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SELECTIVITY IN CYCLOADDITIONS—X[1]

REGIOCHEMISTRY OF CYCLOADDITIONS OF NITRILE OXIDES TO THIOPHENE AND BENZOTHIOPHENE 1, 1-DIOXIDES

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Abstract—Thiophene-1,1-dioxide undergoes regioselective cycloaddition to benzonitrile oxide. In the reaction with the less reactive mesitonitrile oxide the sulfur dioxide deriving from the dimerization of the dipolarophile causes a catalytic decomposition of the nitrile oxide, which competes with the cycloaddition. Benzothiophene-1,1-dioxide and the vinyl sulfone system of 2,3-dihydrothiophene-1,1-dioxide add nitrile oxides with lower regioselectivity. The directing effect of the sulfonyl group has been elucidated with the aid of CNDO/2 calculations.

Previous papers of this series dealt with a comparative study of the dipolarophilic activity of five-membered heteroaromatic compounds in the 1,3-dipolar cycloadditions with nitrile oxides.[3-5]

The aromatic nature of furan, thiophene and their benzo-derivatives is manifest in a sharp decrease of reactivity because of the loss of aromaticity in the cycloaddition transition state. The more stabilized heteroaromatic compounds, thiophene and benzothiophene, are the least reactive.

In spite of the large change in reactivity, which ranges over four powers of ten, the regiochemistry of the cycloadditions to the monocyclic heteroaromatics remains constant and similar to that observed[6] with the isocyclic system, cyclopentadiene, owing to the similar shapes and energies of the frontier orbitals (FOs) of these dipolarophiles. In the cycloadditions to the benzo-derivatives, however, a smooth change of regiochemistry was observed. The change is not related to the reactivity of the dipolarophiles but nicely reflects the variations in the polarization of the FOs.[1b,4,5]

The following is an extension of our study to the cycloadditions of the dioxides of thiophene and benzothiophene, and to the related system of 2,3-dihydrothiophene-1,1-dioxide. The removal of the lone pair of sulfur relieves the aromatic stabilization and restores the polyene behaviour. A high dipolarophilic activity could then be anticipated. Moreover the strong electron withdrawing effect of the sulfone group lowers the energy of the FOs,[7] increasing the electrophilicity of the polyene moiety. Since the electrophilic and nucleophilic centres of nitrile oxides are located at carbon and oxygen, respectively,[8] the enhanced electrophilicity of the diene moiety should lead to a lowering or even a reversal of the regiochemistry observed in the cycloadditions to typical diene systems, i.e. the isocyclic cyclopentadiene,[6] where the diene behaves as the nucleophile, binding the terminal dienic carbon to the nitrile oxide carbon.

The polyene behaviour of thiophene-1,1-dioxide is indeed well documented. The dioxide has been generated by Hofmann elimination of 3-trimethylammonium-2,3-dihydrothiophene-1,1-dioxide salts[9] or dehydrohalogenation of 3,4-dihalotetrahydrothiophene-1,1-dioxide,[10] which are readily available from butadiene sulfone (3-sulfolene). The dioxide dimerizes easily,[9] like the isocyclic cyclopentadiene, and enters Diels–Alder reactions as a diene or a dienophile[11] and 4+6 cycloaddition with fulvenes.[12] Recently its 1,3-dipolar cycloadditions with mesitonitrile oxide and nitrones have been reported.[13] Cycloadditions to the stable benzothiophene-1,1-dioxide have been more extensively investigated.[14,15] 1,3-Dipolar cycloadditions of diazoalkanes,[14a,b] nitrilimines,[14c] nitrones[14d] and nitrile oxides[14d,15] have been reported.

RESULTS

Thiophene-1,1-dioxide is a quite reactive dipolarophile in the 1,3-dipolar cycloaddition with benzonitrile oxide (BNO). The cycloaddition is by far faster than the dimerizations of the dioxide and the dipole. When separately equimolecular solutions of the dioxide and BNO are generated *in situ* by dehydrohalogenation of the precursors with triethylamine in benzene and immediately mixed, an almost quantitative yield of monoadduct **1a** is obtained (Scheme 1). Crystallization affords the pure adduct **1a** with yields over 90%.

The NMR spectrum of the residue of the mother liquors shows exclusively the signals of monadduct **1a** and gives no evidence for the presence of the regioisomeric adduct **2a**. Only traces of the dimer of BNO, diphenylfuroxane, and of bisadduct **3a** are detectable by TLC. These results point out an unusually high dipolarophilic activity of the dioxide as well as a remarkably high regioselectivity of the cycloaddition with BNO. The dioxide is 25 times more reactive than the reference diene system of cyclopentadiene, as shown by competition experiments.

The vinyl sulfone moiety of monoadduct **1a** can add further BNO, although at a significantly lower rate than the initial cycloaddition. In the reaction of thiophene-1,1-dioxide with excess BNO (2 equiv), fair amounts of bisadduct **3a** (42%) are formed, along with monadduct **1a** (48%) and the regioisomeric bisadduct **4a** (0.4%). Treatment of **1a** with BNO similarly gives a mixture of adducts **3a** and **4a** in the same ratio 99:1 observed in the addition to thiophene 1,1-dioxide.

The structures of the adducts rely upon the correlation with the adducts of thiophene[5] shown in Scheme 1 and NMR data (Table 1). The adducts **1a** and **4a** have been independently obtained by oxidation of the thiophene monoadduct **6a** and bisadduct **8a**, respectively, with m-

chloro-perbenzoic acid. The structure of the principal bisadduct **3a** follows then from its formation from **1a** as well as from the symmetrical appearance of its NMR spectrum.

The NMR spectra in $CDCl_3$ closely correspond to the similar adducts to cyclopentadiene[6] and thiophene.[5] The sulfonyl group causes a deshielding of the hydrogens α and β to the sulfonyl of 0.2–1.0 ppm, relatively to a CH_2 group, and usually a slight shielding with respect to the corresponding thiophene adducts. Because of the low solubility of many adducts, the NMR spectra were also recorded in DMSO-d_6 and the chemical shifts are given in Table 1. The isoxazolinic hydrogens are further deshielded in DMSO. In the 4-sulfonyl isoxazolines the downfield shift of the 4-H (0.7–0.8 ppm) is larger than the shift of the 5-H (0.2–0.3 ppm) and almost compensates the difference of chemical shift of the isoxazolinic hydrogens (1.1 ppm),[16] making the assignment sometimes difficult.

Lower yields of cycloadducts have been obtained in

Table 1. Chemical shifts[a] and coupling constants[b] of cycloadducts[c] in $CDCl_3$ (DMSO-d_6)

Comp.	4-H[d]	5-H[d]	$J_{4,5}$	Other signals[e] H_α	H_β
1a	5.11d (5.81d)	6.05dd (6.31dd)	9.91 (9.98)	6.88s (7.28m)	
1b	5.07d (5.58d)	6.05d (6.38dd)	8.97 (9.31)	6.81s (7.62d)	6.81s (7.20dd)
3a	5.04d (6.01s)	5.81d (6.01s)	10.00 ---		
3b	5.00d (5.55d)	5.75d (6.01d)	10.00 (9.31)		
4a	4.69d (5.72s)	5.58d (5.72s)	10.00 ---		
	5.15d (5.84d)	5.76d (6.33d)	10.00 (9.22)		
4b	4.68d (5.28d)	5.32d (5.57d)	9.81 (10.00)		
	5.06d (5.35d)	5.86d (6.36d)	9.62 (9.81)		
13a	4.73d (5.44d)	5.55m (5.73d)	8.81 (9.04)	2.5-3.3m(2.7-3.7m)	
13b	4.66d (5.09d)	5.53m (5.76d)	9.05 (9.98)	2.4-3.2m (3.32s)	
13c	4.78d (5.61d)	5.32dd (5.90d)	9.62 (9.21)	3.25[f] (3.71[f])	5.48m (5.62[g])
13d	4.95d (5.55m)	5.56dd (5.55m)	9.04 ---	3.45[f] (3.72[f])	5.65[g] (5.55[g])
13e	5.52d[h](5.69d)	5.72dd[h](5.89d)	9.31[h](8.61)	3.75[fh](3.85m)	4.98m[h](5.12m)
13f	5.01d (5.51d)	5.64dd (5.89dd)	9.05 (10.11)	3.54[f] (3.84[f])	4.79m (5.09m)
13g	5.55d[h](5.85s)	5.91dd[h](5.85s)	10.40[h] ---	3.84[fh](3.92m)	4.99m[h](5.05m)
13h	5.02d (5.47d)	5.77dd (5.97dd)	9.32 (9.91)	3.65[f] (3.88[f])	4.78m (4.94m)
14a	4.78m (5.15dd)	5.42d (5.75d)	9.32 (9.98)	2.4-3.3m (2.1-2.8m)	
14b	4.63m (4.90d)	5.40d (5.75d)	9.11 (9.84)	2.2-3.5m (3.4s)	
14c	4.76d (5.08d)	5.42d (5.72d)	10.20 (9.60)	2.61[i]3.18[i](2.83[f])	5.47[g] (5.27m)
14d	4.82d	5.60d	10.40 ---	2.93[i]3.40[i]	5.03m
17a	5.36d (6.22d)	6.40d (6.73d)	9.70 (9.31)		
17b	5.32d (5.93d)	6.40d (6.76d)	9.30 (9.30)		
18a	5.73d (6.36s)	5.88d (6.36s)	9.10 ---		
18b	5.46d (5.93d)	6.00d (6.42d)	9.30 (9.30)		

[a] Chemical shifts in parts per million (δ) from internal Me_4Si. Multiplicity: d, doublet; dd, double doublet s, singlet; m, multiplet. Solvent: $CDCl_3$ (DMSO-d_6) unless otherwise stated.

[b] in Hz.

[c] Satisfactory combustion analytical data C, H, N (±0.4%) have been obtained for all the new compounds. Ed.

[d] Numbering refers to the isoxazoline ring.

[e] H_α (or H_β) to the SO_2 group.

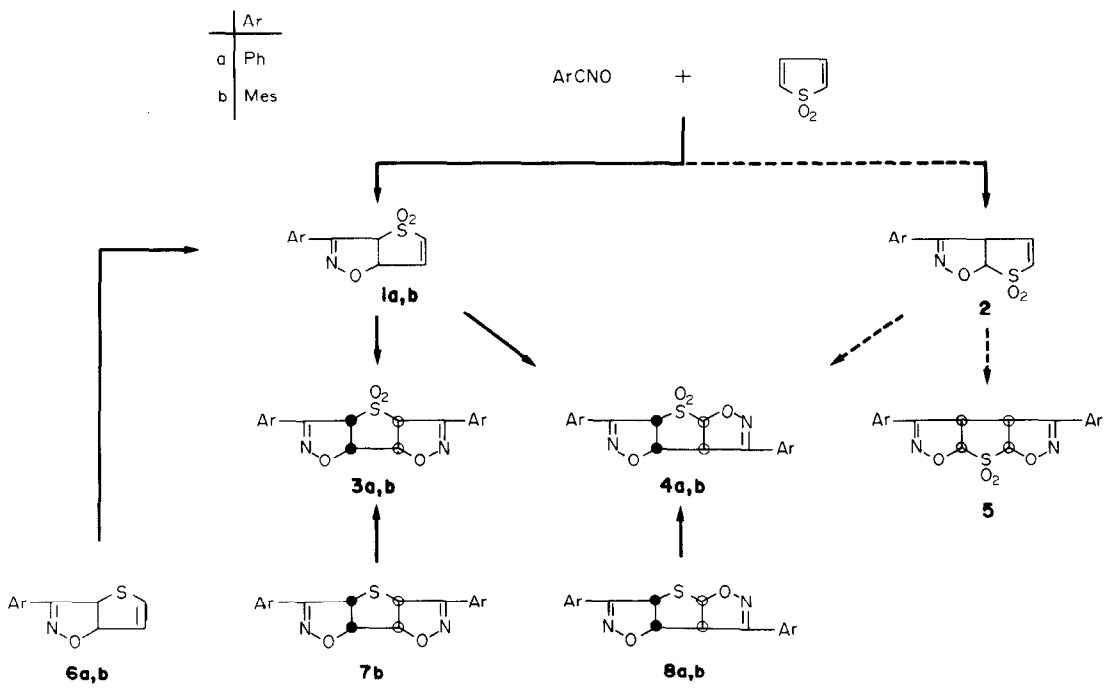
[f] Two geminal protons signals.

[g] Overlapped by isoxazolinic protons.

[h] Acetone-d_6 [i] Part AB of ABX system.

Analytical data for compounds of Table 1

Compound	Formula	Found %			Required %		
		C	H	N	C	H	N
1a	$C_{11}H_9NO_3S$	56.12	3.89	6.07	56.15	3.85	5.95
3a	$C_{18}H_{14}N_2O_4S$	61.04	3.85	8.23	61.00	3.84	7.90
4a	$C_{18}H_{14}N_2O_4S$	61.36	4.12	7.75	61.00	3.84	7.90
4b	$C_{24}H_{26}N_2O_4S$	65.86	6.01	6.37	65.72	5.97	6.38
12a	$C_{18}H_{16}N_2O_4S$	60.54	4.53	7.62	60.67	4.53	7.86
13a	$C_{11}H_{11}NO_3S$	55.97	4.75	5.86	55.69	4.67	5.91
13b	$C_{14}H_{17}NO_3S$	59.90	6.18	5.30	60.18	6.13	5.01
13c	$C_{13}H_{13}NO_5S$	52.63	4.34	5.02	52.88	4.44	4.74
13d	$C_{16}H_{19}NO_5S$	57.07	5.63	4.24	56.97	5.68	4.15
13e	$C_{11}H_{10}NO_3SCl$	48.42	3.77	5.23	48.61	3.70	5.15
13f	$C_{14}H_{16}NO_3SCl$	53.54	5.36	4.89	53.58	5.13	4.46
13g	$C_{11}H_{10}NO_3SBr$	42.18	3.20	4.32	41.78	3.18	4.43
13h	$C_{14}H_{16}NO_3SBr$	46.61	4.37	4.21	46.93	4.50	3.91
14a	$C_{11}H_{11}NO_3S$	55.48	4.76	6.09	55.69	4.67	5.91
14b	$C_{14}H_{17}NO_3S$	59.75	6.31	5.31	60.18	6.13	5.01
14c	$C_{13}H_{13}NO_5S$	52.59	4.28	5.07	52.88	4.44	4.74
14d	$C_{16}H_{19}NO_5S$	57.29	5.78	4.31	56.97	5.68	4.15
17b	$C_{18}H_{17}NO_3S$	66.30	5.36	4.56	66.03	5.21	4.28
18a	$C_{15}H_{11}NO_3S$	72.94	3.90	4.86	63.14	3.88	4.91
18b	$C_{18}H_{17}NO_3S$	65.85	5.27	4.19	66.03	5.21	4.29



Scheme 1.

the cycloaddition of mesitonitrile oxide to thiophene-1,1-dioxide. When equimolecular amounts of the reactants were let to react, a 27% yield of monoadduct **1b** was obtained. With excess mesitonitrile oxide (2 equiv) a 40% of cycloadducts **1b** (10%), **3b** (30%) and **4b** (0.4%) was isolated from the reaction mixture. Cycloadducts **3b** and **4b** were also formed in the same ratio 99:1 from **1b** and mesitonitrile oxide. Cycloadduct **1b** and **3b** have been already obtained by Geneste *et al.*[13] The structures of the adducts have been correlated with the thiophene adducts **6–8b** by oxidation with m-chloro perbenzoic acid.

A large part of mesitonitrile oxide is however transformed under the reaction conditions into dimesitylurea, which was isolated in both reactions with a 58% and 30% yield, resp. Monitoring of the reactions by IR and TLC shows that the disappearance of mesitonitrile oxide is followed by the formation of the adducts as well as by the isomerization of mesitonitrile oxide to mesityl isocyanate, from which the dimesitylurea forms during the isolation. This unexpected and heavily competing isomerization can be ascribed to the formation of SO_2 in the reaction mixtures. The dimerization[9] of thiophene-1,1-dioxide occurs through a transient and never isolated Diels–Alder adduct **9**, which immediately splits off SO_2 (Scheme 2). The bubbling of SO_2 in a benzene solution of mesitonitrile oxide causes indeed a complete isomerization to mesityl isocianate in a few minutes. The cycloadducts **11** of aromatic nitrile oxides with SO_2 have been described.[17] They are rather unstable and fragment by mild heating into aryl isocianate and SO_2, and shown in Scheme 2. The thermal stability of the mesityl derivative **11** should be even lower because of the higher migratory aptitude of mesityl and a fast decomposition at room temperature should occur, as observed. A similar effect of a mesityl substituent on the related fragmentation of oxathiadiazolinones was reported.[18] Thus, the competing formation of dimesitylurea in the cycloadditions of mesitonitrile oxide can be rationalized. Because of the decreased reactivity of this dipole, the dimerization of thiophene dioxide–and hence the formation of SO_2—competes with the cycloaddition and the instability of the mesityl adduct to SO_2, **11**, allows for the recycling of SO_2.

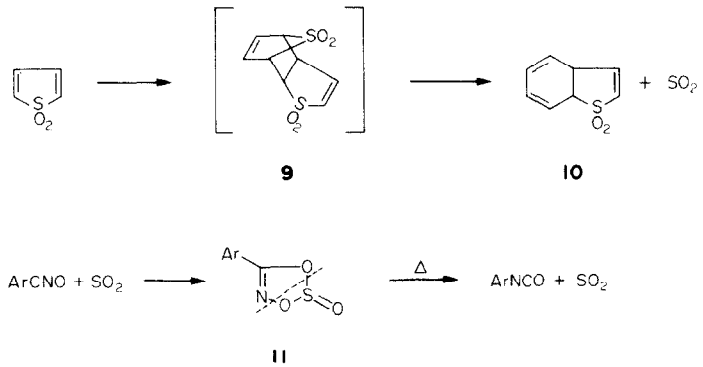
The cycloadditions to thiophene-1,1-dioxide are highly regio selective. On the other hand cycloadditions to the 2,3-dihydrothiophene-1,1-dioxide moiety of the monoadducts **1a,b** occur with lower regioselectivity and both the regioisomeric bisadducts **4a,b** could be isolated or their presence demonstrated, along with the prevailing adducts **3a,b**, in the cycloaddition mixtures. Thus, the directive effect of a sulfonyl group alone is high but unable to suppress the formation of the regioisomer. We have therefore investigated more extensively the behaviour of the dihydrothiophene dioxide systems, which could serve as a route to the missing regioisomers **2** (Scheme 3).

The unsubstituted 2,3-dihydrothiophene-1,1-dioxide adds BNO and mesitonitrile oxide yielding a mixture of cycloadducts **13a,b** and **14a,b** in a ratio 98:2, with a regioselectivity similar to that observed in the cycloadditions to monoadducts **1a,b** (99:1). The regiochemistry of the principal adducts **13a,b** has been confirmed by their formation in the hydrogenation of adducts **1a,b**. A bisadduct, **12a**, was isolated in low yield (6%) from the cycloaddition mixture of BNO. It forms by exposure of adduct **13a** to excess BNO. Similar adducts to the slightly reactive C=N bond of bicyclic isoxazolines have been frequently observed.[3–6]

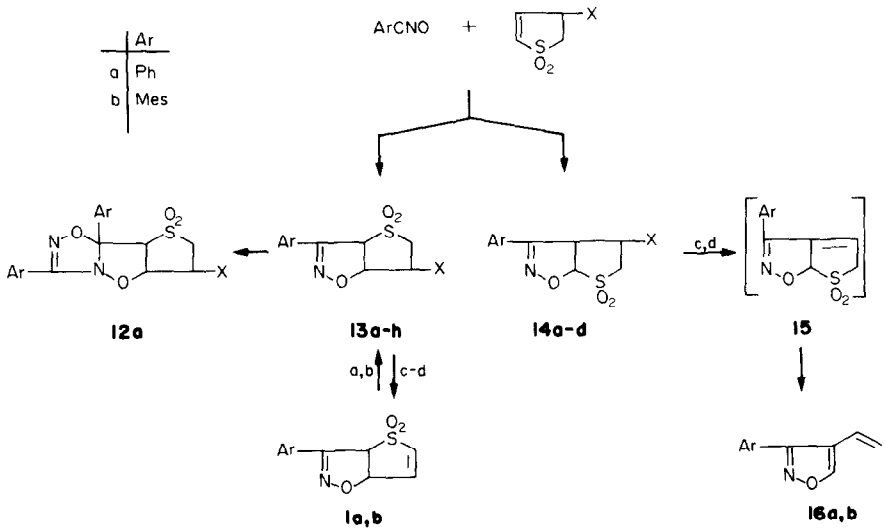
Cycloadditions to 3-acetoxy-2,3-dihydrothiophene-1,1-dioxide similarly yielded a mixture of adducts **13c,d** and **14c,d**. The anti stereochemistry of the adducts follows from the small coupling between 4- and 5-isoxazolinic hydrogens and the adjacent CHOAc. The major adducts **13a,d** undergo elimination with 1,5-diazabicyclo[5.4.0] undec-5-ene in boiling toluene, affording in fair yields adducts **1a,b**. Under the same conditions the minor adducts **14c,d** yield however isoxazoles **16a,b**. Isoxazole **16a** is identical with an authentic specimen[19] and the structure of **16b** follows from its NMR spectrum. The course of the elimination with adducts **14** indicates therefore a preferred formation of the β,γ-unsatured sulfones **15**, conjugated with the isoxazoline C=N. Under the reaction conditions, sulfones **15** undergo a rectrochelotropic reaction, with thermal extrusion of SO_2.[20]

In the cycloadditions to 3-chloro and 3-bromo-2,3-dihydrothiophene-1,1-dioxide the major adducts **13e–h** have been isolated in fair yields. Attempts to generate the 3-halo-2,3-dihydrothiophene dioxides *in situ*, by treatment of 3,4-dihalotetrahydrothiophene dioxides with one equivalent of triethylamine in benzene, afford a mixture of adducts **13** and the cycloadducts on thiophene dioxide.

Benzothiophene-1,1-dioxide is 7 times more reactive toward BNO than the isocyclic indene and a mixture of cycloadducts **17a,b** and **18a,b** (Scheme 4) is formed in the cycloadditions with benzo- and mesitonitrile oxides, in a 99.2:0.8 and 95:5 ratio, resp. The major adducts **17a,b** correspond to the orientation observed by Sauter and



Scheme 2.



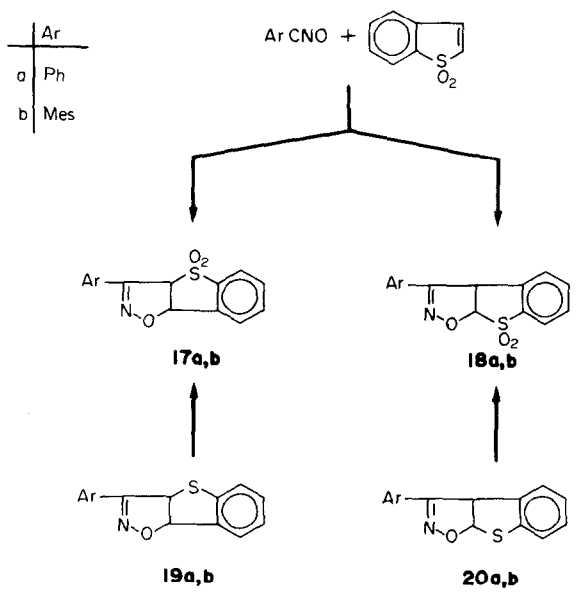
	Ar	X		Ar	X		Ar	X
13a	Ph	H	**13e**	Ph	Cl	**14a**	Ph	H
13b	Mes	H	**13f**	Mes	Cl	**14b**	Mes	H
13c	Ph	$OCOCH_3$	**13g**	Ph	Br	**14c**	Ph	$OCOCH_3$
13d	Mes	$OCOCH_3$	**13h**	Mes	Br	**14d**	Mes	$OCOCH_3$

Scheme 3.

Büyük[14d] with benzonitrile oxide. Adducts **17** and **18** have been independently obtained from the known benzothiophene adducts **19a,b** and **20a,b**.[5]

DISCUSSION

The removal of the lone pair of sulfur on oxidation results in loss of aromaticity in thiophene and in a somewhat enhanced 1,3-dipolar ophilic activity. The addition of BNO to the conjugated double bonds of thiophene and benzothiophene-1,1-dioxides occurs 25 and 7 times faster than the addition to the corresponding isocyclic systems, cyclopentadiene and indene, respectively. 2,3-Dihydrothiophene dioxide is however half as reactive as cyclopentene. The effect of the sulfonyl group on the regioselectivity of the cycloadditions is more straight, even if not constant. As shown in Table 2, substitution of a CH_2 with a sulfonyl group always causes an increase of the ratio I/II, favouring the 4-sulfonyl isoxazoline regioisomer I. The shift of regioselectivity is considerable when comparing cyclopentene with dihydrothiophene dioxide and the changes of $\Delta\Delta G^{\neq}$ amounts to 2.1–2.3 kcal/mol. The change is attenuated in the pair indene/benzothiophene dioxide (0.9–1.1 kcal/mol) and in the pair cyclopentadiene/thiophene dioxide could only be estimated higher than 0.

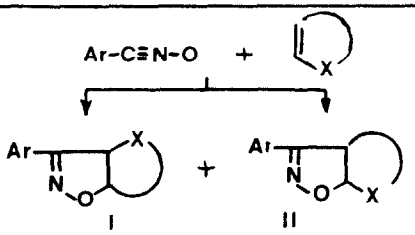


Scheme 4.

The trends in reactivity and regioselectivity discussed above can be satisfactorily rationalized in the framework of the FO treatment of cycloadditions.[21] The CNDO/2[22] eigenvectors and eigenvalues of the FOs of the dioxides and of the relevant isocyclic compounds are given in the Table 3 along with the polarization of the FOs defined as the difference between the squares of the coefficients.

The FOs of the dioxides are lowered in energy, relative to the isocyclic systems. The lowering of the HOMOs is however only moderate (0.3–0.5 eV), whereas the LUMOs are remarkably affected. The drop of LUMO energy is the largest in thiophene dioxide and is somewhat attenuated in benzothiophene dioxide. Thus, the lowering of the LUMOs parallels the increase of 1,3-dipolarophilic activity of thiophene dioxide and benzothiophene dioxide. The higher reactivity of these dioxides can then be ascribed to the increased electrophilicity of their double bonds induced by the sulfonyl group. In dihydrothiophene dioxide the FOs are similarly stabilized. The LUMO remains however too high, so that the main reactivity effect follows from the moderate HOMO

Table 2. Regioisomer distribution in the cycloaddition of nitrile oxides to thiophene dioxide, benzothiophene dioxide, 2,3-dihydrothiophene dioxide and the corresponding isocyclic dipholarophiles

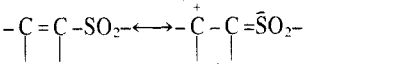


Dipolarophile	X	I/II Ph[c]	I/II Mes[d]	$\Delta\Delta G^{\neq}_{I/II}$[a] Ph	$\Delta\Delta G^{\neq}_{I/II}$[a] Mes	Charge[b] Ph	Charge[b] Mes
Thiophene-1,1-dioxide	SO_2	>99:1	>99:1	>2.48	>2.71	>0	--
Cyclopentadiene	CH_2	99:1	--	2.48	--		
Benzothiophene-1,1-dioxide	SO_2	99.2:0.8	95:5	2.61	1.74	0.89	1.06
Indene	CH_2	96:4	76:24	1.72	0.68		
2,3-dihydrothiophene--1,1-dioxide	SO_2	98:2	98:2	2.10	2.30	2.10	2.30
Cyclopentene	CH_2	50:50	50:50	0	0		

[a] Kcal/mole [b] $\Delta\Delta G^{\neq}_{SO_2} - \Delta\Delta G^{\neq}_{CH_2}$ [c] 0°, ether [d] 25°, benzene

lowering and reactivity decreases. The trends shown by the calculations are consistent with available spectroscopic evidence. The IP and EA of cyclopentadiene are known and are 8.58[23] and −1.05[24] eV, resp. The IP of thiophene dioxide can be estimated at 9.43 eV, assuming the same lowering observed in the di-tert-butyl derivatives,[7] and the EA can be evaluated at 0.33 eV from the empirical relationship $E_{(\pi\pi^*)} = \text{IP-EA-}(J_{ij} - 2K_{ij})$,[21] using the transition energies of cyclopentadiene (5.71 eV)[25] and thiophene dioxide (4.29 eV)[9,26] and the value of $J_{ij} - 2K_{ij}$ derived for cyclopentadiene (4.81 eV).

The shapes of the FOs are displayed in Fig. 1. The HOMOs of thiophene and benzothiophene dioxides look like the butadiene and styrene HOMOs and the polarizations are only slightly decreased with respect to those of cyclopentadiene and indene, as shown in Table 3. The LUMOs of the dioxides differ however significantly from the LUMOs of butadiene and styrene. The LUMOs are still polarized toward the terminal polyene carbon, but the polarization is almost vanished. Thus, the replacement of CH_2 with the sulfonyl group mainly induces a large polarization of the LUMO toward the β-carbon, which almost compensates the opposite effect of the polyenic fragments of these dipolarophiles. The influence of the sulfonyl group on the shapes of the FOs shows up more clearly in dihydrothiophene dioxide. The HOMO is only slightly polarized (toward the α carbon) whereas the LUMO is highly localized on the β carbon. Interestingly enough, the effect of the sulfonyl group on the LUMO polarizations corresponds to the VB representation **21**, which is often drawn to account for the reactivity of vinyl sulfones.[27] In MO terms the effect follows[28] from the availability of low lying vacant $\sigma^*_{SO_2}$ and $\pi^*_{SO_2}$ orbitals.



21

The sulfonyl group has only a small influence on the HOMO polarization. The direction of the effect is however variable and deserves some comments. Thus, substitution of CH_2 with the sulfonyl fragment causes a polarization toward the β carbon in thiophene and benzothiophene dioxides, thereby lowering the HOMO polarizations of the isocyclic systems (see Table 3), whereas in dihydrothiophene dioxide polarization occurs towards the α carbon. These opposite effects depend upon the nodal properties of the dipolarophiles. The HOMO of a diene is antisymmetric with respect to a plane normal to the molecular plane and does not interact with the (symmetric) π orbitals of a CH_2 fragment. An interaction does however occur with a sulfonyl fragment, which possesses an antisymmetric orbital π_{SO_2} rather high in energy (see Fig. 2). This interaction (spiroconjugation)[29] causes a decrease of the HOMO polarization by mixing in the antisymmetric vacant diene orbital in a negative fashion.[28] The inductive effect of the SO_2 fragment stabilizes the diene levels and partially compensates for the dynamic mixing shown in Fig. 2 through the opposing static mixing.[28] In dihydrothiophene dioxide no symmetry restrictions are operative and the interaction with the π orbital of methylene surpasses the composite effect of the sulfonyl, since the influence of the

Table 3. CNDO/2 eingenvectors and eigenvalues of the frontier orbitals[a]

	HOMO				LUMO			
	C_1	C_2	(eV)	P[b]	C_1	C_2	(eV)	P[b]
Thiophene-1,1-dioxide	.517	.367	-12.76	0.13	.438	-.399	0.27	.03
Cyclopentadiene	.575	.413	-12.46	0.16	.502	-.392	3.15	.10
Benzothiophene-1,1-dioxide	.459	.309	-12.19	0.11	.382	-.346	0.61	.03
Indene	.487	.333	-11.71	0.13	.449	-.317	2.70	.10
2,3-dihydrothiophene-1,1-dioxide	.443	.417	-13.82	0.02	.467	-.609	2.72	-.15
Cyclopentene	.494	.494	-12.67	0.00	.631	-.631	4.72	0.00

[a]The geometries of the dioxides have been constructed according to M.H.Palmer and R.H.Findlay, J.C.S. Perkin II, 1223 (1975)

[b]Polarization defined as $C_1^2-C_2^2$

occupied orbitals of the latter fragment is significantly reduced by the action of a low lying orbital $\sigma^*_{SO_2}$ as well as by static mixing.

In cycloadditions of nitrile oxides to thiophene and benzothiophene dioxides, the regiochemistry remains determined by the HOMO (dipolarophile)–LUMO (dipole) interaction. In spite of the lowering of the FOs, the large depolarization of the LUMOs of these dipolarophiles caused by the sulfonyl group reduces the regiochemical influence of the HOMO (dipole)–LUMO (dipolarophile) interaction, which is even less influential than in the isocyclic systems. In cycloadditions to dihydrothiophene dioxides both interactions concur in favouring the formation of adducts I. The regioselective effects of these interactions are not, however, vastly dominating, since the HOMO of the dipolarophile as well as the HOMO of nitrile oxide dipoles[8] are only moderately polarized, and the formation of small amounts of regioisomers II are observed.

The shapes of the FOs discussed above similarly ac-

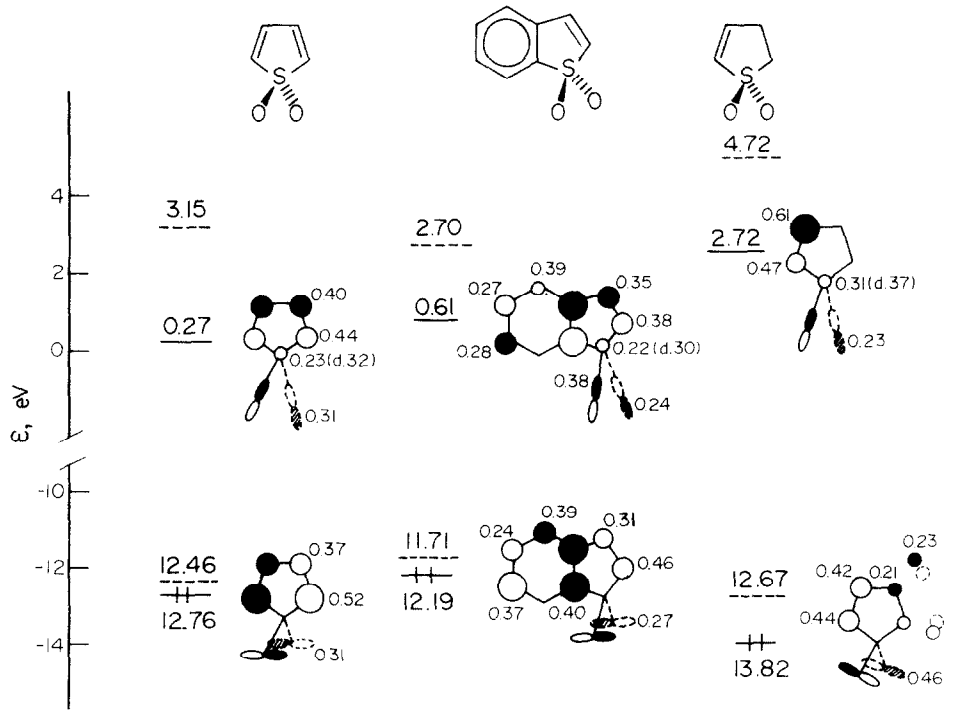


Fig. 1. Frontier orbitals of thiophene dioxide, benzothiophene dioxide and 2,3-dihydrothiophene dioxide (CNDO/2). Dashed lines represent the FO energies of cyclopentadiene, indene and cyclopentene, resp.

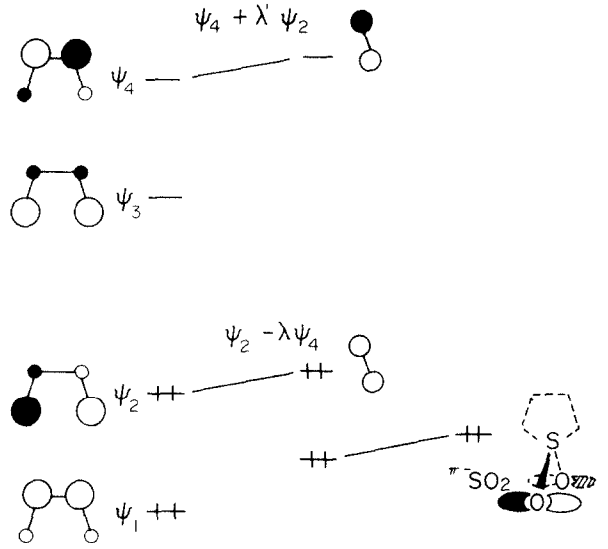


Fig. 2. The antisymmetric π_{SO_2} orbital decreases the HOMO polarization in thiophene dioxide by mixing into ψ_2 the antisymmetric vacant orbital ψ_4 of the diene fragment.

count for the analogous orientation observed in cycloadditions of nitrile imines[14c] and nitrones[13,14d] as well as for the attack of the nucleophilic carbon terminus of the diazoalkanes[14a,b] to the α carbon of benzothiophene dioxide.

CONCLUSIONS

The frontier orbitals discussed above account nicely for the behaviour of the dioxides as dipolarophiles in 1,3-dipolar cycloadditions and clarify other aspects of the chemistry of this interesting class of compounds. Thus, amines add to the β-position of the thiophene dioxide.[9] Since the LUMO of thiophene dioxide is only slightly polarized, the destabilizing HOMO (dioxide)–HOMO (nucleophile) interaction (exchange repulsion),[30] which is not reduced by symmetry in nucleophilic additions, drives the orientation of nucleophilic addition on the β-carbon, which has a significantly lower coefficient in the HOMO.

Thiophene dioxide can be easily trapped with dienes or 1,3-dipoles but trapping with dienophiles in Diels–Alder reactions, in a synthetically useful annelation reaction,[31] usually fails, because of the faster dimerization. The fast dimerization follows from the reduced HOMO–LUMO gap of the dioxide, as discussed above. The tendency toward dimerization can only be overcome in cycloadditions with dienophiles which have similar reduced HOMO–LUMO gaps. Diels Alder reactions occur indeed with highly conjugated dipolarophiles like indene[7] and fulvenes[12] or with strained cyclopropenes.[11] Thus, the FOs give a deeper understanding of the factors involved in cycloadditions and allow for more rational extensions in the applications of these dienes in the synthesis of complex molecules and in drug design.

EXPERIMENTAL

All mps are uncorrected. IR spectra: Perkin–Elmer model 197 spectrophotometer, Nujol mulls. NMR spectra: Perkin–Elmer R-12 and Bruker WP-80 spectrometers. Microanalyses were performed by Dr. L. Maggi Dacrema. Satisfactory analytical data ($\pm$0.4% for C, H, N) were obtained for all new compounds. Quantitative determinations were carried out through gas chromatographic and densitometric analyses. GLC analyses were performed on a glass column, packed with 2% SE 30 and 1% OV-17 on Gas Chrom Q 100/120 mesh on a Hewlett Packard 5720 A instrument. Densitometric determinations were carried out on Vitatron TLD 100/Hg densitometer, using precoated TLC plates silica gel 60 F_{254} (Merck) and HPTLC plates RP-8 F_{254}. Column chromatography and qualitative TLC : silica gel H and GF_{254} (Merck) respectively, eluent cyclohexane : AcOEt 9 : 1 to 7 : 3 unless otherwise specified.

Starting materials. 3,4 - Dibromotetrahydrothiophene - 1,1 - dioxide,[9] 3,4 - dichlorotetrahydrothiophene - 1,1 - dioxide,[32] 3 - bromo - 4 - acetoxytetrahydrothiophene - 1,1 - dioxide,[33] 3 - acetoxy - 2,3 - dihydrothiophene - 1,1 - dioxide,[33] 2,3 - dihydrothiophene - 1,1 - dioxide[9] and benzothiophene - 1,1 - dioxide[34] were prepared according to standard procedures. 3 - Bromo -[9,33] and 3 - chloro - 2,3 - dihydrothiophene - 1,1 - dioxide[32] were obtained by treating 3,4 - disubstitutedtetrahydrothiophene - 1,1 - dioxide, in anhyd benzene, with an equimolecular amount of Et_3N. The triethylammonium salts were filtered off; the benzene solution was washed with water, dried on Na_2SO_4 and evaporated under reduced pressure, giving the unsaturated 3-substituted derivatives.

Cycloadditions to thiophene-1,1-dioxide

(a) *Benzonitrile oxide*; *reactant ratio* 1 : 1. To a stirred soln of benzhydroximic acid chloride (0.155 g, 1 mmole) and 3,4-dibromotetrahydrothiophene-1,1-dioxide (0.277 g, 1 mmole) in anhyd benzene (50 ml), an excess of Et_3N (5 mmole) was added. After 2 days at rt, the triethylammonium salts were filtered off and the filtrate was evaporated under reduced pressure. Crystallization of the residue from EtOH yielded 0.21 g (90%) of monoadduct **1a**, white needles m.p. 165–166°. TLC of the mother liquors showed the presence of monoadduct **1a** along with traces of bisadduct **3a** and 3,4-diphenylfuroxane. In the NMR spectrum of the residue of the mother liquors only the signals of monoadduct **1a** were detectable. In duplicate experiments thiophene dioxide and benzonitrile oxide were generated separately, by treatment of the precursors with Et_3N in benzene. After 5 min, the triethylammonium salts were filtered off and the solutions mixed. Monoadduct **1a** was obtained with a similar yield.

Reactant ratio 2 : 1. Operating as above with benzhydroximic acid chloride (16 mmoles), 3,4-dibromotetrahydrothiophene-1,1-dioxide (8 mmole) and Et_3N (40 mmole) in benzene, the bisadduct **3a**, precipitated along with the Et_3N salts, was filtered off. By treatment with water **3a** was isolated (1.12 g, 42%), white crystals from AcOH, mp 215–216°. The benzene filtrate was evaporated under reduced pressure. The residue consisted of the monoadduct **1a** (48% yield, GLC) along with 3,4-diphenylfuroxane and the bisadducts **3a** (0.26%) and **4a** (0.4%), whose yields were determinated by a densitometric analysis (99 : 1 total ratio, benzene serving as eluent).

Similar results were obtained in the cycloadditions of BNO to 3,4-dichlorotetrahydrothiophene-1,1-dioxide.

Cycloaddition to monoadduct **1a**. Cycloaddition of BNO (10 mmole) to the monoadduct **1a** (1 mmole) in anhyd benzene at rt afforded a 80% yield of bisadduct **3a**, which precipitated along with Et_3NHCl. The mother liquors contained **3a** and the regioisomeric bisadduct **4a** (0.8%, densitometric analysis: **3a** : **4a** total ratio 99 : 1).

(b) *Mesitonitrile oxide*; *reactant ratio* 1 : 1. To a solution of MesCNO (0.19 g, 1.2 mmole) and 3,4-dibromotetrahydrothiophene-1,1-dioxide (0.33 g, 1.2 mmole) in 100 ml of anhyd benzene, an excess of Et_3N (0.6 ml, 4.2 mmole) was added. Et_3NHBr precipitated immediately. The precipitate was filtered off after 12 h and washed with water, leaving a residue of dimesitylurea (0.1 g, 58%). The benzene solution was evaporated under reduced pressure. Crystallization afforded, besides further dimesitylurea, monoadduct **1b** (0.09 g, 27%), white needles from EtOH, m.p. 174–175° (lit[13] 170–171°). The mother liquors contained mainly monoadduct **1b** and only traces of bisadduct **3b**.

Reactant ratio 2 : 1. Mesitonitrile oxide (2.58 g, 16 mmole), 3,4-dibromotetrahydrothiophene-1,1-dioxide (2.24 g, 8 mmole) and Et_3N (8 mmole) were reacted as above. After 1 week, dimesitylurea and Et_3NHBr were filtered off. The benzene solution was evaporated; grinding of the residue with EtOH afforded bisadduct **3b** (1.05 g, 30% yield), white needles m.p. 216–218° (lit[13] 229–230°) from EtOH. The mother liquors contained monoadduct **1b** (10% yield, GLC) and the bisadducts **3b** (0.5%) and **4b** (0.3%), whose yields were determined by densitometric analysis (99 : 1 total ratio), CH_3CN : H_2O 7 : 3 serving as eluent with HPTLC plates.

Similar results were obtained in the cycloadditions of MesCNO to 3,4-dichlorotetrahydrothiophene-1,1-dioxide.

Cycloaddition to monoadduct **1b**. A soln of **1b** and excess mesitonitrile oxide (10 equiv) in benzene was kept 1 month at rt. Adducts **3b** and **4b** were formed in a 99 : 1 ratio as determined by densitometric analysis. Evaporation of the solvent and grinding of the residue with EtOH afforded bisadduct **3b** in a 50% yield.

(c) *Oxidation of the thiophene adducts* **6a,b**, **7b**, **8a,b**. The thiophene adducts[5] were oxidized with a 100% excess of m-chloro perbenzoic acid in benzene soln. After 1 week at rt, the benzene solution was washed with aq $NaHCO_3$ and extracted with chloroform. The organic layer was washed with H_2O, dried on Na_2SO_4 and evaporated under reduced pressure, giving 50–70% of the dioxides **1a,b** and **3b**, identical with the products obtained in the cycloadditions to thiophene-1,1-dioxide, and dioxides **4a**, white needles from acetic acid, m.p. 214–215°, and **4b**, white needles from EtOH, m.p. 215–216°.

Cycloadditions to 2,3-dihydrothiophene-1,1-dioxide derivatives

(a) *Benzonitrile oxide.* To a soln of 1.55 g (10 mmole) of benzhydroximic acid chloride and 1.18 g (10 mmole) of 2,3-dihy-

drothiophene-1,1-dioxide in anhyd benzene, Et_3N (1.7 ml, 12 mmole) was added dropwise. After 2 days, Et_3N.HCl was filtered off and the benzene solution was evaporated at reduced pressure. Grinding of the residue with EtOH afforded cycloadduct **13a** (1.1 g), white needles m.p. 156–157°. Column chromatography of the mother liquors gave (i) bisadduct **12a** (0.1 g, 5.6%), white crystals m.p. 164–165° from EtOH, NMR ($CDCl_3$): CH_2 2.1–3.6 δ,m (4H); 4- and 5-isoxazoline protons 4.39δ,d and 5.05δ,m ($J_{4,5}$4.1 Hz); aromatic protons 7.2–8.2δ,m (10H); (ii) monoadduct **13a** (0.75 g, 78% total yield); (iii) monoadduct **14a** (50 mg, 2%), white crystals m.p. 175–176° from EtOH.

Operating as above with 3 - acetoxy - 2,3 - dihydrothiophene - 1,1 - dioxide and grinding the residue, adduct **13c**, white needles m.p. 191–192° from EtOH, was isolated. Column chromatography (benzene: AcOEt 9:1 as eluents) of the mother liquors gave, besides further **13c** (81% total yield), adduct **14c** (2%), white crystals m.p. 226–227° from EtOH.

The adducts to 3-chloro and 3 - bromo - 2,3 - dihydrothiophene - 1,1 - dioxide can be obtained in fair yields only in the absence of Et_3N. To a stirred solution of benzhydroximic acid chloride (32 mmole) in anhyd benzene, a stoichiometric amount of Et_3N was added. After 5 min, Et_3NHCl was filtered off and the 3 - halo - 2,3 - dihydrothiophene - 1,1 - dioxide (32 mmole) was added to the solution. After keeping 1 day at rt, the adducts **13e** (86%), white crystals m.p. 200–201° from EtOH, and **13g** (84%), soft white needles m.p. 216–217° from THF-benzene were filtered off. Treatment of adducts **13e** and **13g** with Et_3N in anhyd benzene at rt caused an immediate dehydrohalogenation, yielding adduct **1a** in quantitative yield. Mixtures of adducts **13e,g** and the dehydrohalogenation product **1a** were formed upon treatment of a benzene solution of benzhydroximic acid chloride (1 mmole) and 3,4 - dihalo - tetrahydrothiophene - 1,1 - dioxide (1 mmole) with 2 mmole of Et_3N.

(b) *Mesitonitrile oxide.* A soln of MesCNO (1.61 g, 10 mmole) and 2,3 - dihydrothiophene - 1,1 - dioxide (1.18 g, 10 mmole) was left at rt. for 2 weeks. The solvent was evaporated, and the residue was grinded with EtOH, affording adduct **13b** (1.95 g), white crystals, m.p. 169–170°. Column chromatography of the mother liquors ($CHCl_3$ as eluent) gave, besides **13b** (0.5 g, 90% total yield), adduct **14b** (50 mg, 1.8%), white crystals m.p. 154–155° from EtOH.

In the cycloaddition to 3 - acetoxy - 2,3 - dihydrothiophene - 1,1 - dioxide the major adduct **13d** precipitated from the benzene solution, white crystals m.p. 232–233° from EtOH. Column chromatography (benzene: AcOEt 9:1 serving as eluents) of the residue of the mother liquors afforded again **13d** (78% total yield) and the regioisomeric adduct **14d** (1.5%), white crystals m.p. 181–182° from EtOH.

The adducts **13f,h** to 3-chloro and 3 - bromo - 2,3 - dihydrothiophene - 1,1 - dioxide precipitated by concentration of the benzene solutions: **13f** (83%), white silver needles m.p. 225–226° from EtOH and **13h** (79%), white needles m.p. 219–220° from THF. The adducts **13f,h** dehydrohalogenate by treatment with Et_3N in benzene at rt affording the elimination product **1b** in almost quantitative yields.

(c) *Catalytic hydrogenation of monoadducts* **1a** *and* **1b**. A soln of **1a,b** (1 mmole) in ethyl acetate (50 ml) and AcOH (16 ml), with 100 mg of 10% C Pd, was hydrogenated at rt. After 20 min the theoretical amount of H_2 was adsorbed. Evaporation of solvent under reduced pressure gave the saturated dioxides **13a,b** in quantitative yields, identical with the major adducts obtained in the cycloadditions to 2,3-dihydrothiophene-1,1-dioxide.

(d) *Treatment of adducts* **13c,d** *and* **14c,d** *with* 1,5-*diazabicyclo*[5.4.0] *undec-5-ene.* A soln of adduct **13c,d** and 1,5-diazabicyclo[5.4.0] undec-5-ene (1.5 equiv) in anhyd toluene was refluxed 2 h. The mixture was diluted with $CHCl_3$, washed with dil HCl, NaOH and water, dried and evaporated. Crystallization of the residue afforded the elimination products **1a,b** in fair yields (70–80%). Under similar conditions adducts **14c** and **14d** afforded isoxazole **16a** (60%), b.p. (bath) 150–170°/0.1 mm, light yellow crystals m.p. 45° from hexane, identical with an authentic specimen,[19] and **16b** (64%), colorless oil, b.p. (bath) 150–160°/0.1 mm, NMR ($CDCl_3$): olefinic protons 5.04δ,d (1H); 5.09δ,d (1H); 6.10δ,dd (1H); aromatic protons 6.93δ,s (2H) and isoxazole 5-H 8.5δ,s (1H).

Cycloadditions to benzothiophene-1,1-dioxide

(a) *Benzonitrile oxide.* To a stirred soln of benzhydroximic acid chloride (1 g, 6.4 mmole) and benzothiophene-1,1-dioxide (1.05 g, 6.3 mmole) in anhyd benzene (30 ml), a stoichiometric amount of Et_3N was added. After 2 days at rt., the usual work-up yielded a residue. Crystallization from EtOH gave **17a** (1.65 g, 92%), white needles m.p. 175–176° (lit[14d] 175–176°). Column chromatography of the mother liquors (benzene: AcOEt 9:1 as eluents) afforded 10 mg of the regioisomer **18a**, white crystals m.p. 140–141° from EtOH. The ratio of the regioisomeric adducts in the reaction mixture was 99.2:0.8 as determined by densitometric analysis (benzene: AcOEt 9:1).

(b) *Mesitonitrile oxide.* A soln of mesitonitrile oxide (1.61 g, 10 mmole) and benzothiophene-1,1-dioxide (1.66 g, 10 mmole) in anhyd benzene was kept at rt for 2 days. White platelets of **17b** (2.38 g, 73%), m.p. 263–265° from diisopropyl ether, precipitated off. The mother liquors were evaporated. Column chromatography ($CHCl_3$ as eluent) gave, besides traces of unreacted benzothiophene-1,1-dioxide and cycloadduct **17b** (0.55 g, 90% total yield), the regioisomer **18b** (0.16 g, 5% yield), m.p. 220–221° from EtOH. The ratio of the regioisomers in the reaction mixture was 95:5 as determined by a densitometric analysis ($CHCl_3$ as eluent).

(c) *Oxidation of the benzothiophene adducts* **19a,b** *and* **20a,b**. A suspension of benzothiophene cycloadducts **19a,b** and **20a,b**[5] (0.5 mmole) in 15 ml of glacial acetic acid and 12 ml of 30% hydrogen peroxide was heated for 1 h on a steam bath. After cooling, the solution was poured into cold water and neutralized with $NaHCO_3$. The precipitate was filtered off and washed with water, affording in fair yields (70–80%) the dioxides **17a,b** and **18a,b**, identical with cycloadducts obtained in the cycloadditions to benzothiophene-1,1-dioxide.

Competition experiments. BNO (0.1 mmole) and thiophene-1,1-dioxide (0.5 mmole) were generated in diethyl ether solution at 0° in the presence of cyclopentene (2–10 mmole). After keeping two days at 0°, the ratio of the dioxide adduct **1a** and the cyclopentene adduct[35] was determined by densitometric analysis and a reactivity ratio of 50 ± 10:1 of thiophene-1,1-dioxide and cyclopentene was calculated. From the known relative rate of cyclopentadiene and cyclopentene (2.02),[3] a 25-fold increase of reactivity of thiophene-1,1-dioxide relative to cyclopentadiene was computed. The relative rates of 2,3-dihydrothiophene-1,1-dioxide and cyclopentene and that of benzothiophene-1,1-dioxide and indene have been determined similarly (0.5 and 7 respectively), by generating BNO in the presence of mixtures of 2,3-dihydrothiophene-1,1-dioxide (10 equiv) and cyclopentene (5 equiv) and mixtures of benzothiophene-1,1-dioxide (5 equiv) and indene (20 equiv).

Calculations. The calculations were executed with a CNINDO[36] program on a CDC 6600 computer available at the University of Catania.

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