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Cyclization of Phenyl 2,2′-Bithienyl-3-yl Carbene

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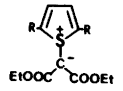
Bamford-Stevens reaction of 3-benzoyl-2,2′-bithienyl tosylhydrazone in diglyme gives 4-phenyl-4*H*-thieno[4′,5′:4,5]cyclopenta[1,2:*b*]-thiophene *7*. Evidence of the involvement of triplet carbene is presented.

In a series of interesting papers Porter *et al.*[1] have shown that suitably substituted carbenoids react with the sulfur atom of simple thiophenes to produce stable ylides. Thus dimethyl diazomalonate reacts with thiophene and 2,5-dichlorothiophene in the presence of rhodium(II) acetate to produce the ylides *1* and *2*.



1 R = H

2 R = Cl

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As a continuation of our work on cyclopentathiophenes[2] we found it challenging to try to realize a *cyclization* of a carbene to the thiophene sulfur atom in order to generate the unknown 6a-thiapentalene *3*, a compound which may also be viewed as a cyclopenta-thiophene.

According to preliminary calculations[3] *3* represents an energy minimum and simple Hückel theory predicts aromatic stabilization due to 10 π-electrons in cyclic conjugation. From models this novel ring system is judged to be almost planar. In order to facilitate its synthesis and isolation, we decided to annelate one aromatic ring to the system and attach another to the ylidic carbon. Our first aim was therefore to attempt to prepare the derivative *4* by ring-closure of carbene *5*. In this paper we report our first results in this field.

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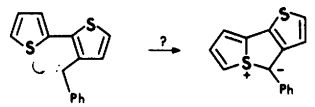

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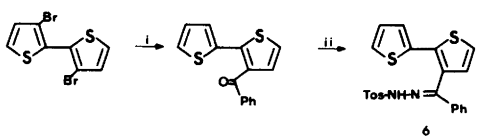
RESULTS AND DISCUSSION

We decided to generate carbene *5* by carrying out a Bamford-Stevens reaction on the corresponding tosylhydrazone *6* prepared according to standard methods as outlined in Scheme 1.

We used two different sets of reaction conditions in the Bamford-Stevens reaction. These are described in the following:

Products from thermal generation of carbene 5. The tosylhydrazone *6* was dissolved in diglyme and placed in flask A (Fig. 1). Sodium hydride was added under nitrogen at ambient temperature. After hydrogen evolution had ceased, the temperature was increased to 180 °C using an oil bath. Evolution of nitrogen from the sodium salt of *6* was complete in a few minutes. The reaction mixture was cooled and filtered into flask B. This removed the sodium sulfonate and gave a clear yellow solution. Usual work-up followed by analyses by HPLC revealed one major and one minor product.



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Scheme 1. Synthesis of the tosyl hydrazone of *6*. Reaction conditions: i. 1. 2BuLi/ether/−70 °C. 2. PhCHO. 3. H_2O, H^+. 4. Chromic acid (Jones reagent). ii. $TosNHNH_2$/2-Propanol/HCl.

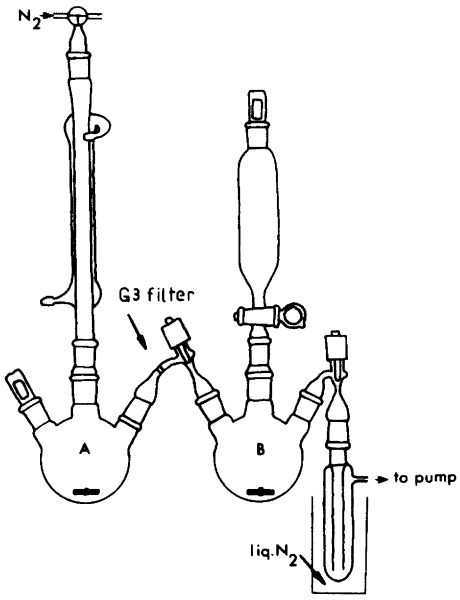
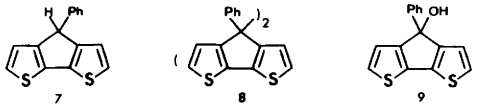


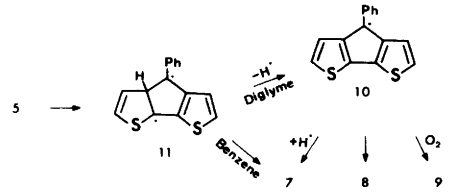
Fig. 1. Experimental arrangement for the Bamford-Stevens reactions.

The major component was identified as an analogue of 9-phenyl-fluorene: 4-phenyl-4*H*-thieno[4′,5′:4,5]cyclopenta[1,2:*b*]thiophene *7* by NMR (^{1}H and ^{13}C) and MS (see Experimental).

The minor component resisted direct identification, but by conducting the decomposition of *6* at 80 °C instead of 180 °C, the only product was this compound. Chemical ionization mass spectrometry proved invaluable in structure elucidation (together with ^{1}H and ^{13}C NMR). The results pointed unequivocally to the dimer 4,4′-bis(4-phenyl-4*H*-thieno[4′,5′:4,5]cyclopenta-[1,2:*b*]thiophene) *8* as the correct structure. Interestingly enough *8* was not formed when decomposition was conducted at the same temperature (80 °C) in benzene solution. Then only the fluorene analogue *7* was produced.



When oxygen was admitted to the diglyme solution in flask B immediately after filtration, the yellow colour disappeared and TLC showed a new product together with some of dimer *8*. This



Scheme 2. Reactions of carbene *5* with the postulation of diradical *11* and radical *10* as intermediates.

new product was isolated by preparative TLC and identified as the alcohol 4-phenyl-4*H*-thieno[4′,5′:4,5]cyclopenta[1,2:*b*]thiophene-4-ol (*9*) by NMR, MS and IR.

These results are summarized in Scheme 2.

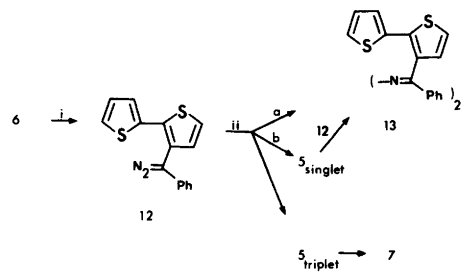
The key intermediate in the reactions in diglyme is postulated to be the phenyl "fluorenyl" radical *10* from which all three products are easily accounted for:

1. Abstraction of a hydrogen atom from the solvent produces *7*.
2. Dimerization gives *8*.
3. Reaction with triplet oxygen (air) produces a peroxy radical which decomposes to an alkoxy radical and gives alcohol *9* after abstraction of a hydrogen atom from the solvent.

The formation of *10* is assumed to occur via the carbene *5* in its triplet state producing the diradical *11* which eliminates hydrogen by abstraction of a hydrogen atom from diglyme. In benzene solution such hydrogen abstraction is not feasible and the diradical therefore rearranges directly to *7*. This accounts for the observed solvent effect.

The reason why carbene *5* did not attack the sulfur to give *4* could be due to its existence in the triplet state. It is for instance well known that diphenylcarbene has a triplet ground state.[4] In order to try to generate a carbene or carbenoid with singlet properties, we decided to make the diazo compound *12* and decompose it in the presence of rhodium(II) acetate. Such reaction conditions would furthermore correspond more closely to those used by Porter as mentioned above.

Products from the catalytic generation of a carbene or carbenoid species. When a benzene solution of *6* was treated with an equivalent amount of sodium hydride at room temperature, a slow decomposition took place. After about



Scheme 3. Postulated routes from the diazomethane derivative *12* to the mixture of *7* and the azine *13*. Reaction conditions: i. NaH/C_6H_6/ 25 °C. ii. $Rh_2(OAc)_4$, C_6H_6.

three days no starting material was detectable by HPLC and the initial faintly yellow solution had turned strongly red. After filtration and evaporation of the solvent, a red semi-crystalline solid was obtained (m.p.~25 °C). The IR spectrum gave clear evidence for the formation of the diazo compound *12* with strong absorption at 2030 cm^{-1} (neat) and ^1H NMR gave a multiplet centered at δ 7.3 ppm (aceton-d_6).

A small amount of rhodium(II) acetate was added to a solution of *12* at room temperature. After 2 h the starting material had disappeared and two products were detected by HPLC. The main product was the azine *13* and the minor component was identical with *7*. They were formed in a proportion of 3:1.

These results are summarized in Scheme 3. Two routes to the azine are envisioned: a). Dimerization of the diazo compound followed by loss of nitrogen.[5] b). A singlet carbene (or carbenoid) *5* reacts with the singlet diazo compound.[6] The first alternative seems more likely in this case as the same mixture of *7* and *13* also was produced without a catalyst after prolonged storage in the refrigerator. This shows that we have probably not succeeded in producing a carbene or carbenoid with singlet properties. This also explains our failure to detect any product resulting from a carbene attack on sulfur. Improvements will concentrate on generating differently substituted carbenes or carbenoids with the right multiplicity.

EXPERIMENTAL

The NMR spectra were recorded on Varian HA 100 and Bruker CX P200 (^1H) and Jeol FX 90 (^{13}C) instruments. The IR spectra were recorded with a Perkin-Elmer 281. The MS spectra were obtained with AEI 902 and VG Micromass 7070 F. GC analyses were carried out with a Hewlett-Pacard 5700 A. HPLC analyses were performed with Perkin-Elmer LC Serie 2 equipped with LC 75 detector and a reverse phase column (5 μm Supelcosil LC 18). Finally were the melting points obtained with a Reichert Thermopan melting point microscope and they are uncorrected.

3-Benzoyl-2,2'-bithienyl. To 3,3'-dibromo-2,2'-bithienyl (19.4 g, 60.0 mmol) dissolved in dry tetrahydrofuran (150 ml) and dry diethyl ether (300 ml) was added butyllithium in hexane (90 ml, 130 mmol, 1.44 M) at −70 °C in nitrogen atmosphere. After stirring for 30 min, benzaldehyde (3.36 g, 60.0 mmol) in dry ether (150 ml) was added during 1 h. When the addition was complete, the temperature was gradually increased to 0 °C. The reaction mixture was then hydrolyzed with an aqueous solution of ammonium chloride and the pH adjusted to about 5. The ether phase was separated and dried ($MgSO_4$). After filtration and evaporation of the ether, the residue was dissolved in acetone (900 ml) and 8 M chromic acid (Jones' reagent) was added untill the colour no longer changed from orange to green. Most of the acetone was then evaporated and the product taken up in ether. After drying and filtration, the crude product was flash chromatographed on a silica (Merck 9385) column with peth.ether/ethyl acetate (15:1) as eluent. This gave 3.6 g (22 %) of a yellow oil which resisted crystallisation.

MS [IP 70 eV; *m/e* (%, rel.int.)]: 270 (100, M), 193 (93, [M−Ph]), 149 (53), 105 (32, PhCHO), 77 (62, Ph).

^1H NMR (98 MHz, $CDCl_3$): δ 6.7−7.7 (m). IR (CS_2): 1660 (s) cm^{-1}.

3-Benzoyl-2,2'-bithienyl tosylhydrazone (6). 3-Benzoyl-2,2'-bithienyl (1.0 g, 4.0 mmol) dissolved in 2-propanol (10 ml) containing 2 % dry hydrogen chloride was placed in a 25 ml's round bottom flask equipped with a Soxlet extractor containing magnesium sulfate. Tosylhydrazine (0.79 g, 4.4 mmol) was added and the mixture was refluxed for 11 h. The reaction mixture was cooled, filtered and the solid product recrystallized from 2-propanol. This gave 1.2 g (68 %) of the hydrazone, m.p. 106−108 °C. MS[IP 70 eV; *m/e* (% rel. int.)]: 438 (8, M), 283 (20, [M−Tos]), 255 (52), 254 (100, [M−Tos−N_2]), 252 (68), 221 (80), 91 (60). ^{1}NMR (60 MHz, $CDCl_3$): δ 2.4 (3H, s), 6.5−7.8 (15H, m).

4-Phenyl-4H-thieno[4',5':4,5]cyclopenta[1,2:b]-thiophene (7). The tosylhydrazone *6* (0.15 g, 0.34 mmol) was dissolved in diglyme (15 ml) and

placed in flask A (Fig. 1). Sodium hydride (0.02 g, 0.5 mmol) 50 % in oil suspension was added and the reaction mixture heated to 180 °C for a few minutes and then cooled. After filtration into flask B (Fig. 1), the solvent was evaporated and the residue crystallized from peth.ether (40–60) to give 0.06 g (69 %) of the title compound m.p. 129–133 °C.

MS[IP 70 eV; *m/e* (% rel. int.)]: 254 (100, M), 253 (53, [M–H]), 221 (38, [M–SH]), 208 (9), 177 (8, [M–Ph]).

^{1}H NMR (200 MHz, acetone-d_6): δ 4.93 (1H, d, J 0.4 Hz), 7.01 (2H, dd, J 4.9 Hz and J 0.4 Hz), 7.25 (5H, m), 7.36 (2H, d, J 4.9 Hz).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ 49.9 (C4), 122.8 (C3,C5), 125.0 (C2,C6), 126.9 (C11), 127.5 (C9,C13), 128.8 (C10,C12), 137.9 (C7a,C7b), 139.2 (C3a,C4a), 154.4 (C8); J (C4,H4) 138.8 Hz, J (C3,H3; C5,H5) 168.0 Hz, J (C2,H2; C6,H6) 186.5 Hz, J (C11,H11) 153.3 Hz, J (C9,H9; C13,H13) 156.3 Hz, J (C10,H10; C12,H12) 162.1 Hz, J (C3,H2; C5,H6) 4.9 Hz, J (C2,H3; C6,H5) 7.8 Hz.

TLC on the crude product also showed the presence of a minor component. This was isolated by conducting the decomposition at a lower temperature (*vide infra*).

*4,4-Bis(4-phenyl-4*H*-thieno[4',5':4,5]cyclopenta[1,2:*b*]thiophene) (8).* Tosylhydrazone *6* (0.50 g, 1.1 mmol) was dissolved in diglyme (70 ml) and placed in flask A (Fig. 1) and then sodium hydride (0.07 g, 1.4 mmol) 50 % in oil suspension was added. The reaction mixture was heated to 80 °C for 1 h. The work-up procedure was similar to the one reported for the preparation of *7* except that preparative TLC (silica, peth.ether/ethyl acetate 7:1) was used to give 0.15 g (55 %) of pure *8*, m.p. 223 °C (dec.).

MS[CI, isobutane, *m/e* (% rel.int.)]: 506 (5, M), 505 (9, [M–H]), 310 (9), 297 (22), 257 (8), 256 (22), 255 (90), 254 (100), 253 (57, M/2), 221 (9,[M/2–SH]), 177 (8,[M/2–Ph]).

^{1}H NMR (60 MHz, $CDCl_3$): δ 6.20 (2H, d, J 5 Hz), 6.85 (2H, d, J 5 Hz), 6.87 (2H, d, J 5 Hz), 7.06 (2H, d, 5 Hz), 7.16 (10H, m).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ 63.1 (C4), 123.2 (C2,C6), 125.1 (C3,C5), 126.8 (C9,C13), 127.3 (C11), 131.7 (C10,C12), 136.8 (C7a,C7b), 138.2 (C3a,C4a), 153 (C8); J (C9,H9; C13,H13) 159.7 Hz, J (C10,H10; C12,H12) 157.2 Hz, J C11, H11) 156 Hz, J (C2,H3; CC6,H5) 7.8 Hz, J (C3,H2; C5,H6) 4.4 Hz, J (C9, H11; C13,H11) 4.4 Hz.

*4-Phenyl-4*H*-thieno[4',5':4,5]cyclopenta[1,2:*b*]thiophene-4-ol (9).* Tosylhydrazone *6* (0.30 g, 0.68 mmol) was dissolved in diglyme (40 ml) and placed in flask A (Fig. 1) and then sodium hydride (0.04 g, 0.8 mmol) 50 % in oil suspension was added. Decomposition was carried out at 80 °C as in the previous case. Immediately after the filtration into flask B, dry oxygen was let into the filtrate. The product was worked up by preparative TLC (silica, light petroleum–ethyl acetate 5:1) to give 0.14 g (78 %) of the title compound, m.p. 115–123 °C. MS [IP 70 eV, *m/e* (% rel.int.)]: 270 (100, M), 269 (30 [M–H]), 253 (47, [M–OH]), 237 (40, [M–SH]), 193 (30, [M–Ph]), 77 (32, Ph). ^{1}H NMR (98 MHz, $CDCl_3$): δ 2.53 (1H, s), 6.95 (2H, d, J 5.0 Hz), 7.19 (2H, d, J 5.0 Hz), 7.32 (5H, m). Addition of D_2O removed the signal at δ 2.53 ppm. IR (KBr): 3410 (m) cm^{-1}.

Phenyl 2,2'-bithienyl-3-yl diazomethane (12). Tosylhydrazone *6* (0.20 g, 0.46 mmol) was dissolved in benzene (40 ml) and placed in flask A (Fig. 1) and then sodium hydride (0.02 g, 0.45 mmol) 50 % in oil suspension was added under nitrogen with magnetical stirring. After 3 d the red solution no longer contained any starting material. The reaction mixture was filtered and the benzene solution was evaporated to give 0.11 g (85 %) of a red semi-crystalline solid, m.p. ~25 °C. ^{1}H NMR (60 MHz, acetone-d_6): δ 7.3 (m). IR (neat): 2030 (s) cm^{-1}.

Catalytic decomposition of phenyl 2,2'-bithienyl-3-yl diazomethane (12). When a small amount of rhodium(II) acetate was added to a solution of *12* (1 mg) in benzene (5 ml) at room temperature, the colour first turned more intensively red before gradually disappearing. After 2 h two products were detected by HPLC (at 254 nm) with 90 % methanol in water as eluent. The two products were separated by flash column chromatography. The main product was indentified as *phenyl 2,2'-bithienyl-3-yl azine (13).*

MS [IP 70 eV, *m/e* (% rel.int.)]: 254 (100, [$\frac{1}{2}$(M–N_2)]), 253 (65), 221 (42). MS [CI, isobutane, *m/e* (% rel.int.)]: 537 (15, [M+1]), 311 (15), 297 (27), 271 (40), 270 (28), 268 (23), 255 (100). ^{1}H NMR (200 MHz, acetone-d_6): δ 6.90 (1H, dd, J 5.1 and J 3.6 Hz), 6.90 (1H, d, J 5.3 Hz), 6.98 (1H, dd, J 3.6 and 1.2 Hz), 7.29 (3H, m), 7.31 (1H, dd, J 5.1 and J 1.2 Hz), 7.49 (2H, dd, J 8.0 and J 1.7 Hz), 7.54 (1H, d, J 5.3 Hz).

The second product was identical with *4-phenyl-4*H*-thieno[4',5':4,5]cyclopenta[1,2:*b*]-thiophene 7* according to TLC and HPLC. *13* and *7* were formed in the approximate proportion of 3:1 (due to the small scale of operation, the absolute yield was not determined).

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