Synthesis of 2,2'-Bithienyl Derivatives

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A series of 2,2'-bithienyl derivatives were synthesized starting from the coupling of 2,2'-bithienyl and 2-(2-iodoethyl)-1,3-dioxolane.

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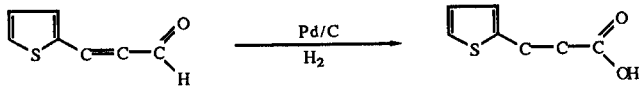
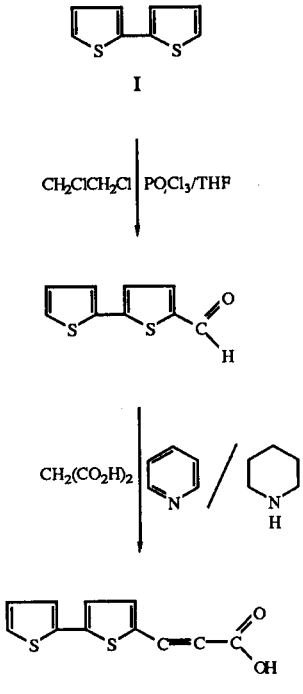
In connection with our studies on the bio-interested coordination compounds with tridentate ligands, we were interested in the synthesis of functional derivatives of 2,2'-bithienyl as potential polydentate ligands. It has been reported that 2,2'-bithienyl derivatives display interesting biological properties [1-4]. Moreover, the chemistry of such π-excessive heteroaromatic compounds remains to be explored in detail. In fact, there is little information in literature on open chain π-excessive heteropolyaromatic compounds and much less on their reactivity and functionalization due to the lack of efficient preparative methods.

According to Atkinson's method for the syntheses of *trans*-β-(5-bifuryl)acrylic acid [5], we had successfully synthesized 3-[5-(2,2'-bithienyl)]acrylic acid in a fairly good yield. However, hydrogenation with 1% and 10% palladium on charcoal as the catalyst to convert **XI** to its corresponding propionic acid were unsuccessful. But 3-[2-thienyl)acrylic acid can be converted to 3-(2-thienyl)acrylic acid under the same conditions [6]. This phenomena may be due to the more rapid formation of a 5-membered chelate ring between the more easily coordinate bithienyl



group (with two soft sulfur donors) and the soft metal center, palladium, which produces great steric hindrance for the catalytic reduction of the external double bond even in the presence of excess palladium. In order to illustrate the complexing capability of the bithienyl moiety, we have synthesized the 3-[5-(2,2'-bifuryl)]acrylic acid analog. This compound can be hydrogenated smoothly to 3-[5-(2,2'-bifuryl)]propionic acid in good yield as the bifuryl moiety has poor complexing ability [7].

We herein describe an efficient method for the syntheses of 3-[5-(2,2'-bithienyl)]propionic acid starting from the coupling of bithienyl and 2-(2-iodoethyl)-1,3-dioxolane. The coupling product **II** thus formed can also be converted to some other interesting potential tridentate ligands as described in the following scheme.

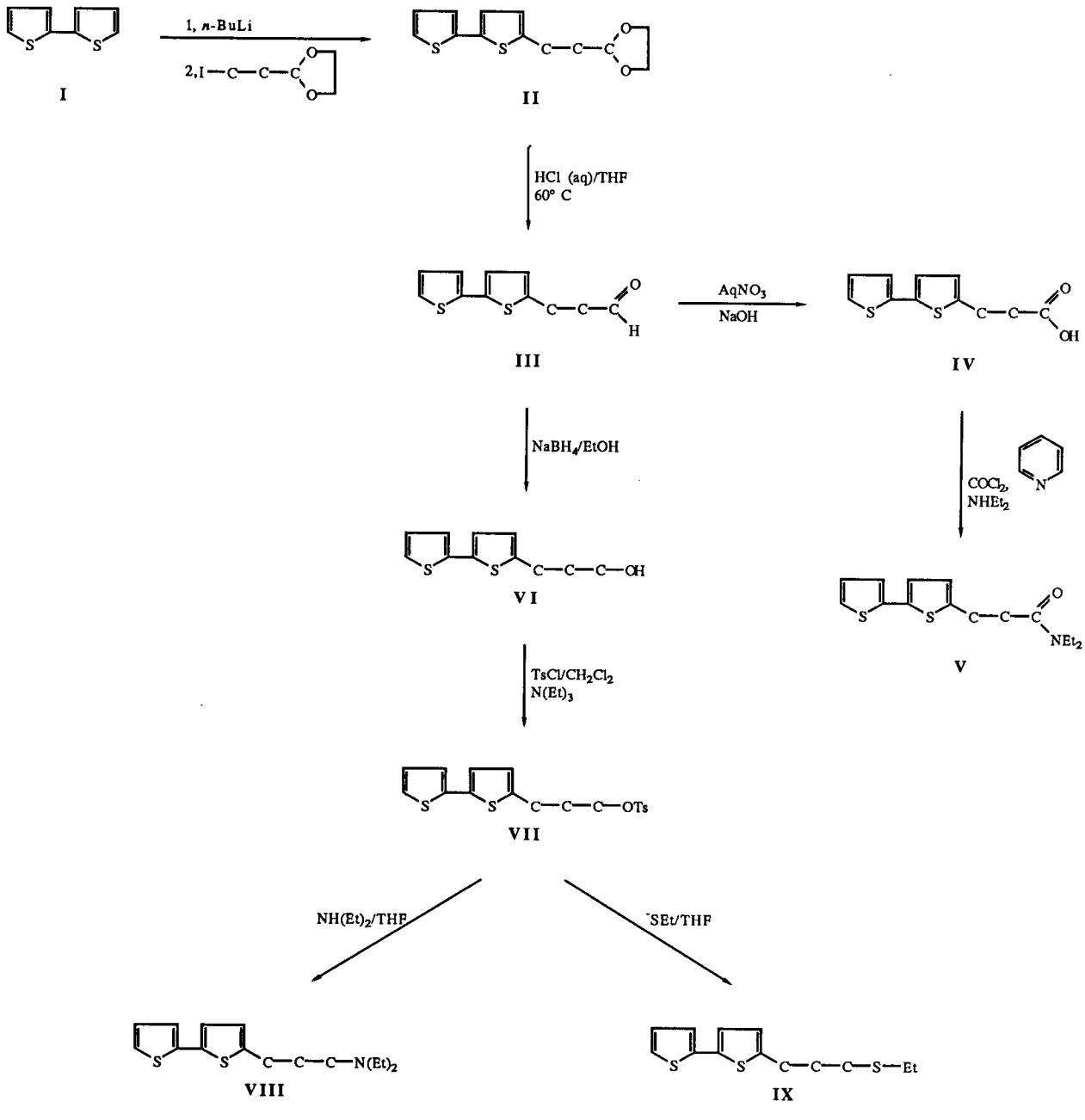


EXPERIMENTAL

The ^{1}H nmr spectra were recorded on a Varin EM-390 spectrometer. Infrared spectra were determined on a Perkin-Elmer 1330 spectrometer. Mass spectra were determined on a Hitachi M-52 instrument. Elemental analysis were done on a Heraeus CHN-O Rapid Analyzer. Melting points were uncorrected.

2,2'-Bithienyl (**I**) was prepare according to Gronowitz and Carlsson [8]. With prolonging the reflux time to 4 hours the yield can be raised to 72%. 2-[2-(5-(2,2'-Bithienyl))ethyl]-1,3-dioxolane (**II**). *n*-Butyllithium (45 ml, 1.6 *M*) was dropwise added to a stirred solution of 10 g (0.06 mole) of 2,2'-bithienyl in 150 ml of dry ether at −78° under nitrogen gas. After the addition was completed, the cold bath was removed and the reaction mixture was allowed to stir for 2 hours. The reaction mixture was cooled to −78° again and 17 g (0.07 mole) of 2-(2-iodoethyl)-1,3-dioxolane [9] in 60 ml of dry ether was dropwise added. The reaction mixture was then refluxed for 12 hours, quenched with aqueous saturated ammonium chloride solution, and then extracted with ether. The extracts were dried over sodium sulfate and concentrated *in vacuo*.

Scheme



The residue was chromatographed on a silica gel column. Elution with *n*-hexane/ethyl acetate (1/10) gave 6.1 g of **II** (40% yield), mp 61-61.5°; ^{1}H nmr (deuteriochloroform): δ 6.9-7.2 (m, 4H) 6.7 (d, 1H), 4.9 (t, 1H), 3.9 (broad d, 4H), 2.9 (t, 2H), 1.9-2.2 (quin, 2H); ms: 266 (M^+), 238, 179, 100, 73, 45.

Anal. Calcd. for $C_{13}H_{14}O_2S_2$: C, 58.56; H, 5.26; S, 24.06. Found: C, 58.57; H, 5.29; S, 24.10; ir: ν max 2850, 1420, 1240, 1130, 1040, 1020, 890, 810.

3-[5-(2,2'-Bithienyl)]propionaldehyde (**III**).

To a 5.0 g (0.019 mole) of **II** in 50 ml of THF solution, 5 ml of 2*N* hydrochloric acid was added and the reaction mixture was refluxed for 16 hours. After concentrated, the residue was extracted with dichloromethane and was chromatographed on a silica gel column. Elution with *n*-hexane/ethyl acetate (1/10) gave 1.6 g (37% yield) of **III**; ^{1}H nmr (deuteriochloroform): δ 9.66 (s,

1H), 6.8-7.1 (m, 4H), 6.57 (d, 1H), 3.0 (t, 2H), 2.67 (t, 2H).

Anal. Calcd. for $C_{11}H_{10}OS_2$: C, 59.43; H, 4.53; S, 28.84. Found: C, 59.38; H, 4.55; S, 28.88.

3-[5-(2,2'-Bithienyl)]propionic Acid (**IV**).

Silver nitrate (4.6 g, 0.027 mole) in 40 ml of water was added slowly to a 30 ml of an 1.8*N* aqueous sodium hydroxide solution with stirring at 0°. To the reaction mixture, 3 g (0.0135 mole) of **III** was added at room temperature and stirred for 1 hour. The brown suspension was removed and washed with several portions of hot water. The combined filtrates were acidified with concentrated hydrochloric acid. The milk-white precipitate was filtered and recrystallized from ether/*n*-hexane solution to give 1.8 g (56% yield) of **IV**, mp 97-98°; ^{1}H nmr (deuteriochloroform): δ 8.33 (broad s, 1H), 6.9-7.2 (m, 4H), 6.7 (d, 1H), 3.14 (t, 2H), 2.74 (t, 2H); ir: ν max 3250, 2950, 1050, 840, 790; ms: 238 (M^+), 179.

Anal. Calcd. for $C_{11}H_{10}O_2S_2$: C, 55.46; H, 4.20; S, 26.89. Found: C, 55.43; H, 4.22; S, 27.07.

3-[5-(2,2'-Bithienyl)]propanol (**VI**).

Reduction of 4.0 g (0.018 mole) of the corresponding aldehyde **III** with 3 g (0.09 mole) of sodium borohydride in a 50 ml of ethanol gave 3.2 g (80%) of **VI**, mp 45-46.5°; ^{1}H nmr: δ 6.76-7.07 (m, 4H), 6.55 (d, 1H), 3.25 (t, 2H), 3.04 (s, 1H), 2.74 (t, 2H), 1.8 (quin, 2H); ir: ν max 3250, 1710, 1430, 1270, 1050, 840, 790; ms: 224 (M^+), 179.

Anal. Calcd. for $C_{11}H_{12}OS_2$: C, 58.93; H, 5.36; S, 28.57. Found: C, 58.90; H, 5.38; S, 28.68.

3-[5-(2,2'-Bithienyl)]propyl *p*-Toluenesulfonate (**VII**).

By following the general sulfonation procedure compound **VII** was obtained in 90% yield from **VI** and *p*-toluenesulfonyl chloride, mp 75-76.5°; ^{1}H nmr δ 7.8 (broad d, 2H), 7.35 (broad d, 2H), 7.27-6.9 (m, 4H), 6.6 (d, 1H), 4.1 (t, 2H), 2.9 (t, 2H), 2.5 (s, 3H), 2.05 (quin, 2H); ms: 378 (M^+), 206, 179, 91, 65.

Anal. Calcd. for $C_{18}H_{18}O_3S_3$: C, 57.14; H, 4.76; S, 25.39. Found: C, 57.10; H, 4.76; S, 25.60.

1-(Diethylamino)-3-[5-(2,2'-bithienyl)]propane (**VIII**).

One half g (0.0013 mole) of **VII** and 1 ml (0.0097 mole) of diethylamine in 20 ml of THF was refluxed for 4 hours. The solution turned from dark green to a brown color. The solution and unreacted diethylamine was removed by rotary evaporation and the residue was extracted with dichloromethane, washed with saturated sodium carbonate aqueous solution and saturated sodium chloride solution. After concentrated *in vacuo*, the residue was chromatographed on a silica gel column. Elution with *n*-hexane/ethyl acetate (5/3) gave 0.3 g (90% yield) of **VIII**; ^{1}H nmr: δ 7.2-6.9 (m, 4H) 6.65 (d, 1H), 2.8 (t, 2H), 2.77 (quin, 4H), 2.38-2.63 (m, 4H), 1.0 (t, 6H); ir: ν max 2960, 1380, 840, 800; ms: 279 (M^+), 206, 179, 98, 72.

Anal. Calcd. for $C_{15}H_{21}NS_2$: C, 64.45; H, 7.52; N, 5.02; S, 22.94. Found: C, 64.13; H, 7.54; N, 4.96; S, 22.78.

3-Thia-6-[5-(2,2'-bithienyl)]hexane (**IX**).

Sodium hydride (0.38 g, 0.016 mole) in 80 ml of dry THF was added slowly to 2 ml (0.0264 mole) of ethanethiol with stirring. After 30 minutes the solution was cooled to 0° and 5.0 g (0.013 mole) of **VIII** in 20 ml of dry THF was added. After 6 hours of reaction at room temperature, the reaction mixture was filtrated and the filtrate was concentrated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with *n*-hexane/ethyl acetate (19/1) gave 3.2 g of **IX** (92% yield); ^{1}H nmr: δ 6.9-7.2 (m, 4H), 6.6 (d, 1H), 2.85 (t, 2H), 2.37-2.66 (m, 4H), 1.9 (quin, 2H), 1.2 (t, 3H); ir: ν max 2920, 1430, 840, 800; ms: 268 (M^+), 206, 179.

Anal. Calcd. for $C_{13}H_{16}S_3$: C, 58.15; H, 5.96; S, 35.87. Found: C, 58.18; H, 6.02; S, 35.98.

N,N-Dimethyl-3-[5-(2,2'-bithienyl)]propionamide (**V**).

Oxalyl chloride (1.5 ml, 0.016 mole) was added slowly to 2 g (0.008 mole) of **IV** in 10 ml of dry THF solution at 0°. After one hour of reflux, the reaction mixture was cooled to 0° again and 0.65 ml(0.008 mole) of pyridine was added with stirring. The reaction mixture was stirred for another 5 minutes and 8.5 ml (0.008 mole) of diethylamine in 10 ml of THF was added. After 70 minutes of reaction at room temperature the solvent and pyridine was removed and the residue was extracted with dichloromethane. The extract was concentrated *in vacuo* and the residue was chromatographed. Elution with *n*-hexane/ethyl acetate (4/1) gave 1.24 g of **V** (53% yield); ^{1}H nmr: δ6.85-7.13 (m, 4H), 6.67 (d, 1H), 3.05-3.5 (m, 6H), 2.6 (t, 2H), 1.1 (t, 6H); ms: 293 (M^+), 192, 179, 166.

Anal. Calcd. for $C_{15}H_{19}NOS_2$: C, 61.39; H, 6.53; N, 4.77; S, 21.85. Found: C, 61.28; H, 6.58; N, 4.81; S, 21.79.

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