THE SYNTHESIS OF 2,2':5',3"-TERTHIOPHENE

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Abstract - 2,2':5,3"-Terthiophene has been synthesized by two different routes. One utilized the Cadiot-Chodkiewicz coupling of 2-(bromoethynyl)thiophene with 3-ethynylthiophene, followed by sodium sulfide treatment of the resulting 1-(2-thienyl)-4-(3'-thienyl)-1,3-butadiyne. The other featured a Grignard reaction starting from 5-iodo-2,2'-bithiophene and 3-oxotetrahydrothiophene, followed by thermal aromatization with sulfur. The new terthiophene was an efficient singlet oxygen sensitizer.

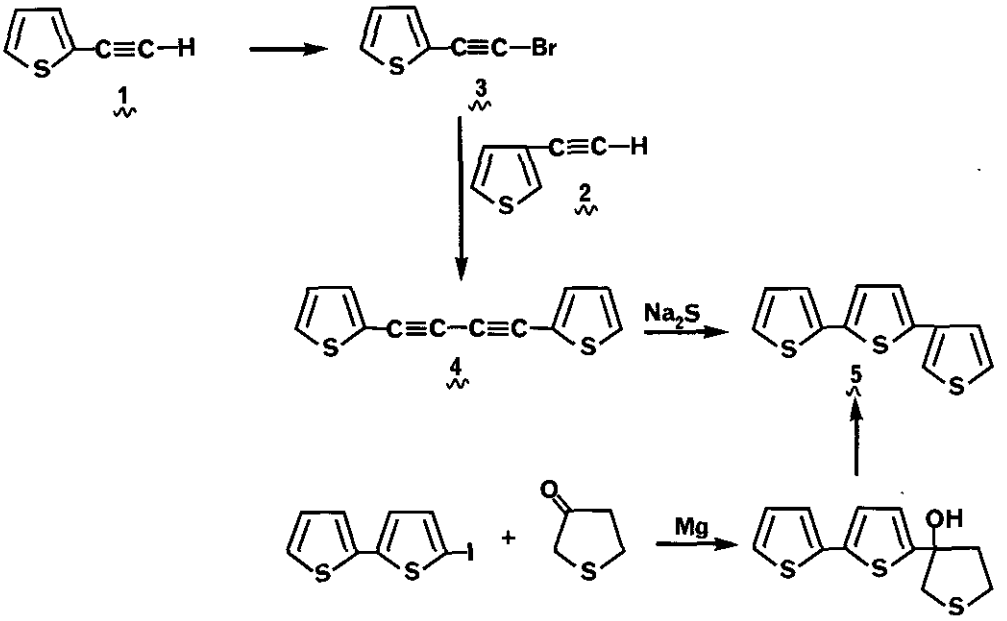
No directed syntheses of 2,2':5',3"-terthiophenes have been recorded in the literature, but there is a claim that the treatment of 2-chlorothiophene with sulfuric acid in the cold yielded, among other oligomerization products, a compound presumed to be 5,5"-dichloro-2,2':5',2"-terthiophene or 5,5"-dichloro-2,2':5',3"-terthiophene.[1] The synthetic value of this approach is still uncertain.

A number of symmetrical terthiophenes, including the previously unknown 3,2':5',3"-terthiophene, were recently synthesized from the appropriate 2-thienyl-carboxaldehyde.[2] Conversion into a 2-ethynylthiophene was followed by oxidative coupling, yielding a symmetrical 1,4-dithienyl-1,3-butadiyne which was finally transformed into the desired terthiophene by treatment with sodium sulfide.

Since unsymmetrical 1,3-butadiynes are readily available by the Cadiot-Chodkiewicz coupling of terminal acetylenes with bromoacetylenes,[3] the unambiguous synthesis of the 2,2':5',3"-terthiophenes appeared possible. This has now been

demonstrated by the synthesis in excellent yield of the parent compound in this series. The starting materials were 2-ethynylthiophene (1) and 3-ethynylthiophene (2). The former, which is the more readily available, was converted into the bromoacetylene derivative 3, and the coupling of 2 with 3 in the presence of cuprous chloride gave 1-(2-thienyl)-4-(3'-thienyl)-1,3-butadiyne (4) in 91% yield. Its treatment with sodium sulfide produced 2,2':5',3"-terthiophene (5) in 87% yield.

The same compound could also be obtained by another approach, modeled after the synthesis of 2,3'-bithiophene described by Wynberg et al..[4] The Grignard reagent derived from 5-iodo-2,2'-bithiophene was condensed with 3-oxotetrahydrothiophene, and the alcohol thus obtained in about 80% yield was aromatized by heating in the presence of potassium hydrogen sulfate and sulfur, yielding a product identical to that obtained by the first method.



The new terthiophene 5 is an isomer of alpha-terthienyl (2,2':5',2"-terthiophene, 6), a natural product originally investigated because of its nematicidal activity,[5] which was later shown to have herbicidal activity,[6] and to be a powerful photosensitizer.[7] Like 6 and its 3,2':5',3" isomer (7), 5 was found to be an excellent singlet oxygen sensitizer, judging by the extent of photosensitized conversion of adamantylideneadamantane into adamantanone.[8] Under identical conditions, using light sources which had their maximum emission at 350 nm,

these three terthiophenes were compared to methylene blue, a standard singlet oxygen sensitizer. The extent of conversion into adamantanone was 1.75, 2.05, and 1.89 times greater with the 2,2':5',2", 3,2':5',3", and 2,2':5',3"-terthiophenes respectively than with methylene blue.

The light-induced hemolysis of human erythrocytes is a reaction characteristic of photodynamic molecules.[9] In this case, however, we observed that although 6[10] and the newly obtained 5 were readily sensitizing the hemolysis of human erythrocytes in the presence of light, the isomeric compound 7 did not, even after prolonged irradiations. The reasons for these differences in behavior are not clear at this time, and will be investigated further. There was a difference in the rates of hemolysis induced by the two active isomers, and alpha-terthienyl was always producing the hemolysis of the erythrocytes more rapidly. For example, when photolyzed simultaneously under conditions which led to hemolysis of 50% of the erythrocytes in the presence of 6 in 18 min, an identical sample containing 5 required 35 min to reach the same extent of hemolysis. No hemolysis was observed following more than 2 h of photolysis in the presence of 7.

Both 4 and 5 displayed strong photoantibiotic properties when tested by our standard procedure, using Candida utilis, Saccharomyces cerevisiae, E. coli, and Bacillus subtilis.[11]

EXPERIMENTAL

The melting points were determined with a Koffler apparatus and are not corrected. The nmr spectra were recorded on a Varian A-60A or T-60, with an internal standard of tetramethylsilane. The mass spectra were obtained on a AEI MS-30, or HP-5985. The microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois. The hemolysis experiments were carried out using 0.2 mL of blood, which was washed 3 times with 1 mL of buffer solution, and was suspended in 2 mL of phosphate buffer, pH 7.42. The sensitizer (0.150 mL of a DMSO solution containing 1 g/L) was added, and buffer was added to bring the final volume to 4 mL. The mixture was kept overnight in the dark, and was irradiated in the beam of a 1000-W Hanovia lamp, filtered through a Pyrex vessel containing circulating cold water. Magnetic stirring was maintained during the irradiations, and all three terthiophene isomers were irradiated simultaneously. The extent of hemolysis was determined by spectroscopic analysis of the supernatent obtained after centrifugation of an ali-

quot from the photolysis mixtures.[12]

1-(2-Thienyl)-4-(3'-thienyl)-1,3-butadiyne (4). Cuprous chloride (111 mg), one crystal of hydroxylamine hydrochloride, and 70% aq. ethylamine (2.77 mL) were added to a well stirred solution of 3-ethynylthiophene (2.16 g, 0.02 mol) in methanol-ether (1:1, 30 mL). A solution of 1-bromo-2-thienylacetylene (3.74 g, 0.02 mol) in methanol (20 mL) was added dropwise at room temperature. After stirring for 1 hr, sodium cyanide (44 mg in 50 mL of water) was added. The mixture was extracted with CH_2Cl_2 (4 x 25 mL), which was washed with water (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum to yield 3.9 g (91%) of 4 after crystallization from CH_3OH; m.p. 96-97°C, u.v. (CH_3OH) 266, 322 nm; n.m.r. ($CDCl_3$) 6.9-7.6 ppm (m, 6 H); mass spec. m/e 214 (M^+, 100%).

Anal. Calcd for $C_{12}H_6S_2$: C, 67.25; H, 2.82; S, 29.92. Found: C, 67.07; H, 2.91; S, 29.69.

2,2':5',3"-Terthiophene (5). A mixture of the butadiyne 4 (1.000g, 4.6 mmol), $Na_2S.9H_2O$ (4.517 g, 18.4 mmol), and methanol (150 mL) was refluxed and the progress of the reaction was monitored by tlc. After 18 hr, the reaction mixture was cooled and the solvent was removed under vacuum. The crude product was washed with water, filtered, and recrystallized from 95% ethanol to give 1.11 g (90%) of 5. Another crystallization from methanol furnished the title compound in 87% yield, m.p. 158-160°C; u.v. (CH_3OH) 243 and 331 nm; n.m.r. ($CDCl_3$) 7.0-7.6 ppm (m); mass spec. m/e 248 (M^+, 100%).

Anal. Calcd for $C_{12}H_8S_3$: C,58.03; H, 3.25; S, 38.73. Found: C, 58.19; H, 3.20; S, 38.78.

Synthesis of 5 from 5-iodo-2,2'-bithiophene. To the Grignard reagent prepared from 5-iodo-2,2'-bithiophene[13] (730 mg, 2.5 mmol) and Mg turnings (72 mg, 3 mmol) in anhydrous ether (20 ml) was added 2-oxotetrahydrothiophene (252 mg, 2.5 mmol) in ether (10 mL) over a 30 min period. The gummy product initially formed turned into a yellow powder by continuous stirring at room temp for 1.5 hr. After addition of ice-cold dilute HCl, the organic layer was washed with aq $NaHCO_3$, dried over $MgSO_4$, and concentrated under vacuum to give 500 mg (80.7%) of a viscous oil (6), which was heated at 160-170°C with $KHSO_4$ (200 mg, 0.15 mmol) and sulfur (400 mg, 12.5 mmol). The temperature was slowly raised to 225°C, and gas evolution ceased after 20 min. After cooling, the mixture was extracted with ether, which was then washed with aq $NaHCO_3$ and with water, dried over $MgSO_4$, and concentrated under vacuum. The gummy residue was flash chromato-

graphed (Hexane-$CHCl_3$, 9:1) to give 80 mg (18%) of 5, m.p. 157-160°C. A mixture m.p. with the material obtained by the other procedure was not depressed, and the i.r and n.m.r. spectra were superimposable. Both samples had undistinguishable tlc and hplc behavior.

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