A General Synthetic Route to 4-Substituted-2,2'-Bithiophenes

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A new synthetic route to 4-substituted-2,2'-bithiophenes has been developed utilizing 4-bromo-2,2'-bithiophene (**1**). Formation of the bithienyllithium adduct *via* halogen-metal exchange was found to be problematic and resulted in complex mixtures of products. The Grignard reagent of **1** can be obtained easily *via* the "entrainment" method, allowing the production of 4-substituted-2,2'-bithiophenes (where substituent = octyl, hydroxyethyl, hydroxymethyl, carboxy, carbomethoxy, acetoxyethyl, and acetoxymethyl).

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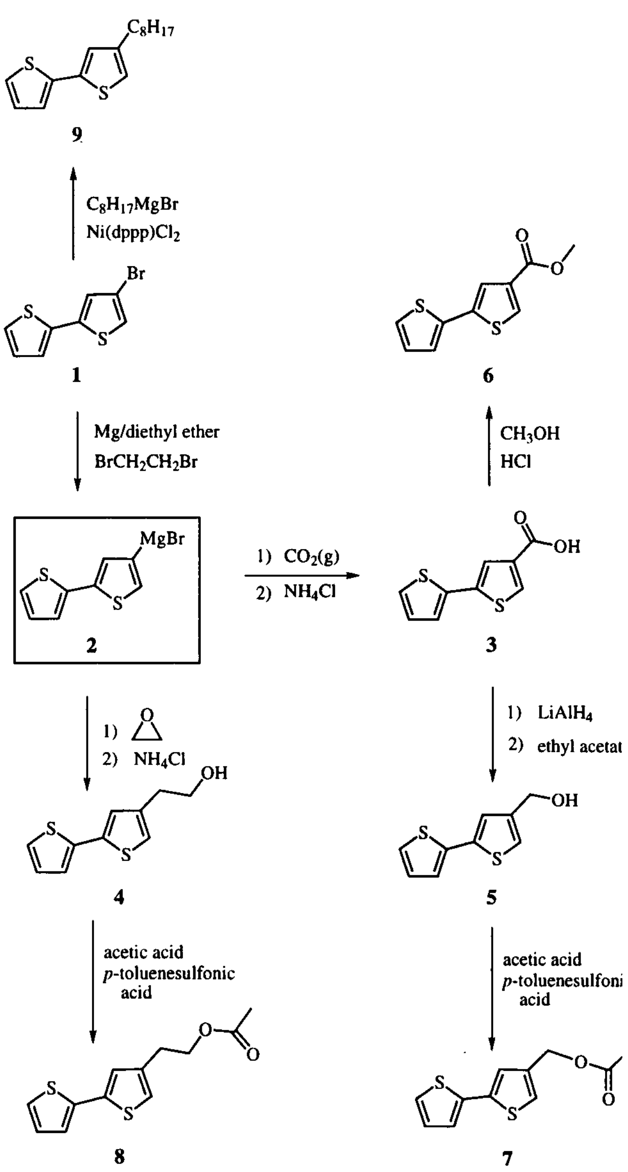
Introduction.

Substituted thiophenes and bithiophenes are useful synthons for the synthesis of a number of naturally occurring and biologically active bi- and terthiophenes [1-3], and the preparation of oligo- and polythiophenes [4-11]. The chemical, optical, and electronic properties of polythiophenes can be tuned by the incorporation of functional groups at the β-positions of the thiophene rings. For example, monomeric thiophenes derivatized with alkyl substituents produce conducting polymers soluble in common organic solvents [4-10]. Thus, the syntheses of a large number of β-substituted thiophene and bithiophene monomers have been reported [4-15].

In our present research, we require 4-substituted-2,2'-bithiophenes as precursors for substituted polythiophenes, but found that very few *singly* β-substituted bithiophenes have been reported [1,7-13]. Of those reported, these compounds are 3-substituted bithiophenes, with the single exception of 4-bromo-2,2'-bithiophene [11-13]. Here we report general synthetic routes to 4-substituted-2,2'-bithiophenes from 4-bromo-2,2'-bithiophene (**1**, Scheme 1).

Scheme 1

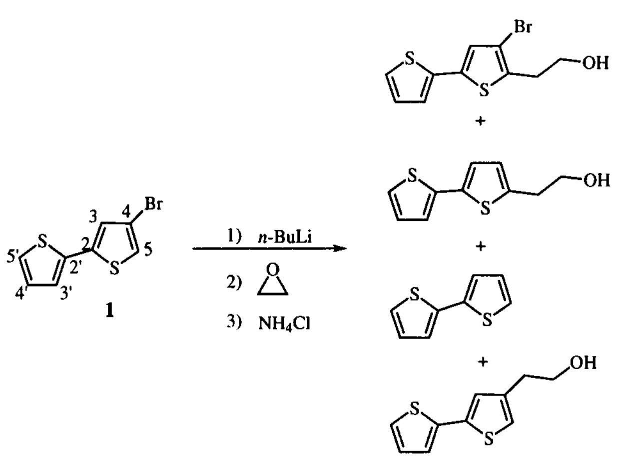


Results and Discussions.

Synthesis of a large variety of 3-substituted thiophenes is generally accomplished through lithiation of 3-bromothiophene at -70° followed by reaction with an appropriate electrophile [16,17]. Extension of this method to 4-bromo-2,2'-bithiophene **1** was unsuccessful. Lithiation of **1** at -70° with *n*-butyllithium followed by immediate addition of ethylene oxide, resulted in a complex mixture of bithiophenes (Scheme 2) [18]. The major product isolated was 4-bromo-5-hydroxyethyl-2,2'-bithiophene. This mixture is similar to that reported by Gronowitz for 3-thienyllithium at room temperature [19], and suggests that deprotonation at the 5 position competes with halogen-metal interconversion.

The lack of selective halogen-metal interconversion of **1** can be explained by chelation of the bithiophene to the lithium cation. It is well known that the addition of Lewis bases to alkyllithiums reduces the degree of lithium aggregation and thus increases the basicity of the organolithium compound [21-23]. This effect is greatly

Scheme 2



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increased when the Lewis base is a bidentate ligand such as *N,N,N',N'*-tetramethylethylenediamine [23,24]. Sulfur coordination of the lithium cation has been proposed as the first step of thiophene metallation and has been thought responsible for the exclusive α-lithiation of most thiophenes [20]. The increased basicity of the bithiophene-chelated organolithium reagent would result in an enhanced rate of halogen-metal interconversion relative to metallation at the acidic 5 position, even at -70°. Chelation in the reaction of **1** would also explain the difference in reactivities between **1** and its relative 3,3'-dibromo-2,2'-bithiophene, which undergoes halogen-metal interconversion smoothly at -70° [25]. The steric bulk of the bromides in 3,3'-dibromo-2,2'-bithiophene hinders rotation to the *s-cis* conformation, thus inhibiting chelation and resulting in reactivity similar to 3-bromothiophene.

Gronowitz has previously reported the formation of the Grignard reagent of 3-bromothiophene *via* the "entrainment" method [26-28]; however, the Grignard reagent is seldom used due to the difficulty of its preparation and inferior yields in comparison to 3-thienyllithium [20]. Application of the "entrainment" method to **1**, though, gave very favorable results. Although the reaction is slow to initiate, the Grignard reagent of **1** can be obtained, and when quenched with carbon dioxide produces the 4-carboxy-2,2'-bithiophene (**3**) in 78% yield. A similar reaction with ethylene oxide produces the 4-hydroxyethyl-2,2'-bithiophene (**4**) in 44% yield. Because monomeric Grignard species normally predominate, chelation should have little effect on the reactivity of the Grignard reagent obtained from **1** [29].

The production of **3** and **4** allowed a number of desired 4-substituted-2,2'-bithiophenes to be obtained (Scheme 1). The reduction of carboxybithiophene **3** produced the 4-hydroxymethyl-2,2'-bithiophene (**5**) and **3-5** were converted to the corresponding acetates **6-8**. In addition, the synthesis of 4-octyl-2,2'-bithiophene (**9**) demonstrates the ability of **1** to undergo conventional nickel catalyzed heterocoupling [30,31] in the same fashion as previously reported for 3-bromo-2,2'-bithiophene [10] and 4,4'-dibromo-2,2'-bithiophene [6]. It should be possible to produce a large variety of 4-alkyl-2,2'-bithiophenes by this method. Polymerization of the functionalized bithiophenes **6-9** will allow elucidation of conditions for polymerization of compounds containing more elaborate ester and alkyl sidechains. Physical investigations of the resulting polymers will enable us to determine the dependence of the chemical, optical, and electronic properties of these new polythiophenes upon the type and spacing of the polymer sidechains.

EXPERIMENTAL

Materials used in this work were reagent grade and were used without further purification. 2-Bromothiophene, [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride, [1,3-bis(diphenylphosphino)propane]nickel(II) chloride, 1-bromooctane and 1,2-dibromoethane were purchased from Aldrich Chemical Company. Magnesium used in the Grignard reactions was dried and stored at 140° for a minimum of 5 days. *p*-Toluenesulfonic acid was recrystallized from concentrated hydrochloric acid and dried under vacuum. Silica gel used in the chromatographic separations was 60 Å 230-400 mesh and purchased from Whatman. Anhydrous diethyl ether was freshly distilled from sodium benzophenone and deoxygenated prior to use. All other solvents were used without further drying. All synthetic reactions described were carried out under inert atmosphere. Unless otherwise noted, the ^{1}H and ^{13}C nmr spectra were obtained in deuteriochloroform on a Varian 300 MHz spectrometer and referenced to the chloroform signal. The ir measurements were obtained on a Nicolet Magna 550 spectrometer.

4-Bromo-2,2'-bithiophene (**1**).

4-Bromo-2,2'-bithiophene was prepared through the modification of previously reported procedures [12,26,28] resulting in improved yields, purity, and ease of purification. 2-Bromothiophene (4.75 ml, 0.0491 mole) was combined with magnesium turnings (1.80 g, 0.0741 mole) and 100 ml of diethyl ether. Dibromoethane (6.28 ml, 0.0729 mole) in 50 ml of ether was added rapidly dropwise until the reaction initiated, thereafter the addition was continued dropwise. Once the addition was complete, the mixture was heated at reflux for one hour.

A second flask containing 2,4-dibromothiophene [6] (10.0 g, 0.0413 mole), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (0.200 g, 0.270 mmole), and 100 ml of diethyl ether was cooled to 0°. The Grignard solution was added dropwise over 1 hour, stirred for an additional 3 hours, and the reaction allowed to warm to room temperature. Saturated aqueous ammonium chloride (100 ml) was added slowly, and the ether layer separated. The aqueous layer was extracted once with diethyl ether and the combined ether layers were dried over magnesium sulfate and concentrated. The resulting oil was added to hexane to induce precipitation of residual salts, filtered, concentrated, and flash chromatographed on silica using *n*-hexane. The product eluted first to give 9.2 g (91%) of a slightly yellow oil; ^{1}H nmr (deuteriobenzene): δ 6.53 (1H, d, J = 1.2 Hz), 6.57 (1H, dd, J = 5.1, 3.6 Hz), 6.68 (1H, dd, J = 5.1, 1.2 Hz), 6.80 (1H, dd, J = 3.6, 1.2 Hz), 6.86 (1H, d, J = 1.2 Hz), consistent with lit spectrum [11]; ^{1}H nmr: δ 7.03 (1H, dd, J = 5.1, 3.6 Hz), 7.09 (1H, d, J = 1.4 Hz), 7.11 (1H, d, J = 1.4 Hz), 7.18 (1H, dd, J = 1.2, 3.6 Hz), 7.26 (1H, dd, J = 5.1, 1.2 Hz); ^{13}C nmr: δ 110.4, 121.4, 124.4, 125.3, 126.1, 127.9, 136.0, 138.6; ms: m/z 246 (M$^+$), 244, 121; ir (neat): 3109, 1496, 837, 817, 727, 588 cm^{-1}.

Grignard Reagent of **1** (**2**).

Magnesium turnings (5.0 g, 0.206 mole) and **1** (10.0 g, 0.0410 mole) were combined in 200 ml of diethyl ether. About 5 ml of a solution consisting of dibromoethane (14.0 ml, 30.6 g, 0.163 mole) and 100 ml ether was then added to initiate the reaction [32]. Once the reaction initiated, addition was continued dropwise over one hour, and the mixture subsequently heated at reflux for an additional hour. The solution was allowed to cool to room temperature and used immediately.

4-Carboxy-2,2'-bithiophene (**3**).

Carbon dioxide was bubbled through the Grignard solution **2** for one hour and the mixture heated at reflux for an additional hour. After cautious addition of 100 ml of 10% hydrochloric acid, the ether layer was extracted with three 100 ml portions of 10% sodium hydroxide. The combined aqueous basic layers were acidified with 10% hydrochloric acid yielding 6.7 g (78%) of a tan solid which was purified by recrystallization from ethanol/water, mp 171-172°; ^{1}H nmr: δ 7.04 (1H, dd, J = 5.1, 3.6 Hz), 7.22 (1H, dd, J = 3.6, 1.2 Hz), 7.28 (1H, dd, J = 5.1, 1.2 Hz), 7.60 (1H, d, J = 1.1 Hz), 8.10 (1H, d, J = 1.1 Hz); ^{13}C nmr: δ 124.0, 124.8, 125.5, 128.0, 133.2, 133.3, 136.2, 138.6, 167.0; ms: m/z 210 (M$^+$); ir (potassium bromide): 3300-2500, 3109, 1700, 1467, 1270, 743, 684 cm^{-1}.

Anal. Calcd. for $C_9H_6O_2S_2$: C, 51.41; H, 2.88. Found: C, 51.30; H, 2.79.

4-Hydroxyethyl-2,2'-bithiophene (**4**).

Following the preparation of the Grignard solution **2**, the flask was fitted with a mechanical stirrer and cooled to 0°. Ethylene oxide (~1 ml, ~ 0.02 mole) was slowly transferred to the Grignard solution *via* cannula inducing precipitation. Additional aliquots (1 ml) of ethylene oxide were added until precipitate was no longer formed. The reaction was heated at reflux for 1 hour, the reaction quenched with saturated ammonium chloride, and the aqueous layer extracted three times with ether. The combined ether extractions were washed at least 5 times with 10% hydrochloric acid, twice with water, dried over sodium sulfate, and concentrated. The crude oil was purified by Chromatotron using 6:1 (v/v) hexanes/ethyl acetate. The desired product eluted as the third band. The combined Chromatotron elutions were concentrated to give 3.8 g (44%) of a light yellow oil; ^{1}H nmr: δ 1.59 (1H, s), 2.86 (2H, dt, J = 6.5, 0.8 Hz), 3.87 (2H, t, J = 6.5 Hz), 6.93 (1H, dt, J = 0.8, 1.5 Hz), 7.01 (1H, dd, J = 5.1, 3.6 Hz), 7.06 (1H, d, J = 1.5 Hz), 7.16 (1H, dd, J = 1.2, 3.6 Hz), 7.21 (1H, dd, J = 5.1, 1.2 Hz); ^{13}C nmr: δ 34.0, 62.9, 120.9, 123.8, 124.5, 125.2, 127.9, 137.5, 137.9, 139.8; ms: m/z 210 (M$^+$), 179; ir (neat): 3349, 3104, 2940, 2878, 1417, 1049, 832, 743 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}OS_2$: C, 57.11; H, 4.79. Found: C, 57.00; H, 4.73.

4-Hydroxymethyl-2,2'-bithiophene (**5**).

A suspension of carboxybithiophene **3** (0.5 g, 2.4 mmoles) in 60 ml of diethyl ether was added dropwise over one hour to a suspension of lithium aluminum hydride (0.35 g, 9.2 mmoles) in 100 ml of diethyl ether and then heated at reflux for 5 hours. After cooling to room temperature, the reaction was quenched with ethyl acetate and the aluminum salts decomposed with 75 ml of ice cold 10% hydrochloric acid. The organic layer was then separated and the aqueous layer extracted with three 30 ml portions of ether. The combined organic layers were washed once with 50 ml 5% sodium bicarbonate, water, and dried over magnesium sulfate. The solution was concentrated and purified by Chromatotron using 1:1 (v/v) hexanes/ethyl acetate. The product eluted second after a minor by-product to give 0.4 g (85%) of **5** as an oil; ^{1}H nmr: δ 1.76 (1H, s), 4.66 (2H, s), 7.01 (1H, dd, J = 5.1, 3.6 Hz), 7.09 (1H, s), 7.16 (2H, overlapping resonances), 7.22 (1H, dd, J = 5.1, 0.9 Hz); ^{13}C nmr: δ 143.1, 138.2, 137.5, 127.9, 124.6, 123.9, 123.5, 120.7, 60.5; ms: m/z 196 (M$^+$); ir (neat): 3342, 3104, 2928, 2870, 1420, 1000, 832, 695 cm^{-1}.

Anal. Calcd. for $C_9H_8OS_2$: C, 55.07; H, 4.11. Found: C, 55.47; H, 4.32.

4-Carbomethoxy-2,2'-bithiophene (**6**).

The carboxybithiophene **3** (1.0 g, 4.8 mmoles) and concentrated hydrochloric acid (1 ml) were added to 60 ml of methanol and heated at reflux overnight. Removal of the solvent *in vacuo* resulted in an oil which was dissolved in methylene chloride and washed with five 20 ml portions of 2*N* sodium hydroxide. The combined aqueous layers were extracted once with methylene chloride (20 ml). The combined organic fractions were washed once with water, dried over magnesium sulfate, and concentrated to yield the crude ester. The ester was purified by Chromatotron using 1:1 (v/v) ethyl acetate/hexanes. The product eluted as the first band to give a low melting solid, mp <25°. Vacuum sublimation gave 0.87 g (81%) of a white crystalline solid, mp. 38-39°; ^{1}H nmr: δ 3.88 (3H, s), 7.02 (1H, dd, J = 5.3, 3.8 Hz), 7.19 (1H, dd, J = 3.8 Hz, 1.1 Hz), 7.25 (1H, dd, J = 5.3, 1.1 Hz), 7.56 (1H, d, J = 1.5 Hz), 7.95 (1H, d, J = 1.5 Hz); ^{13}C nmr: δ 51.0, 123.8, 124.5, 125.3, 127.9, 131.2, 134.0, 136.3, 138.1, 163.0; ms: m/z 224 (M$^+$); ir (potassium bromide): 3114, 2961, 1733, 1461, 1252, 1098, 993, 847, 742, 679 cm^{-1}.

Anal. Calcd. for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59. Found: C, 53.52; H, 3.50.

4-Acetoxymethyl-2,2'-bithiophene (**7**).

Glacial acetic acid (6 ml), hydroxymethylbithiophene **5** (0.74 g, 3.8 mmoles), *p*-toluenesulfonic acid (~ 50 mg), and 100 ml of toluene were added to a flask equipped with a Dean-Stark trap and heated at reflux for two hours. After cooling to room temperature, the solution was washed with two 40 ml portions of water, four 40 ml portions of 10% sodium hydroxide, and dried with sodium sulfate. The solution was concentrated and purified by Chromatotron using 2:1 (v/v) hexanes/ethyl acetate. The product eluted as the first band to give 0.63 g (75%) of **7** as an oil; ^{1}H nmr: δ 2.11 (3H, s), 5.06 (2H, s), 7.01 (1H, dd, J = 4.8, 3.6 Hz), 7.16 (2H, br s), 7.18 (1H, dd, J = 1.2, 3.6 Hz), 7.22 (1H, dd, J = 4.8, 1.2 Hz); ^{13}C nmr: δ 21.2, 61.6, 123.4, 124.2, 124.3, 124.9, 128.0, 137.2, 137.7, 138.5, 171.0; ir (neat): 2954, 1743, 1375, 1227, 1027, 836, 700 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}O_2S_2$: C, 55.44; H, 4.23. Found: C, 55.69; H, 4.22.

4-Acetoxyethyl-2,2'-bithiophene (**8**).

The acetoxyethylbithiophene **8** was prepared as for **7** substituting **4** (0.80 g, 3.8 mmoles) for **5** and extending the heating time to four hours. This produced 0.63 g (66%) of **8** as an oil; ^{1}H nmr: δ 2.07 (3H, s), 2.93 (2H, t, J = 6.9 Hz), 4.29 (2H, t, J = 6.9 Hz), 6.91 (1H, d, J = 1.2 Hz), 7.00 (1H, dd, J = 5.1, 3.6 Hz), 7.04 (1H, d, J = 1.2 Hz), 7.15 (1H, dd, J = 3.6, 1.2 Hz), 7.20 (1H, dd, J = 5.1, 1.2 Hz); ^{13}C nmr: δ 21.3, 30.1, 64.4, 120.9, 124.0, 124.7, 125.2, 128.1, 137.9, 139.1, 171.3; ms: m/z 252 (M^+), 192; ir (neat): 3105, 2963, 2927, 1738, 1242, 1035, 837, 703 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}O_2S_2$: C, 57.11; H, 4.79. Found: C, 57.03; H, 4.75.

4-Octyl-2,2'-bithiophene (**9**).

The octylbithiophene **9** was prepared through the modification of previously reported procedures [30,31]. A mixture of magnesium turnings (0.620 g, 25.6 mmoles), 1-bromooctane (4.0 ml, 23.2 mmoles), and 10 ml of diethyl ether was treated with a few drops of a solution of dibromoethane (0.20 ml, 2.32 mmoles) in diethyl ether (5 ml) to initiate the Grignard reaction. The remaining dibromoethane solution was added periodically when the reaction started to subside. Once no further reaction was observed, the mixture was heated at reflux for 30 minutes.

This Grignard solution was added to mixture of bromobithiophene **1** (2.0 g, 8.16 mmoles) and [1,3-bis(diphenylphosphino)-propane]nickel(II) chloride (25 mg, 0.05 mmole) in 25 ml of diethyl ether over 10 minutes and allowed to stir at room temperature overnight. The reaction was quenched with 10% hydrochloric acid at 0° and the aqueous layer extracted twice with diethyl ether. The combined ether layers were washed once with water, saturated sodium bicarbonate, water again, and dried over sodium sulfate. The solution was concentrated to give a red oil and purified by Chromatotron using hexanes. The product eluted as the first band and combined elutions gave 1.5 g (66%) of **9** as an oil. Further purification by vacuum distillation removed a small impurity of 2,2'-bithiophene, bp 110° (70 mTorr); ^{1}H nmr: δ 0.89 (3H, t), 1.2-1.4 (10H, overlapping resonances), 1.63 (2H, m), 2.58 (2H, t, J = 7.5 Hz), 6.80 (1H, s), 7.00 (1H, dd, J = 5.1, 3.6 Hz), 7.02 (1H, s), 7.15 (1H, dd, J = 3.6, 1.2 Hz), 7.19 (1H, dd, J = 5.1, 1.2 Hz); ^{13}C nmr: δ 14.4, 23.0, 29.6, 29.6(3), 29.7, 30.7, 30.8, 32.2, 119.3, 123.7, 124.4, 125.5, 128.0, 137.3, 138.1, 144.4; ms: m/z 278 (M^+), 180; ir (neat): 3112, 3080, 2954, 2925, 2830, 1465, 835, 820, 691 cm^{-1}.

Anal. Calcd. for $C_{16}H_{22}S_2$: C, 69.01; H, 7.96. Found: C, 68.89; H, 7.85.

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