

THE SYNTHESIS OF ALPHA-THIOPHENE OLIGOMERS BY  
OXIDATIVE COUPLING OF 2-LITHIOTHIOPHENES

Jacques Kagan and Sudershan K. Arora

Department of Chemistry, University of Illinois at Chicago  
P.O. Box 4348, Chicago 60680, Illinois, USA

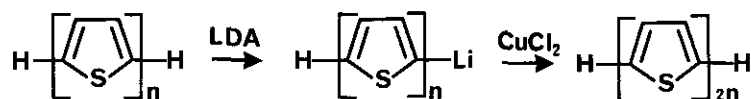
**Abstract** - Alpha-thiophene oligomers containing an even number of thiophene rings can be obtained with very good yields by reacting a suitable thiophene precursor with 0.5 equivalent of lithium diisopropylamide in dry THF, followed by the oxidation of the  $\alpha$ -lithio derivative with cupric chloride. The Scheme is illustrated with the synthesis of 2,2'-bithienyl,  $\alpha$ -quaterthienyl, and  $\alpha$ -sexithienyl in 83, 85, and 73% yields from thiophene, 2,2'-bithienyl, and  $\alpha$ -terthienyl respectively.

A number of thiophene oligomers and their derivatives have shown interesting biological properties<sup>1</sup>, the best known member in this series being  $\alpha$ -terthienyl (1).<sup>2</sup>

Although  $\alpha$ -terthienyl has now been made by different routes, it was originally synthesized by reacting 2-iodothiophene with copper, a procedure which gives a complex mixture of products, from which the oligomers possessing 2 to 7 thiophene ring could be obtained individually in low yields after tedious purification steps.<sup>3,4</sup> Related reactions in which two different iodothiophenes were reacted with copper also produced complex mixtures.<sup>5</sup> Other coupling methods gave mediocre yields of products. For example, 2,2'-bithienyl (2) was produced by a reaction of cobaltous chloride with the Grignard reagent from 2-bromothiophene (26% yield),<sup>6</sup> or with 2-thienyllithium (30% yield),<sup>7</sup> and  $\alpha$ -quaterthienyl (3) was obtained in 30% yield when 5-iodo-2,2'-bithienyl was treated with cuprous acetate.<sup>8</sup>

Efficient syntheses of individual alpha-thiophene oligomers are clearly needed, if the chemistry and biological properties of these molecules are to be investigated.

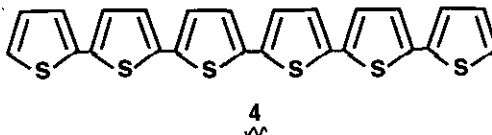
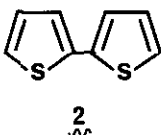
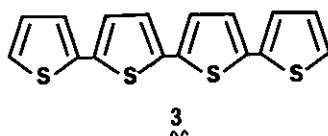
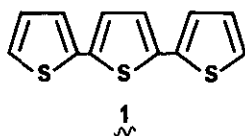
We now report that individual alpha-thiophene oligomers can be obtained with vastly improved yields utilizing a simple approach which is based on the much greater acidity of the  $\alpha$ -protons compared to the  $\alpha$ -protons in thiophenes,<sup>9</sup> and on the ability of cupric chloride to oxidatively couple organolithium compounds.<sup>10</sup>



The stoichiometry requires an equimolar relationship of the starting material and lithium diisopropylamide (LDA), but these conditions always led to a mixture of the desired product and its dimer. For example the treatment of 2-lithiothiophene with LDA in these conditions produced a mixture of 2,2'-dithienyl (41% yield) and  $\alpha$ -quaterthienyl (30% yield). The trimer  $\alpha$ -terthienyl was not formed, in contrast to the results observed in the coupling reactions of 2-iodothiophene.<sup>3</sup> Presumably, the equilibrium obtained in a mixture of 2,2'-bithienyl with unreacted 2-lithiothiophene favors the lithium salt of the bithienyl. This problem was minimized when a two-fold excess of thiophene was used. In this manner, under otherwise identical conditions, the yield of distilled 2,2'-bithienyl based on the LDA used was 83%, and only a very small amount of  $\alpha$ -quaterthienyl was obtained (0.15% yield). The 2,2'-bithienyl had nmr, ir and mass spectra identical to those of an authentic sample. The excess of thiophene was recovered (85% yield) and could be recycled.

Similarly, the reaction of 2 equivalents of 2,2'-bithienyl with 1 equivalent of LDA and then with 1 equivalent of  $\text{CuCl}_2$  yielded  $\alpha$ -quaterthienyl (3) in 85.8% yield, and the excess of bithienyl was recovered in 85% yield.

The reaction of 2 equivalents of  $\alpha$ -terthienyl with 1 equivalent of LDA followed by 1 equivalent of  $\text{CuCl}_2$  produced  $\alpha$ -sexithienyl (4) in 73% yield after purification.



The experimental procedure used for the synthesis of  $\alpha$ -thiophene oligomers is exemplified here with the synthesis of  $\alpha$ -sexithienyl. *n*-Butyllithium (0.005 mol, 1.5 M in hexane) was added dropwise to a stirred solution of diisopropylamine (0.505g, 0.005 mol) in dry THF (10 ml) at  $-78^{\circ}\text{C}$  under  $\text{N}_2$ .  $\alpha$ -Terthienyl (2.480g, 0.01 mol) in dry THF (10ml) was added dropwise, the mixture was stirred for 30 min at  $-78^{\circ}\text{C}$ , and anhydrous  $\text{CuCl}_2$  (0.672g, 0.005 mol) in dry DMF (10ml) was added. The mixture was stirred for 1 h at  $-78^{\circ}\text{C}$ , and also while it returned to room temperature. After addition of 3% aqueous HCl, a solid was formed, which was filtered off and washed successively with water and with ether. The ether phase was dried and concentrated, and yielded 1.000g of unreacted starting material. The solid reaction product was purified by sublimation, and afforded 0.905g (73% yield) of  $\alpha$ -sexithienyl, mp  $304\text{--}305^{\circ}\text{C}$  (lit mp  $304^{\circ}\text{C}$ ),<sup>3</sup> mass spec  $m/e$  494 ( $\text{M}^+$ , 100%), identical to an authentic sample.

In conclusion, a simple method is available for the synthesis of  $\alpha$ -thiophene oligomers, where individual members may be obtained in excellent yield. By its very design the method herein described is limited to the synthesis of oligomers with an even number of thiophene units.

ACKNOWLEDGMENTS We are grateful to the National Institutes of Health (GM 24144) for financial support.

#### REFERENCES

1. Downum, K, R. E. W. Hancock and G.H.N. Towers, Photochem. Photobiol., 1982, 36, 517, and references cited.
2. Beny, J.-P., S. N. Dawan, J. Kagan and S. Sundlass, J. Org. Chem., 1982, 47, 2201, and references cited.
3. Steinkopf, W. R. Leitsmann, and K. H. Hofmann, Justus Liebigs Ann. Chem., 1982, 546, 180.
4. Sease, J. W., and L. Zechmeister, J. Am. Chem. Soc., 1947, 69, 270.
5. Steinkopf, W., H. J. V. Petersdorff, and R. Gording, Justus Liebigs Ann. Chem., 1937, 527, 272.
6. Morizur, J. P. and R. Pallaud, Compt. Rend., 1962, 254, 1093.
7. Morizur, J. P., Bull. Soc. Chim. France, 1964, 1331.

8. Atkinson, R. E., R. F. Curtis, and G. T. Phillips, *J. Chem. Soc. (C)* 1967, 2011.
9. Wynberg, H. and A. Bentjes, *J. Am. Chem. Soc.* 1960, 82, 1447.
10. Ito, Y., T. Konoike, T. Harada, and T. Saegusa, *J. Am. Chem. Soc.*, 1977, 99, 1487.

Received, 20th June, 1983