Electrocyclic Aromatic Substitution by the Diazo Group. Part 5.[1] The Reactions of α-(2-Arylthienyl)diazoalkanes

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3-Diazoalkyl-2-phenyl- and 2-diazoalkyl-3-phenyl-thiophenes have been generated from tosylhydrazone sodium salts. Neither species undergoes 6π or 8π electrocyclisation reactions of the diazo group and both give only carbene-derived products. The products from the 3-diazoalkylthiophenes (1; R = H, Me) depend on the nature of R, thus, (16) gives the carbene 'dimer' and azine while (21) reacts *via* an intramolecular path to give (22). The carbenes from the 2-diazoalkylthiophenes react *via* ring cleavage to give oligomers of γ,δ-acetylenic thioaldehydes.

This work is concerned with diazo-compounds of types (1) and (2) and was carried out as part of our programme investigating the reactions of 1,3-dipolar intermediates conjugated with systems of 4 π electrons. Two pieces of earlier work provide the background: (i) diazo-compounds of types (3) and (4), analogous to (1)/(2) but having an alkenyl rather than aryl double bond in the γ,δ position, cyclise readily *via* an 8π electron 1,7 electrocyclisation to give thieno[1,2]diazepines, *e.g.* (6) from (3),[2] (ii) diazo-compounds of type (7), analogous to (1)/(2) but having a cyclopentenyl rather than a thiophene ring, undergo ring closure by both 8π and 6π electron cyclisations to give the 1,2-benzodiazepine (9) and the pyrazole (8)—which rearranges thermally to give (9)—and some (*ca.* 20%) carbene-derived product (10).[3] The reactions of (1) and (2) were studied in the hope that they would undergo 1,7 electrocyclisation and so provide a direct route to fused 1,2-benzodiazepine systems such as (12) and (13) which are structurally similar both to (14) and to a large range of fused 1,4-benzodiazepine systems such as (15) which have proved to be highly effective CNS agents.

Results and Discussion

The diazo compounds (1) and (2) were generated at *ca.* 80 °C from tosylhydrazone salt precursors in both 1,2-dimethoxyethane (DME) and cyclohexene but in the event gave no products resulting from cyclisation of the diazo group. The products from the 3-diazoalkyl compounds (1; R = H and Me) were typical of inter- and intra-molecular carbene reactions but it is of interest to note that the reaction paths depended strongly on the nature of the substituent (R) at the carbene centre. Thus the carbene in (16) gave no product *via* interaction with the adjacent phenyl group but only the azine (18) and 'dimer' (17) resulting from reaction with its diazo precursor. However the methyl substituted analogue (21) reacted only by substitution in the phenyl ring to give (22)—even in the presence of cyclohexene as a carbene trap. The failure of (21) to react *via* hydrogen migration to give (20) is also noteable since such reactions are known to be of very low activation energy and normally dominate the reactivity of methyl substituted singlet carbenes.[4] The cyclisation (21) to (22) must be very rapid. The reaction is formally a C–H insertion but it seems likely that the reaction path parallels that of the similar nitrene to carbazole reaction [5] and involves a 6π electron electrocyclisation to give (23) followed by a [1,5] sigmatropic hydrogen shift. Such a mechanism would require a formally disrotatory approach to the transition state from a conformation (24) in which a doubly occupied σ-type orbital of the carbene is conjugated with the π-system. This conformation would be favoured for carbenes with bulky substituents because of the steric interaction of R with the 4-H of the thiophene ring (25). A similar dependence of the course of reaction on the nature of R was observed for the carbene derived from (7).[3]

It appears from these results that the presence of two conjugated aromatic groups raises the activation energy for the 1,7-electrocyclisation (1)→(11) to an extent which makes it uncompetitive with carbene formation. An attempt was made to reduce this effect by replacing the benzene ring in (1) with a thiophene ring. Thiophene is known from recent work [1] to be more reactive to electrocyclic substitution than benzene but even so the diazo compound (26) failed to cyclise and gave only carbene-derived products (27), (28), and (29).

The 2-diazoalkyl thiophenes (2; R = H and Me) reacted predominantly *via* ring cleavage of the carbenes (30; R = H and Me) to give oligomers (32) of the γ,δ-acetylenic thioaldehydes (31). Similar reactions have recently been described by Shechter for furyl and thienyl carbenes.[6] The products from (30) showed similar i.r. spectral characteristics to those reported by Shechter and in addition (32; R = H) gave a strong peak in its mass spectrum at *m/z* 344 indicating the presence of the dimer of (31).

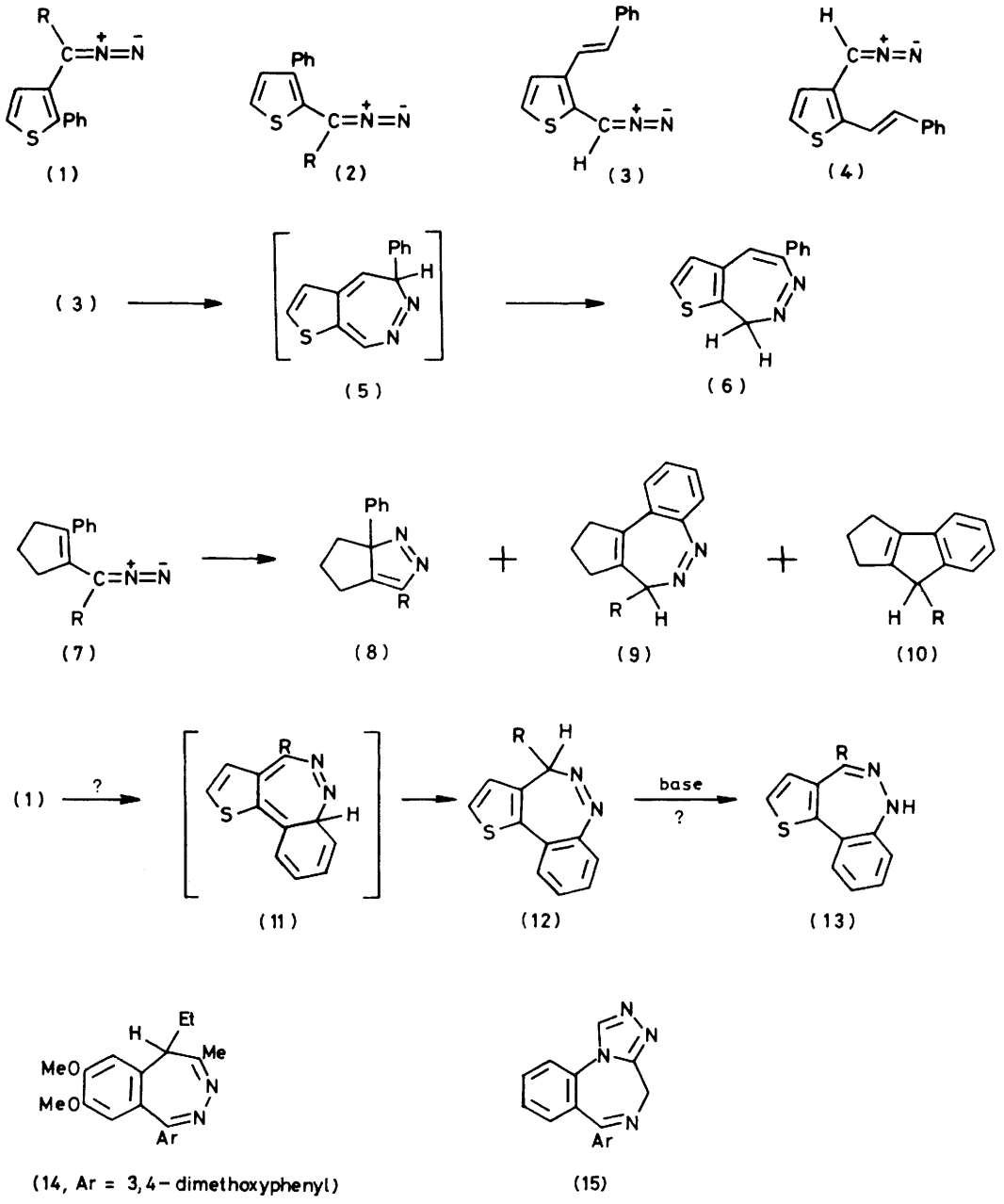
It must be concluded that although diazo groups conjugated with two alkenyl groups [7] or with one alkenyl and one aryl group [3,8] can be readily cyclised to give 1,2-diazepines, the presence of two aryl groups precludes this reaction path.

Experimental

^{1}H N.m.r. spectra were obtained on a Varian HA100 spectrometer and ^{13}C n.m.r. spectra on a Varian CFT20 spectrometer. All samples were run as solutions in deuteriochloroform and chemical shifts are recorded as p.p.m. downfield from internal tetramethylsilane. Mass spectra were obtained on an AEI MS902 instrument operated at 70 eV. Preparative chromatography was carried out by the medium pressure technique (<100 lb in^{-2}) using either 2.5 × 100 or 1.5 × 100 cm columns packed with Merck Kieselgel 60.[9] Light petroleum was the fraction b.p. 40—60 °C unless otherwise stated.

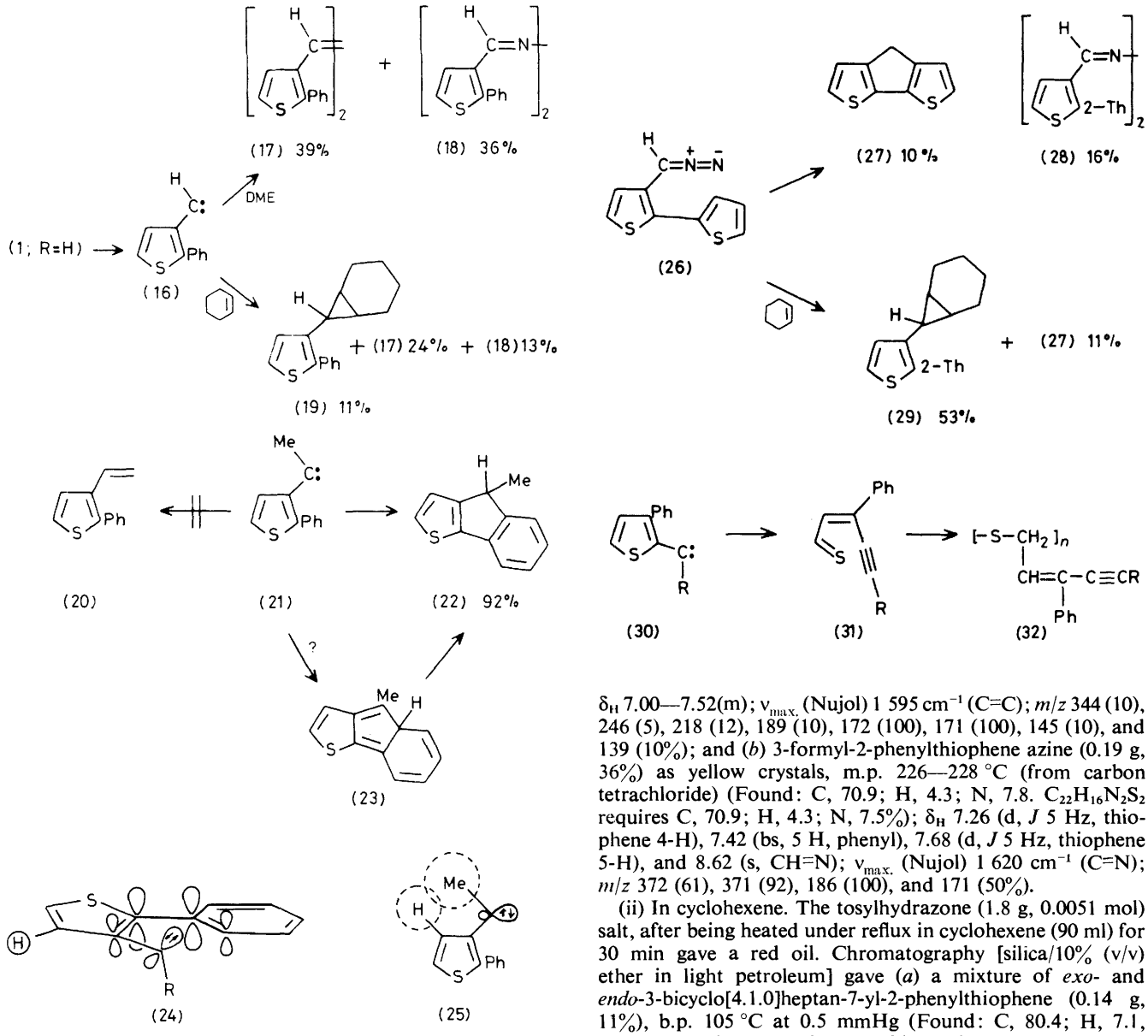
Reagents and Starting Materials.—1,2-Dimethoxyethane (DME) and cyclohexene were freshly distilled from calcium hydride under nitrogen as required. The following were prepared by literature routes: 2,3,5-tribromothiophene,[10] 2,3-dibromothiophene,[11] 3-bromothiophene,[12] 3-phenylthiophene,[13] 2-formyl-3-phenylthiophene,[14] 2-acetyl-3-phenylthiophene,[14] 3-formyl-2-phenylthiophene,[15] 3-acetyl-2-phenylthiophene,[15] 3-bromo-2,2′-bithienyl.[16]

3-Formyl-2,2′-bithienyl. A solution of n-butyl-lithium in ether (50 ml; 1.5M) was added with stirring to a solution of 3-bromo-2,2′-bithienyl (9.0 g, 0.037 mol) in ether (100 ml) at



−60 °C. After 5 min a solution of *N,N*-dimethylformamide (5.0 g, 0.065 mol) in ether (50 ml) was added and the mixture was stirred at −60 °C for 30 min and then allowed to stand at room temperature overnight. The reaction mixture was poured into water, extracted with ether, and the ether solution washed successively with 1M-hydrochloric acid (150 ml), aqueous sodium hydrogencarbonate (20% w/v; 2 × 100 ml), and water (150 ml); it was then dried. The ether was evaporated under reduced pressure and the residue chromatographed on silica when elution with 20 vol% ether in light petroleum gave a yellow oil which was distilled to give 3-formyl-2,2′-bithienyl (2.5 g, 35%), b.p. 120 °C at 0.7 mmHg (Found: C, 55.5; H, 3.3. $C_9H_6OS_2$ requires C, 55.7; H, 3.1%); δ_H 6.91—7.48 (m, 5 H), and 10.00 (s, CHO); $\nu_{max.}$ (film) 1 665 cm^{-1} (C=O).

Tosylhydrazones of thienyl aldehydes and ketones. The aldehyde derivatives were prepared by mixing warm (45 °C) equimolar ethanolic solutions of the aldehyde and toluene-*p*-sulphonohydrazide and allowing the mixtures to stand, and the product crystallise, at room temperature; the reactions with ketones were carried out at reflux temperature for the time given using a few drops of hydrochloric acid as catalyst. *2-Formyl-3-phenylthiophene tosylhydrazone* (75%), m.p. 62—63.5 °C (from ethanol) (Found: C, 60.7; H, 4.5; N, 7.8. $C_{18}H_{16}N_2O_2S_2$ requires C, 60.7; H, 4.5; N, 7.8%); $\nu_{max.}$ (Nujol) 3 180 cm^{-1} (NH). *3-Formyl-2-phenylthiophene tosylhydrazone* (81%), m.p. 55—57 °C (from ethanol) (Found: C, 60.9; H, 4.5; N, 7.9. $C_{18}H_{16}N_2O_2S_2$ requires C, 60.7; H, 4.5; N, 7.8%); $\nu_{max.}$ (Nujol) 3 170 cm^{-1} (NH). *3-Formyl-2,2′-bithienyl tosylhydrazone* (*ca.* 95%), a yellow noncrystalline solid, m.p. 152—156 °C which could not be crystallised (Found: M^+, 362.019894. $C_{16}H_{14}N_2O_2S_3$ requires *M*, 362.021 739). *2-Acetyl-3-phenylthiophene tosylhydrazone* (1 h reflux) (86%), m.p. 183.5—184.5 °C (from ethanol) (Found: C, 61.7; H, 4.9; N, 7.5. $C_{18}H_{18}N_2O_2S_2$ requires C, 61.6; H, 4.9; N, 7.6%); $\nu_{max.}$ (Nujol) 3 185 cm^{-1} (NH). *3-Acetyl-2-phenylthiophene tosylhydrazone* (1.5 h reflux) (82%), m.p. 150—151 °C (from ethanol) (Found: C, 61.5; H, 5.0; N, 7.5. $C_{18}H_{18}N_2O_2S_2$



requires C, 61.6; H, 4.9; N, 7.6%); $\nu_{max.}$ (Nujol) 3 198 cm^{-1} (NH).

Preparation and Decomposition of the Tosylhydrazone Sodium Salts.—The sodium salts were prepared and dried as described previously[6] and decomposed in either 1,2-dimethoxyethane or cyclohexene under reflux, under nitrogen, in the dark. The reactions were continued for the times given until t.l.c. showed that all the reactant had been consumed and any red colour due to the diazo-compound had been discharged. After cooling, the precipitated sodium toluene-*p*-sulphinate was filtered off, the reaction solvent evaporated off under reduced pressure, and the other products isolated as described.

3-*Formyl*-2-*phenylthiophene tosylhydrazone.* (i) In DME. The tosylhydrazone (1.02 g, 0.0028 mol) salt after being heated under reflux in DME (45 ml) for 10 min gave a red oil. Chromatography [silica/25% (v/v) ether in light petroleum] gave (*a*) *E*-1,2-di-3-(2-phenyl)thienylethene (0.19 g, 39%) as colourless crystals, m.p. 128.5—130 °C (from ethanol) (Found: C, 76.6; H, 4.7. $C_{22}H_{16}S_2$ requires C, 76.7; H, 4.7%); δ_H 7.00—7.52(m); $\nu_{max.}$ (Nujol) 1 595 cm^{-1} (C=C); *m/z* 344 (10), 246 (5), 218 (12), 189 (10), 172 (100), 171 (100), 145 (10), and 139 (10%); and (*b*) 3-formyl-2-phenylthiophene azine (0.19 g, 36%) as yellow crystals, m.p. 226—228 °C (from carbon tetrachloride) (Found: C, 70.9; H, 4.3; N, 7.8. $C_{22}H_{16}N_2S_2$ requires C, 70.9; H, 4.3; N, 7.5%); δ_H 7.26 (d, *J* 5 Hz, thiophene 4-H), 7.42 (bs, 5 H, phenyl), 7.68 (d, *J* 5 Hz, thiophene 5-H), and 8.62 (s, CH=N); $\nu_{max.}$ (Nujol) 1 620 cm^{-1} (C=N); *m/z* 372 (61), 371 (92), 186 (100), and 171 (50%).

(ii) In cyclohexene. The tosylhydrazone (1.8 g, 0.0051 mol) salt, after being heated under reflux in cyclohexene (90 ml) for 30 min gave a red oil. Chromatography [silica/10% (v/v) ether in light petroleum] gave (*a*) a mixture of *exo*- and *endo*-3-bicyclo[4.1.0]heptan-7-yl-2-phenylthiophene (0.14 g, 11%), b.p. 105 °C at 0.5 mmHg (Found: C, 80.4; H, 7.1, $C_{17}H_{18}S$ requires C, 80.3; H, 7.1%); δ_H 0.51—2.05 (m, 11 H) and 6.56—7.72 (m, 7 H); *m/z* 254 (100), 211 (13), 197 (16), 185 (33), and 173 (83%); (*b*) *E*-1,2-bis(2-phenyl-3-thienyl)-ethene (0.21 g, 24%), m.p. 130—131 °C (from ethanol); and (*c*) 3-formyl-2-phenylthiophene azine (0.12 g, 13%), m.p. 226—228 °C.

3-*Acetyl*-2-*phenylthiophene tosylhydrazone.* (i) In DME. The tosylhydrazone (1.02 g, 0.0027 mol) salt after being heated under reflux in DME (45 ml) for 30 min gave an oil which was distilled to give 4-methyl-4*H*-indeno[1,2-b]thiophene (0.50 g, 92%), b.p. 155 °C at 0.25 mmHg (Found: C, 77.4; H, 5.5. $C_{12}H_{10}S$ requires C, 77.4; H, 5.4%); δ_H 1.35 (d, *J* 7 Hz, Me), 3.62 (q, *J* 7 Hz, 4-H), and 6.83—7.41 (m, 6 H); *m/z* 186 (100) and 171 (90%).

(ii) In cyclohexene. The tosylhydrazone (0.5 g, 0.0013 mol) salt after being heated under reflux in cyclohexene (25 ml) for 3 h gave only 4-methyl-4*H*-indeno[1,2-b]thiophene (0.21 g, 78%).

3-*Formyl*-2,2′-*bithienyl tosylhydrazone* (i). In DME. The tosylhydrazone salt (2.0 g, 0.0052 mol) after being heated under reflux in DME (90 ml) for 20 min gave a red oil. Chromatography (silica/graded elution ether [0—20% (v/v) in light petroleum] gave (*a*) 4*H*-cyclopenta[1,2-*b*:3,4-*b*′]dithiophene

(0.09 g, 10%), m.p. 71—73 °C (from ethanol) (lit.,[17] 74—75 °C); δ_H 3.50 (s, 4-CH_2), 6.97 (d, *J* 5 Hz, 2 H), 7.11 (d, *J* 5 Hz, 2 H); and (*b*) 3-formyl-2,2′-bithienyl azine (0.162 g, 16%) as yellow crystals, m.p. 202—204 °C (from carbon tetrachloride) (Found: M^+, *m/z* 383.988 337. $C_{18}H_{12}N_2S_4$ requires M^+, 383.988 334); δ_H 7.02—7.71 (m, 5 H) and 8.84 (s, CH=N); $\nu_{max.}$ (Nujol) 1 615 cm^{-1} (C=N); *m/z* 384 (35), 192 (62), 174 (100), 148 (15), and 121 (30%).

(ii) In cyclohexene. The tosylhydrazone salt (1.0 g, 0.0026 mol) after being heated under reflux in cyclohexene (45 ml) for 5 h gave an oil. Chromatography as in (i) above gave (*a*) a mixture of *exo*- and *endo*-3-bicyclo[4.1.0]heptan-7-yl-2,2′-bithienyl (0.3575 g, 53%), b.p. 92 °C at 0.3 mmHg (Found: C, 69.1; H, 6.0. $C_{15}H_{16}S_2$ requires C, 69.2; H, 6.2%); δ_H 0.40—2.05 (m, 11 H), 6.53 (d, *J* 5 Hz, 1 H), and 6.92—7.30 (m, 4 H); *m/z* 260 (100), 227 (17), 217 (13), 203 (20), 191 (33), 179 (43), and 147 (14%); and (*b*) 4*H*-cyclopenta[1,2-*b*:3,4-*b*′]-dithiophene (0.05 g, 11%), m.p. 72—74 °C (from ethanol).

2-*Formyl*-3-*phenylthiophene tosylhydrazone*. (i) In DME. The tosylhydrazone (1.02 g, 0.0028 mol) salt after being heated under reflux in DME (45 ml) for 20 min gave a red oil. Chromatography (silica/light petroleum) gave a very unstable yellow oil (0.20 g, 41%) which contained a dimer of 3-phenylpent-2-en-4-yne-1-thiol (Found: M^+, *m/z* 344.068 835. $C_{22}H_{16}S_2$ requires M^+, 344.069 340); δ_H 3.55 (s, C≡CH) and 6.70—8.02 (m, 7 H); $\nu_{max.}$ (film) 3 310 (C≡CH) stretch, 2 080 cm^{-1} (C≡C); *m/z* 344 (46), 312 (100), 311 (33), 188 (26), 187 (24), 80 (61), 79 (77), 78 (51), and 77 (90%).

(ii) In cyclohexene. The tosylhydrazone (1.02 g, 0.0028 mol) salt after being heated under reflux in cyclohexene (45 ml) for 15 min gave a red oil. Chromatography (silica/light petroleum) gave (*a*) *exo*-2-bicyclo[4.1.0]heptan-7-yl-3-phenylthiophene (0.07 g, 10%), b.p. 120 °C at 0.8 mmHg (Found: M^+, *m/z* 254.112 175. $C_{17}H_{18}S$ requires M^+, 254.112 917); δ_H 0.60—1.98 (m, 10 H), 2.11 (t, *J* 8 Hz, 1 H), and 7.00—7.62 (m, 7 H); *m/z* 254 (100), 211 (16), 197 (28), 186 (25), 185 (72), 184 (25), 173 (47), and 171 (28%); (*b*) *endo*-2-bicyclo[4.1.0]heptan-7-yl-3-phenylthiophene (0.13 g, 19%), b.p. 120 °C at 0.8 mmHg (Found: C, 80.5; H, 6.8. $C_{17}H_{18}S$ requires C, 80.3; H, 7.1%); δ_H 0.95—2.12 (m, 11 H) and 6.88—7.55 (m, 7 H); *m/z* 254 (100), 211 (17), 197 (30), 186 (28), 185 (73), 184 (33), 173 (100), and 171 (53%); (*c*) the dimer of 3-phenylpent-2-en-4-yne-1-thiol (0.19 g, 39%).

2-*Acetyl*-3-*phenylthiophene tosylhydrazone* (i) In DME. The tosylhydrazone (1.02 g, 0.0027 mol) salt after being heated under reflux in DME (45 ml) for 4 h gave a black gum. Chromatography (silica/ether) gave a very unstable yellow oil which contained a dimer of 3-phenylhex-2-en-4-yne-1-thiol (0.24 g, 48%) (Found: M^+, *m/z* 372.681 956. $C_{24}H_{20}S_2$ requires M^+, 372.682 160); δ_H 1.87 (s, CH_3) and 6.47—7.68 (m, 7 H); $\nu_{max.}$ (film) 2 210 cm^{-1} (C≡C); *m/z* 372 (6), 340 (100), 352 (21), 310 (20), 292 (12), 211 (10), 184 (14), 115 (16), 91 (16), and 77 (16%).

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