

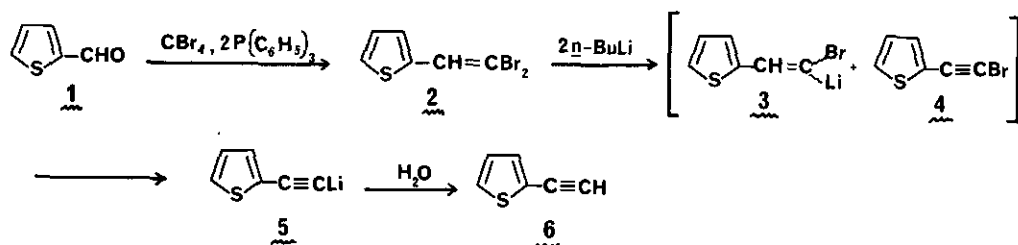
A SIDE REACTION IN THE SYNTHESIS OF 2-ETHYNYLTHIOPHENE  
FROM 2-THIOPHENECARBOXALDEHYDE BY THE COREY PROCEDURE  
AND AN IMPROVED SYNTHESIS OF 2,2':5',2"-TERTHIOPHENE

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**Abstract** - The conversion of thiophenecarboxaldehyde to thienylacetylene by the Corey procedure is associated with a concentration-dependent polymerization process and an alkylation of the thiophene at the 2 position. Improvements in the synthesis of 2,2':5',2"-terthiophene and its 5,2"-dibutyl derivative are reported.

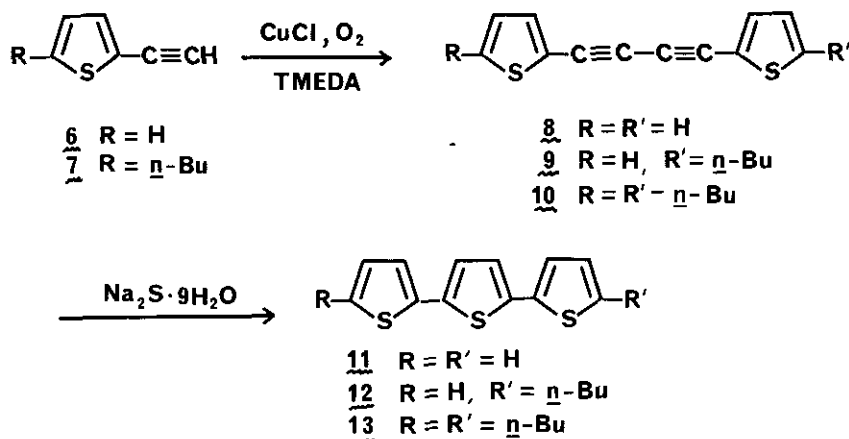
The Corey procedure<sup>1</sup> for converting an aldehyde to its acetylenic homologue has been used to synthesize thienylacetylenes in good yield (Scheme 1).<sup>2-5</sup> These compounds have been intermediates in the synthesis of terthiophenes.<sup>3-5</sup>



SCHEME 1

Wishing to possess multigram quantities of 2,2':5',2"-terthiophene, 11, for continuing studies of phototoxicity,<sup>6</sup> the reported synthesis<sup>3</sup> was scaled up. No difficulties were encountered in preparing 2 from 1 on a 70 g scale in excellent yield. The conversion of 45 g of 2 into 6 was then attempted, using for convenience an approximately 10-fold increase (over the published procedure<sup>3</sup>) in the concentration of reactants 2 and  $n\text{-BuLi}$ . Following the usual workup, where the product is purified by distillation, over 90% of the reaction mixture was in the form of an intractable, apparently oligomeric, residue which displayed several dozen peaks on HPLC.

The low-boiling fractions in this distillation, assumed from NMR to be the mixture of 1-BrBu (from metalation of 4 by *n*-BuLi) and 6 encountered at this stage in previous runs, were subjected without further purification to Glaser coupling conditions. The material which crystallized spontaneously from the concentrated reaction mixture proved by NMR, IR, MS, and elemental analysis to be bis(5-butyl-2-thienyl)butadiyne, 10; only trace amounts of the expected 8 could be detected by HPLC, but the unsymmetrical product 9 was not found. Compound 10, in turn, readily formed 2,5"-dibutyl-2,2':5',2"-terthiophene (13, 70% yield of analytically pure product) in 82% yield, upon exposure to Na<sub>2</sub>S·9H<sub>2</sub>O (reflux, 1 h, 2-methoxyethanol). These products were previously unknown.



SCHEME 2

The assignment of the butyl substituents to the 5 and 5' positions in 10 was based on the NMR spectrum, which displayed the thiophene protons as two doublets, at 6.6 and 7.1 ppm. This ruled out any unsymmetrical structures, and the magnitude of *J* (3.5 Hz) suggested that the adjacent protons were at the 3 and 4 positions.<sup>7</sup> This was unequivocally confirmed by subjecting 13 to Raney nickel desulfurization: the sole product, isolated in 83% yield, was *n*-eicosane, identical with an authentic sample by mmp, GC, NMR, and MS. The possibility that 10 had been produced after 8 had been generated was ruled out by a second experiment. A mixture of 8 and 1-bromobutane was subjected to the conditions of Glaser coupling which had produced 10; 8 was recovered quantitatively. The simplest explanation for the introduction of a butyl substituent at the 5 position is based on the much greater acidity of  $\alpha$  over  $\beta$  hydrogens in a thiophene ring. The intermediacy of a 5-lithio derivative of 2, 3, 4, or 5, followed by alkylation with 1-bromobutane formed *in situ*, would yield 7. The alkylation of 2-lithiothiophene by alkyl halides is a well-known process.<sup>8</sup>

The polymerization process appears to be concentration dependent: when the reaction was

repeated on a 12- and 24-g scale in the concentrations (about 0.1 M in **2** and 1.0 M in *n*-BuLi) employed by previous workers,<sup>1-3,5</sup> reliably high yields of **6** were obtained, with no observable polymerization or formation of **7**.

A final improvement was realized. The formation of **6** in the successful conversions from **2** was monitored by HPLC, disclosing that some of the volatile **6** was removed along with the solvent in a rotary evaporator during workup. This loss occurred even when the reaction of **2** with *n*-BuLi was carried out in the more volatile Et<sub>2</sub>O instead of THF. (An attempt to couple **6** in ether failed; this is consistent with the observation that the reaction was significantly solvent dependent.)

The loss of material can be obviated by removing the ether by distillation before the reaction mixture is quenched; at this stage, **6** is entirely in the form of its nonvolatile lithium salt, **5**. Subsequent addition of a mixture of water and DME, the solvent to be used in the subsequent reaction, results in partitioning into two phases. The DME organic phase containing **6** is sufficiently pure for immediate use in the coupling reaction. In this manner, the overall yield from **2** to **11** was 77%, a significant improvement over the previous value of 46%.<sup>3</sup>

#### EXPERIMENTAL

Melting points, uncorrected, were determined on a Reichert hot stage. The following instruments were used: NMR, Varian T-60 ( $\delta$ -scale, internal TMS); IR, Perkin-Elmer 700; UV, Coleman-Hitachi 124; MS, AEI MS-30 or Hewlett-Packard 5985 (70 eV); HPLC reverse phase 25 cm column, 10 Alltech C-18 (80:20 MeCN:H<sub>2</sub>O or MeOH eluant, 254 nm detector); GC, Hewlett-Packard 402 with a 2m x 2mm column OV-101 on Chromosorb W-HP, 80/100 mesh. *n*-Eicosane was from Applied Science Laboratories, State College, Penn. Elemental analyses were by Micro-Tech Laboratories, Skokie, IL.

**1,4-Bis(5-butyl-2-thienyl)butadiyne (10).** To a stirred solution of 45.0 g (0.17 mol) of **2** in 150 ml of THF (1.13 M), 35 ml of 10.5 M *n*-BuLi in hexane (0.37 mol, 2.1 eq) was added dropwise under N<sub>2</sub> at -78°C over a period of 45 min. Stirring at -78°C was continued for 1.25 h further, then the temperature was allowed to rise over 0.5 h to 25°C, where it was maintained for 1.0 h further. The mixture was then quenched with water and extracted with 3 x 50 ml of Et<sub>2</sub>O. The ether extracts were dried (MgSO<sub>4</sub>) and removed in vacuo; the distillate, which showed peaks on HPLC for **6** and other compounds, was retained. The residue was distilled under aspirator vacuum and 3 fractions were collected: 1.4 g, bp 32-46°C; 2.35 g, bp 52-70°C; 15.3 g, bp 72-131°C. All fractions had strong <sup>1</sup>H NMR signals for thiophene and acetylene and weaker olefinic signals at 5-6 ppm; the residue in the pot showed at least 50 peaks on HPLC and was discarded. The reserved Et<sub>2</sub>O distillate was stripped of THF and hexane by spinning band fractional distillation, the distillates showing no traces of thiophene components (HPLC, NMR). The residue (4 g) was combined with the 3 fractions from the aspirator distillation and dissolved in 50 ml of dimethoxyethane (DME). This was added dropwise over 20 min to a solution of 30 mmol (3.0 g) CuCl in 10.0 ml (66 mmol) of N,N,N',N'-tetramethylethylenediamine and 100 ml of DME stirred by vibromixer in a current of air and protected from volatilization by an acetone-dry ice trap. The reaction was allowed to proceed

for 1 h at 30-35°C.<sup>9</sup> The mixture was then filtered, washed with water and dilute HCl, the washings back extracted with Et<sub>2</sub>O, and the combined organic layers dried. After solvent removal a thick brown oil remained. When dissolved in a small amount of EtOH and chilled overnight, a mass of crystals separated. After several recrystallizations to constant mp (47-48°C), and 100% purity (HPLC), there was obtained 2.5 g of 10 as white crystals: NMR (CDCl<sub>3</sub>) δ 0.92 (m, 6H), 1.50 (m, 8H), 2.8 (t, 4H), 6.6 (d, J = 3.5 Hz, 2H), 7.1 (d, J = 3.5 Hz, 2H); MS m/e 326.2 (M<sup>+</sup>, 62%), 283.1 (100%), 240 (54.4%); IR (melt) 2945, 2880, 2160, 1455, 1150, 810 cm<sup>-1</sup>; UV (EtOH) λ<sub>max</sub> 344 nm (ε 16,600). Anal. Calcd for C<sub>20</sub>H<sub>22</sub>S<sub>2</sub>: C, 73.57; H, 6.79; S, 19.64. Found: C, 73.73; H, 6.81; S, 19.53.

**5,5'-Dibutyl-2,2':5',2''-terthiophene (13).** A mixture of 1.0 g of 10 (3.1 mmol), 2.9 g of Na<sub>2</sub>S<sub>9</sub>H<sub>2</sub>O (9.0 mmol), and 100 ml of 2-methoxyethanol was warmed with stirring. At reflux temperature (110°C), all solids had dissolved and the mixture was allowed to reflux overnight. After cooling and neutralization with aq HCl, crystals formed. They were extracted with 3 x 100 ml of Et<sub>2</sub>O, the organic layer dried (MgSO<sub>4</sub>) and concentrated in vacuo. The crude product was recrystallized first from 95% EtOH to yield 0.90 g of material having mp 68-75°C, then from abs. EtOH to give 0.77 g (70.1% yield) of 13 as golden yellow crystals, mp 76-77°C, NMR (CDCl<sub>3</sub>) δ 0.92 (m, 6H), 1.50 (m, 8H), 2.8 (t, 4H), 6.6 (d, J = 3.5 Hz, 2H), 6.9 (d, J = 3.5 Hz, 2H), 6.9 (s, 2H); MS m/e 360 (M<sup>+</sup>), 317, 274; IR (5% in CS<sub>2</sub>) 2945, 2880, 1235, 1195, 1030, 790 cm<sup>-1</sup>; UV (EtOH) λ<sub>max</sub> 360 nm (ε 26,200). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>S<sub>3</sub>: C, 66.62; H, 6.71; S, 26.68. Found: C, 66.84; H, 6.80; S, 26.48.

**Raney Ni Desulfurization of 13.** 0.51 g of 13 was dissolved in 45 ml of warm abs. EtOH under N<sub>2</sub> with magnetic stirring. A slurry of ca. 2.5 ml of Raney Ni W-7<sup>10</sup> in abs. EtOH was added, and the mixture was heated to reflux. Within 1 h, no 13 remained (HPLC). The mixture was filtered and the filtrate quenched with water. A white flocculent precipitate formed, which was extracted into Et<sub>2</sub>O; the extract was washed with water, dried (MgSO<sub>4</sub>), and evaporated to yield 0.33 g (83%) of waxy product which was pure by GC. A recrystallized sample, mp 34-35°C, was identical with an authentic sample of *n*-eicosane by mmp, GC, NMR, and MS.

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