THE SYNTHESIS OF 2,2',5',2''-[2',5'-$^{14}C_2$]TERTHIENYL AND 1,4-BIS(2-THIENYL)[1,4-$^{14}C_2$]BUTADIYNE.

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SUMMARY

2,2',5',2"-[2',5'-$^{14}C_2$]Terthienyl and 1,4-bis(2-thienyl)[1,4-$^{14}C_2$]butadiyne were synthesized from [^{14}C]formic acid.

Key words: α-Terthienyl, dithienylbutadiyne, thienylacetylene.

INTRODUCTION

Alpha terthienyl,(αT), first isolated in the plant Tagetes erecta (family Compositae),[1] has been shown to have a variety of biological effects in the presence of long wavelength ultraviolet light,[2,3] and more recently 1,4-bis(2-thienyl)-butadiyne (DTB) was also reported to have photoantibiotic properties similar to those of αT.[4] Since butadiynes and thiophenes are closely related, both chemically and biologically, we took advantage of this relationship to prepare the ^{14}C-labelled samples which were needed in order to study the photochemistry of αT and DTB in vivo.

RESULTS AND DISCUSSION

Several procedures have been reported in the literature for preparing αT.[5-8] The first synthesis of ^{14}C-labelled αT followed Kooreman and Wynberg's procedure,[4] but this method is lengthy and its overall yield poor, primarily because of a low yield in the very last step.

It is known that αT can be obtained from DTB by reaction with hydrogen sulfide,[6] but the utility of this method is limited by the availability of 2-ethynylthiophene,[9-11] the immediate pre-

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cursor which is to be oxidatively dimerized to DTB. The standard syntheses are either lengthy or not applicable to small scale work, and the yields are frequently unsatisfactory.

A key step in our synthetic approach was the preparation of a ^{14}C-labelled 2-ethynylthiophene from 2-thiophenecarboxaldehyde and carbon tetrabromide, using Corey and Fuchs' procedure[12] which is known to give good results with thienyl compounds[13], and which is particularly convenient for small scale work. In this approach a consideration of the availability of starting materials[14] led us to select the method described in Figure 1, where the label was introduced into the aldehyde.

2-Thiophene-[^{14}C]carboxaldehyde was obtained by a Vilsmeier-Haack reaction,[15] where the yield was increased by replacing N-methylformanilide with N-methyl-N-toluidylformamide.[16] After conversion of this aldehyde into 1,1-dibromo-2-(2-thienyl)-[2-^{14}C]ethylene, dehydrobromination with n-butyllithium yielded (2-thienyl)[1-^{14}C]acetylene, which was then oxidatively coupled in the presence of cupric ion, generated from cuprous chloride and air.[17] The desired di(2-thienyl)[1,4-$^{14}C_2$]butadiyne (DTB*, 5) could be obtained in a yield ranging from 32.6 to 36.4% from formic acid, which was used in excess in the synthesis of N-methyl-N-toluidylformamide.

The labelled αT, 2,2',5',2"-[2',5'-$^{14}C_2$]terthienyl was synthesized by reacting DTB* with aqueous sodium sulfide in refluxing methanol. The overall yield for the synthesis of αT from formic acid by this procedure on the scale employed was as high as 26% in some preliminary runs with non-radioactive materials. It was 10-12% in the actual synthesis of αT* which is herein described, and which had a poorer yield in the first three steps than in the preliminary experiments.

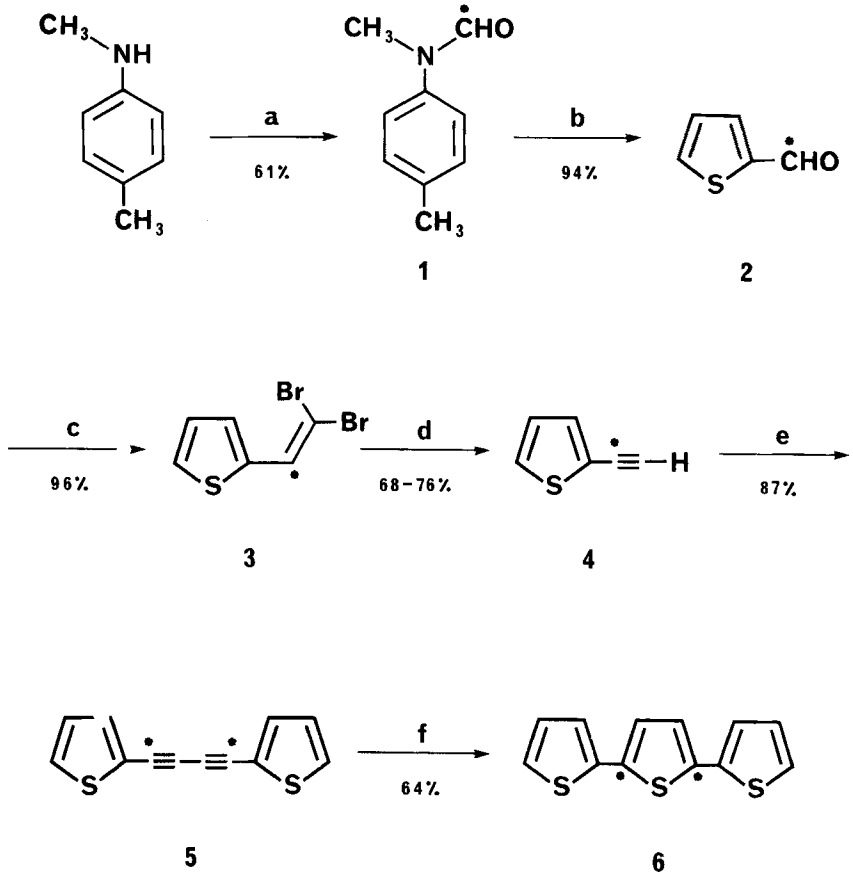

Figure 1. Scheme for the synthesis of DTB* and αT*.
Reagents: a) $H\overset{*}{C}OONa$, HCOOH; b) 1.$POCl_3$, 2. thiophene, 3. H_2O; c) $P(C_6H_5)_3$, CBr_4; d) 1. n-BuLi, 2. H_2O; e) CuCl, O_2, $(Me_2NCH_2)_2$; f) Na_2S.

EXPERIMENTAL

Melting points were determined with a Koffler apparatus and are uncorrected. ^{1}H N.M.R. spectra were recorded on Varian A-60 or T-60 spectrometers in chloroform-d with tetramethylisilane (TMS) as an internal standard. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois on non-radioactive samples produced under conditions identical to those reported for

the labelled materials. The purity of DTB* and αT* was determined by HPLC chromatography (Lichrosorb Si-60, 10μ, eluent: hexane); these products were characterized by comparison of U.V. spectra and melting points with authentic samples.

Radioactivity measurements were obtained with a Nuclear-Chicago 6819 liquid scintillation counter using a cocktail of 120 g of naphtalene, 4 g of PPO, and 75 mg. of POPOP per liter of dioxane.

Sodium[^{14}C]Formate (54.8 mCi/mmol, 1mCi) was purchased from Amersham Corp., Arlington Heights, IL, and diluted with 700 mg of 88% formic acid prior to use.

N-[^{14}C]Formyl-N-methyltoluidine (1). In a 50-ml round-bottomed flask were placed 1.210 g (10 mmol) of freshly distilled N-methyltoluidine, 700 mg (13.5 mmol) of formic acid (88%), and 25 ml of toluene. The solution was magnetically stirred and distilled slowly to remove the water azeotropically. The process was continued until approximately 24 ml of distillate had been collected, then the toluene was completely removed by evaporation under vacuum (15 Torr) at room temperature. The yield evaluated by N.M.R. was 61% based on formic acid, and the crude product was satisfactory for the preparation of the aldehyde 2.

2-Thiophene[^{14}C]carboxaldehyde (2). To the crude product obtained in the previous step was added 1.300 g (8.5 mmol) of phosphorus oxychloride, and the mixture was stirred slowly for 30 min at room temperature. Freshly distilled thiophene (1 ml) was added, the mixture was warmed at 35-40 °C for 2 hr and then allowed to stand at room temperature overnight. The red, viscous solution was poured into a vigorously stirred mixture of crushed ice and water, and was extracted with five 20-ml portions of ether. The ether extracts were combined and washed twice with dilute HCl (2M, 20 ml) to remove all traces of amine. The aqueous

washings were in turn extracted twice with ether (40 ml). The combined ether extracts were washed twice with a saturated sodium bicarbonate solution (20 ml), then with water (10 ml) and dried ($MgSO_4$). The yellow oil (about 1 g) obtained by concentrating the ether solution was used without further purification.

1,1-Dibromo-2-(2-thienyl)[2-^{14}C]ethylene (3). Triphenylphosphine (5.24 g, 20 mmol) was added under nitrogen to a well stirred solution of carbon tetrabromide (3.32 g, 10 mmol) in dry dichloromethane (25 ml distilled from P_2O_5) placed in a 50 ml, three-necked, round bottomed flask. The mixture was stirred at 0 °C for 5 min, the 2-formylthiophene from the previous step was added, and stirring was continued for 1 hr at room temperature. Pentane (10 volumes) was added to the reaction mixture, which was then filtered to remove the insoluble material, and concentrated. The insoluble fraction was treated by additional cycles of CH_2Cl_2 extraction and pentane precipitation to remove all the olefinic product. The dibromoolefin 3 was in mixture (1.660g) with unreacted triphenylphosphine in the ratio 3:1 and was used without further purification for the next step. However, a pure sample was obtained by column chromatography (silica gel 60-200 mesh, 15 g/g, eluent: hexane-$CHCl_3$ 9:1) yielding white crystals; m.p. 57-8 °C; ir (CCl_4): 1210, 860, 700 cm^{-1}; mass spec. m/e: 266, 268,270 (M^+), 186-191 (M-Br, -HBr), 108 ($M-Br_2$); n.m.r. ($CDCl_3$) 7.60 (1H,s), 7.34 (1H, dd, J=4.9 and 1.4), 7.17 (1H, dd, J=3.7 and 1.4) and 6.99 ppm (1H, dd, J=4.9 and 3.7).

Anal. Calcd. for $C_6H_4Br_2S$; C, 26.89; H, 1.50; Br, 59.64; S, 11.96. Found: C, 26.71; H, 1.48; Br, 59.66; S, 11.52.

(2-Thienyl)[1-^{14}C]acetylene (4). A solution of 0.834 g (3.36 mmol) of 3 (1.112 g of the above mixture) in 35 ml of dry ether was cooled to -78 °C under dry nitrogen, and n-butyllithium in ether (6.3 ml, 1.45 M, 9.1 mmol) was added dropwise. After stirring for 1 hr at -78 °C, the mixture was allowed to warm up to

room temperature and stirring was maintained for 1 hr longer. The mixture was poured into water (10 ml) and extracted with ether (30 ml). Drying over $MgSO_4$ followed by concentration and transfer under vacuum (0.1 Torr) furnished 0.192 g of a colorless liquid (53%); b.p. 46 °C/15mm (lit[11] 54-60 °C/20mm); n.m.r. ($CDCl_3$): 7.22 (2H,m), 6.93 (1H,dd) and 3.13 ppm (1H,s).

1,4-Di(2-thienyl)[1,4-$^{14}C_2$]butadiyne (5). To a magnetically well-stirred suspension of cuprous chloride (66 mg, 0.66 mmol) in dimethoxyethane (5 ml) in a 25-ml, two-necked, round-bottomed flask equipped with a condenser, was added 190 µl of N,N,N',N'-tetramethylethylenediamine (1.00 mmol). After 10 min at room temperature to allow the formation of the blue complex the thienylacetylene 4 from the previous step in 2-3 ml of DME was added and the mixture was warmed at 30-35 °C for 1 hr. while air was bubbled through the solution. The solution turned black rapidly. The mixture was then poured into water (30 ml) and extracted with ether (100 ml). The organic layer was washed twice with dilute HCl (20 ml) and the aqueous washing extracted again with ether (30 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated, yielding 109 mg (0.51 mmol) of crude product. Two recrystallizations from 95% ethanol gave 34 mg of 5 (over 99% pure) as pale beige needles; m.p. 92-92.5 °C (lit[6] 92 °C); U.V. (CH_3OH): λ_{max} 235 (ε17,700), 287 (ε24,000), and 354 nm (ε16,300); n.m.r. ($CDCl_3$): 7.2-7.4 (4H,m) and 7.0 (2H,dd,J=4.9 and 3.7). Concentration of the mother liquor yielded another 45 mg of practically pure 5; specific activity 0.125 mCi/mmol (calculated 0.148 mCi/mmol).

2,2',5',2"-[2',5'-$^{14}C_2$]Terthienyl (6). A mixture of 45 mg (0.21 mmol) of 5 and 300 mg of $Na_2S \cdot 9H_2O$ was dissolved in 20 ml of methanol and refluxed for 5 hr. The solution was cooled to room temperature and evaporated to dryness. The crude product was washed with water, filtered and recrystallized in 95% ethanol,

yielding 24 mg (0.10 mmol) of 6 (over 99% pure) as yellow plates; m.p. 93.5-94.5 °C (lit[6] 95 °C); U.V. (CH_3OH): λ_{max} 254 (ε 7,100) and 350 nm (ε 21,300); n.m.r. ($CDCl_3$): 6.95-7.25 (m); specific activity 0.128 mCi/mmol (theoretical value: 0.148 mCi/mmol). Anal. Calcd. for $C_{12}H_8S_3$: C, 58.08; H, 3.24; S, 38.72; Found: C, 57.86; H, 3.29; S, 38.44.

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