

**THE SYNTHESIS OF 2,3':2',3"-, 2,3':4',3"-, 2,3':5',3"-,
AND 2,2':4',3"-TERTHIENYLS**

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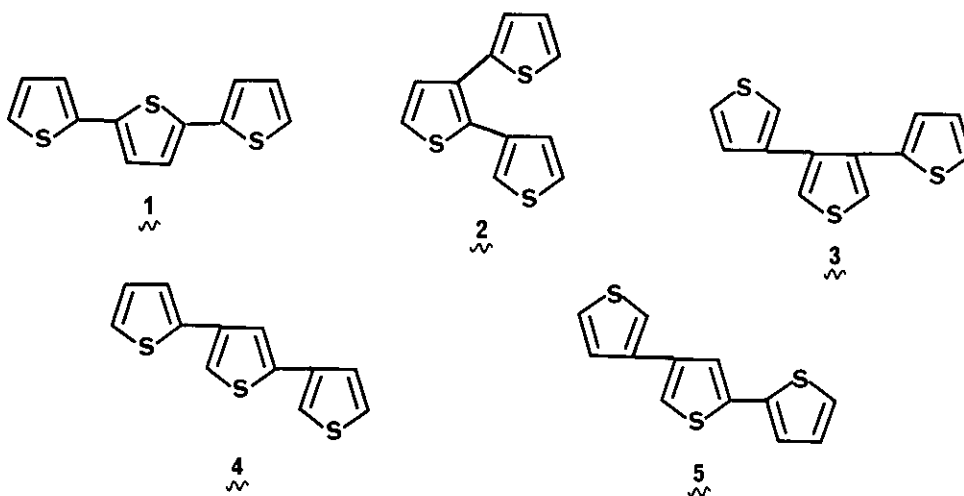
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Abstract - The coupling of thienyl Grignard reagents with the appropriate bromobithiophenes in the presence of Ni(dppp)Cl_2 gave the title compounds with yields ranging between 72 and 95%.

INTRODUCTION

Alpha-terthienyl (1) a molecule frequently found in plants of the family Compositae, displays powerful light-dependent cytotoxic properties in many organisms.¹ In order to perform a comprehensive study on the relationship between structures and activity in terthiophenes, it was necessary to secure samples of all fourteen isomers theoretically possible when three non-fused thiophene rings are directly attached to each others.

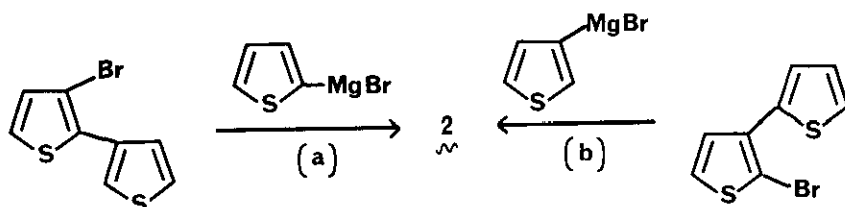
Following the synthesis of other isomers in several laboratories, including ours, we recently reported on the nickel-catalyzed coupling reaction of 2-thienyl and 3-thienyl Grignard reagents with dibromothiophenes, which brought to 10 the number of known unsubstituted terthiophenes.² We now describe the synthesis of the remaining four isomers, 2 to 5.



DISCUSSION

Terthiophenes which possess either two alpha or two beta thienyl units attached to the central thiophene ring can be prepared very conveniently by coupling two equivalents of either the 2-thienyl or the 3-thienyl Grignard reagent with the appropriate dibromothiophene in the presence of a catalytical amount of $\text{Ni}(\text{dppp})\text{Cl}_2$ (dppp = 1,3-bis(diphenylphosphino)propane) as described earlier.² However, this approach, which utilizes a procedure introduced by Kumada *et al.*,³ is not applicable to the synthesis of the isomers 2 to 5 because, with this catalyst, there is not enough difference in the rates of the two successive coupling reactions of the Grignard reagent. It is difficult, therefore, to interrupt the process after coupling of the first thiophene ring, and to introduce the second Grignard reagent to be coupled in order to complete the synthesis of the desired terthiophene. Furthermore, even if stepwise coupling reactions were possible, the necessary regioselectivity requirements may not be met easily in all cases.

We now report that the coupling of an appropriate bromobithiophene with either 2- or 3-thienyl Grignard reagent provides a simple approach for the synthesis of the compounds 2 to 5, which were obtained with yields ranging from 72 to 95%. In each case two possibilities existed for creating the desired terthiophene from a bromobithiophene, and the actual choice of reagents was based on the availability of the required starting materials. The synthesis of 2, for example, could have been approached by reactions involving either 2- or 3-thienylmagnesium bromide.



Because 2-thienylmagnesium bromide is much more readily accessible than its 3-isomer, path a was followed in this case, and the reaction of 3-bromo-2,3'-bithienyl⁴ with this Grignard reagent in the presence of a catalytical amount of $\text{Ni}(\text{dppp})\text{Cl}_2$ led to the isolation of 2,3':2',3''-terthienyl (2) in 95% yield. The same 2-thienyl Grignard reagent was also reacted with 4-bromo-3,3'-bithienyl⁴ and with 4-bromo-2,3'-bithienyl⁵ to give 2,3':4',3''-terthienyl (3) and 2,3':5',3''-terthienyl (4) in 83 and 94% yield respectively.

The synthesis of 2,2':4',3''-terthienyl (5) required access to either 5-bromo-3,3'-bithienyl or 4-bromo-2,2'-bithienyl, to be coupled with 2-thienyl or 3-thienylmagnesium bromide respectively. The latter choice appeared preferable, even though it uses the less readily available Grignard reagent, because the alternative required a bromobithiophene which is difficult to obtain.

Carpita and Rossi recently described the preparation of bromobithiophenes by coupling of a thienyl Grignard reagents with dibromothiophenes in the presence of a palladium catalyst.⁵ This procedure

has now been used for the synthesis of the previously unknown 4-bromo-2,2'-bithienyl, and the reaction of 1 equivalent of 2-thienylmagnesium bromide with 2,4-dibromothiophene⁶ in the presence of $\text{Pd}(\text{dppf})\text{Cl}_2$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) at 0 °C gave the expected bromo-bithiophene in 88% yield. The coupling reaction took place predominantly at the more reactive 2-position, and the product was proved to be 4-bromo-2,2'-bithienyl by performing a halogen-metal exchange reaction with *n*-butyllithium at -78 °C, followed by quenching of the lithio derivative with water. The product formed was identified as 2,2'-bithienyl by comparison with an authentic sample (mp, glc retention time, nmr, ir and mass spectral data).

The coupling of 4-bromo-2,2'-bithienyl with 3-thienylmagnesium bromide in the presence of $\text{Ni}(\text{dppp})\text{Cl}_2$ gave 2,2':4',3"-terthienyl (5) in 72% yield.

In this as well as in the earlier work involving metal-mediated coupling syntheses of terthiophenes, the structural assignments were based on the premise that no structural rearrangements had occurred during the coupling step. This assumption is now better supported by the observation that single products have been obtained in each reaction, and that they are all different.

With the synthesis of all fourteen isomeric unsubstituted terthiophenes finally completed, we are now proceeding with the comparison of the photochemical and biological properties of these molecules.

EXPERIMENTAL

2,3':2',3"-terthienyl (2). Under N_2 , a solution of 2-bromothiophene (3.6 g, 0.022 mol) in 15 ml of ether was added dropwise over Mg turnings (0.9 g, 0.037 mol) in 45 ml of ether. The reaction started upon warming. After the addition was complete, the mixture was refluxed for 30 min, and cooled to room temperature. The Grignard reagent was then added slowly into a mixture of 3-bromo-2,3'-bithienyl (4.0 g, 0.0163 mol) and $\text{Ni}(\text{dppp})\text{Cl}_2$ (65 mg, 0.12 mmol) in 25 ml of ether. Gentle refluxing took place during the addition, and the resulting solution was refluxed for 15 h before it was quenched with 50 ml of 2 M HCl. The ether layer was separated, washed with satd NaCl, dried over MgSO_4 , and concentrated to give a yellowish brown oil which was flash chromatographed over silica gel using hexane, and gave 4.05 g of a solid which was recrystallized from pentane/ether to yield 3.85 g (95%) of 2 as white crystals, mp 39-40 °C, mass spec 248 (M^+ , 100%), uv (MeOH) 207 (14,400), 244 (14,800) and 292 nm (10,900). Anal. Calcd for $\text{C}_{12}\text{H}_8\text{S}_3$: C, 58.03; H, 3.25; S, 38.73. Found C, 57.94; H, 3.15; S, 38.45.

2,3':4',3"-terthienyl (3). Under N_2 , 2-thienylmagnesium bromide (from 0.041 mol of Mg and 0.0245 mol of 2-bromothiophene in 60 ml of ether) was added dropwise into a mixture of 4-bromo-3,3'-bithienyl (4.0 g, 0.016 mol) and $\text{Ni}(\text{dppp})\text{Cl}_2$ (70 mg, 0.13 mol) in 25 ml of ether. The resulting reddish brown solution was refluxed for 18 h and worked up as above. The residue was flash chromatographed on silica gel using hexane, to give 3.7 g of a slightly colored solid. Recrystallization from petroleum ether (bp 35-60 °C) gave 3.38 g (83%) of 3 as white crystals, mp 68-69 °C, mass spec 248 (M^+ , 100%), uv (MeOH) 210 (17,300) and 242 nm (14,900). Anal. Found C, 58.16; H, 3.36; S, 38.45.

2,3':5',3"-terthienyl (4). Under N_2 , 2-thienylmagnesium bromide (from 0.049 mol of Mg and 0.0245 mol of 2-bromothiophene in 60 ml of ether) was added dropwise into a mixture of 4-bromo-2,3'-bithienyl (4.0 g, 0.016 mol) and $Ni(dppp)Cl_2$ (70 mg, 0.13 mol) in 25 ml of ether. The resulting reddish brown solution was refluxed for 18 h and worked up as above. The residue was recrystallized from hexane to yield 3.8 g (94%) of 4 as faintly yellow crystals, mp 103-104 °C, mass spec 248 (M^+ , 100%), uv (MeOH) 205 (9700) and 272 nm (14,700). Anal. Found C, 58.11; H, 3.23; S, 39.00.

4-Bromo-2,2'-bithienyl. Under N_2 , 2-thienylmagnesium bromide (from 0.0491 mol of 2-bromothiophene and 0.0741 mol of Mg in 125 ml of ether) was added over 1 h into a mixture of 2,4-dibromothiophene (10.0 g, 0.0413 mol) and $Pd(dppf)Cl_2$ (200 mg, 0.27 mol) in 100 ml of ether at 0 °C. After stirring for 3 h at 0 °C, 75 ml of satd NH_4Cl was added, and the ether layer was separated, dried over $MgSO_4$, and concentrated. The residual oil was flash chromatographed over silica gel using hexane, to yield 9.0 g (88%) of 4-bromo-2,2'-bithienyl as a colorless oil which was 98.5% pure by glc. An analytical sample was prepared by bulb-to-bulb distillation under vacuum; mass spec 246 (100%), 245 (17%), 244 (79.6%), 121 (95.7%). Anal. Calcd for $C_8H_5BrS_2$: C, 39.19; H, 2.06; S, 26.16; Br, 32.60. Found C, 39.08; H, 2.14; S, 26.55; Br, 32.74. On standing, the colorless oil turned green.

2,2':4',3"-terthienyl (5). Under N_2 , 3-bromothiophene (4.66 g, 0.0286 mol) was added dropwise to $n-BuLi$ (0.0286 mol, 2.6 M in hexane) in ether (20 ml) at -78 °C. After 10 min the white suspension was rapidly transferred into a flask containing $MgBr_2$ (0.0372 mol) in ether at room temp. The resulting homogeneous solution was stirred for 30 min and was added dropwise into a mixture of 4-bromo-2,2'-bithienyl (4.8 g, 0.0196 mol) and $Ni(dppp)Cl_2$ (65 mg) in 20 ml of ether. The mixture was refluxed for 17 h, and was worked up as usual. The residual solid was flash chromatographed over silica gel using hexane, giving 3.7 g of pale yellow solid which was recrystallized from hexane, yielding 3.5 g (72%) of 5 as white crystals, mp 101-102 °C, mass spec 248 (M^+ , 100%), uv (MeOH) 210 (29000), 263 (23600) and 310 nm (9800). Anal. Found C, 58.12; H, 3.22; S, 38.59.

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