THE SYNTHESIS OF BITHIENYLS AND TERTHIENYLS BY NICKEL-CATALYZED COUPLING OF GRIGNARD REAGENTS

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Abstract - The coupling of thienyl Grignard reagents and bromothiophene derivatives in the presence of $Ni(dppp)Cl_2$ is particularly good for linking one thiophene derivative to the beta position of another one, as illustrated by the synthesis of 2,3′- and 3,3′-bithienyl. The same procedure was used for the synthesis of 3,2′:3′,3"-, 3,2′:4′,3"-, 3,3′:4′,3"-, 2,2′:3′,3"-, and 2,2′:3′,2"-terthienyls, in yields ranging between 61 and 93%.

INTRODUCTION

Alpha-terthienyl (2,2′:5′,2"-terthiophene, 1), found in many plants of the family Compositae, displays a wide range of biocidal properties which have been recently reviewed by Cooper and Nietsche.[1] Even more recent publications document a new phenomenon, the very high phototoxicity of 1 in fish and other aquatic organisms.[2]

Our interest in the light-dependent toxicity of 1 and related molecules made us explore a number of different approaches for synthesizing polythiophenes.[3] While coupling of thiophene moieties via alpha-positions is easy, coupling at beta positions was desirable for obtaining the eight isomers which remained unknown. The coupling of 2-thienylmagnesium bromide with 2-bromothiophene, 3-bromothiophene, and 2,5-dibromothiophene by the procedure of Kumada et al.,[4] in the presence of catalytical amounts of $Ni(dppp)Cl_2$ (dppp = $Ph_2P(CH_2)_3PPh_2$), was known to give excellent yields of 2,2′-bithienyl, 2,3′-bithienyl, and alpha-terthienyl respectively, without positional isomerization during this reaction. However, related reactions of 3-thienyl magnesium bromide had not been investigated. We succeeded in coupling the beta position of one thiophene ring to either the alpha or the beta position of another. In this paper we report the synthesis of five terthiophenes in yields ranging from 61 to 93%. As this manuscript was prepared, the synthesis of three of the above terthiophenes appeared in print.[5] The approach was similar, but used a palladium instead of a nickel catalyst.

RESULTS AND DISCUSSION

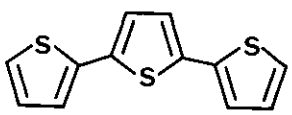
3-Bromothiophene is rather unreactive toward magnesium, and the Grignard reagent is therefore best prepared by transmetallation of 3-lithiothiophene with magnesium bromide etherate as described by Gronowitz.[6] The 3-lithiothiophene, in turn, is easily obtained by the reaction of 3-bromothiophene

with n-butyllithium at -78 °C.[7]

The reaction of 3-thienylmagnesium bromide with 3-bromothiophene in ether in the presence of a catalytical amount of Ni(dppp)Cl_2 yielded a single product, the known 3,3′-bithienyl, which was isolated in over 88% yield. The traditional synthesis of this compound, with a yield of ca. 50%, is by oxidative coupling of 3-lithiothiophene with $CuCl_2$.[8] Although the halogen-metal exchange reaction of 3-bromothiophene with n-butyllithium produces 1-bromobutane, its Ni(dppp)Cl_2-catalyzed coupling with the Grignard reagent was not competitive with the coupling reaction between two sp^2 centers, since the formation of 3-butylthiophene was not detected.

Similarly, the 3-thienyl Grignard reagent coupled readily with 2-bromothiophene in the same conditions to yield a single bithiophene, 2,3′-bithienyl, isolated in 77% yield.

The Ni(dppp)Cl_2-catalyzed coupling reaction of the 3-thienyl Grignard reagent with dibromothiophenes constituted an attractive approach to the synthesis of terthiophenes in which at least one thiophene ring was attached in the molecule by a bond at a beta position. We observed that in three different cases the coupling reaction between 2 equivalents of Grignard reagent and one equivalent of dibromothiophene gave a single product in high yield. Barring unprecedented rearrangement reactions, the structural assignments, which are fully consistent with the spectroscopic and analytical data, are straightforward. Thus, the reaction of the 3-thienyl Grignard reagent with 3,4-dibromothiophene,[9] 2,4-dibromothiophene,[10] and 2,3-dibromothiophene[11] gave 3,3′:4′,3″-terthienyl (**2**), 3,2′:4′,3″-terthienyl (**3**), and 3,2′:3′,3″-terthienyl (**4**) respectively, with yields of 85, 61 and 77% respectively. Other isomeric compounds were also obtained by Ni(dppp)Cl_2-catalyzed coupling of the 2-thienyl Grignard reagent with 2,3-dibromothiophene and with 2-bromo-3,3′-bithienyl,[12] namely 2,2′:3′,2″-terthienyl (**5**, 83% yield) and 2,2′:3′,3″-terthienyl (**6**, 93% yield) respectively.



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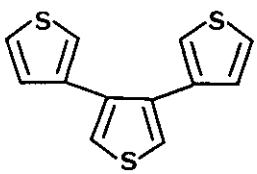

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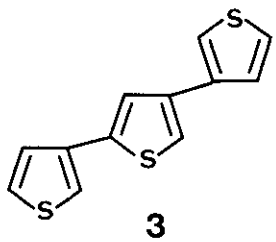

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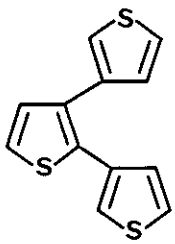

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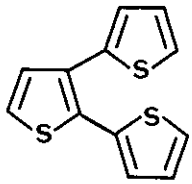

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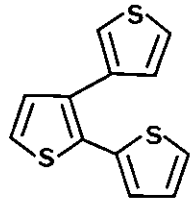

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The comparison of our results with Carpita and Rossi's[5] using Pd(dppf)Cl_2-mediated coupling reactions suggests that the Nickel catalyst may have distinct advantanges, both in terms of yields and cost. One disadvantage, however, is in the difficulty experienced in performing stepwise coupling reactions. When 2,3-dibromothiophene was reacted with 1 equivalent of 3-thienyl magnesium bromide, for example, the major product was **4**, in about ten-fold excess over the expected bromobithienyl.

The phototoxicity of the three terthiophenes which have significant absorption in the near ultraviolet range (between 300 and 400 nm) was determined with Daphnia magna. The 24-h LC_{50} values following 1 h of incubation of the mature organisms in the presence of the sensitizer, prior to 1 h of irradiation, were 0.45 mg/L for **4**, 0.06 mg/L for **5**, and 0.02 mg/L for **6**. These compounds are distinctly less phototoxic than alpha-terthienyl, which gave a LC_{50} value of 0.0013 mg/mL under identical conditions.

EXPERIMENTAL

3,3'-Bithienyl. Under N_2, 3-bromothiophene (20 g, 0.123 mol) was added dropwise to n-BuLi (0.125 mol, 2.5 M in hexane) in ether (75 ml) at -78°C. After 10 min, the suspension was rapidly transferred into a flask containing $MgBr_2$ (0.15 mol) in ether (150 ml) at room temperature. The resulting homogeneous solution was stirred for 0.5 h, and was added over 1 h into a flask containing 3-bromothiophene (16 g, 0.098 mol) and Ni(dppp)Cl_2 (550 mg, 0.001 mol) in 50 ml of ether. Gentle boiling of the solvent took place during this addition, and a yellow-brown solution was obtained, which was refluxed for 20 h, then cooled and quenched with 200 ml of 2M HCl. The ether layer was washed successively with 10% $NaHCO_3$, water, and sat. NaCl, was dried over $MgSO_4$, and was concentrated in vacuo. The residue was treated with charcoal, and was recrystallized from hexane to yield 14.4 g (88.3%) of 3,3'-bithienyl as white crystals, mp 133-134 °C (Lit.[8] mp 132-134 °C).

2,3'-Bithienyl. The same procedure was used for the reaction of 2-bromothiophene (10 g, 0.061 mol), Ni(dppp)Cl_2 (200 mg), and 3-thienylmagnesium bromide (prepared from 0.0875 mol of $MgBr_2$ and 0.074 mol of 3-lithiothiophene in 100 ml of ether). After overnight reflux and work-up as above, and recrystallization of the crude product from hexane, there was obtained 7.8 g (77%) of 2,3'-bithienyl as pale yellow crystals, mp 66-67 °C (lit.[13] mp 68-68.5 °C).

3,3':4',3"-Terthienyl (2). A solution of 3-thienylmagnesium bromide (0.147 mol) in 175 ml of ether was added dropwise to a mixture of 3,4-dibromothiophene (15 g, 0.062 mol) and Ni(dppp)Cl_2 (350 mg) in 50 ml of ether. After a 20-h reflux and work-up as above, the crude reaction mixture was flash chromatographed on silica gel using hexane-acetone (19:1), to produce 14.3 g of slightly impure product, which was recrystallized from pentane-ether to yield 13.0 g (85%) of pure **2** as white needles, mp 81-82 °C (lit.[5] mp 83.5-84.5 °C), mass spec. 248 (M^+, 100%); UV (MeOH) 210 (32,400) and 250 nm (15,900). Anal. Calcd for $C_{12}H_8S_3$: C, 58.03; H, 3.25; S, 38.73. Found C, 57.95; H, 3.30; S, 38.90.

3,2':4',3"-Terthienyl (3). The same procedure was applied to 7.5 g (0.031 mol) of 2,4-dibromothiophene. After 48 h of reflux, the reaction mixture was worked up as usual. The residue was treated with charcoal, and recrystallized from heptane to yield 4.7g (61%) of **3** as white crystals, m.p. 157.5-158.5 °C (lit.[5] mp 156-158 °C); mass spec. 248 (M^+, 100%); UV (MeOH) 222 (24,000) and

262 nm (22,400). Anal. Found C, 57.81; H, 3.24; S, 38.75.

3,2′:3′,3″-Terthienyl (4). The same procedure applied to 7.5 g (0.031 mol) of 2,3-dibromothiophene gave 6.3 g of product after chromatography, which was recrystallized from pentane-ether to yield 5.9 g (77%) of **4** as white crytals, m.p 49-50°C; mass spec. 248 (M^+, 100%); UV (MeOH) 210 (20,400) 255 (11,300), and 275 nm (10,700). Anal. Found C, 58.09; H, 3.26; S, 38.71.

2,2′:3′,2″-Terthienyl (5). To a mixture of 2,3-dibromothiophene (6.05 g, 0.025 mol) and Ni(dppp)Cl_2 (150 mg) in 30 ml ether, 2-thienylmagnesium bromide (from 0.070 mol Mg and 0.055 mol 2-bromothiophene in 100 ml of ether) was added dropwise. The resulting brown solution was refluxed for 12 h, and worked up as usual. The residue was treated with charcoal, and recrystallized from hexane to yield 5.15 g (83%) of 5 as yellow crystals, mp 59-60 °C (lit.[5] mp 60-61 °C); mass spec 248 (M^+, 100%); UV (MeOH) 205 (18,600), 254 (13,400) and 296 nm (9,400). Anal. Found C, 57.89; H, 3.26; S, 38.63.

2,2′:3′,3″-Terthienyl (6). The same procedure was applied to 3.8 g (0.016 mol) of 2-bromo-3,3′-bithienyl and 0.020 mol of 2-thienylmagnesium bromide, using 60 mg of Ni(dppp)Cl_2. After chromatography, the product (3.7 g) was recrystallized from pentane-ether to yield 3.6 g (93%) of **6** as white crystals, mp 38-39 °C; mass spec 248 (M^+, 100%); UV (MeOH) 203 (18,600), 250 (12,500) and 295 nm (7,900). Anal. Found C, 57.87; H, 3.18; S, 38.61.

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