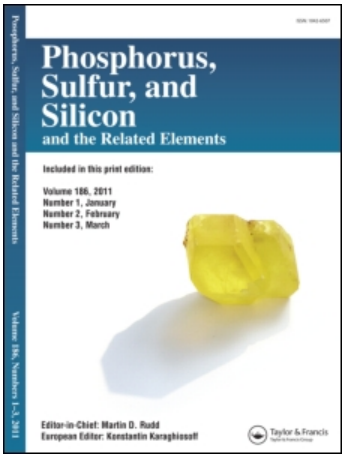

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Synthetic Uses of Ring-Opening and Cycloaddition Reactions of Thiophene-1,1-Dioxides

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SYNTHETIC USES OF RING-OPENING AND CYCLOADDITION REACTIONS OF THIOPHENE-1,1-DIOXIDES

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Abstract The reaction of 3-bromo-2,5-thiophene-1,1-dioxides with various nucleophiles has been studied. Organolithium derivatives gave hexenynes by a 1,6-Michael addition followed by ring-opening and elimination of sulfur dioxide and lithium bromide. In a competing reaction lithium enyne sulphinates were formed. Grignard reagents gave cage compounds through a series of Michael type additions, while organocopper reagents gave 3-alkyl or 3-aryl substituted derivatives.

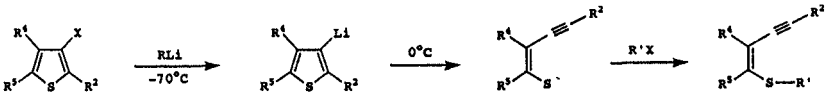
Reaction with secondary cyclic amines in refluxing benzene resulted in a 1,4-Michael type addition to the *exo*methylene tautomer providing 3-bromo-6-amino-(2Z,4E)-2,4-hexadienes as main products and dialkylaminomethyl substituted *cis* 2,3-dihydrothiophene-1,1-dioxides. Reactions in aqueous piperidine on the other hand resulted in a normal 1,4-Michael addition producing 3-bromo-2,5-dimethyl-4-piperidino-4,5-*trans*-dihydrothiophene-1,1-dioxide. The reaction of the thiophene-1,1-dioxides with thiolates and alkoxides under various conditions were also studied. New high yielding methods for the preparation of pentasubstituted and 1,2,3-trisubstituted benzenes were discovered in a tandem dimerization ring-opening reaction of 3-halo-2,5-dialkylthiophene-1,1-dioxides and 2-alkyl- and 2-aryl-3-bromothiophene-1,1-dioxides, respectively. From 3,5-dibromo-2-methyl- and 3,5-dibromo-2-phenylthiophene-1,1-dioxide as well as 4-bromo-2-methylthiophene-1,1-dioxide, benzo[b]thiophene-1,1-dioxides were obtained

INTRODUCTION

The aromaticity of thiophene makes it possible to introduce various functional groups through electrophilic substitution reactions, in addition to metalation and halogen-metal exchange with organolithium derivatives followed by reaction of the thienyllithium derivatives with various electrophiles. With the help of these reactions, a manifold of mono- to tetra-substituted derivatives can conveniently be prepared. The late Professor Gol'dfarb and coworkers at the Zelin-

sky Institute in Moscow realized that the combination of the convenient synthesis of substituted thiophenes with Raney-nickel desulfurization made possible the syntheses of various otherwise unavailable saturated hydrocarbons, alcohols, acids and amino acids. The limitations are of course that during Raney-nickel desulfurization reduction of double bonds, halogens, carbonyl and nitro groups may occur. (For review cf [1].)

In the beginning of the 1970's, we discovered that 2,5-dialkyl-3-thienyllithium derivatives were not stable at room temperature, but opened smoothly to lithium enynethiolates, which could be trapped with various electrophiles.



X = Br, I

Yields 50-70%

R^2, R^4, R^5 = alkyl, aryl heterocycles, vinyl
R^4, R^5 = OCH_3, SCH_3 etc.

The ring-opening was stereospecific. The scope and limitations of the reaction were studied in detail, and it was found that it was quite general. An exception was 3-thienyllithium derivatives with intra- and intermolecularly chelating groups in the 2-position, which did not ring-open. (For review cf [2].)

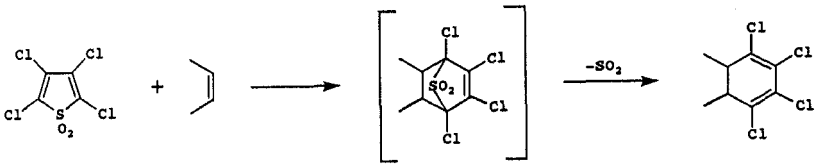
We used the ring-opening in combination with Pd(0)-catalyzed reaction to prepare a number of naturally-occurring unsaturated compounds[3-5].

In our continued attempts to use thiophene derivatives as templates for synthesis of other classes of compounds, we recently turned to thiophene-1,1-dioxides. This class of compounds was studied between 1937-1950 by Professor Backer and his coworkers in Groningen. They prepared these compounds by oxidation with peracids, especially *meta*-chloroperbenzoic acid[6-8].

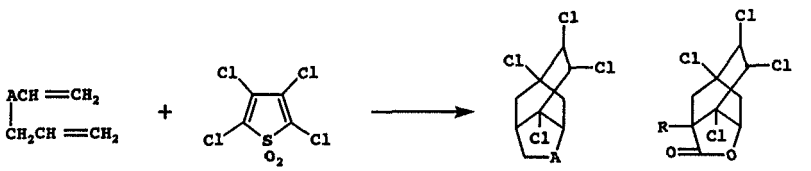
They found that thiophene-1,1-dioxide itself could not be isolated as it underwent dimerization by 4+2 cycloaddition, as shown by Bailey and Cummins[9]. This was also true for simple mono-substituted derivatives. However, most di- and higher substituted derivatives

gave reasonably stable dioxides, especially if they contained electron-donating substituents. Some reactions of these dioxides were studied by Backer and his coworkers, and by other groups. (For a recent review cf [10].)

A revival of interest in thiophene-1,1-dioxide chemistry ocurred when Dr Raasch at Dupont discovered that tetrachlorothiophene-1,1-dioxide was highly reactive in the Diels-Alder reaction, giving cycloaddition with simple olefins such as 2-butene, to yield tetrachlorocyclohexadienes after elimination of sulfur dioxide.

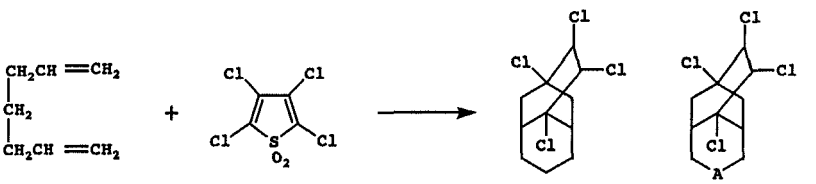


Interesting cage-like compounds were obtained using various types of diolefins, due to a second Diels-Alder reaction with the tetrachlorocyclohexadiene[11,12].



a A = O b A = S

a R = H
b R = CH_3



A = O, S, NHAc
NCH, NCH_2CH

PREPARATION OF THIOPHENE-1,1-DIOXIDES

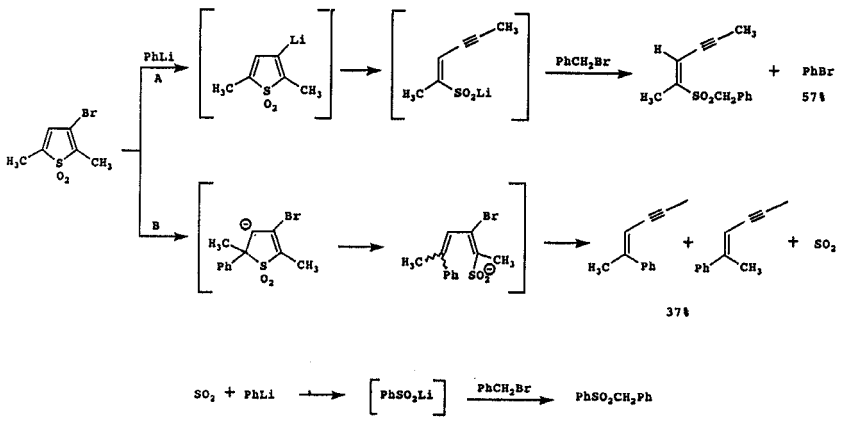
Due to the uncertain commercial availability of *meta*-chloroperbenzoic acid, we have recently studied alternative methods for

converting thiophenes to thiophene-1,1-dioxides using 3-bromo-2,5-dimethylthiophene as model compound. We found that the use of selenium dioxide and 30 % hydrogen peroxide[13] also gave the dioxide, but in somewhat lower yields. Ethyl cyanoformate and hydrogen peroxide[14] could also be used, and a 24 % yield of the dioxide was obtained. On the other hand, trimethylamine-N-oxide and catalytic amounts of osmium tetroxide[15] gave only trace amount of the dioxide.

We also found that 5-trimethylsilyl-2,3- and 2,4-disubstituted thiophene-1,1-dioxides were very stable and could be transformed to reactive 2,3- and 2,4-disubstituted thiophene-1,1-dioxides by desilylation under mild conditions.

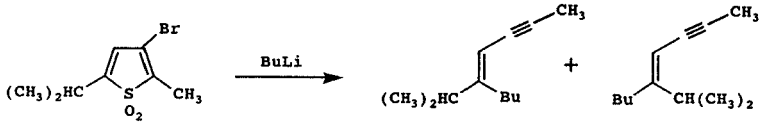
REACTION WITH ORGANOLITHIUM REAGENTS

In our first investigations, we reacted 3-bromo-2,5-dialkylthiophene-1,1-dioxides with organolithium reagents in order to compare their reactivity with those of the parent thiophenes. When the dioxides were reacted with methyl-, ethyl-, butyl-, t-butyl- and phenyllithium, two competing ring-opening reactions were found. One reaction path, via halogen-metal exchange, followed by ring-opening, led to lithium enynesulphinates, which were trapped with electrophiles such as benzyl bromide. The ring-opening was so fast that the 3-lithiothiophene-1,1-dioxide could not be trapped even at -100 °C with carbon dioxide. The other path is a Michael type 1,6-addition of the organolithium reagent to the 5-carbon of the thiophene-1,1-dioxi-



de, followed by ring-opening and loss of sulphur dioxide and lithium bromide to give enynes.

Unfortunately, the ring-opening is not stereospecific, and a mixture of enynes is formed. If the size of the 5-alkyl group is increased, the enyne with the larger group *trans* to the acetylene function is favoured.



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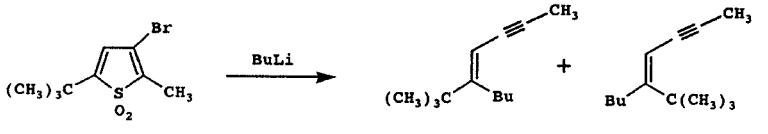
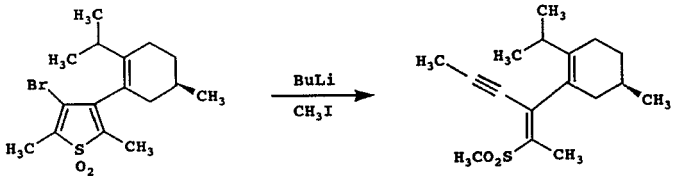


10 : 1

low total yields

The corresponding chloro derivatives, such as 3-chloro-2,5-dimethylthiophene-1,1-dioxide, gave only 1,6-addition and no halogen-metal exchange[16,17]. Tetrachlorothiophene-1,1-dioxide gave 5-butyl-6-chlorododeca-5-en-6-yne as main product. Reaction of 3-bromo-2,5-dimethyl-4-menthenylthiophene-1,1-dioxide with butyllithium gave most- ly halogen-metal exchange, and the lithium enynesulphinate which was formed was trapped with methyl iodide to give a compound showing hindered rotation[18].

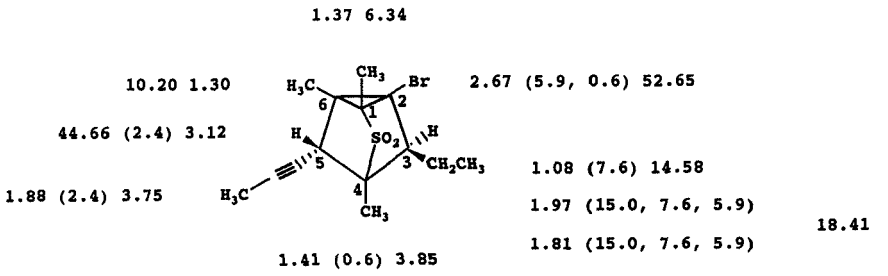


$\triangle G^{\ddagger}$ = 18,4 kcal/mol

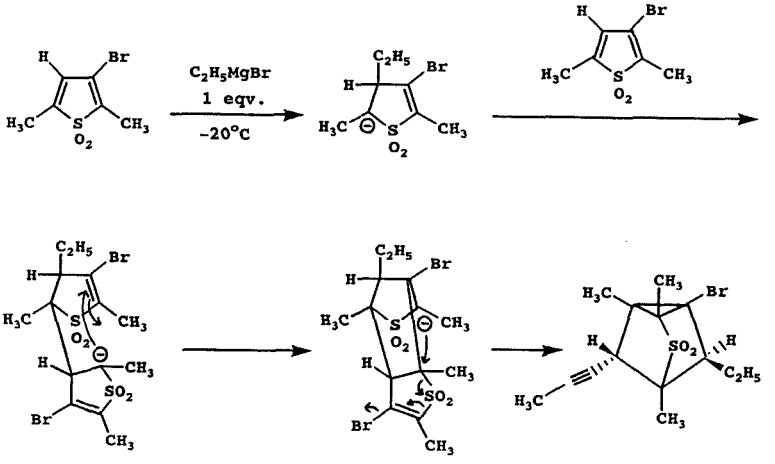
REACTION WITH GRIGNARD REAGENTS

We found that Grignard reagents reacted quite differently with thiophene-1,1-dioxides. For example the reaction of ethylmagnesium

bromide with 3-bromo-2,5-dimethylthiophene-1,1-dioxide gave a product in high yield which analyzed correctly for $C_{14}H_{19}BrO_2S$, and thus appears to be formed from two moles of the dioxide and one mole of ethylmagnesium bromide. Detailed NMR studies could not give a definite structure, so an X-ray investigation was undertaken, which showed the structure to be 2-bromo-*exo*-3-ethyl-1,4,6,-trimethyl-*endo*-(1-propynyl)-7-thiatricyclo[2,2,1,0^{26}]heptane-7,7-dioxide[19].



In contrast to organolithium reagents, the Grignard reagent primarily attacks the 4-position of a second molecule of 3-bromo-2,5-dimethylthiophene-1,1-dioxide with its 5-carbon, which after two additional carbon-carbon bond-forming reactions gives the product with elimination of sulfur dioxide and bromide ion.

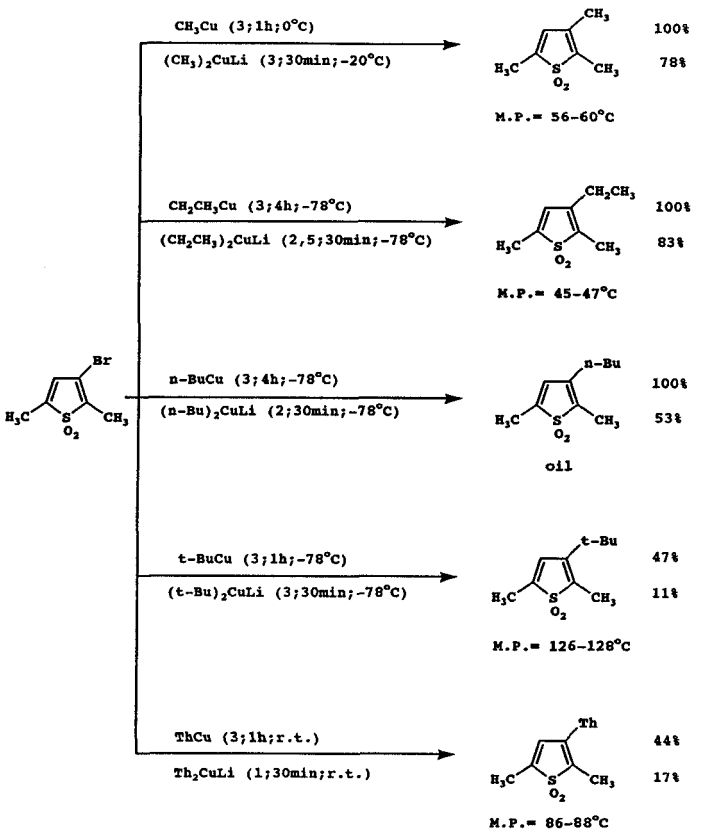


Propylmagnesium chloride reacted similarly, but no simple products were obtained from methylmagnesium iodide or phenylmagnesium

bromide. The mercury(II)sulphate-catalyzed hydration of the methylacetylenic group of the cage compound gave a somewhat unexpected result. According to the literature the carbonyl group could be formed next to a secondary or tertiary carbon. Instead, we obtained the 5-acetonyl derivative in 91 % yield.

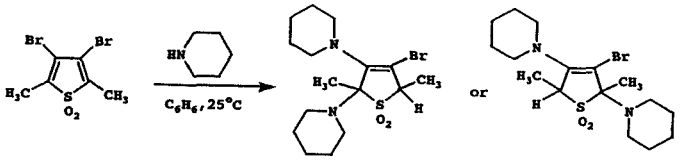
REACTION WITH ORGANOCOPPER REAGENTS

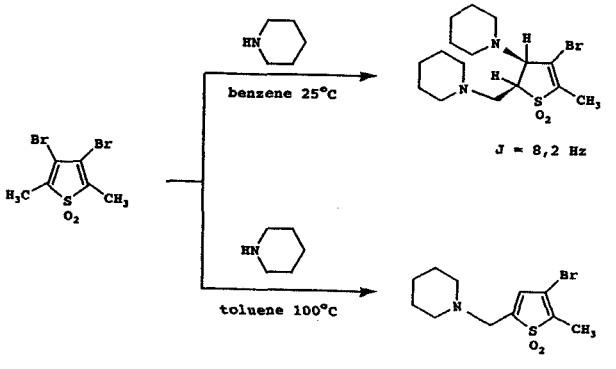
Organocopper reagents react in a third way with 3-bromo-2,5-dimethylthiophene-1,1-dioxide. Not unexpectedly, they did not give conjugate addition, but instead substitution of the bromine with alkyl or aryl groups was obtained, yielding 3-alkyl and 3-aryl substituted 2,5-dimethylthiophene-1,1-dioxides in 50-100 % yields. The less stable organocopper reagents reacted faster and at lower temperatures. It is therefore more convenient to use alkylcopper than lithium dialkylcuprates, which gives higher yields without side-reactions[20].



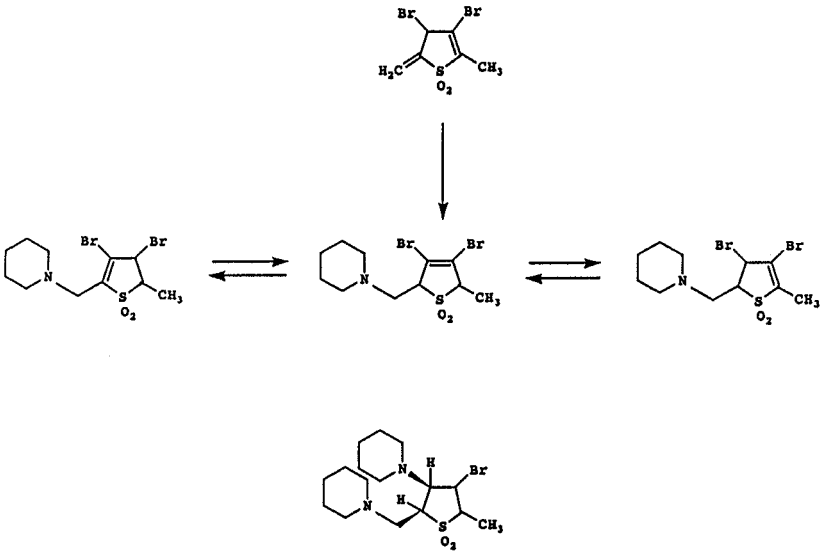
REACTIONS WITH SECONDARY AMINES

The reaction of some thiophene-1,1-dioxides with secondary amines has previously been studied by Melles[21] in Backer's group. In the reaction of 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide with piperidine in benzene he obtained a crystalline compound, which he believed to be either 4-bromo-2,5-dimethyl-2,3-dipiperidino-2,5-dihydrothiophene-1,1-dioxide or 3-bromo-2,5-dimethyl-2,4-dipiperidno-2,5-dihydrothiophene-1,1-dioxide. The reaction represented a 2,5-addition of one mole of piperidine across the diene system and substitution of one bromine atom with another molecule of piperidine. Repeating Melles', work we obtained the same crystalline compound. However, its ^1H NMR spectrum revealed that the dihydrothiophene ring in the product had two vicinal hydrogens with a coupling constant of 8.2 Hz, indicating a *cis* arrangement. In order to ascertain that the introduction of the substituent did not cause large changes in the geomery, and in the coupling constants, an X-ray investigation was undertaken which unambiguously confirmed the *cis* relationship between the piperidino and the piperidinomethyl group. Thus, the product was 3-bromo-2-methyl-4-piperidino-5-piperidinomethyl-*cis*-4,5-dihydrothiophene-1,1-dioxide[22].





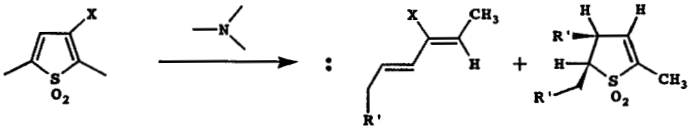
The formation of this product can be explained by assuming that an *exo*methylene tautomer of the starting material, present in minute amounts in the equilibrium, is involved as reactive intermediate, which is attacked in a Michael-type reaction by the piperidine followed by substitution of one bromine with piperidine. Similar tautomers have been suggested to be involved in the reaction of 3,4-dimethylthiophene-1,1-dioxide with secondary amines[23].

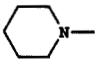
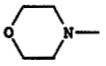
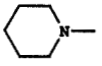
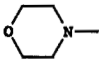
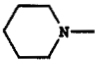


When the reaction of 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide with piperidine was performed at 100 °C for 10 min 3-bromo-2-methyl-5-piperidinomethylthiophene-1,1-dioxide was formed in 84 % yield.

In our continued investigations of the reactions of cyclic secondary amines, such as piperidine, pyrrolidine, morpholine, with 3-chloro- and 3-bromo-2,5-dimethylthiophene-1,1-dioxide in refluxing toluene, we discovered a new synthetically useful reaction leading to dialkylaminomethyl-substituted halobutadienes, such as 3-chloro-6-piperidino(2Z,4E)-2,4-hexadiene. In addition, dialkylamino-substituted *cis*-2,3-dihydrothiophene-1,1-dioxides were obtained as byproducts in up to 15 % yield[24]. They all had J_{23}-coupling constants between 8.3 and 9.1 Hz. In a previous NMR investigation of 2,3-dihydrothiophene-1,1-dioxides, it was shown that the *cis*-vicinal coupling constant was about 9.0 Hz while the *trans*-vicinal coupling constant

was about 4.20 Hz[25]. This type of compound was as mentioned above, the main product in the reaction with 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide. The ring-opening was highly stereoselective and resulted in only one of the four theoretically possible dienes, according to GLC and careful analyses of the ^{1}H NMR spectra. The reaction of 2,5-dimethylthiophene-1,1-dioxide with piperidine gave 1-piperido-[2E,4E]-2,4-hexadiene in 92 % yield. The high stereoselectivity is somewhat unexpected as in the reaction with alkyllithium derivatives, in which similar anionic intermediates are assumed, stereospecificity is lost, as mentioned above.

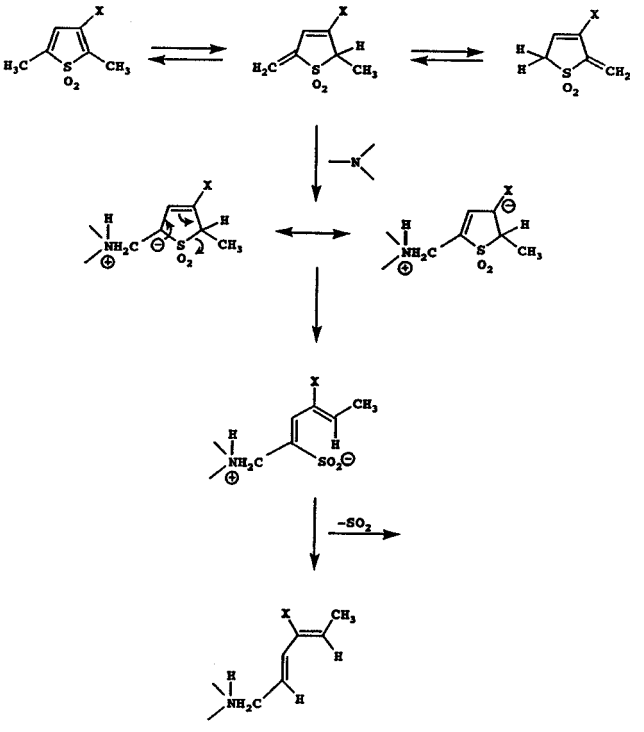


Entry	Time,h	X	R'	Yield %	
1	3	Cl		58	<5
2	24	Cl		48	10
3	72	Cl		42	10
4	3	Br		52	13
5	24	Br		39	14
6	72	Br		31	10
7	72	H		92[a]	<5

a glc yields

We first suggested a stepwise reaction for the ring-opening. As

for 3,4-dimethylthiophene-1,1-dioxide, we suggest the existence of two tautomeric forms in equilibrium with the 3-halo-2,5-dimethyl-1,1-dioxides. For steric and/or electronic reasons, the 5-exomethylene tautomer is more reactive than the 2-exomethylene tautomer. It could also be possible that the former tautomer is present in higher concentrations. The reaction starts with a 1,4-Michael addition to the formal α,β-unsaturated sulphone group giving an intermediate resonance -stabilized allylic anion. Such anions have previously been obtained by treatment of 2,5-dihydrothiophene-1,1-dioxides with strong bases, such as sodium hydride in dimethyl sulfoxide[26], alcoholic potassium hydroxide[27], Grignard reagents [28,29] or organolithium derivatives[30] and they easily ring-open to butadienylsulfinates. The reactions of such anions are however strongly dependent on the conditions, as recently demonstrated for deprotonation reactions of 2,5-dihydrothiophene-1,1-dioxides with various bases. After subsequent alkylation, alkylsulfolenes are obtained[31-40]. The extrusion of sulfur dioxide from the butadienyl sulfinate occurs at higher temperature in our case and the vinylic carbanion intermediate formed was protonated to the product.



We considered first chelotropic disrotatory elimination of sulfur dioxide from the allylic group or its protonated form less likely, since such reactions require temperatures higher than 200 °C[41-47]. The great preparative value of chelotropic disrotatory elimination reactions was recently demonstrated in the synthesis of some natural products[48-52].

However, we could not trap the butadienyl sulphinate, and recent discovery that elimination of sulfur dioxide from substituted 2,5-dihydrothiophene dioxides occurred under relatively mild conditions, such as heating in toluene at 110 °C[40,53-55] means that we cannot exclude a chelotropic disrotatory elimination reaction. Our reactions are in some aspects analogous to the ring-opening of 3-thienyllithium derivatives mentioned in the introduction.

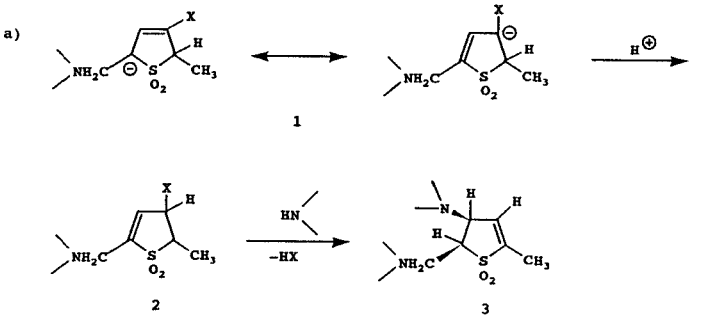
Dihydrothiophene-1,1-dioxides[29,30,31,32,33], 1-substituted dihydrothiophenes[26,56,57] and thiophene-1,1-dioxides[17,18,26,28] show similar reactions upon treatment with base, although the steric outcome differs. For instance the reaction of *trans* 2,5-dimethyl-2,5-dihydrothiophene-1-methylthiophenium hexafluorophosphate with butyllithium at -78 °C produced a *cis,trans* 2,4-hexadiene exclusively, whereas the reaction with the *cis* compound resulted in a mixture of *trans,trans* and *cis,cis* 2,4-hexadienes in a ratio of 1:2. The reaction of *trans* 2,5-diethyl-3,4-dicarbomethoxy-2,5-dihydro-1-methylthiophenium tetrafluoroborate with LDA in THF at room temperature gave only one isomer of the 3-methylthio-4,5-bismethoxycarbonylocta-3,5-diene[56]. The stereochemistry of both double bonds could not be established with certainty. The 3-double bond was assigned the E-configuration based on NMR and by application of the principle of least motion in organic reactions[58].

One might also note that the initially formed (Z)-1-(methylsulfinyl)buta-1,3-diene formed in the treatment of 2,5-dihydrothiophene-oxide with aqueous sodium hydroxide is almost quantitatively converted to the (E)-isomer in the presence of LDA[26]. The isomerization was explained by removal of the proton from the 1-position and subsequent inversion of the vinylic carbanion. Inversion of such carbanions with α-sulfur substituents has been observed[59-61].

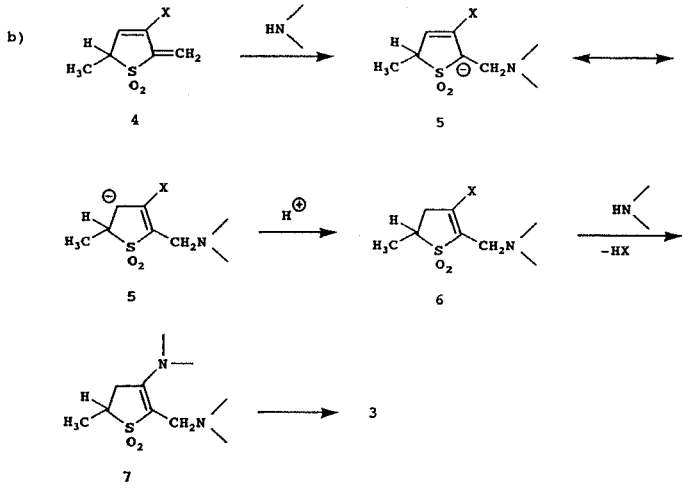
The regiospecificity in the ring-opening reaction with secondary

amines was lost when unsymmetrical 3-bromo-2,5-dialkylthiophene-1,1-dioxide was used in the reaction. Thus, from 3-bromo-5-ethyl-2-methylthiophene-1,1-dioxide and piperidine, 3-bromo-6-piperidino-(2Z,4E)-2,4-heptadiene and 3-bromo-1-piperidino-(2Z,4E)-2,4-heptadiene were formed in a ratio of 7:3. On the other hand, reaction of 3-bromo-2-ethyl-5-methylthiophene-1,1-dioxide gave only 4-bromo-1-piperidino-(2E,4Z)-2,4-heptadiene.Piperazine reacted with two molecules of 3-bromo-2,5-dimethylthiophene-1,1-dioxide to give 1,4-di[4-bromo-(2E,4Z)-2,4-hexadienyl]piperazine[62].

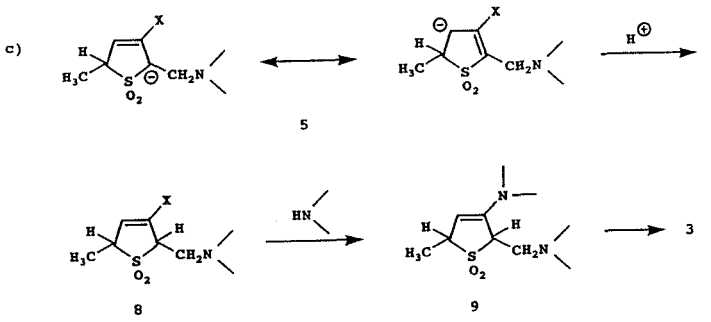
Several mechanistic pathways can be imagined for the formation of the minor products, the *cis* 2,3-dihydrothiophene-1,1-dioxide: a) protonation of the intermediate 1 at position 3 to give 2 followed by Michael addition and elimination of HX to give the minor product 3;



b) nucleophilic attack on the tautomer 4 resulting in 5, followed by protonation at position 3 to 6. Michael addition and elimination of HX gives 7 followed by double bond isomerization to 3;



and c) protonation of 5 at position 5 leads to 8 followed by substitution and isomerization of the double bond to give 3.



The most likely pathway seems to be a). Path c) seems least likely, since vinylic substitution must occur. 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 of various substituents in the α- and β-positions (via aromatic substitution and metalation), followed by ring-opening.

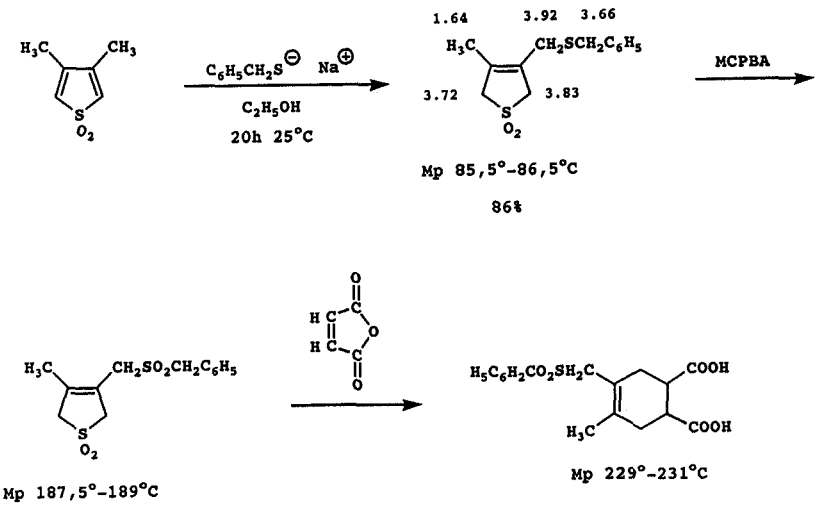
In aqueous piperidine, the thiophene-1,1-dioxides reacted quite differently. 2,5-Dimethylthiophene-1,1-dioxide yielded 2,5-dimethyl-3-piperidino-*trans*-2,3-dihydrothiophene-1,1-dioxide in almost quantitative yield. 3-Chloro- and 3-bromo-2,5-dimethylthiophene-1,1-dioxide reacted analogously to give 3-chloro- 3-bromo-2,5-dimethyl-4-piperidino-trans-4,5-dihydrothiophene-1,1-dioxide. The products are formed by a 1,4-Michael reaction, piperidine attacking at the β-position.The *trans* structure was evident from the J_{23}-coupling constants of 3.6 to 4.4 Hz. The formation of the *trans* isomer is somewhat unexpected as in Michael additions to double bonds in cyclic systems the *cis* isomers are formed preferentially. However, the formation of the *trans*-isomer might be due to the fact that in the 1,4-Michael addition reactions the thermodynamically most stable isomer is preferentially formed.

REACTIONS WITH THIOLATES

We have reinvestigated the reaction of 3,4-dimethylthiophene-

1,1-dioxide with sodium benzylthiolate in ethanol. According to Melles[21] the reaction gave an oily product, which was oxidized to a crystalline derivative. The latter was suggested to be 2-benzylsulfonyl-3,4-dimethyl-2,5-dihydrothiophene-1,1-dioxide. This was based on the observation that the product was different from that obtained from 3-bromo-3,4-dimethyl-2,5-dihydrothiophene-1,1-dioxide with benzylthiolate followed by oxidation with perbenzoic acid. Further evidence was that the product underwent a cycloaddition reaction with maleic anhydride with elimination of sulfur dioxide to provide a compound suggested to be 1,2-dimethyl-3-benzylsulfonyl-1-cyclohexene-4,5-dicarboxylic acid.

When we repeated Melles' procedure we obtained a crystalline compound in 55 % yield. Carrying out the reaction at room temperature increased the yield to 86 %. NMR proved the structure to be 3-benzylthiomethyl-4-methyl-2,5-dihydrothiophene-1,1-dioxide. Oxidation with *m*-CPBA gave a compound with the same melting point as that obtained by Melles, namely 3-benzylsulfonylmethyl-4-methyl-2,5-dihydrothiophene-1,1-dioxide. Thus, the primary product obtained by Melles was propably impure 3-benzylthiomethyl-4-methyl-2,5-dihydrothiophene-1,1-dioxide. We also repeated the Diels-Alder reaction and obtained after hydrolysis a product with the same mlting point as Melles. NMR comfirmed that the Diels-Alder product was 1-benzylsulfonylmethyl-2-methyl-1-cyclohexene-4,5-dicarboxylic acid[63].



Thus the reaction with sodium benzylthiolate proceeds in the same manner as the reaction of 3,4-dimethylthiophene-1,1-dioxide with secondary amines[23], through 1,6-addition to the exomethylene tautomer. On the other hand, 2,5-dimethylthiophene-1,1-dioxide behaved differently under the same conditions. A normal 1,4-addition of the thiolate to the β-position followed by double bond isomerization led to 3-benzylthio-2,5-dimethyl-4,5-dihydrothiophene-1,1-dioxide in 40 % yield. The reaction is thus analogous to that with piperidine in aqueous media. However, in that case no double bond isomerization occurred.

Substitution of a bromine in the 3-position of 2,5-dimethylthiophene-1,1-dioxide led to different results. Two isomeric products were obtained, which were separated by HPLC. NMR showed them to be 2-benzylthiomethyl-4-ethoxy-5-methyl-2,3-dihydrothiophene-1,1-dioxide and 2-benzylthiomethyl-3-ethoxy-5-methyl-4,5-dihydrothiophene-1,1-dioxide. The ratio of the products depends on the reaction temperature. At room temperature the ratio was 2:3, while in refluxing ethanol a ratio of 3:1 was obtained. In order to account for the positions of the benzylthio group it seems likely that both exomethylene tautomers of 3-bromo-2,5-dimethylthiophene-1,1-dioxide are involved in the reaction. However, we do not know if this step occurs before or after the exchange of the bromine for alkoxy groups.

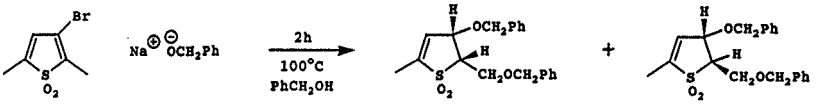
When 3-bromo-2,5-dimethylthiophene-1,1-dioxide was stirred at room temperature with potassium benzylthiolate in DMF[64] nucleophilic substitution occurred, giving 3-benzylthio-2,5-dimethylthiophene-1,1-dioxide.

REACTIONS WITH ALKOXIDES

The reaction of 3-bromo-2,5-dimethylthiophene-1,1-dioxide with sodium ethoxide in ethanol was fast, and after only a few minutes at room temperature all the starting material had disappeared. From GLC, mass- and NMR-spectra, it was evident that the two isomers formed were the *trans* and *cis* isomers of 2-ethoxymethyl-3-ethoxy-5-methyl-2,3-dihydrothiophene-1,1-dioxide, in a ratio of 4:1. The reaction is thus related to that of 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide

with piperidine in benzene at room temperature, which gave predominantly the *cis* compound. The formation of the *trans* isomer might be due to isomerization of the thermodynamically more stable isomer by the stronger alkaline medium[63].

The reaction of 3-bromo-2,5-dimethylthiophene-1,1-dioxide with sodium benzyloxide in benzyl alcohol was slower and required heating to 100 °C for two hours, but yielded similar products as the reaction with sodium ethoxide in ethanol. The *trans* and *cis* 2-benzyloxymethyl-3-benzyloxy-5-methyl-2,3-dihydrothiophene-1,1-dioxides were obtained in the proportion of 4:1 and in 61 % yield.



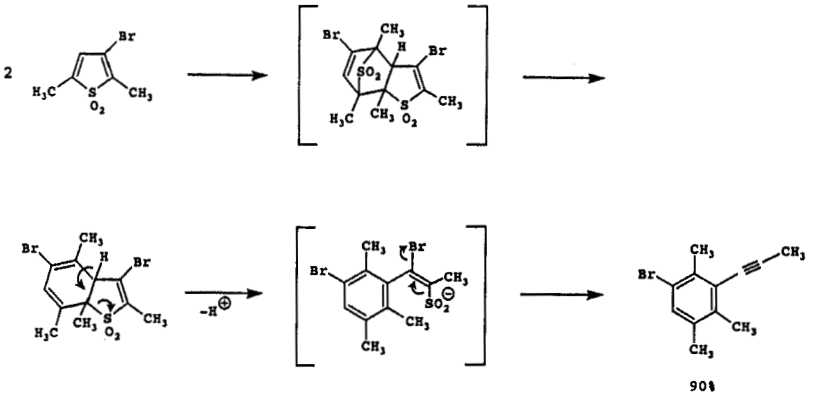
1 : 1 20 : 80

61% yield

TANDEM DIMERIZATION RING OPENING

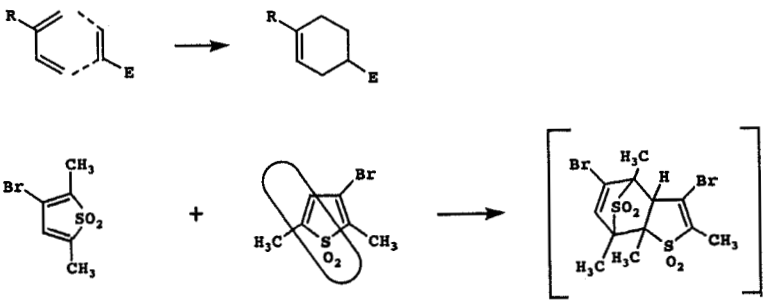
During an investigation of the reaction of 3-bromo-2,5-dimethylthiophene-1,1-dioxide with sodium *t*-butoxide in *t*-butanol, we discovered a new reaction. Instead of obtaining an addition product of the same type as described above, we isolated a crystalline compound,which analyzed correctly for $C_{12}H_{13}Br$. Its IR-spectrum showed a weak band at 2230 cm^{-1}, indicating the presence of a disubstituted acetylene. The ^{13}C NMR (DEPT) spectra indicated the presence of four non-equivalent methyl groups, six aromatic carbons, one of which is bonded to a hydrogen atom. Upon reaction of the compound with butyllithium, followed by hydrolysis, a new derivative having two benzenic *ortho* hydrogens with a coupling constant of 7.9 Hz was obtained. Thus the primary product is either 1-(3-bromo-2,5,6-trimethylphenyl)propyne or 1-(4-bromo-2,3,6-trimethylphenyl)propyne[65]. By analyzing the INADEQUATE NMR spectra, the structure was proven to be the 3-bromo derivative. It is formed by dimerization followed by extrusion of sulfur dioxide, which yields 3,5-dibromo-2,4,7,7a-tetramethyl-3a,7a-dihydrobenzo[b]thiophene-1,1-dioxide. The 3a hydro-

gen is removed by base and the ring opens with loss of bromide ion and sulfur dioxide to give the product. The aromatization of the benzene ring is of course a strong driving force for the ring-opening. We have previously observed related ring-opening reactions with loss of bromide ion and sulfur dioxide[16,17,18]. The intermediate dihydrobenzo[b]thiophene-1,1-dioxide shown below could be isolated if shorter reaction times were used.



90%

Thus 3,5-dibromo-2,4-diethyl-7,7a-dihydrobenzo[b]thiophene-1,1-dioxide was obtained on heating 3-bromo-2-ethyl-5-methylthiophene-1,1-dioxide in t-butanol for 100 h. Heating this intermeiate for 45 h in t-butanol then gave 1-(3-bromo-5,6-dimethyl-2-ethylphenyl)-1-butyne in quantitative yield. It was later found that treatment with ethylmagnesium bromide at -70 °C for 2 h also gave the product in quantative yield[66]. The dimerization is regiospecific because the 4,5-bond in the dienophilic molecule is more reactive than the 2,3-bond



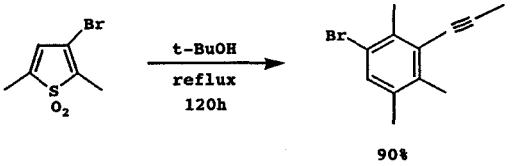
Unsymmetrical diene

Electron-withdrawing dienophile

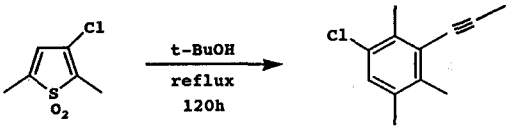
for steric reasons. Furthermore, a dienophile with one electron withdrawing group and an unsymmetrical diene with a 2-substituent are

expected to react in such a way that the two substituents are *para* oriented, in agreement with the observed results.

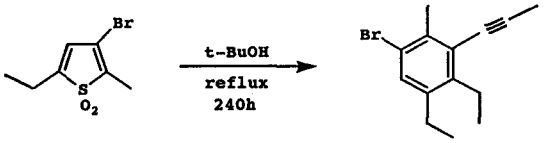
The reaction is quite general and the products were isolated in 75-94 % yield.



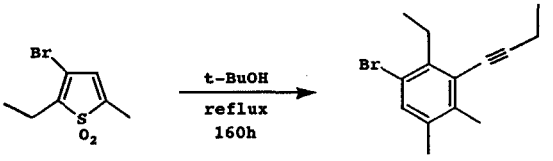
90%



75%



83%

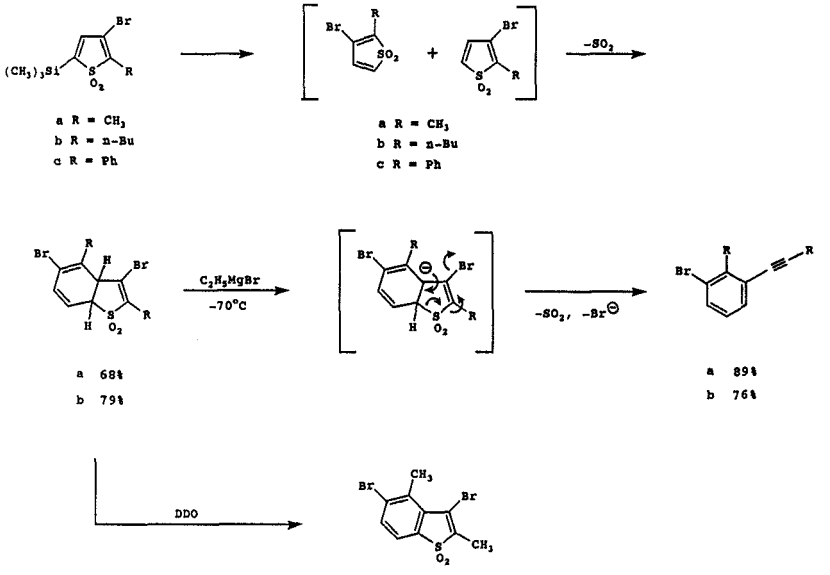


74%

We also attempted mixed dimerization reactions. Refluxing a mixture of 3-bromo-2,5-dimethylthiophene-1,1-dioxide and 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide in *t*-butanol gave a mixture of 1-(3-bromo-2,5,6-trimethylphenyl)propyne and predominantly 1-(3,4-dibromo-2,5,6-trimethylphenyl)propyne[62].

We also extended the dimerization-ring-opening reaction to 2,3-substituted thiophene-1,1-dioxide, which as mentioned before is formed by desilylation of 5-silylated derivatives. Treatment of 3-bromo-2-methyl- and 3-bromo-2-butyl-5-trimethylsilylthiophene-1,1-dioxide with basic alumina in pentane/dichloromethane led to cyclodimeriza-

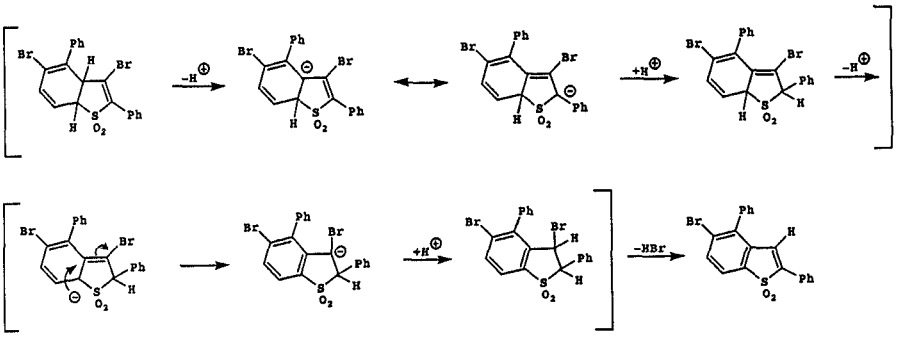
tion and expulsion of sulfur dioxide to give 3,5-dibromo-2,4-dimethyl- and 3,5-dibromo-2,4-dibutyl-*cis*-3a,7a-dihydrobenzo[b]thiophene-1,1-dioxide in 68 % and 79 %, respectively[66]. The cyclodimerization was again regiospecific as only one product was obtained. The coupling constant H_{3a}-H_{7a} was in agreement with the *cis* coupling of 8.0 Hz previously found for the parent compound[67].



Treatment of 3,5-dibromo-2,4-dimethyl-*cis*-3a,7a-dihydrobenzo-[b]thiophene-1,1-dioxide with DDQ in refluxing benzene led to aromatization, resulting in the formation of 3,5-dibromo-2,4-dimethylbenzo[b]thiophene-1,1-dioxide in 71 % yield. Reacting the dihydrobenzo[b]thiophene-1,1-dioxides with a strong base such as ethylmagnesium bromide or refluxing the silylated thiophene-1,1-dioxides with basic alumina in pentane/dichloromethane for a longer period, caused ring-opening to 1,2,3-unsymmetrically substituted benzenes. In this way 1-(3-bromo-2-methylphenyl)-1-propyne and 1-(3-bromo-2-butylphenyl)-1-hexyne were obtained in 89 % and 76 % yield, respectively[66].

3-Bromo-2-phenyl-5-trimethylsilylthiophene-1,1-dioxide behaved somewhat differently. Reaction at room temperature with basic alumina in pentane/dichloromethane gave a 52 % yield of 5-bromo-2,4-diphenyl-

benzo[b]thiophene-1,1-dioxide. A possible pathway for the formation of the last mentioned compound consists in a series of allylic rearrangements, followed by hydrogen bromide elimination, as indicated in the scheme below. As in previous cases, aromatization of the benzene



ring is a strong driving force. Apparently in this case the initially formed anion is stabilized by the phenyl group in the 2-position and is not prone to undergo ring-opening. However, refluxing of 3-bromo-2-phenyl-5-trimethylsilylthiophene-1,1-dioxide with basic alumina caused ring-opening and the expected 3-bromo-2-phenyltolane was obtained in 69 % yield, together with 27 % of 5-bromo-2,4-diphenylthiophene-1,1-dioxide.

Refluxing of 3-bromo-5-methyl-2-phenylthiophene-1,1-dioxide in decalin gave cyclodimerization with elimination of sulfur dioxide, leading to a compound with the composition $C_{22}H_{18}Br_2O_2S$ in 66 % yield. X-ray structure determination showed it to be 3,5-dibromo-7,7a-dimethyl-2,4-diphenyl-*cis*-3a,7a-dihydrobenzo[b]thiophene-1,1-dioxide. Attempts to ring-open this compound with different bases such as ethylmagnesium bromide or sodium *t*-butoxide were not successful. The isomeric 3-bromo-2-methyl-5-phenylthiophene-1,1-dioxide resisted cyclodimerization.

PREPARATION OF BENZO[b]THIOPHENE-1,1-DIOXIDE

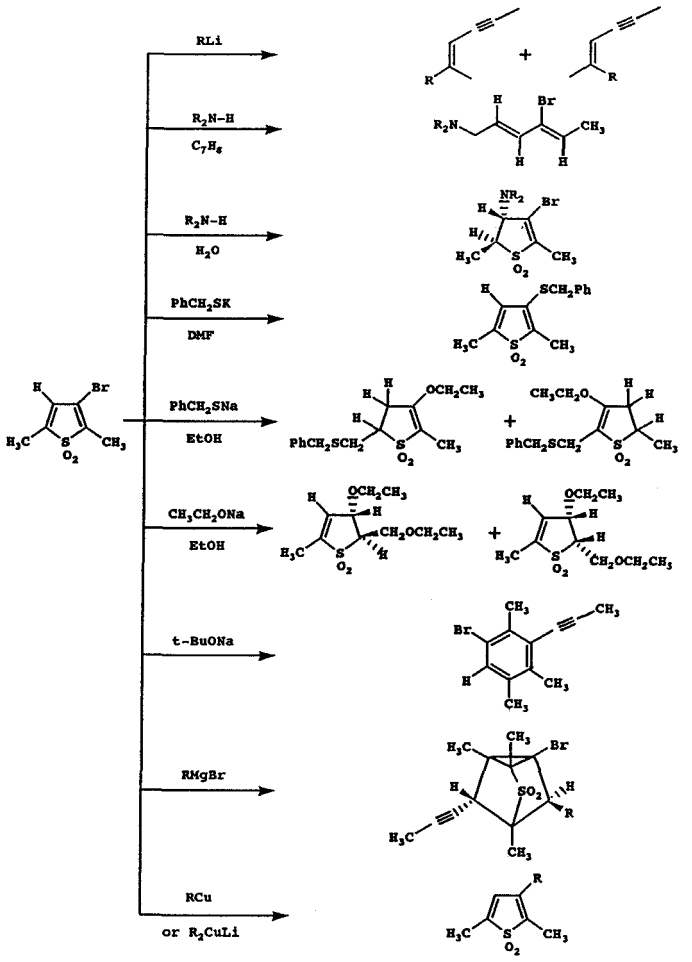
Finally, appropriately substituted thiophene-1,1-dioxides can be used for the direct preparation of benzo[b]thiophene-1,1-dioxides[68]. Such compounds can of course, as mentioned previously, be obtained by

oxidation of dihydrobenzo[b]thiophene-1,1-dioxides. Thus, refluxing 3,5-dibromo-2-methylthiophene-1,1-dioxide for 100 h in *t*-butanol afforded after dimerization followed by elimination of sulfur dioxide and hydrogen bromide a tribromodimethylbenzo[b]thiophene-1,1-dioxide in 65 % yield. The product could be either 3,5,7-tribromo-2,4-dimethylbenzo[b]thiophene-1,1-dioxide or 3,4,6-tribromo-2,7-dimethylbenzo[b]thiophene-1,1-dioxide depending upon the relative orientation of the diene and dienophile. ^{1}H and ^{13}C NMR could not differentiate between these structures, and due to the low solubility of the product, INADEQUATE experiments were not possible. The structure was therefore proven chemically by debrominationn with zink in acetic acid. A dibromo compound and two monobromo derivatives were obtained and the structure of the dibromo compound was proven to be 5,7-dibromo-2,4-dimethylbenzo[b]thiophene-1,1-dioxide by NOE experiments, proving that the primary product was the 3,5,7-tribromo derivative.

The regiospecificity depends on the fact that only the monosubstituted side reacts as a dienophile. A crude solution of 3,5-dibromo-2-phenylthiophene-1,1-dioxide reacted similarly in refluxing ethanol, yielding 3,5,7-tribromo-2,4-diphenylthiophene-1,1-dioxide in 86 % yield. The structure determination was based on comparison with the analogous methyl case. In contrast to 3,5-dibromo-2-methylthiophene-1,1-dioxide the isomeric 2,3-dibromo-5-methylthiophene-1,1-dioxide did not give dimerization even after 10 days' refluxing.

In order to elucidate which side of 2,4-dithiophene-1,1-dioxide was acting as dienophile we studied the dimerization of 4-bromo-2-methylthiophene-1,1-dioxide, in which the two substituents are of similar size, in refluxing *t*-butanol. Two products, 6-bromo-2,4-dimethylbenzo[b]thiophene-1,1-dioxide and 5-bromo-2,7-dimethylbenzo-[b]thiophene-1,1-dioxide had been formed by dimerization followed by sulfur dioxide and hydrogen bromide elimination. It is thus clear that the side with the bromine substituent acts as dienophile and the formation of two isomers depends upon the loss of selectivity in the orientation of diene and dienophile in the cycloaddition.

In the following scheme, I have summerized the manyfold of reactions that thiophene-1,1-dioxide undergoes. All the products are derived from 2,5-dimethylthiophene-1,1-dioxide.



I hope that this convinces you of the synthetic possibilities of combining the aromatic chemistry of thiophenes with the cyclodimerization and ring-opening of thiophene-1,1-dioxides.

ACKNOWLEDGEMENTS

Finally, I would like to thank my very gifted students, who made it possible for me to tell you this fascinating story. Dr Torbjörn Frejd, now Professor at the University of Umeå, discovered the ring-opening of 3-thienyllithium derivatives at the beginning of his graduate work, and developed it very successfully. Dr Ander Hallberg, now Professor of medicinal chemistry at the University of Uppsala,

took part in the first investigations on thiophenedioxides as a graduate student, together with Olle Karlsson and Arne Svensson, and assisted in the supervision of Dr Grigorios Nikitidis, who did most of the experimental work I have told you about. Dr Zorica Bugarcic, a post-doc from Yugoslavia, recently worked on the reaction of thiophene-1,1-dioxides with organocopper reagents and Mr Anders Tsirk is at present successfully engaged in continuing research in this field.

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