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CYCLOADDITION REACTIONS OF 3-VINYLTHIOPHEN

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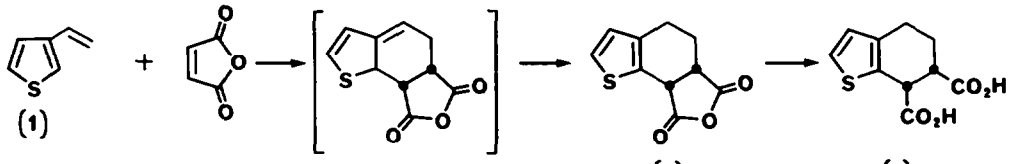
Abstract - Cycloaddition reactions between 3-vinylthiophen and the dienophiles maleic anhydride, methyl acrylate, dimethyl acetylene - dicarboxylate, and methyl propiolate give products including methyl benzo[b]thiophen-7-carboxylate (11) and its dihydroderivative (10), the 6,7-dicarboxylic acid (3), its dimethyl ester (7) and dihydroester (6); the naphtho[a,b]dithiophen (14), and the novel ethano bridged benzo[b]thiophen (15).

Interest in benzo[b]thiophen and in other condensed thiophen ring systems has been considerable in view of their pharmaceutical potential.[1] We have reported[2] that 2-vinylthiophen reacts as a diene with various dienophiles to give a number of products, in particular benzo[b]thiophens with unusual patterns of substitution in the six membered ring. We have now extended our studies to 3-vinylthiophen (1), observing a number of new types of cycloadduct. The only precedent for diene activity with 3-vinylthiophen (1) were the conventional Diels-Alder adduct from p-benzoquinone[3] and an intramolecular cycloaddition using an alkyne suitably placed in a chain substituted on the β-carbon of the vinyl group.[4]



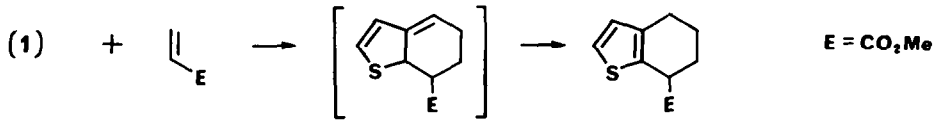
(1) (2) (3)

Scheme 1

The most simple and straightforward of our cycloaddition reactions was obtained using maleic anhydride to give, in high yield, the 1:1 adduct (2). The n.m.r. spectrum showed an AB pattern at δ6.7 and 7.2 (J = 5Hz) characteristic of a 1,2-disubstituted thiophen, and confirming that re-aromatisation of the initial adduct had taken place. Multiplets at δ3.65 and 4.35 (each 1H, major coupling 10Hz) were assigned to H6 and H7 being in good agreement with a cis (a,e) arrangement. The anhydride proved unstable to moisture and was converted for analysis into the dicarboxylic acid (3).

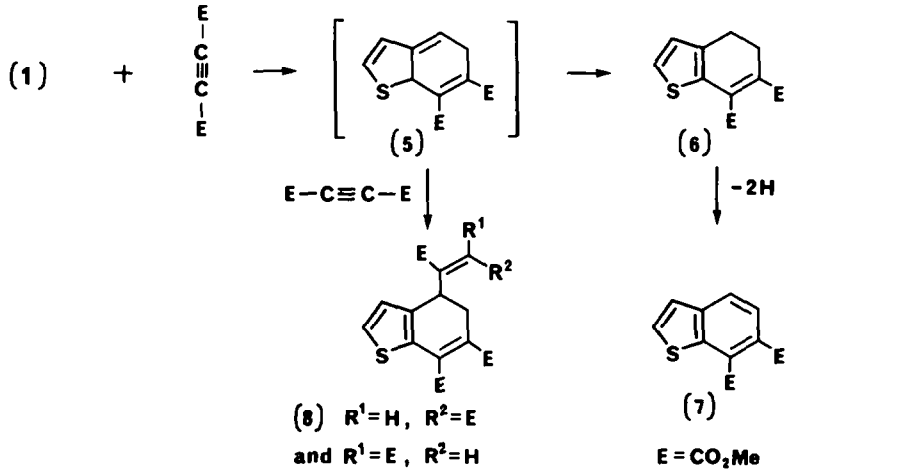
Reaction between 3-vinylthiophen (1) and methyl acrylate was slow, even at 160 °C, and only one product was isolated, in 31% yield. Analysis showed the product to be a 1:1 adduct, with a methyl singlet in the n.m.r. at δ3.6 and infrared maximum at 1750 cm^{-1}.

The AB system at δ6.5 and δ6.85 indicates that the initial adduct has again aromatized. A series of multiplets at δ1.6-2.1 (4H), 2.3-2.7 (2H), and at δ3.4-3.7 (1H, concealed by the ester singlet but revealed by addition of $Eu(fod)_3$) confirmed that the ester is in position 7, and that the cycloaddition is regiospecific, in the sense predicted by simple Hückel MO calculations, giving compound (4).



Scheme 2

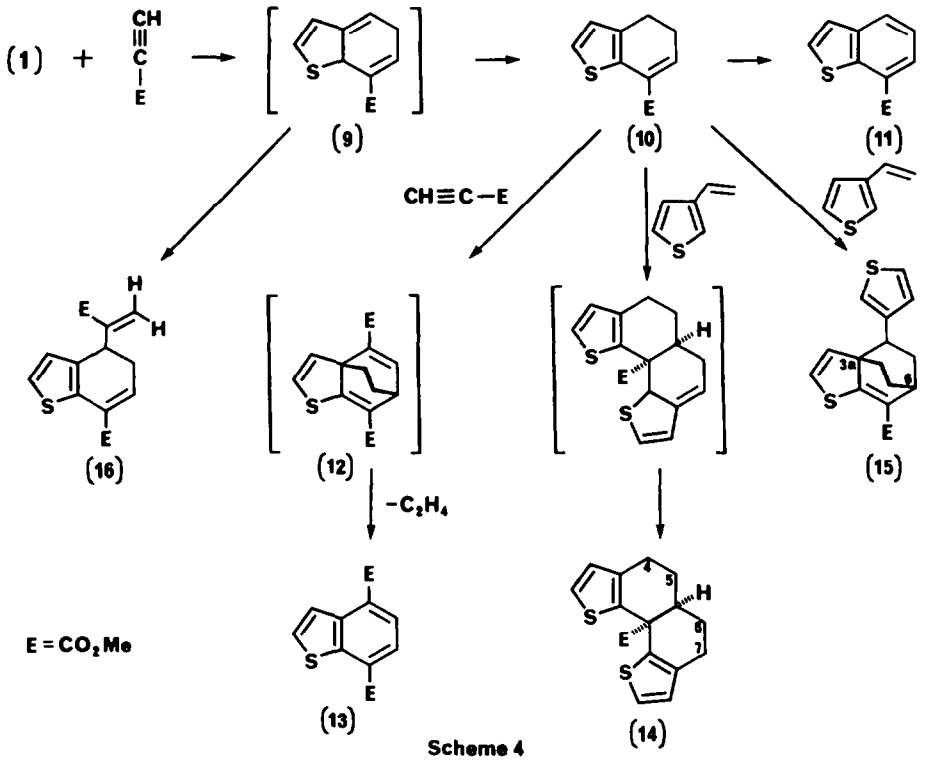
Dimethyl acetylenedicarboxylate (DMAD) reacted slowly with 3-vinylthiophen (1) to give a mixture of two major products, separated by HPLC. The first product, $C_{12}H_{12}O_4S$, was identified as dimethyl benzo[b]thiophen-6,7-dicarboxylate (7) by its simple n.m.r. spectrum which showed two AB systems in the aromatic region. One AB system at δ7.3 and 7.6 (J = 6Hz) was due to a 2,3-disubstituted thiophen, and the other, at δ7.65 and 7.75 (J = 8Hz) was due to H4 and H5. The second product was a dihydroderivative of the first, with an AB quartet (J = 6Hz) at δ6.8 and 7.25 (H2. H3), and a multiplet (4H) at δ2.8. These data accord with the structure (6) in which the initial adduct (5) has rearomatized in the thiophen ring, and dehydrogenation of ester (6) gave ester (7). A small amount of a mixture was also isolated, which we believe to be the Z and E ethenedioates (8), formed by ene addition of DMAD to the initial adduct (5); the spectrum showed a considerable similarity to that of the corresponding compounds obtained from 2-vinylthiophen and DMAD.[2]



Scheme 3

The most interesting reaction products were obtained from 3-vinylthiophen (1) and methyl propiolate. From the crude mixture by crystallization was obtained dimethyl benzo[b]thiophen-4,7-dicarboxylate (13), previously isolated in small yield from 2-vinylthiophen[2]. The diester (13) is presumably obtained by addition of a second molecule of methyl propiolate to the adduct (10), followed by retro Diels-Alder ejection of ethene from the second intermediate (12) (Scheme 4). The second product, a 1:1 adduct, obtained by p.l.c. and h.p.l.c. was the ester (10), formed by normal addition to give adduct (9) with subsequent rearomatization. We have been unable to obtain an analytically pure sample of ester (10) but the n.m.r. spectrum is quite unambiguous, showing a singlet at δ3.7 (3H, s), a thiophen AB system at δ6.65 and 7.0 (J = 6Hz) a triplet (J = 5Hz) at δ6.7 (H6), and a 4H multiplet at δ2.3-2.8. Such an adduct was not observed among the products of reaction between 2-vinylthiophen and methyl propiolate. In one experiment the fully aromatic methyl benzo[b]thiophen-7-carboxylate (11) was also isolated. The n.m.r. spectrum showed in the downfield section two double doublets (J = 8 and 1Hz) which could be assigned to H4 and H6.

The fourth adduct had a formula $C_{16}H_{16}O_2S_2$, but had only one ester group. The n.m.r. spectrum showed that the molecule had a high degree of symmetry with an AB quartet at δ6.5 and 7.0 (thiophen H3 and H2) integrating for four protons, and two multiplets at δ1.4-2.0 (4H). This adduct is formed by addition of a second molecule of vinylthiophen to the intermediate (10); of the two possible modes of cycloaddition only that producing compound (14) gives two thiophen rings with identical n.m.r. signals. The most interesting compound, of a type not previously observed with either vinlythiophen, was again of formula $C_{16}H_{16}O_2S_2$ and hence formed from two molecules of vinylthiophen and one of propiolate. In the downfield region of the n.m.r. spectrum at δ6.5-6.8 (2H) and δ6.9-7.15 (1H) were signals characteristic of a 3-substituted thiophen. At δ5.8 and 6.05 were doublets due to an AB system (J = 5Hz) which would agree well with those expected for a vinyl sulphide, leading to the conclusion that the second thiophen ring was unaromatized, with an exocyclic bond as in intermediate (12). The structure most consistent with this data is (15), derived from intermediate (10) by normal Diels-Alder addition of a second molecule of 3-vinylthiophen. Two signals in the n.m.r. spectrum, a broadened triplet at δ3.6 and a double doublet at δ3.2-3.5 (J = 5.5 and 9Hz) are assigned to bridgehead protons (H3a and H6) the latter clearly coupled to an upfield broadened doublet at δ1.8-2.0. The final compound, isolated in one experiment and characterized spectroscopically, was the α-(dihydrobenzthienyl)acrylate (16). The n.m.r. spectrum showed a downfield doublet at δ7.25 (J = 5Hz, H2), and a multiplet at δ6.75-7.05 due to the H3 and H6 signals. The very characteristic pair of singlets (one broadened) at δ6.15 and 5.15 are almost identical with those found in a similar compound from 2-vinylthiophen.[2] A triplet at δ4.15 is assigned to H4, and the rest of the spectrum consisted of two singlets (each 3H) at δ3.75 and 3.8 and a two proton multiplet at δ2.6-2.9. Thus we have been able to identify a further product from the first 1:1 adduct (9) (the product (16) of one reaction); from the rearranged 1:1 adduct (10) products in which compound (10) acts as diene (adducts (13) and (15)) or as a dienophile (compound (14)) have been isolated. Products of type (14) and (15) have not been isolated from reaction between methyl propiolate and 2-vinylthiophen.



Scheme 4

EXPERIMENTAL

M.p.s. were determined on a Kofler heated stage and are uncorrected. Column chromatography was performed on Merck silica or alumina. P.l.c. plates were 20 x 20 or 20 x 40 cm, of Merck silica gel PF_{254}. HPLC was performed on a Waters instrument, using a semi preparative Porasil column, eluting with a mixture of hexane and ethyl acetate (10:1). N.m.r. spectra were determined in CCl_4 unless otherwise stated.

1-(3-Thienyl)ethanol was prepared from 3-bromothiophen and n-butyllithium (in ether as solvent), by addition of acetaldehyde. The yield was 52%, b.p. 65-70 °C/2 mm Hg (lit.[5] b.p. 98 °C/12 mm Hg).

3-Vinylthiophen (1) was prepared from the 3-thienylethanol by distillation at atmospheric pressure as reported[3] though our yield was poor, and also by distillation through a heated (250 °C) alumina column at 50 mm Hg pressure. The vinylthiophen had b.p. 160 °C/760 mm Hg (lit.[2] b.p. 155-158 °C/760 mm Hg).

Reaction between 3-Vinylthiophen and Maleic Anhydride. - A solution of 3-vinylthiophen (1) (1.5 g) and maleic anhydride (1.4 g) in anhydrous benzene (15 ml) was boiled under reflux (18 h) then left at room temperature (24 h). Evaporation gave the anhydride (2) (2.8 g) as an oil, apparently pure by n.m.r., but giving inconsistent analyses $\delta(CDCl_3)$ 1.8-2.3 (2H, m),

2.5-2.8 (2H, m), 3.3-3.8 (1H, d of t, J = 10 and 6Hz), 4.35 (1H, d of t, J = 10 and 1Hz), 6.7 (1H, d, J = 5Hz), 7.2 (1H, d, J = 5 Hz). The anhydride was hydrolyzed in aqueous NaOH (20%) at room temperature (16 h). Acidification at ice-bath temperature gave the acid (3), (from chloroform-methanol) (0.2 g), m.p. 142-146.5 °C (Found: C, 52.5; H, 4.45. $C_{10}H_{10}O_4S$ requires C, 53.1; H, 4.55%). δ(CD_3COCD_3) 1.5-2.0 (2H, m), 2.0-2.7 (3H, m), 3.75 (1H, d, J = 6Hz, H7), 6.25 (1H, d, J = 5Hz, H3), 7.25 (1H, d, J = 5Hz, H2), 7.7 (2H, brs, CO_2H).

Reaction between 3-Vinylthiophen (1) and Methyl Acrylate. - A solution of 3-vinylthiophen (1) (0.9 g) and methyl acrylate (0.75 g) in dichloromethane (10 ml) was heated at 160 °C (sealed tube) for 3 days. Evaporation gave a crude product, purified by p.l.c. (hexane), to give methyl 4,5,6,7-tetrahydrobenzo[b]thiophen-7-carboxylate, (4) as an oil (0.5 g, 31%). (Found: C, 61.0; H, 5.9. $C_{10}H_{12}O_2S$ requires C, 61.2; H, 6.1%). ν_{max} (CCl_4) 1750 cm^{-1}. δ1.7-2.2 (4H, m), 2.4-2.8 (2H, m), 3.6-3.9 (1H, m), 3.7 (3H, s), 6.8 (1H, d, J = 5Hz, H3), 7.0 (1H, d, J = 5Hz, H2).

Reaction between 3-Vinylthiophen (1) and Dimethyl Acetylenedicarboxylate (DMAD). -

A solution of 3-vinylthiophen (1) (0.5 g) and DMAD (0.64 g) in anhydrous benzene (15 ml) was boiled and stirred under reflux (48 h) and then left at room temperature (48 h). Evaporation gave crude product (1.2 g), purified on a column of silica (eluent hexane/ethylacetate, 8:2). The first fraction was a mixture of starting materials (0.5 g). The second fraction (0.35 g) was a mixture of esters (6) and (7), separated by h.p.l.c. First eluted was dimethyl benzo[b]thiophen-6,7-dicarboxylate (7) (1.5 ml/min, retention time 29 min.), (0.1 g, 9%), identical with that obtained from ester (6) and DDQ in boiling benzene. δ3.85 (3H, s), 3.95 (3H, s), 7.3 (1H, d, J = 5Hz, H3), 7.6 (1H, d, J = 5Hz, H2), 7.4 (1H, d, J = 8Hz, H4), 7.65 (1H, d, J = 8Hz, H5). The second product eluted was dimethyl 4,5-dihydrobenzo[b]thiophen-6,7-dicarboxylate (6), (retention time 32 min), (0.1 g, 9%). (Found: C, 57.25; H, 4.8. $C_{12}H_{12}O_4S$ requires C, 57.15; H, 4.75%). δ2.6-2.9 (4H, m), 3.7 (3H, s), 3.8 (3H, s), 6.8 (1H, d, J = 5Hz, H3), 7.25 (1H, d, J = 5Hz, H2). A third fraction from the column was tentatively identified as a mixture of esters (8), having n.m.r. signals at δ2.8-3.2 (m), 3.2-4.1 (m), 3.6 (s), 3.7 (s), 3.75 (s), 3.8 (s), 5.5 (s, maleate H), 6.8 (d, J = 5Hz), 7.1 (d, J = 5Hz), 7.3 (d, J = 5Hz), 7.5 (s, fumarate H).

Reaction between 3-Vinylthiophen (1) and Methyl Propiolate. - A solution of 3-vinylthiophen (1) (2.9 g) and methyl propiolate (2.5 g) in dichloromethane (20 ml) was heated in a pressure reactor at 100 °C (5 atmospheres pressure) (75 h). Evaporation gave a crude product (4.2 g) which was treated with carbon tetrachloride, precipitating dimethyl benzo[b]thiophen-4,7-dicarboxylate (13), m.p. 137-139 °C (from petroleum) (lit.[2] m.p. 128-130 °C). Further quantities of this ester were obtained from various chromatography fractions - total yield was 12.5%. The residue after removal of CCl_4 was separated on an alumina column, (eluent petroleum/ethyl acetate 98:2) to give four major fractions. The first fraction was separated on the chromatotron (eluent petroleum, then increasing amounts of ethyl acetate) to give two compounds. The first eluted was methyl benzo[b]thiophen-7-carboxylate (11), b.p. 138 °C/0.5 mm Hg (bulb tube). (0.3 g, 6%). (Found: C, 63.1; H, 4.4. $C_{10}H_8O_2S$ requires C, 62.5; H, 4.15%). δ3.85 (3H, s), 7.0-7.5 (3H, m), 7.85 (1H, dd, J = 8 and 1Hz, H6), 7.95 (1H, dd, J = 8 and 1Hz, H4). The second compound was

methyl 2,5,5a,6,7,10-hexahydrothieno[2,3-a]thieno[3,2-h]naphthalene-10-carboxylate (14), m.p. 153-157 °C (CCl_4) (with further material from other chromatographic fractions, total yield 3.5%). (Found: C, 62.85; H, 5.25. $C_{16}H_{16}O_2S_2$ requires C, 63.15; H, 5.2%). δ1.6-2.0 (4H, m), 2.5-3.0 (5H, m), 3.65 (3H, s), 6.5 (2H, d, J = 5Hz, H3 and H8), 7.0 (2H, d, J = 5Hz, H2 and H9). The second major fraction from the alumina column was further purified by Chromatotron, giving more of compound (14), and a band which was separated by HPLC (ϕ 2 ml/min, eluent 1% ethyl acetate in hexane) to give a final sample of compound (14), and a further amount of ester (13), followed by adduct (15) (Rt 1 hr 20 min) (total yield, with subsequent fractions 0.039 g, 0.5%). Recrystallized from petroleum ether b.p. 60-80 °C, after a further purification by HPLC, the adduct (15) had an indistinct m.p., softening at 115 °C, melting at 130 °C. (Found: C, 62.6; H, 5.1. $C_{16}H_{16}O_2S_2$ requires C, 63.15; H, 5.25%). δ1.0-1.7 (4H, m), 1.8-2.0 (1H, brd, J = 8Hz), 2.05-2.3 (1H, dd, J = 11.5 and 3Hz), 3.25-3.5 (1H, dd, J = 9.7 and 5.7 Hz), 3.5-3.6 (1H, m), 3.8 (3H, s), 5.8 (1H, d, J = 5Hz), 6.1 (1H, d, J = 5Hz), 6.5-6.8 (2H, m), 6.9-7.15 (1H, dd, J = 5.5 and 3Hz9. m/z ($C_{16}H_{16}O_2S_2$ requires M^+ = 304). The third major fraction from the column was compound (13), and the fourth gave more compound (13) and, after Chromatotron and HPLC, dimethyl 4-(2-propenoato)4,5-dihydrobenzo[b]thiophen-7-carboxylate (16), (150 mg, 2%). δ2.6-2.9 (2H, m), 3.75 (3H, s), 3.8 (3H, s), 4.15 (1H, t, J = 7Hz, H4), 5.15 (1H, brs, H9) 6.15 (1H, s, H10), 6.75-7.05 (2H, m, H3 and H6), 7.25 (1H, d, J = 5Hz, H2). Still more ester (13) was obtained from the last fraction from column chromatography.

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