Bromoalkane (58.1 mmol) in dry ether (65 ml) was reacted with Mg (1.70 g, 69.9 mmol) activated with iodine in a dry atmosphere at room temperature for 1 h and cooled. The resultant Grignard reagent was then added to an ice-cooled solution of 3,3'-dibromo-2,2'-bithiophene (6.30 g, 19.4 mmol) in ether (55 ml) containing $NiCl_2$.dppp (0.11 g, 0.20 mmol). The mixture was stirred overnight at room temperature, ice-cooled and treated with saturated NH_4Cl solution. After drying with $MgSO_4$, the solvent was removed to give the crude product. Purification by flash chromatography using hexane as solvent gave the 3,3'-dialkyl-2,2'-bithiophenes as yellow liquids or semi-solids (90-95%). The products were used in the next synthesis step without further treatment (Analyses were performed on pure 3,3'-dialkyl-2,2'-bithiophene samples obtained by distillation at reduced pressures).

5a: bp 60 °C (0.03 mmHg); ^{1}H nmr 7.47 (2H, d, J = 5.4 Hz), 7.21 (2H, d, J = 5.1 Hz), 2.74 (4H, t, J= 7.4 Hz), 1.92-1.31 (8H, m), 1.08 (6H, t, J = 6.7 Hz); m/z 278 (M^+:100%); Anal. Calcd for $C_{16}H_{22}S_2$: C, 69.01, H, 7.97, S, 23.03; Found: C, 68.56, H, 8.13, S, 23.32.

5b: bp 82 °C (0.03 mmHg); ^{1}H nmr 7.27 (2H, d, J = 5.2 Hz), 6.95 (2H, d, J = 5.2 Hz), 2.49 (4H, t, J = 7.8 Hz), 1.56-1.23 (16H, m), 0.85 (6H, t, J = 6.7 Hz); m/z 334 (M^+: 100%); Anal. Calcd for $C_{20}H_{30}S_2$: C, 71.80, H, 9.04, S, 19.17; Found: C, 71.77, H, 9.20, S, 18.53.

5c: bp 108 °C (0.03 mmHg); ^{1}H nmr 7.24 (2H, d, J = 5.1 Hz), 6.98 (2H, d, J = 5.3 Hz), 2.50 (4H, t, J = 7.3 Hz), 1.69-1.23 (24H, m), 0.86 (6H, t, J = 5.6 Hz); m/z 390 (M^+: 100%); Anal. Calcd for $C_{24}H_{38}S_2$: C, 73.78, H, 9.80, S, 16.42; Found: C, 74.10, H, 10.24, S, 16.38.

5d: bp 116 °C (0.03 mmHg); ^{1}H nmr 7.28 (2H, d, J = 5.2 Hz), 6.97 (2H, d, J = 5.2 Hz), 2.50 (4H,t, J = 7.8 Hz), 1.57-1.24 (32H, m), 0.89 (6H, t, J = 6.7 Hz); m/z 446 (M^+: 100%); Anal. Calcd for $C_{28}H_{46}S_2$: C, 75.27, H, 10.38, S, 14.35; Found: C, 75.51, H, 10.77, S, 13.87.

5e: mp 42-43 °C; ^{1}H nmr 7.28 (2H, d, J = 5.3 Hz), 6.96 (2H, d, J = 5.3 Hz), 2.49 (4H,t, J = 7.8 Hz), 1.54-1.22 (40H, m), 0.88 (6H, t, J = 6.7 Hz); m/z 502 (M^+: 100%); Anal. Calcd for $C_{32}H_{54}S_2$: C, 76.43, H, 10.82, S, 12.75; Found: C, 76.43, H, 11.00, S, 12.77.

3,3'-Dialkyl-5,5'-dinitro-2,2'-bithiophene. A solution of 3,3'-dialkyl-2,2'-bithiophene (13.5 mmol) in chloroform (65 ml) was added over 1.5 h at 10 °C (50 °C for alkyl = decyl and dodecyl) to a mixture of 70% HNO_3 (95 ml), glacial acetic acid (52.5 ml) and chloroform (10 ml). The mixture was stirred at room temperature until tlc showed the complete disappearance of the dialkylated compound (ca. 1 h). Concentrated H_2SO_4 (13 ml) was then added dropwise at 10 °C and the mixture stirred at room temperature until complete nitration was achieved. The mixture was poured into ice-water and chloroform was removed. The residue was washed with saturated $NaHCO_3$ solution, extracted with ether, washed again successively with deionized water and brine, dried with $MgSO_4$ and finally ether was removed to give solid crude products. Recrystallization yielded pure yellow 3,3'-dialkyl-5,5'-dinitro-2,2'-bithiophenes (50-60%).

6a: mp 57-58 °C; ^{1}H nmr 7.83 (2H, s), 2.54 (4H, t, J = 7.3 Hz), 1.66-1.19 (8H, m), 0.87 (6H, t, J = 7.0 Hz); m/z 368 (M^+:100%); FTir $\nu_{max(NO_2)}$1510, 1330 cm^{-1}; Anal. Calcd for $C_{16}H_{20}N_2O_4S_2$: C, 52.15, H, 5.47, N, 7.61, S, 17.40; Found: C, 51.96, H, 5.59, N, 7.60, S, 17.18.

6b: mp 50-51 °C; ^{1}H nmr 7.82 (2H, s), 2.53 (4 H, t, J =7.8 Hz), 1.55-1.26 (16H, m), 0.87(6H, t, J =6.8 Hz); m/z 424 (M^+: 100%); FTir $\nu_{max(NO_2)}$1504, 1332 cm^{-1}; Anal. Calcd for $C_{20}H_{28}N_2O_4S_2$: C, 56.58, H, 6.65, N, 6.60, S, 15.10; Found: C, 56.75, H, 6.79, N, 6.62, S, 14.83.

6c: mp 56-57 °C; ^{1}H nmr 7.83 (2H, s), 2.54 (4H, t, J = 7.4 Hz), 1.65-1.23 (24H, m), 0.87(6H, t, J = 5.6 Hz); m/z 480 (M^+: 100%); FTir $\nu_{max(NO_2)}$1510, 1329 cm^{-1}; Anal. Calcd for $C_{24}H_{36}N_2O_4S_2$: C, 59.97, H, 7.55, N, 5.83, S, 13.34; Found: C, 60.00, H, 7.70, N, 5.88, S. 13.35.

6d: mp 63.5-64.5 °C; ^{1}H nmr 7.82 (2H, s), 2.53 (4H, t, J =7.8 Hz), 1.57-1.24 (32H, m), 0.88 (6H, t, J =6.7 Hz); m/z 536(M^+: 100%); FTir $\nu_{max(NO_2)}$1503, 1331 cm^{-1}; Anal. Calcd for $C_{28}H_{44}N_2O_4S_2$: C, 62.65, H, 8.26, N, 5.22, S, 11.95; Found: C, 62.54, H, 8.41, N, 5.29, S, 11.95.

6e: mp 71-72 °C; ^{1}H nmr 7.82(2H, s), 2.53 (4H, t, J = 7.8 Hz), 1.54-1.24 (40H, m), 0.88(6H, t, J = 6.7 Hz); m/z 592 (M^+: 100%); FTir $\nu_{max(NO_2)}$1506, 1333 cm^{-1}; Anal. Calcd for$C_{32}H_{52}N_2O_4S_2$: C, 64.82, H, 8.84, N, 4.73, S, 10.82; Found: C, 64.63, H, 9.12, N, 4.92, S, 10.32.

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