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A STEREOSELECTIVE SYNTHESIS OF DIALKYLAMINOMETHYL SUBSTITUTED HALOBUTADIENES VIA AMINE INDUCED RING-OPENING OF THIOPHENE-1,1-DIOXIDES

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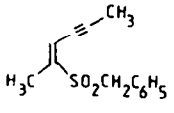
Abstract - 2,5-Dimethylthiophene-1,1-dioxide and 3-chloro-2,5-dimethylthiophene-1,1-dioxide react with aqueous piperidine at room temperature in a Michael addition fashion to give respectively 2,5-dimethyl-3-piperidino-trans-2,3-dihydrothiophene-1,1-dioxide and 3-chloro-2,5-dimethyl-4-piperidino-trans-4,5-dihydrothiophene-1,1-dioxide in good yields. The reaction of 3-chloro- and 3-bromo-2,5-dimethylthiophene-1,1-dioxide with piperidine, pyrrolidine and morpholine at 100 °C in toluene on the other hand gave only one of the four possible isomeric dialkylaminomethyl-substituted halobutadienes as main products and dialkylamino-substituted cis-2,3-dihydrothiophene-1,1-dioxides as by-products. Possible reaction paths are discussed. This useful preparation of dialkylaminomethyl substituted halobutadienes is another example of the synthetic strategy using thiophenes for the regio- and stereospecific syntheses of highly functionalized unsaturated aliphatic compounds.

This paper is dedicated to Professor Hans Wynberg on the occasion of his sixty-fifth birthday.

INTRODUCTION

Substituted thiophene-1,1-dioxides are rather stable and constitute useful starting materials for organic syntheses.[1] We have previously found that 3-bromo-2,5-dialkylthiophene-1,1-dioxides react with various organolithium derivatives in two competing ways: halogen-metal exchange followed by ring-opening leads to lithium enynesulphinates, which could be trapped with benzyl bromide to give benzylsulphonyl enynes (such as 1); addition of the organolithium derivative to the 5-carbon followed by ring-opening and bromide and sulphur dioxide elimination gave alkylated or arylated enynes (such as 2).[2] 3-Chloro-2,5-dimethylthiophene-1,1-dioxide reacted only according to the second pathway.[3]



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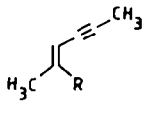
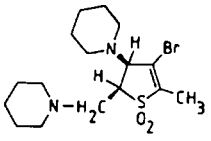


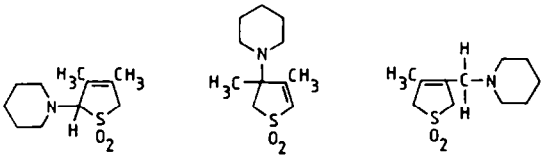
2

The reactions of thiophene-1,1-dioxides with other nucleophiles have been studied only to a very limited extent. Melles allowed 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide to react with excess piperidine in benzene at room temperature, and obtained a crystalline product,[4] to which he assigned an erroneous structure. Based on NMR spectroscopy and X-ray crystallography, we found that compound 3 was formed.[5]



3

Melles also examined the reaction of 3,4-dimethylthiophene-1,1-dioxide in excess piperidine and, assuming 1,4-addition over the diene system, assigned structure 4 to the product melting at 68-69 °C.[4] He showed that this product was different from 5, m.p. 120.5-121 °C, obtained by dehydrobromination of 3,4-dibromo-3,4-dimethyl-tetrahydrothiophene-1,1-dioxide, followed by reaction with piperidine. Wrobel and Kabzinska[6] showed twenty years later that 5 could also be obtained by the reaction of 3,4-dimethylthiophene-1,1-dioxide in aqueous piperidine, but that the product obtained in pure piperidine had not structure 4, but was 6, as proven by NMR and mass spectrometry.



4 5 6

7 8

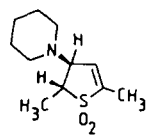
They assumed that during these reaction conditions tautomerization of 3,4-dimethylthiophene-1,1-dioxide to 7 or 8 occurred, which was attacked by the nucleophile on the exomethylene group. The reaction pattern of thiophene-1,1-dioxides with secondary amines thus is rather complex and we were therefore interested in studying this reaction with 2,5-dialkylthiophene-1,1-dioxide and its ß-halo derivatives.

RESULTS

The reaction of 2,5-dimethylthiophene-1,1-dioxide in aqueous piperidine proceeded smoothly and a 92% yield of 2,5-dimethyl-3-piperidino-2,3-trans-dihydrothiophene-1,1-dioxide (9) was obtained. The NMR spectrum at 300 MHz combined with selective decoupling experiments allowed complete assignment of shifts and coupling constants and showed that J_{23} = 4.4 Hz. A detailed and careful analysis of the spectrum of 2,3-dihydrothiophene-1,1-dioxide showed that the couplings of the CH_2-CH_2 grouping were 9.00 Hz for the cis vicinal coupling and 4.20 Hz for the trans coupling.[7] These assignments are supported by the X-ray structure determination of 3, for which a coupling constant J_{23} = 8.2 Hz has been observed.[5]

The addition in aqueous medium thus follows the same reaction patterns as for 3,4-dimethylthiophene-1,1-dioxide, being a Michael type 1,4-addition to a formal vinyl sulphone. The formation of the trans isomer is not unexpected, as in Michael additions the thermodynamically most stable isomer usually is formed.

When this reaction was carried out on 3-chloro-2,5-dimethylthiophene-1,1-dioxide, attack of piperidine occurred at the 4-position and 3-chloro-2,5-dimethyl-4-piperidino-4,5-trans-dihydrothiophene-1,1-dioxide (10) was obtained in 62% yield, as was evident from mass and its NMR spectra (J_{45} = 3.6 Hz). It is interesting to note that aqueous piperidine and organolithium compounds attack 3-chloro-2,5-dimethylthiophene-1,1-dioxide in different positions.



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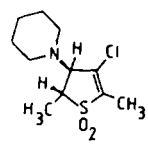
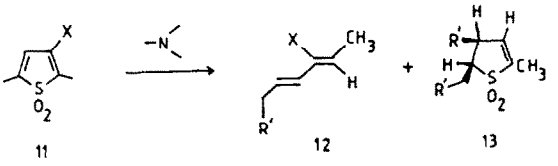


10

The reaction of 3-chloro- and 3-bromo-2,5-dimethylthiophene-1,1-dioxides (11) with piperidine, pyrrolidine and morpholine at 100 °C in toluene proceeded quite differently and gave different reaction products as shown in Scheme 1. The main products were dialkylaminomethyl-substituted halobutadienes (12), while as by-products the dialkylamine-substituted cis-2,3-dihydrothiophene-1,1-dioxides (13) were obtained. The reaction was highly stereoselective. According to GLC and NMR, only one of the four theoretically possible dienes was obtained.

The structure of the dienes was proven by NMR spectroscopy. The NMR spectrum of (12, X = H) showed two CH=CH groups with coupling constants of 15 Hz, indicating trans arrangements for the vinylic hydrogen, the isomer thus being the E,E-isomer. In the compound (12, X = Cl or Br), the coupling constants (J = 15 Hz) were present in the $N\text{-}CH_2CH{=}CH$ fragment, proving the trans-relation of the hydrogens, and by analogy with the parent compound it is assumed that the other double bond has the Z-configuration.

The configuration of the by-products (13) was evident from the magnitude of the J_{23} coupling constant (8.3-9.1 Hz). The rate of the reaction depended upon the structure of the sec. amine and was related to the base strength.



11 12 13

Entry	Time, h	X	R′	Yield %	
1	3	Cl		58	<5
2	24	Cl		48	10
3	72	Cl		42	10
4	3	Br		52	13
5	24	Br		39	14
6	72	Br		31	10
7	72	H		92[a]	<5

a glc yields

Scheme 1

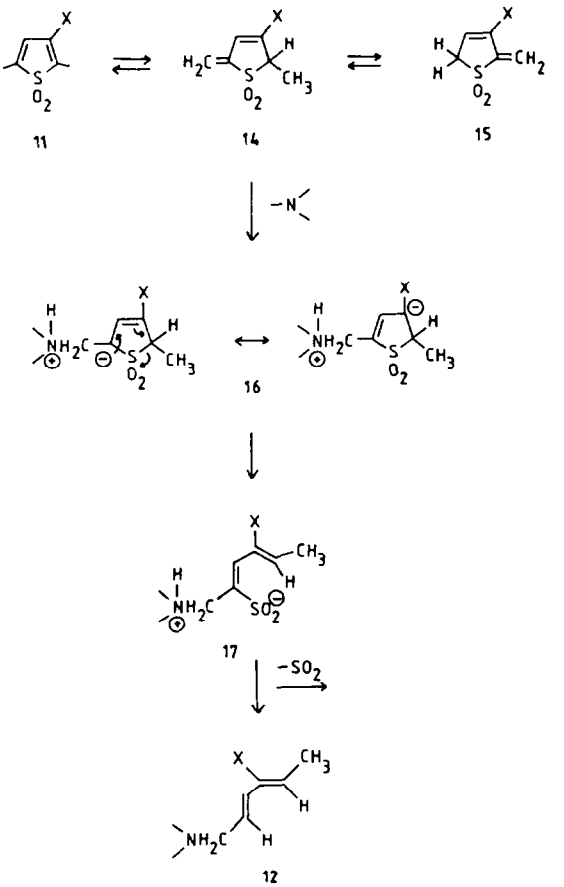
Reaction pathway

The formation of compounds 12 could be explained in a similar way as the formation of 6 from 3,4-dimethylthiophene-1,1-dioxide. Two tautomeric forms (14 and 15) might be in equilibrium with 11 in non-aqueous solutions.

Form 14 is more reactive toward sec. amines than 15 and/or is present in higher concentration and is attacked at the formal α,β-unsaturated sulphone group as indicated in Scheme 2.

There is precedent for the facile ring-opening of the intermediate anion of type 16 to butadienyl sulphinates 17, usually obtained through the treatment of 2,5-dihydrothiophene-1,1-dioxide with strong bases such as Grignard reagents[8,9] or organolithium derivatives.[10] The ring-opening of the anion from the 2,5-dihydrothiophene-1,1-dioxide occurred already at -70 °C and the butadienylsulphinate was trapped as the sulphone by alkylation with benzyl chloride.[10] The fate of the anion is however strongly dependent on the conditions under which it is formed. Thus it was recently found that 2,5-dihydro-thiophene-1,1-dioxides are easily deprotonated by sodium hydride in N,N-dimethylformamide to form the α-anion, which was stable enough to allow the preparation of 2-alkylsulpholenes, (2-alkyl-2,5-dihydrothiophene-1,1-dioxides and 2-alkyl-4,5-dihydrothiophene-1,1-dioxides).[11] Alternatively, lithium bis(trimethylsilyl)amine in THF has also been used successfully in connection with the alkylation of 2,5-dihydrothiophene-1,1-dioxides.[12]

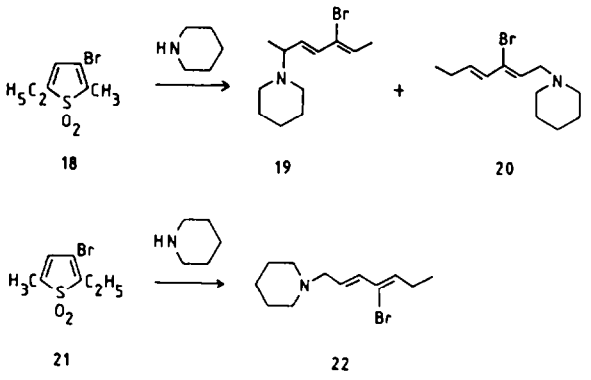
In our case sulphur dioxide is split off from 17 at the higher temperature and the vinylic carbanion is protonated to give 12.



Scheme 2

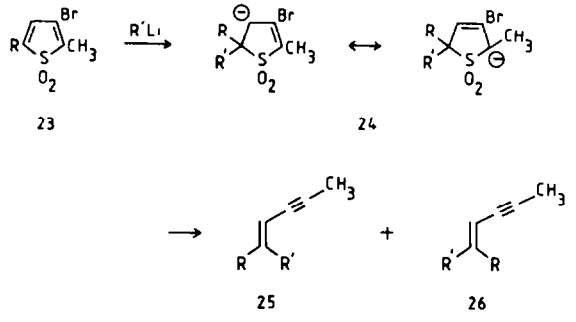
An alternative reaction path for the formation of 12, consisting in the protonation of 16 followed by chelotropic disrotatory elimination of sulphur dioxide,[13-15] seems less likely as such reactions normally require temperatures of over 200 °C, but are preparative useful as recently demonstrated by the synthesis of trans β-ocimene and α-farnesene[16] hydroindanes and hydronaphthalenes[12] and (±)-lupenine and (±)epilupine[17]. However, the recent finding that elimination of sulphur dioxide from 3,4-diphenylthio-2,5-dihydrothiophene-1,1-dioxide occurred already upon heating to 110 °C,[18] seems to indicate that some caution is necessary. There could also be the possibility that the allylic anion 16 has pyramidal configuring at C-2 and undergoes chelotropic disrotatory elimination of sulphur dioxide. In order to explain the stereochemical outcome, cis-arrangement of the aminomethyl and methyl group in 12 has to be assumed, which seems unlikely.

The regioselectivity, however, was lost when certain unsymmetrical 3-bromo-2,5-dialkylthiophene-1,1-dioxides are used. Thus, 3-bromo-5-ethyl-2-methylthiophene-1,1-dioxide (18) reacted with piperidine in toluene to give 19 and 20 in the proportions 7:3, being derived from the exocyclic tautomers of type 14 and 15, respectively (Scheme 3), while 3-bromo-2-ethyl-5-methylthiophene-1,1-dioxide (21) only reacted as one tautomer to give 22.



Scheme 3

The high stereospecificity in our reaction is somewhat unexpected. We found, for instance, that in the reaction of 3-bromo-2,5-dialkylthiophene-1,1-dioxides with alkyllithium derivatives in which anionic intermediates similar to 16 are assumed to be formed, 25 and 26 were obtained in varying proportions depending upon the nature of R and R' (Scheme 4).[2]



Scheme 4

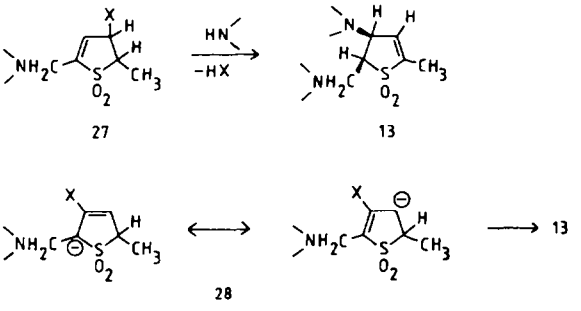
Also the reaction of 2,4-dimethyl-2,5-dihydrothiophene-1,1-dioxide with two equivalents of Grignard reagents proceeding via similar anions, a mixture of E (predominantly) and Z-isomer were formed.[9]

A similar anionic cycloreversion as for the 2,5-dihydrothiophene-1,1-dioxides has been observed for the ylide derived from 2,5-dihydrothiophenium salts, however, with different results with regard to stereospecificity. Trost et al.[19] found that the reaction of cis- and trans-2,5-dimethyl-2,5-dihydro-1-methylthiophenium hexafluorophosphates with n-butyllithium at -78^0 gave a mixture of stereoisomeric 2-methylthio-2,4-hexadienes in a ratio of 4:1 as the minor product formed via the ylide. The main product came from a complete stereospecific fragmentation reaction leading to cis, trans 2,4-hexadiene from trans-2,5-dimethyl-2,5-dihydro-1-methylthiophenium hexafluorophosphate, while the corresponding cis compound only gave trans,trans and cis,cis 2,4-hexadiene as main products. The fragmentation was shown to proceed via the sulphurane as butyl methyl sulphide was obtained as a product.

In a more recent study of the reactions of 3,4-dimethyl- and 3,4-dicarbomethoxy-2,5-dihydro-1-methylthiophenium tetrafluborate as well as trans-2,5-diethyl-3,4-dicarbomethoxy-2,5-dihydro-1-methylthiophenium tetrafluoborate with LDA in THF only one stereoisomer was obtained[20] and stereochemistry of the double bond carrying the methylthio group was assigned by the principle of least motion.[21] Assuming in our case that 17 is formed from 16 in accordance with the principle of least motion and the splitting of sulphur dioxide and protonation occurs with retention, one can understand the stereospecificity at the 2-position, while the reason for the specificity at the 5-position is not quite clear but might be due to isomerization to the thermodynamically most stable olefin during some stage of the reaction. It should perhaps be pointed out that concerted elimination in the anion 16 or in the protonated form of 16, the 2,5-dihydrothiophene-1,1-dioxide cannot explain the stereoselectivity since two diastereomeric forms (two cis-trans isomers) should be present, especially in the 2,5-dihydrothiophene-1,1-dioxides.

Several mechanistic pathways can be imagined for the formation of the by-products 13.

Protonation of 16 to 27 followed by Michael-addition of the sec. amine to the 3-position and elimination of HX could yield 13 (Scheme 5). An alternative route to 13 could be imagined via the tautomer 15, which upon reaction with the sec. amine would give 28, which upon protonation, nucleophilic substitution and isomerization of the double bond yields 13 (Scheme 5).



Scheme 5

The reaction of thiophene-1,1-dioxides with secondary amines, leading stereospecifically to dialkylamino-substituted halobutadienes is another example of the synthetic strategy, using thiophene as a template for the introduction (via aromatic substitution or metallation) of various substituents in the α- and β- positions, followed by ring-opening. We have previously extensively used this strategy for the stereospecific ring-opening of 3-thienyllithium derivatives to alkylthiovinylacetylenes (for review cf. Ref. 22). In the present case, after oxidation to the 1,1-dioxides, the ring is opened by nucleophilic attack giving the possibility for the preparation of various specifically substituted butadienes.

EXPERIMENTAL

General:

Infrared spectra were recorded on a Perkin Elmer 298 spectrometer and were in accordance with the proposed structures. ^{1}H NMR spectra were recorded on a Varian XL 300 spectrometer. Quantitative gas chromatographic analyses were performed on a Perkin Elmer 900 gas chromatograph equipped with a 2.5 m column of 3% OV 101 on Gaschrom. Q, 100-120 mesh and a flame ionization detector. Dodecane was used as internal standard. Mass spectra were obtained on a Finnigan 4021 (Data system Incos 2100) gas chromatograph mass spectrometer operating at 70 eV. Elemental microanalyses were performed at Dornis und Kolbe, Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, West Germany. Column Chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM) and hexane 68-69 °C, ethylacetate and triethylamine TEA, 15/15/1, as eluent.

Preparation of 3-Bromo-2-ethyl-5-methylthiophene-1,1-dioxide (21)

To a stirred solution of 0.05 mol (10.2 g)of 3-bromo-2-ethyl-5-methylthiophene[23] in 500 ml of dry methylene chloride, 0.15 mol (25.8 g) of m-chloroperbenzoic acid was added in portions and the solution was stirred 25 h at room temperature. After separation of m-chlorobenzoic acid, the methylene chloride phase was cooled to - 55 °C and the precipitate (benzoic acid) collected by means of a cooled glass filter. The resulting solution was washed several times with saturated bicarbonate and water and then dried with magnesium sulphate. After evaporation 9.6 g (81%) of the title compound 22 was isolated as an oil.
^{1}H-NMR ($CDCl_3$): δ 6.31 (bq, 1H, 4H J = 2.0 Hz), 2.58 (bq, 2H, CH_2, J = 7.6 Hz), 2.14 (bd, 3H,5-CH_3, J = 2.0 Hz), 1.28 (t, 3H, CH_3, J= 7.6 Hz).
Mass spectrum: m/e 236/238. Anal calcd for $C_7H_9BrO_2S$: C 35.5; H 3.83; Br 33.7. Found: C 35.5, H 3.90; Br 33.6

Diene Reactions. General Prodecure. Entries 1-9

To a solution of 10 mmol of the appropriate thiophene-1,1-dioxide in 50 ml of toluene, 40 mmol of the amine was added under vigorous stirring. For entries 1-9 the reaction temperature was 100 °C. The reaction time for entries 1, 4, 8 and 9 was three hours, for 2 and 5 one day, and for 3, 6 and 7 three days. The precipitated amine salts were filtered off. After hydrolysis, the aqueous phase was extracted three times with ether and the combined ether-toluene phase was washed with saturated bicarbonate and then dried over magnesium sulphate. After filtration samples from the organic phases were removed for GLC and MS analyses. The remaining part of the organic phases was evaporated and chromatographed for isolation of analytically pure samples of the dienes.

The crude products were chromatographed on silica gel columns using ethyl acetate, hexane and triethylamine (TEA), 15/15/1 as eluent. Mixtures of the dienes were obtained for entry 8. The isomer distribution was determined by analyses of the NMR spectra, including decoupling techniques.

Entry 1. 3-Chloro-6-piperidino-(2Z,4E)-2,4-hexadiene (12.1)

From 8.9 g (50 mmol) of 3-chloro-2,5-dimethylthiophene-1,1-dioxide[24] and following the general procedure. 5.8 g (58%) of the title compound was obtained after distillation b.p. 118-120 °C/10 mm Hg.
^{1}H NMR ($CDCl_3$): δ 6.5 (d, 1H, 4-H, J = 15 Hz), 6.08 (m, 1H, 5-H, J = 15, 6.8 Hz), 5.80 (q, 1H, 2-H, J = 6.8 Hz), 3.17 (d, 2H, 6-CH_2, J= 6.8 Hz), 1.85 (d, 3H, 1-CH_3, J = 6.8 Hz);
Mass spectrum: m/e 199/201. Anal. calcd. for $C_{11}H_{18}ClN$: C66.2, H 9.08; Cl 17.8; N 7.01. Found: C 66.2, H 9.08; Cl 17.8, N 6.97.

Entry 2. 3-Chloro-6-pyrrolidino-(2Z,4E)-2,4-hexadiene (12.2)

From 6.25 g (35 mmol) of 3-chloro-2,5-dimethylthiophene-1,1-dioxide[24] and following the general procedure. 3.1 g (48%) of the title compound was obtained after distillation b.p. 112-116 °C/12 mm Hg. ^{1}H NMR ($CDCl_3$)): δ 6.23 (d, 1H, 4-H, J = 15 Hz), 6.13 (m, 1H, 5-H, J = 15, 6.6 HZ), 5.77 (q, 1H, 2-H, J= 6.8 HZ) 3,19(d, 2H, 6-CH_2, J = 6.8 Hz), 1.85(d, 3H, 1-CH_3, J = 6.8 Hz).
Mass spectrum: m/e 185/187. Anal. calcd. for $C_{10}H_{16}ClN$: C 64.7; H 8.69; Cl 19.1; N 7.54. Found: C 64.8; H 8.74; Cl 19.0; N 7.60.

Entry 3. 3-Chloro-6-morpholino-(2Z,4E)-2,4-hexadiene (12.3)

From 1.79 g (10 mmol) of 3-chloro-2,5-dimethylthiophene-1,1-dioxide 0.85 g (42%) of the title compound was obtained following the general procedure.
^{1}H NMR ($CDCl_3$): δ 6.22(d, 1H, 4-H, J = 15 Hz) 6.04(m, 1H, 5-H, J = 15, 6.8 Hz) 5.78(q, 1H, 2-H, J = 6.8 Hz) 3.07(d, 2H, 6-CH_2, J = 6.8 Hz) 1.82(d, 3H, 1-CH_3, J = 6.8 Hz).
Mass spectrum: m/e 201/203. Anal. calcd. for $C_{10}H_{16}ClNO$: C 59.5; H 8.00; Cl 17.6; N 6.94.
Found: C 59.5; H 7.89; Cl 17.6; N 6.88.

Entry 4. 3-Bromo-6-piperidino-(2Z,4E)-2,4-hexadiene (12.4)

From 3.35 g (15 mmol) of 3-bromo-2,5-dimethylthiophene-1,1-dioxide[2] following the general procedure. 1.9 g (52%) of the title product was obtained. ^{1}H NMR ($CDCl_3$): δ 6.15(d, 1H, 4-H, J = 15 Hz) 6.09(m, 1H, 5-CH_2, J = 15, 5.6 Hz) 5.97(q, 1H, 2-H, J = 6.8 Hz) 3.06(d, 2H, 6-CH_2, J = 5.6 Hz) 1.87(d, 3H, 1-CH_3, J = 6.8 Hz).
Mass spectrum: m/e 243/245. Anal. calcd for $C_{11}H_{18}BrN$: C 54.1; H 7.43, Br 32.7; N 5.74. Found: C 54.1; H 7.61; Br 32.6; N 5.78

5-Methyl-2-piperidinomethyl-3-piperidino-cis-2,3-dihydrothiophene-1,1-dioxide (13.4) was obtained as a by-product (0.6 g, 13%), m.p. 159-160 °C.
^{1}H NMR ($CDCl_3$): δ 6.35(m, 1H, 4-H, J = 3.6, 2.0 Hz) 3.82(dm, 1H, 3-H, J = 8.6, 3.6, 1.2 Hz) 3.36(m, 1H, 2-H, J = 8.6, 6.6, 4.4 Hz) 3.09 (dd, 1H, 2-CH_2, J = 14.2, 4.4 Hz) 2.89(dd, 1H, 2-CH_2, J = 14.2, 6.6 Hz) 2.10(t, 3H, 5-CH_3, J = 2.0, 1.2 Hz).
Mass spectrum: m/e 312. Anal. calcd. for $C_{16}H_{28}N_2O_2S$: C 61.5; H 9.03; N 8.97; O 10.2; S 10.3.
Found: C 61.7; H 9.03; N 8.91; O 10.2; S 10.3

Entry 5. 3-Bromo-6-pyrrolidino-(2Z,4E)-4-Hexadiene (12.5).
From 2.23 g (10 mmol) of 3-bromo-2,5-dimethylthiophene-1,1-dioxide 0.90 g (39%) of the title compound was obtained following the general procedure.
^{1}H NMR ($CDCl_3$): δ 6.19(d,1H, 4-H, J = 15 Hz) 6.10(m, 1H, 5-H, J = 15, 6.3 Hz) 5.98(q, 1H, 2-H, J = 6.8 Hz) 3,19(d, 2H, $6CH_2$, J = 6.3 Hz) 1.87(d, 3H, 1-CH_3, J = 6.8 Hz).
Mass spectrum: m/e 229/231. Anal. calcd. for $C_{10}H_{16}BrN$: C 52.2; H 7.01; Br 34.7; N 6.09. Found: C 52.2; H 6.98; Br 34.8; N 5.99.

5-Methyl-2-pyrrolidinomethyl-3-pyrrolidino-cis-2,3-dihydrothiophene-1,1-dioxide (13.5).
was obtained as a by-product (0.35 g, 12%), m.p. 83-85 °C.
^{1}H NMR ($CDCl_3$): δ 6.22(m, 1H, 4-H, J = 4.4, 1.8 Hz) 3.82(m, 1H, 3-H, J = 9.1, 4.4, 1.6 Hz) 3.29(m, 1H, 2-H, J = 9.1, 7.8, 6.6 Hz) 3.13(dd, 1H, 2-CH_2, J = 13.2, 7.8 Hz) 3.06(dd, 1H, 2-CH_2, J = 13.2, 6.6 Hz) 2.05(t, 3H, 5-CH_3. J = 1.8. 1.8 Hz).
Mass spectrum: m/e 284. Anal. calcd. for $C_{14}H_{24}N_2O_2S$: C 59.1; H 8.51; N 9.85.
Found: C 59.1, H 8.48; N 9.74

Entry 6. 3-Bromo-6-morpholino-(2Z,4E)-hexadiene (12.6)
From 2,23 g (10 mmol) of 3-bromo-2,5-dimethylthiophene-1,1-dioxide 0.80 g (33%) of the title compound was obtained following the general procedure.
^{1}H NMR ($CDCl_3$): δ 6.19(d, 1H, 4-H, J = 15 Hz) 6.07(m, 1H, 5-H, J = 15, 6.6 Hz) 6.00(q, 1H, 2-H, J = 6.6 Hz) 3.09(d, 2H, 6-CH_2, J = 6.6 Hz) 1.87(d, 3H, 1-CH_3, J = 6.6 Hz).
Mass spectrum: m/e 245/247. Anal. calcd for $C_{10}H_{16}BrNO$: C 48.8; H 6.55; Br 32.5; N 5.69.
Found: C 48.8; H 6.60; Br 32.5; N 5.75

5-Methyl-2-morpholinomethyl-3-morpholino-cis-2,3-dihydrothiophene-1,1-dioxide (13.6). was obtained as a by-product (0.32 g, 10%), m.p. 144-146 °C.
0.32 g (10%) was obtained m.p. 144-146 C.
^{1}H NMR ($CDCl_3$): δ 6.37(q, 1H, 4-H, J = 4.1, 2.0 Hz) 3.81(dm, 1H, 3-H, J = 8.3, 4.1, 1.5 Hz) 3.41(m, 1H, 2-H, J = 8.3, 7.8, 4.6 Hz) 3.03(dd, 1H, 2-CH_2, J = 13.9, 4.6 Hz) 2.91(dd, 1H, 2-CH_2, J = 13.9, 7.8 Hz) 2.13(t, 3H, 5-CH_3, J = 2.0, 1.5 Hz).
Mass spectrum: m/e 316. Anal calcd. for $C_{14}H_{24}N_2O_4S$: C 53.1; H 7.65; N 8.86. Found: C 53.2, H 7.70; N 8.75

Entry 7. 1-Piperidino-(2E,4E)-2,4-hexadiene (12.7).
92% yield by GLC, unstable when heated or evaporated. Evaporation of the solvent under nitrogen gave 12.7 in pure form. ^{1}H NMR (C_7D_8): δ 6.12(m, 1H, 4-H, J = 15, 10.5, 2.4 Hz) 6.00(m,1H, 3-H, J = 15, 10.5, 2.7 Hz) 5.62(m,1H, 5-H, J = 15, 6.6 Hz) 5.47(m, 1H, 2-H, J = 15, 6.4 Hz) 2.89(dd, 2H, 1-CH_2. J= 6.4, 2.7 Hz) 1.60(dd, 3H, 6-CH_3, J = 6.6, 2,4 Hz).
Mass spectrum: m/e 165.

Entry 8. 3-Bromo-6-piperidino-(2Z,4E)-2,4-heptadiene (19). 3-Bromo-1-piperidino-(2Z,4E)-2,4-heptadiene (20).
From 0.48 g (2 mmol) of 3-bromo-5-ethyl-2-methylthiophene-1,1-dioxide[2] following the general procedure, 0.30 g (58%) of the titled compound was obtained. The ratio of 19/20 was 2.4.
^{1}H NMR ($CDCl_3$): 19; δ 3.06(qv, 1H, 6-CH) 1.87(d, 3H, 1-CH_3) 1.20(d, 3H, 7-CH_3)
20; δ 3.24(d,2H, 1-CH_2) 2.18(qv, 2H, 6-CH_2) 1.04(t, 3H, 7-CH_3).
The structures were determined by using decoupling techniques.

Entry 9. 4-Bromo-1-piperidino-(2E,4Z)-2,4-heptadiene (22)
From 3-bromo-2-ethyl-5-methylthiophene-1,1-dioxide following the general procedure 1.42 g (55%) of 22 was obtained. ^{1}H NMR ($CDCl_3$): δ 6.15(d, 1H, 3-H, J = 15 Hz) 6.08(dt, 1H, 2-H, J = 15, 5.7 Hz) 5.89(t, 1H, 5-H, J = 7.0 Hz) 3.06(d, 2H, 1-CH_2, J = 5.7 Hz) 1.59(qv, 2H, 6-CH_2, J= 7.6, 7.0 Hz) 1.03(t, 3H, 7-CH_3, J = 7.6 Hz). Anal. calcd for $C_{12}H_{20}BrN$: C 55.8; H 7.81; Br 30.9; N 5.43. Found: C 55.8; H 7.77; Br 30.8; N 5.48

2,5-Dimethyl-3-piperidino-trans-2,3-dihydrothiophene-1,1-dioxide (9)
To a solution of 0.5 g (3.5 mmol) of 2,5-dimethylthiophene-1,1-dioxide[25] in 10 ml of water was added 2 ml (20 mmol) of piperidine followed by vigorous stirring for three days at room temperature. The solvent was extracted three times with ether and the combined ethereal phase was washed with water,dried over magnesium sulphate and evaporated.
The title product (0,73 g, 92%) was obtained. ^{1}H NMR ($CDCl_3$): δ 6.18(m, 1H, 4-H, J = 2.8, 1.5 Hz) 3.55(m, 1H, 3-H, J = 4.4, 2.7, 2.2 Hz) 3.26(qd, 1H, 2-H, J = 7.0, 4.4 Hz) 2.06(g, 3H, 5-CH_3, J = 2.2, 1.5 Hz) 1.45(d, 3H, 2-CH_3, J = 7.0 Hz). Mass spectrum: m/e 229. Anal. calcd for $C_{11}H_{19}NO_2S$: C 57.6; H 8.35; N 6.11. Found: C 57.6.; H 8.31; N 6.19.

3-Chloro-2,5-dimethyl-4-piperidino-trans-4,5-dihydrothiophene-1,1-dioxide (10)
To a solution of 0.5 g (2.8 mmol) of 3-chloro-2,5-dimethylthiophene-1,1-dioxide[24] in 10 ml of water was added 1.6 ml (16 mmol) of piperidine, under vigorous stirring for 24 hours at room temperature. The crude product was recrystallised from water, yielding 0.45 g (62%) of the title compound, m.p. 120-122 °C. ^{1}H NMR($CDCl_3$): δ 3.62(m, 1H, 4-H, J = 3.6, 1.9 Hz) 3.42(qd, 1H, 5-H, J = 7.8, 3.6 Hz) 2.08(d, 3H, 2-CH_3, J = 1.9 Hz) 1.48(d, 3H, 5-CH_3, J = 7.5 Hz). Mass spectrum: m/e 263/265

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