Photochemical Synthesis of Bithienyl Derivatives

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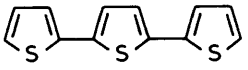
The application of a photochemical arylation of thienyl derivatives to the synthesis of bithienyl compounds is reported. The syntheses of 5-phenyl-2-propynylthiophene and 5-but-3-en-1-ynyl-2,2'-bithienyl are described using as starting materials a phenylthienyl and a bithienyl derivative obtained by this method. Furthermore, the photochemical synthesis of halogenobithienyl ketones *via* the photochemical coupling of a halogenothiophene and 2-acetyl-5-iodothiophene is described. This methodology furnishes a new approach to the synthesis of natural bithienyls. All the synthesized compounds are singlet oxygen photosensitizers, and are, therefore, potentially bioactive compounds.

Bithienyls and terthienyls were first isolated in *Tagetes minuta*;[1,2] later on, these compounds, biogenetically related to the natural acetylenes, were isolated in numerous members of the genus *Compositae*. The nematocidal properties of compounds of type (**1**) have been well known since 1958; however,



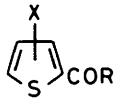
(**1**)

they were not used for this purpose because of their inactivity in soil tests.[3,4] Only recently Gommers[5] showed that the nematocidal activity of α-terthienyl increases in presence of sunlight, and since then there have been many contributions related to the bioactivity of this type of compounds in the presence of u.v. light. Thus, these compounds exhibit antibiotic activity against *Candida albicans*,[6] *Candida utilis*, and *Escherichia coli*;[7] furthermore, they show ovicidal,[8] algicidal,[9] and larvicidal properties:[10] the latter is an important feature since all larvae must return to the surface of water to breathe, and it is unlikely that they could avoid in the course of a day, the relatively small toxic dose of sunlight required for total mortality in presence of compound (**1**). They also show an antifeedant activity on the larvae of *Euxoa messoria*; when polythienyl compounds were incorporated into artificial diets, they reduced feeding and growth of the phytophagous.[11] Compound (**1**) inhibits germination[12] and growth[13] of some plants. These compounds also promote haemolysis[14] and phototoxic dermatitis:[15] however, they are unable to induce chromosome damage.[16]

In conclusion, these compounds appear to be part of the defence system of the host plant and the mechanism of their phototoxic activity has been studied extensively. Under aerobic conditions, bithienyls and terthienyls inhibit glucose-6-P dehydrogenase and acetylcholinesterase: these enzymes are usually protected against photoactivated polythienyls by singlet oxygen quenchers such as histidine, methionine, and tryptophan, indicating that the protection is a singlet oxygen mediated process.[7] It is clear therefore, that the biological inhibitory activity of polythienyls is strictly related to their singlet oxygen photosensitizer properties.

Recently we have reported[17] that halogenothiophenecarbaldehydes or ketones (**2**) can be converted into the corresponding phenyl derivatives (**3**) *via* a photochemical reaction in benzene solution.

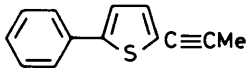
In this paper we report our first results on the synthetic utility of this reaction in the preparation of naturally occurring thiophenes and, in particular, in the synthesis of bithienyl compounds.



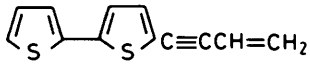
(**2**) X = halogen
(**3**) X = Ph

Results and Discussion

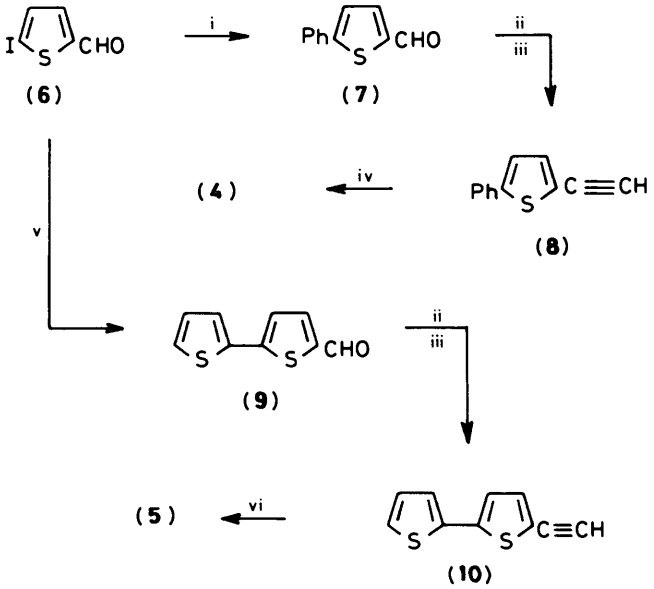
Typical members of this class of compounds are the thiophene (**4**) and the bithienyl (**5**), isolated from *Coreopsis grandiflora*[18] and from *Tagetes minuta* L.[19] respectively.



(**4**)



(**5**)



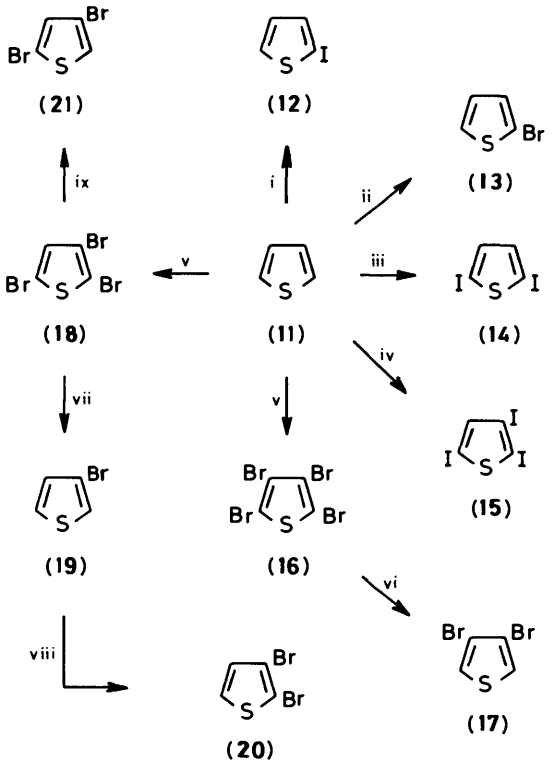
Scheme 1. *Reagents and conditions:* i, *hν*, C_6H_6; ii, Zn, Ph_3P, CBr_4; iii, BuLi, H_2O; iv, Li, Me_2SO_4; v, *hν*, C_4H_4S; vi, CH_2CHBr, $[Pd(PPh_3)_4]$, CuI, C_6H_6, $BuEt_3N^+ Cl^-$, 2.5M NaOH

By using our photochemical approach we obtained the precursors (**7**) and (**9**) in 94 and 70% yields, respectively (Scheme 1). Acetonitrile was used as the solvent on the basis of analogous reactions with furan carried out previously.[20]

Both compounds (**7**) and (**9**) can be converted into the corresponding acetylenes using Corey's procedure.[21] Thus, compound (**8**) furnished the target product on reaction with lithium and $(MeO)_2SO_2$[22] while (**10**) was converted into (**5**) by an alkenylation reaction with vinyl bromide in the presence of Pd^0 under phase-transfer conditions.[23]

However, our effective goal was the direct synthesis of more complex bithienyls by photochemical coupling of suitable thiophene precursors *via* the production of halogenobithienylcarbaldehydes or ketones that could be converted into the natural bithienyls.

In order to obtain this type of compounds we investigated the photochemical reaction of 2-acetyl-5-iodothiophene with various halogenothiophenes. The latter compounds were prepared as described in Scheme 2. The photochemical reaction was carried out in acetonitrile solution in an immersion apparatus, and in the presence of a Pyrex filter. The results are given in the Table.

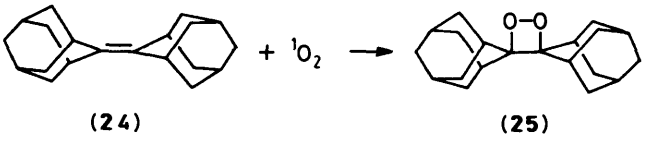


Scheme 2. *Reagents and conditions:* i, I_2, HgO; ii, Br_2, AcOH; iii, I_2, HNO_3; iv, I_2, HIO_3; v, Br_2, $CHCl_3$; vi, Mg, $(CH_2Br)_2$; vii, Zn, AcOH; viii, Br_2, dioxane; ix, BuLi, H_2O

A Pyrex filter was necessary to avoid the formation of thienyl radicals by direct irradiation of halogenothiophenes. The lower than expected yield reported for 2-iodothiophene (**12**) (Table, entry 2) is probably due to the decomposition of the product under these reaction conditions. Furthermore, the reaction works only with α-unsubstituted halogenothiophenes; when 2,5-di-iodothiophene (**14**) or 2,3,5-tri-iodothiophene (**15**) (Table, entries 4 and 5) were used no reaction was observed.

As described above, the biological properties of bithienyls are related to the ability of these compounds to act as singlet oxygen sensitizers, therefore, this feature was tested on our compounds.

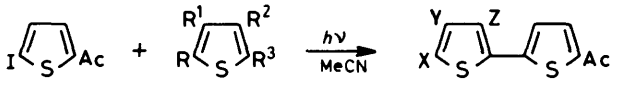
The u.v. spectrum of 5-but-3-en-1-ynyl-2,2′-bithienyl (**5**), a natural compound, gives a band at 341 nm (ε 22 930):[24] absorption at this wavelength is responsible for the photobioactivity of this compound in sunlight; our compounds showed similar absorption bands: for example, 5-acetyl-5′-iodo-2,2′-bithienyl (**23b**) has this band at 363 nm (ε 21 000), and 5-acetyl-5′-bromo-2,2′-bithienyl (**23c**) at 356 nm (ε 21 300). To monitor the formation of singlet oxygen we utilized a known reaction with biadamantanylidene which furnishes the stable endoperoxide.[25] Compound (**24**) was dissolved in a 3×10^{-5} M solution of a bithienyl compound in CH_2Cl_2. Under O_2 we irradiated this solution in the presence of a Pyrex filter for 1 h, after which time, for all the bithienyl compounds (**23a–f**), g.l.c. analysis of the mixture failed to show any starting material but indicated the formation of adamantan-2-one [derived from the thermal decomposition of compound (**25**)].



Experimental

M.p.s were obtained with a Kofler block, and with a Mettler FP81 MBC Cell equipped with a Mettler FP80 Central Processor. ^{1}H N.m.r. spectra were recorded with a Varian EM-360 spectrometer, using CCl_4 or $CDCl_3$ as solvent with Me_4Si as internal standard. I.r. spectra were obtained on a Perkin-Elmer 457 spectrometer. Mass spectra were obtained with a Kratos instrument at 70 eV, by using direct insertion at a source temperature of 150 °C. U.v. spectra were recorded with a Varian DMS-90 and Cary 291 spectrophotometers. Commer-

Table.



Entry	Thiophene	R	R^1	R^2	R^3	Product	X	Y	Z	Yields (%)
1	(**11**)	H	H	H	H	(**23a**)	H	H	H	91
2	(**12**)	I	H	H	H	(**23b**)	I	H	H	66
3	(**13**)	Br	H	H	H	(**23c**)	Br	H	H	80
4	(**14**)	I	H	H	I	—				—
5	(**15**)	I	I	H	I	—				—
6	(**17**)	H	Br	Br	H	(**23d**)	H	Br	Br	86
7	(**20**)	Br	Br	H	H	(**23e**)	Br	Br	H	94
8	(**21**)	Br	H	Br	H	(**23f**)	Br	H	Br	99.8

cial Merck silica gel and alumina were used for column chromatography. Merck pre-coated silica gel plates were used for t.l.c. G.l.c. analyses were performed on a Hewlett-Packard 5880A instrument (flame ionization detection).

Starting Materials.—5-Iodothiophene-2-carbaldehyde (**6**) was prepared from 2,5-di-iodothiophene (**14**) by reaction with BuLi and dimethylformamide (DMF).[26] Compound (**14**) was obtained from 2-iodothiophene (**12**) through a disproportionation reaction in the presence of 18-crown-6[27] or by the reaction of thiophene (**11**) with iodine and HNO_3.[28] 2-Iodothiophene (**12**) was prepared from thiophene by reaction with I_2 and HgO.[29] 2-Bromothiophene (**13**) was obtained by the bromination of (**11**) in AcOH.[30] Iodination of thiophene in the presence of iodic acid furnished tri-iodothiophene (**15**). 3,4-Dibromothiophene (**17**) was obtained from tetrabromothiophene (**16**) *via* a Grignard reaction.[31] Compound (**16**) was obtained through bromination of thiophene in $CHCl_3$.[32] Similarly we obtained 2,3,5-tribromothiophene (**18**).[33,34] By reaction with zinc in AcOH, compound (**18**) was transformed into 3-bromothiophene (**19**)[34] which was brominated with bromine in dioxane to give 2,3-dibromothiophene (**20**).[32] Lithiation of thiophene (**18**) with BuLi followed by quenching in water, furnished 2,4-dibromothiophene (**21**). 2-Acetyl-5-iodothiophene (**22**) was prepared from thiophene (**12**) by reaction with Ac_2O in presence of H_3PO_4.[35] For the physical data for 2-iodothiophene (**12**), 2,5-di-iodothiophene (**14**), 2,3,5-tri-iodothiophene (**15**), 2,3,5-tribromothiophene (**18**), 3-bromothiophene (**19**), 5-iodothiophene-2-carbaldehyde (**6**), and 2-acetyl-5-iodothiophene (**22**) see ref. 17.

2-*Bromothiophene* (**13**). B.p. 60—62 °C/30 mmHg (lit.,[30] 42—46 °C/13 mmHg); $\nu_{max.}$ 1 782, 1 710, 1 640, 1 580, 1 510, 1 405, 1 340, 1 220, 1 080, 1 043, 972, 841, 818, and 785 cm^{-1} (identical with reported spectrum[36]).

Tetrabromothiophene (**16**). M.p. 114.8—116.1 °C (lit.,[32] 114 °C).

3,4-*Dibromothiophene* (**17**). B.p. 118—122 °C/30 mmHg (lit.,[32] 108—110 °C/10 mmHg).

2,3-*Dibromothiophene* (**20**). B.p. 102—104 °C/20 mmHg (lit.,[32] 80 °C/10 mmHg); δ_H 7.08 (1 H, d, *J* 6 Hz) and 6.72 (1 H, d, *J* 6 Hz); $\nu_{max.}$ 1 503, 1 406, 1 343, 1 175, 1 151, 1 123, 1 090, 995, 980, 853, 810, and 768 cm^{-1}; *m/z* 244, 242, and 240.

2,4-*Dibromothiophene* (**21**). B.p. 105—108 °C/25 mmHg (lit.,[37] 83—85 °C/9 mmHg); δ_H 6.92 (1 H, d, *J* 1.5 Hz), and 6.80 (1 H, d, *J* 1.5 Hz); $\nu_{max.}$ 1 502, 1 405, 1 226, 1 174, 1 087, 980, 858, 820, and 810 cm^{-1}; *m/z* 244, 242, and 240.

5-*Phenylthiophene*-2-*carbaldehyde* (**7**).—5-Iodothiophene-2-carbaldehyde (**6**) (2 g) was dissolved in MeCN (270 ml) and benzene (30 ml). The mixture was outgassed with nitrogen for 1 h and then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a quartz water-jacket. After 4 h the mixture was dissolved in chloroform and washed successively with 0.1M $Na_2S_2O_3$ and then with brine. The organic phase was dried (Na_2SO_4), and evaporated to yield a crude product which was chromatographed on SiO_2. Elution with $CHCl_3$–hexane (3:2) gave pure compound (**7**) (1.48 g, 94%), m.p. 92—93 °C (lit.,[38] 93—93.5 °C) (Found: C, 70.2, H, 4.2. Calc. for $C_{11}H_8OS$: C, 70.19; H, 4.28%); δ_H 9.92 (1 H, s) and 7.6 (7 H, m); $\nu_{max.}$ 1 660, 1 449, 1 438, 1 381, 1 348, 1 107, and 1 052 cm^{-1}; *m/z* 188 (71%), 187 (51), 177 (86), 175 (100), 131 (30), 115 (30), and 73 (21).

5-*Ethynyl*-2-*phenylthiophene* (**8**).—Zn (1.3 g), Ph_3P (5.24 g), and CBr_4 (6.63 g) were suspended at room temperature in anhydrous CH_2Cl_2 (30 ml). The mixture was stirred for 48 h after which compound (**7**) (1.3 g) was added and the mixture stirred for a further 2 h. Pentane was added and the mixture filtered. The filtrate was evaporated, the crude product was dissolved in anhydrous THF (100 ml), and BuLi (1.38M; 10 ml) was added under nitrogen, at −78 °C. The mixture was stirred for 1 h at −78 °C and for a further 1 h at 25 °C after which it was diluted with water and extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and evaporated to yield a crude product which was chromatographed on SiO_2, using hexane as eluant to give pure compound (**8**) (1.1 g); δ_H 7.2 (7 H, m) and 3.20 (1 H, s); $\nu_{max.}$ 3 314, 3 080, 3 060, 3 022, 2 958, 2 922, 2 870, 2 855, 2 100, 1 598, 1 490, 1 450, 1 070, 1 026, and 950 cm^{-1}; *m/z* 184.

5-*Phenyl*-2-*propynylthiophene* (**4**).—Thiophene (**8**) (1 g) in dioxane (10 ml), was added to a solution of lithium (0.5 g) in NH_3 (liq.) (25 ml). Dioxane (20 ml) was added and the mixture heated under nitrogen at 90 °C until evolution of ammonia had ceased. $(MeO)_2SO_2$ (1 g) was added and the mixture was stirred at 90 °C for 1 h, after which it was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). Evaporation of the solvent yielded a crude product which was chromatographed on neutral Al_2O_3BI using hexane as eluant to give the pure thiophene (**4**) (0.6 g), m.p. 42—44 °C (lit.,[22] 43—44 °C) (Found: C, 78.6; H, 4.9. Calc. for $C_{13}H_{10}S$: C, 78.75; H, 5.10%); δ_H 7.6—6.8 (7 H, m) and 2.02 (3 H, s); $\nu_{max.}$ 3 080, 3 060, 3 020, 2 960, 2 920, 2 840, 2 220, 1 600, 1 490, 1 450, 1 440, 1 370, 1 260, 1 190, 1 070, 1 050, 1 025, 955, 900, 800, 750, 680, and 640 cm^{-1}; *m/z* 198.

2,2′-*Bithienyl*-5-*carbaldehyde* (**9**).—Compound (**6**) (2 g) was dissolved in MeCN (250 ml) in the presence of thiophene (15 ml). The reaction was carried out as described above to give compound (**9**) (74%), m.p. 57—58 °C (lit.,[39] 59 °C) (Found: C, 55.6; H, 3.1. Calc. for $C_9H_6OS_2$: C, 55.64; H, 3.11%); δ_H 9.57 (1 H, s), 7.45 (1 H, d, *J* 4 Hz), and 7.0 (4 H, m); $\nu_{max.}$ 1 673, 1 507, 1 452, 1 227, 1 200, 1 055, 841, and 698 cm^{-1}; *m/z* 194.

5-*Ethynyl*-2,2′-*bithienyl* (**10**).—Zn (1.3 g), Ph_3P (5.24 g), and CBr_4 (6.63 g) were suspended at room temperature in anhydrous CH_2Cl_2 (30 ml). The mixture was stirred for 48 h, after which compound (**9**) (1.3 g), dissolved in CH_2Cl_2, was added and the mixture stirred for a further 2 h. Work-up as described gave a crude product which was dissolved in anhydrous THF (100 ml) under nitrogen at −78 °C. 1.3M BuLi (15 ml) was added, and the mixture was stirred for 1 h at −78 °C and then for a further 1 h at 25 °C. It was then diluted with water and extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give a crude product which was chromatographed on SiO_2 using hexane as eluant to give compound (**20**) as an oil (710 mg), δ_H 7.2—6.8 (5 H, m) and 3.20 (1 H, s); $\nu_{max.}$ 3 300, 3 110, 3 070, 2 960, 2 930, 2 875, 2 860, 2 100, 1 618, 1 502, 1 451, 1 424, 1 200, 1 142, 1 080, 1 048, 1 032, 887, 840, 800, and 758 cm^{-1}; *m/z* 194.

5-*But*-3-*en*-1-*ynyl*-2,2′-*bithienyl* (**5**).—A deaerated solution of compound (**10**) (355 mg) and bromoethene (0.1 ml) was added to a mixture of benzyltriethylammonium chloride (7 mg), CuI (8 mg), and $[Pd(Ph_3P)_4]$[40] (23 mg). 2.5M NaOH (1.5 ml) was added and the mixture was stirred for 6 h after which NH_4Cl was added and the mixture stirred for a further 1 h. The mixture was extracted with Et_2O and the extract washed with brine, dried (Na_2SO_4), and evaporated to afford a crude product which was chromatographed on SiO_2 using hexane as eluant to give compound (**5**) as an oil in 90% yield; δ_H 7.3—6.6 (5 H, m) and 6.3—5.2 (3 H, m); $\nu_{max.}$ 2 195, 1 600, 1 505, 1 455, 1 425, 1 410, 1 290, 1 240, 1 225, 1 190, 1 070, 1 050, 1 035, 965, 915, 835, 790, and 650 cm^{-1}; *m/z* 216.

General Procedure for the Photochemical Synthesis of Halogenobithienyls.—2-Acetyl-5-iodothiophene (1 g) was

dissolved in acetonitrile (300 ml) in the presence of the halogenothiophene (5 ml). The solution was outgassed with nitrogen for 1 h and then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water-jacket. After 3 h the mixture was dissolved in chloroform and the solution washed with 0.1M $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and evaporated to yield a crude product that was chromatographed on SiO_2 using $CHCl_3$–hexane (3:2) as eluant to give the pure product (Table).

5-Acetyl-2,2′-bithienyl (**23a**). M.p. 110—111 °C (lit.,[41] 108—111 °C) (Found: C, 57.5; H, 3.7. Calc. for $C_{10}H_8OS_2$: C, 57.66; H, 3.87%); δ_H 7.43 (1 H, d, *J* 4 Hz), 7.0 (4 H, m), and 2.44 (3 H, s); $\nu_{max.}$ 1 660, 1 445, 1 361, 1 314, 1 278, and 1 075 cm^{-1}; *m/z* 208.

5-Acetyl-5′-iodo-2,2′-bithienyl (**23b**). M.p. 205—207 °C (Found: C, 36.0; H, 2.0. $C_{10}H_7IOS_2$ requires C, 35.94; H, 2.11%); δ_H 7.2 (4 H, s) and 2.5 (3 H, s); $\nu_{max.}$ 1 660, 1 401, 1 358, 1 314, 1 270, 1 070, 1 030, and 960 cm^{-1}; *m/z* 334.

5-Acetyl-5′-bromo-2,2′-bithienyl (**23c**). M.p. 160—161 °C (lit.,[41] 170—172 °C) (Found: C, 41.9; H, 2.3. Calc. for $C_{10}H_7BrOS_2$: C, 41.82; H, 2.46%); δ_H 7.42 (1 H, d, *J* 4 Hz), 6.92 (1 H, d, *J* 4 Hz), 6.90 (2 H, s), and 2.48 (3 H, s); $\nu_{max.}$ 1 655, 1 445, 1 360, 1 290, 1 270, 1 070, and 970 cm^{-1}; *m/z* 288 and 286.

5-Acetyl-3′,4′-dibromo-2,2′-bithienyl (**23d**). Viscous oil (Found: C, 38.6; H, 1.4. $C_{10}H_6Br_2OS_2$ requires C, 38.81; H, 1.65%); δ_H 7.47 (1 H, d, *J* 4 Hz), 6.92 (1 H, d, *J* 4 Hz), 7.12 (1 H, s), and 2.48 (3 H, s); $\nu_{max.}$ 1 660, 1 445, 1 405, 1 360, 1 270, 1 070, and 910 cm^{-1}; *m/z* 368, 366, and 364.

5-Acetyl-4′,5′-dibromo-2,2′-bithienyl (**23e**). Viscous oil (Found: C, 39.0; H, 1.5. $C_{10}H_6Br_2OS_2$ requires C, 38.81; H, 1.65%); δ_H 7.48 (1 H, m), 7.28 (1 H, d, *J* 4 Hz), 6.90 (1 H, d, *J* 4 Hz), and 2.50 (3 H, s); $\nu_{max.}$ 1 660, 1 445, 1 410, 1 360, 1 270, and 910 cm^{-1}; *m/z* 368, 366, and 364.

5-Acetyl-3′,5′dibromo-2,2′-bithienyl (**23f**). Viscous oil (Found: C, 37.8; H, 1.8. $C_{10}H_6Br_2OS_2$ requires C, 38.81; H, 1.65%); δ_H 7.47 (1 H, d, *J* 4 Hz), 7.18 (1 H, d, *J* 4 Hz), 6.88 (1 H, s), and 2.48 (3 H, s); $\nu_{max.}$ 1 665, 1 445, 1 415, 1 365, 1 278, and 910 cm^{-1}; *m/z* 368, 366, and 364.

Reactions of Compounds (**23a**—**f**) *with Biadamantanylidene in the Presence of Oxygen.*—Biadamantanylidene[42] (40 mg) was dissolved in a 3.0×10^{-5}M solution of a halogenobithienyl derivative (**23a**—**f**) in anhydrous CH_2Cl_2 (100 ml). The solution was irradiated in a Pyrex tube in the presence of oxygen (2 ml/min) with a high-pressure mercury arc (Helios-Italquartz). After 1 h, the mixture was analysed by g.l.c. (Carbowax; injection temperature, 250 °C; column, 205 °C).

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