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SELECTIVITY IN CYCLOADDITIONS—XI[1]

CYCLOADDITIONS OF NITRILE OXIDES TO METHYL STYRYL SULFIDES, SULFOXIDES AND SULFONES. REGIOCHEMISTRY

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Abstract—*E* and *Z* methyl styryl sulfides undergo highly regioselective cycloadditions with benzo and mesitonitrile oxide. The regioselectivity is lower with sulfoxides and is reversed in the case of sulfones. The directing effect of the thio moieties has been clarified in the framework of the frontier model of cycloaddition reactions. The lower effect of the thio substituents in the cycloadditions of cyclic dipolarophiles depends upon the nodal properties of their FOs.

In previous papers we have dealt with the reactivity of heteroaromatic compounds in the 1,3-dipolar cycloaddition with nitrile oxides. In spite of the large decrease of dipolarophilic activity of the heteroaromatics because of the loss of aromaticity in the cycloaddition transition states, the regiochemistry of the cycloadditions fits the frontier orbital (FO) approach well and parallels the changes of the FO polarizations.[3] Thus, in cycloadditions with the moderately electrophilic benzonitrile oxide (BNO), benzothiophene[4] and its non aromatic 1,1-dioxide derivative[1] differ in dipolarophilic activity by more than two powers of ten. The regiochemistry of these cycloadditions, however, nicely reflects the low and high polarizations of their HOMOs.

The following is a study of the regioselectivity of the cycloadditions of BNO and mesitonitrile oxide (MNO) to the related (*E*)- and (*Z*)-styryl sulfides, sulfoxides and sulfones. Aside from providing reference data for the evaluation of the influence of the cyclic conjugation upon the regioselectivity and eventually a clarification of the effect in FO terms, the set of these dipolarophiles allows for the assessment of the effect of the $S(O)_nR$ moieties upon the regioselectivity. No systematic comparison is available in the literature of cycloaddition reactions, in spite of the synthetic utility of the S containing moieties. Only scattered studies dealt with the directive effect of sulfide[4] and sulfoxide[5] substituents. The influence of the sulfonyl group has been more extensively studied. Vinyl sulfones add nitrile oxides to yield mainly 5-sulfonyl isoxazolines[6] whereas β-alkyl[1,7] and phenyl[8] substituents cause a reversal of regiochemistry. A similar behaviour is observed with the more nucleophilic nitrones,[9] which show an increased preference for reversal.[7,9,10] Diazoalkanes behave differently. A regiospecific cycloaddition occurs with vinyl[11,12] and propenyl sulfones,[11] yielding the cycloadducts which arise by binding the nucleophilic dipole carbon to the unsaturated carbon β to the sulfone substituent, whereas mixtures of cycloadducts are formed with styryl[11] and strained[13] sulfones.

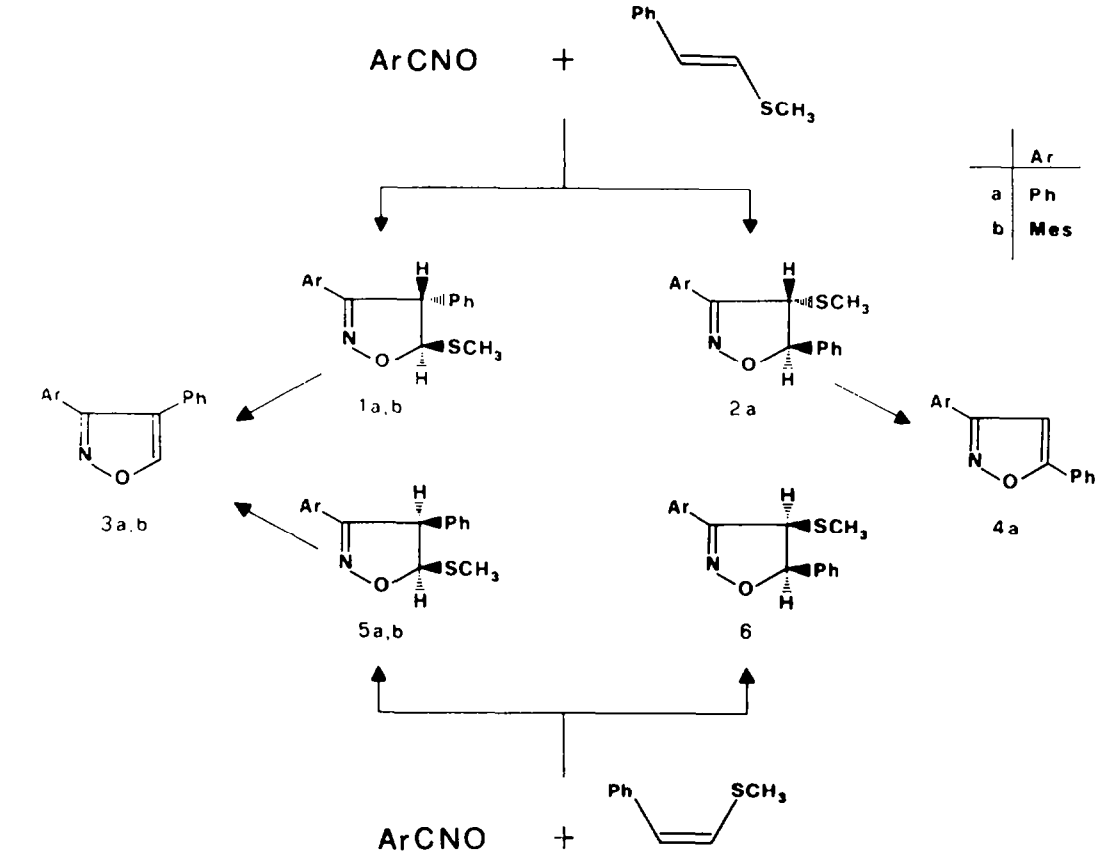
RESULTS

The dipolarophilic activity of the *trans* (*E*)-methyl styryl sulfide, sulfoxide and sulfone toward nitrile oxides is only moderate. The ω-thiomethyl substituent causes a 70-fold decrease of the dipolarophilic activity of styrene toward BNO and a similar decrease occurs with the sulfoxide and the sulfone. The drop compares well to those observed in similar *trans* disubstituted dipolarophiles.[14] The rather low reactivity of these styryl derivatives causes the dimerization of the dipole[15] to complete heavily in the preparative experiments, which were run with only a slight excess of the dipolarophiles to avoid complications in the separation procedures. Fair yields are obtained with mesitonitrile oxide, which is stable toward dimerization.

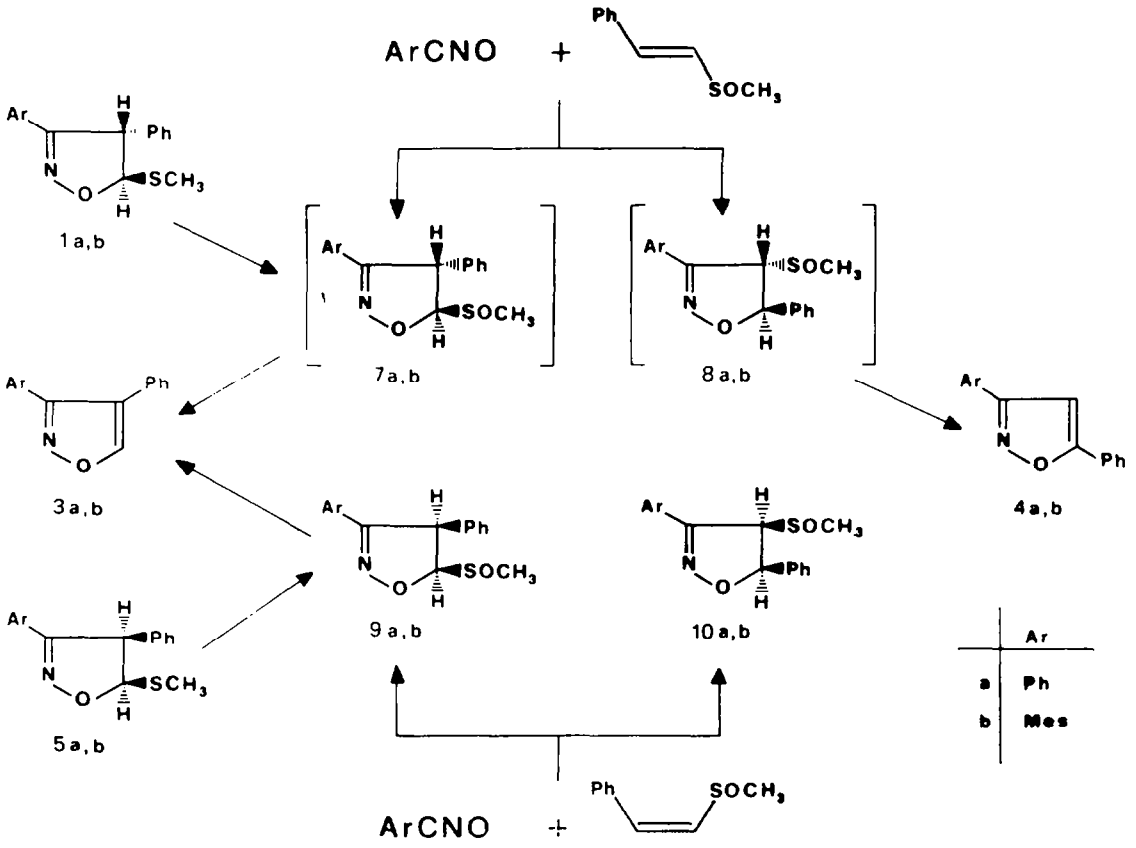
The (*E*)-sulfide undergoes a highly regioselective cycloaddition with BNO and mesitonitrile oxide. The major cycloadducts **1a, b** (Scheme 1) crystallized out from the reaction mixtures with a 23 and 90% yield, resp. Along with **1a** the minor regioisomer **2a** was formed in a 97 : 3 ratio and a sample was isolated by column chromatography. The less reactive (*Z*)-sulfide similarly yielded the *cis*-isoxazolines **5a, b** as the principal adducts, albeit with lower yields.

The structures of the adducts **1a, b** and **5a, b** rely upon the conversion to the known isoxazoles **3a, b** by acid catalyzed elimination while isoxazole **4a** was formed by oxidation of **2a** with *m*-chloroperbenzoic acid. The NMR spectra of the adducts are fully consistent with the assignments and are gathered in Table 1. The stereochemistry follows from the comparison of the isoxazolinic coupling constants ($J_{cis} > J_{trans}$)[16] and the regiochemistry from the spacings between the isoxazolinic hydrogens. Because of the higher deshielding effect of a phenyl relative to a thiomethyl substituent,[17] the spacing of a 5-phenyl substituted isoxazoline is larger than that of the 4-phenyl regioisomer. The trend becomes more manifest in the spectra of the isoxazolines carrying sulfoxide and sulfone substituents, allowing for a ready assignment. Noteworthy is the solvent dependence of the chemical shifts of these S containing isoxazolines. In DMSO the isoxazolinic protons of sulfides and sulfoxides are deshielded (0.2–0.5 ppm) and the effect becomes remarkable larger (1 ppm) in the sulfones.

In the cycloaddition of BNO and mesitonitrile oxide to the (*E*)-sulfoxide, a mixture of the isoxazoles **3a, b** and **4a, b** was obtained in a 45 : 55 and 79 : 21 ratio, resp. The



Scheme 1.



Scheme 2.

Table 1. Chemical shifts[a] and coupling constants[b] of cycloadducts

Comp.	H_4[d]	H_5[d]	$J_{4,5}$	R
1a	4.58d (5.09d)	5.59d (5.83d)	3.3 (3.3)	CH_3 2.28 (2.26)
1b	4.29d (4.58d)	6.01d (6.28d)	3.2 (3.7)	" 2.38 (2.35)
2a	4.46d (5.08d)	5.79d (5.91d)	3.6 (3.4)	" 2.12 (2.12)
5a	4.88d (5.30d)	6.00d (6.12d)	9.5 (9.3)	" 2.21 (2.17)
5b	5.03d (5.34d)	6.09d (6.27d)	9.0 (9.3)	" 2.22 (2.26)
9a	5.36s (5.48d)	5.36s (5.75d)	- (9.8)	" 2.70 (2.59)
9b	5.22s (5.08s)	5.22s (5.68s)	- -	" 2.65 (2.69)
10a	4.79d	6.02d	9.3	" 2.59
10b	4.37d (5.07d)	6.04d (6.19d)	9.9 (9.9)	" 2.48 (2.69)
11a	5.27d (5.89d)	5.45d (6.20d)	4.0 (3.3)	" 3.01 (3.60)
11b	5.29d (5.25d)	5.66d (6.42d)	3.9 (3.9)	" 3.09 (3.21)
11c	5.28d	5.51d	3.5	
11d	5.48d	5.73d	4.6	
12a	4.93d (6.11d)	6.38d (6.47d)	2.8 (2.9)	" 2.85 (3.12)
12b	4.82d (5.59d)	6.32d (6.37d)	5.3 (5.3)	" 2.53 (2.59)
12c	5.07d (6.23d)	6.39d (6.32d)	3.3 (3.9)	
12d	5.04d (5.52d)	6.39d (6.21d)	6.6 (6.4)	
12e	4.91d (6.06d)	6.37d (6.42d)	3.3 (3.6)	
12f	4.81d (5.47d)	6.37d (6.36d)	5.4 (5.1)	
13a	5.43d (5.89d)	5.62d (6.17d)	10.0 (10.6)	" 2.60 (2.73)
13b	5.71s (6.11d)	5.71s (6.23d)	- (10.6)	" 2.84 (2.82)
13e	5.42d	5.71d	10.6	
13f	5.63s	5.63s	-	
14e	5.08d (6.13s)	6.09d (6.13s)	9.3 -	" 2.53 (2.29)
14b	4.95d (5.72d)	6.09d (6.22d)	10.6 (9.9)	" 2.47 (2.41)
14e	5.08d (6.05s)	6.01d (6.05s)	8.6 -	
14f	4.98d (5.62d)	6.03d (6.19d)	10.3 (10.3)	

a) Chemical shifts in parts per million (δ) from internal Me_4Si. Multiplicity: d, doublet; s, singlet. Solvent: $CDCl_3$ ($DMSO-d_6$).

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.

Analytical data for compounds of Table 1.

Compound	Formula	Found % C	H	N	Required % C	H	N
1a	$C_{16}H_{15}NOS$	71.51	5.80	5.38	71.36	5.61	5.20
1b	$C_{19}H_{21}NOS$	73.42	6.81	4.61	73.29	6.80	4.50
2a	$C_{16}H_{15}NOS$	71.20	5.43	5.32	71.36	5.61	5.20
5a	$C_{16}H_{15}NOS$	71.25	5.48	5.41	71.36	5.61	5.20
5b	$C_{19}H_{21}NOS$	73.21	6.79	4.61	73.29	6.80	4.50
9a	$C_{16}H_{15}NO_2S$	67.28	5.24	4.98	67.36	5.30	4.91
9b	$C_{19}H_{21}NO_2S$	69.74	6.52	4.25	69.70	6.47	4.28
10a	$C_{19}H_{21}NO_2S$	69.80	6.55	4.33	69.70	6.47	4.28
11a	$C_{16}H_{15}NO_3S$	63.51	5.24	4.51	63.78	5.02	4.65
11b	$C_{19}H_{21}NO_3S$	66.27	6.26	4.36	66.46	6.16	4.08
12a	$C_{16}H_{15}NO_3S$	64.06	4.84	4.40	63.78	5.02	4.65
12b	$C_{19}H_{21}NO_3S$	66.29	6.14	4.22	66.46	6.16	4.08
12d	$C_{24}H_{23}NO_3S$	70.95	5.69	3.49	71.09	5.72	3.46
12f	$C_{22}H_{27}NO_3S$	68.37	7.06	3.68	68.55	7.06	3.63
13a	$C_{16}H_{15}NO_3S$	63.66	5.09	4.81	63.78	5.02	4.65
13b	$C_{19}H_{21}NO_3S$	66.58	6.25	4.17	66.46	6.16	4.08
14a	$C_{16}H_{15}NO_3S$	63.53	4.95	4.77	63.78	5.02	4.65
14b	$C_{19}H_{21}NO_3S$	66.55	6.18	4.23	66.46	6.16	4.08
14f	$C_{22}H_{27}NO_3S$	68.43	7.01	3.72	68.55	7.06	3.63

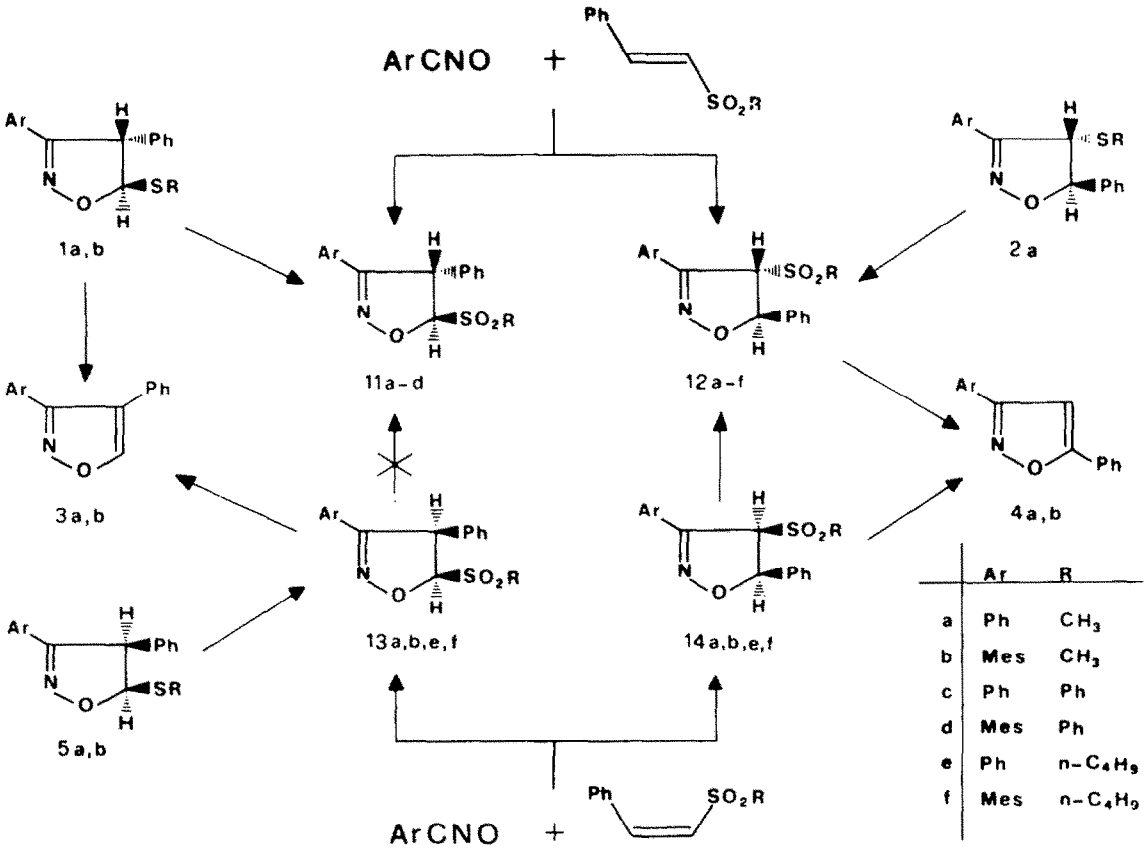
elusive formation of the cycloadducts 7 and 8 (Scheme 2) was proved by oxidation of the methylthio adducts **1a, b** and **2a** with *m*-chloroperbenzoic acid, yielding mainly the isoxazoles. By slow addition of a solution of the sulfides to a solution containing excess peracid, consistent amounts of the sulfones (30–40%) are however formed, along with the isoxazoles. The *syn* retroenic fragmentation of the sulfoxides usually occurs by heating at 100–150°.[18] The remarkable ease with which these isoxazolinic sulfoxides fragment can then be attributed to the formation of the aromatic isoxazole ring.

Cycloadditions to the (*Z*)-sulfoxide afford more stable cycloadducts since their stereochemistry prevents *syn* fragmentation. Only two of the four possible diastereomeric and regioisomeric cycloadducts are discernible in the NMR spectra of the reaction mixtures in a 9 : 1 and 7 : 3 ratio, resp. The major adducts **9a, b** have been isolated by fractional crystallization in fair yields and are identical with the products obtained by oxidation of the *cis*-sulfides **5a, b** with *m*-chloroperbenzoic acid. The assignment for the minor adducts **10a, b** follows from their NMR spectra.

The (*E*)-sulfone adds BNO and mesitonitrile oxide to yield a mixture of adducts **11a, b** and **12a, b** (Scheme 3) in a ratio 29 : 71 and 57 : 43 resp. Adducts **11a, b** and **12a** are identical with the sulfones obtained by oxidation of the sulfides **1a, b** and **2a** resp. The regiochemistry of adducts **12a, b** was secured by base catalyzed elimination with NaOH in EtOH to isoxazoles **4a, b**.

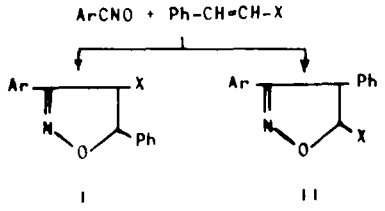
The (*Z*)-sulfone yields a mixture of the highly base sensitive cycloadducts **13** and **14**. When the reactions are run in the absence of bases, i.e. using preformed benzonitrile oxide or mesitonitrile oxide, cycloadducts **13a, b** and **14a, b** are formed in a 22 : 78 and 2 : 98 ratio, resp. In the presence of base (NEt_3), adducts **13a, b** undergo fast elimination at room temperature to yield isoxazoles **3a, b**, whereas adducts **14a, b** epimerize to the *trans*-isoxazolines **12a, b**. The behaviour follows because of the high acidity of the 4-isoxazolinic hydrogen. Attack of the base to this proton cause a concerted detachment of the sulfinate anion, as suggested by the lack of epimerization to sulfones **11**, which are stable under comparable conditions. On the other hand adducts **14** epimerize through 4-isoxazoline anions, which are efficiently stabilized by conjugation with the isoxazoline C=N as well as by the sulfonyl group, as shown by the ready exchange of the 4-isoxazoline proton with D_2O. Adducts **13a, b** have been independently obtained by oxidation of the *cis*-sulfides **5a, b** with excess *m*-chloroperbenzoic acid.

Mixtures of cycloadducts are also formed in the cycloadditions of BNO to (*E*)-phenyl and (*Z*)-*n*-butyl styryl sulfones already described.[8] Along with the major cycloadducts **12c** and **14e**, the NMR spectra of the cycloaddition mixtures show the presence of regioisomers **11c** and **13e**. The ratio of regioisomers **11c/12c** and **13c/14c** are 16 : 84 and 21 : 79, resp. With mesitonitrile oxide the phenyl styryl sulfone adducts **11d** and **12d** and the butyl styryl sulfone adducts **13f** and **14f** are formed in a 38 : 62 and 5 : 95 ratio, resp. By treating the *cis* adducts **13e, f** and **14e, f** with NEt_3, elimination to isoxazoles **3a, b** and epimerization to the *trans*-isoxazolines **12e, f**, resp., occur.



Scheme 3.

Table 2. Regioisomer distribution in the cycloadditions of nitrile oxides to styrene, (*E*) and (*Z*) styryl sulfides, sulfoxides and sulfones and to cyclic analogs



I II

X	I/II ($\Delta\Delta G^{\neq}$, Kcal/mole) BNO[a]		MNO[b]		Change[c]
H	99.5:0.5	(2.86)	98:2	(2.30)	0.6
(*E*)-dipolarophiles					
SO_2Ph	84:16	(0.89)	62:38	(0.38)	0.5
SO_2CH_3	71:29	(0.48)	43:57	(-0.17)	0.6
$SOCH_3$	55:45	(0.11)	21:79	(-0.78)	0.8
SCH_3	3:97	(-1.88)	II[d]		-
(*Z*)-dipolarophiles					
SO_2nBu	79:21	(0.72)	95:5	(1.73)	-1.0
SO_2CH_3	78:22	(0.68)	98:2	(2.30)	-1.6
$SOCH_3$	10:90	(-1.19)	30:70	(-0.50)	-1.7
SCH_3	II[d]		II[d]		-
Cyclic					
Benzothiophene 1,1 dioxide	99:1	(2.48)	95:5	(1.74)	0.7
Benzothiophene	78:22	(0.68)	26:74	(-0.62)	1.3

a) diethyl ether, 0-5°C
b) benzene, 25°C
c) $\Delta\Delta G^{\neq}_{I} - \Delta\Delta G^{\neq}_{II}$, Kcal/mole
d) only adduct II was detected

DISCUSSION

A wide and somewhat regular variation of regioselectivity occurs within the set of the thiodipolarophiles, as displayed in Table 2. In the cycloadditions of benzonitrile oxide to the (*E*)-isomers, the styryl sulfones maintain the orientation I, typical of the unsubstituted styrene itself.[19] The high regioselectivity of the cycloaddition to styrene seems to be only somehow reduced by the presence of the β-sulfonyl substituent. The styryl sulfoxide undergoes an almost unregioselective cycloaddition whereas with the sulfide the regiochemistry is definitely reversed toward regioisomer II. The same trend shows up in the cycloadditions to the sterically congested (*Z*)-dipolarophiles. Only the (*Z*)-sulfoxide shows a sizeable change of the I/II ratio. In the corresponding cyclic dipolarophiles, i.e. benzothiophene 1,1-dioxide and benzothiophene, the shift of regiochemistry parallels the order $H > SO_2 > (SO) > S$ observed within the styryl derivatives. The ratios I/II for the cyclic dipolarophiles are however remarkable higher than those of the corresponding (*E*)- and (*Z*)-linear dipolarophiles.

The change of regioselectivity along the series does not appear to be simply related to any accepted reactivity parameter of the thio moieties. Thus, the increase of II does not meet with the steric effect of the substituents. On the other hand, the regular increase of regioisomer I with the oxidation state of S follows the electron withdrawing ability of the substituents (σ or σ_R),[20] in agreement with the idea of the increasing feasibility of the nucleophilic attack of the dipole oxygen on the C located β to the substituent. Aside from the question of the irregular position of H (styrene) in the correlation, which could be accomodated by invoking steric effects, the above explanation implies an increase of the I/II ratios, with more nucleophilic dipoles.

On going from BNO to the more nucleophilic mesitonitrile oxide, the regiochemistry of the cycloadditions to the (*E*)-dipolarophiles are regularly shifted toward regioisomer II instead, similar to that observed with styrene itself and with the cyclic dipolarophiles. Likewise the definitely nucleophilic diazomethane attacks styryl sulfones in both directions and the regioisomeric pyrazolines arising from attack of the dipole C to the α-sulfonyl C are slightly prevailing (3 : 1).[11] Surprisingly enough, an increase of the ratios I/II occurs in the cycloadditions of mesitonitrile oxide to the (*Z*)-dipolarophiles and the increase is remarkable large with (*Z*)-sulfones.

In spite of the wide variations of steric effects and polarities of these dipolarophiles, a simple FO treatment accounts satisfactorily for the selectivity effects of the $S(O)_nR$ moieties as well as for the changes caused by annelation. The MINDO/3[21] and CNDO/2[22] eigenvalues and eigenvectors of the dipolarophiles are gathered in Table 3. The first three entries compare the FOs of styrene, methyl styryl sulfide and benzothiophene as

Table 3. Eigenvectors and eigenvalues for the frontier orbitals[a].

$C_6H_5-\overset{1}{C}H=\overset{2}{C}H-X$

Dipolarophile	HOMO C_1	HOMO C_2	HOMO ϵ(eV)	HOMO p^b	LUMO C_1	LUMO C_2	LUMO ϵ(eV)	LUMO p^b
MINDO/3								
Styrene	.318	.465	-8.53	0.12	.302	-.445	0.82	0.11
Benzothiophene	.387	.482	-8.38	0.08	.267	-.468	0.82	0.15
(E) methyl styryl sulfide	.417	.404	-8.11	-0.01	.294	-.467	0.81	0.13
CNDO/2								
Styrene	.315	.486	-12.21	0.14	.325	-.475	2.87	0.12
Benzothiophene 1,1-dioxide	.309	.459	-12.19	0.11	.346	-.382	0.61	0.03
(E) Methyl styryl sulfone	.319	.463	-12.48	0.11	.436	-.442	1.66	0.01
(E) Methyl styryl sulfoxide[c]	.278	.414	-12.35[d]	0.09	.438	-.361	1.49	-0.06
(E) Methyl styryl sulfoxide	.250	.344	-12.18[d]	0.05	.355	-.486	2.44	0.11
(E) Methyl styryl sulfide	.340	.282	-10.69	-0.04	.414	-.439	2.13	0.08
Methyl vinyl sulfone	.392	.321	-14.78	0.05	.588	-.431	2.83	0.16
(E) Methyl propenyl sulfone	.454	.478	-14.00	-0.02	.589	-.445	2.79	0.15

a) Standard geometries have been used. The geometry of the thio fragments have been constructed on the s-cis conformer of the sulfide according to ref. 25a. The spd basis has been used for the sulfones. b) Polarization defined as $C_2^2-C_1^2$. c) Calculation with spd basis. d) SHOMO

obtained by MINDO/3 which correctly reproduce the orbital sequence of the latter dipolarophile.[4] The influence of the oxidation of S was estimated with the aid of CNDO/2 calculations, which were successfully used in the assignment of the photoelectron spectra of sulfoxides[23] and sulfones.[24] In the case of sulfones d orbitals are essential in describing bonding[25,26] because of the contraction induced by the electronegative substituents and have been therefore included in the basis set. The results with the sp and spd basis are given for the sulfoxide and an average of the values should be enough reliable to our purposes.

The FOs change in energy rather regularly, depending upon the main donor and acceptor character of the substituents, i.e. the FOs of methyl styryl sulfide are raised with respect to styrene whereas those of the corresponding sulfone are lowered. Noteworthy and large are the raising of the HOMO of sulfide and the lowering of the sulfone LUMO. The trends in the FO energies shown by the calculations compare favourably with available experimental data. Thus, the IP of styrene (8.55)[27] is remarkably lowered in styryl methyl sulfide (7.75)[28] and slightly raised in the corresponding sulfones (8.8).[29] The EAs of sulfide and sulfone can be evaluated at -0.35 eV and $\times 0.29$ eV from the empirical relationship $E_{\pi\pi^*} = IP - EA - (J_{ij} - 2K_{ij})$,[30] using the transition energies of the sulfide (4.34 eV)[31] and the sulfone (4.75 eV)[32] and the value of $(J_{ij} - 2K_{ij})$ derived for styrene (3.76 eV)[33] from the EA (-0.25 eV)[34] and transition energy (5.04 eV)[35] of styrene. The sulfone LUMO is lowered by 0.54 eV with respect to styrene, whereas only a slight raising results with the sulfide.

More important in determining the regioselectivity phenomena, are the changes in the shapes of the FOs, which vary dramatically along the series. The changes can be qualitatively understood by deriving the FOs of the dipolarophiles from those of styrene and the substituents (Fig. 1). Upon interaction, the orbitals split apart and change in shape. According to the mixing rules,[36] the occupied orbitals of the substituents cause a decrease of the HOMO polarization and a slight increase of the LUMO polarization (Fig. 1a). The vacant orbitals, on the other hand, decrease the LUMO polarization and slightly increase the HOMO polarization (Fig. 1b). Within the styryl dipolarophiles we are dealing with, the overlaps of the thio fragments with the styrene FOs are comparable and the degree of mixing is inversely proportional to the energy difference between the substituent orbitals and the styrene orbital to be polarized. Thus, the familiar HOMO polarization of styrene decreases and switches by raising the occupied orbitals of the substituent, i.e. on going from styrene to the sulfone, sulfoxide and sulfide. Similarly the LUMO polarization decreases by lowering the vacant orbitals of the substituent, i.e. on going from styrene and the sulfide to sulfoxide and sulfone. The numbers above the levels of Fig. 1 are the negative of the styrene IP and EA whereas the numbers in parentheses, near the symbols of the fragments, refer to their highest occupied orbital of π symmetry, estimated from the photoelectron spectra of dimethylsulfone,[24] sulfoxide[23] and sulfide,[28] and to the lowest vacant orbitals of π symmetry of the sulfoxide and sulfone fragments determined by accurate *ab initio* calculations.[37] A question mark, placed near SCH_3, summarizes our difficulties in finding reliable estimates for the (high) energy of d orbitals in sulfides.

The simple scheme of Fig. 1 also accounts for the lower changes in polarizations relatively to styrene

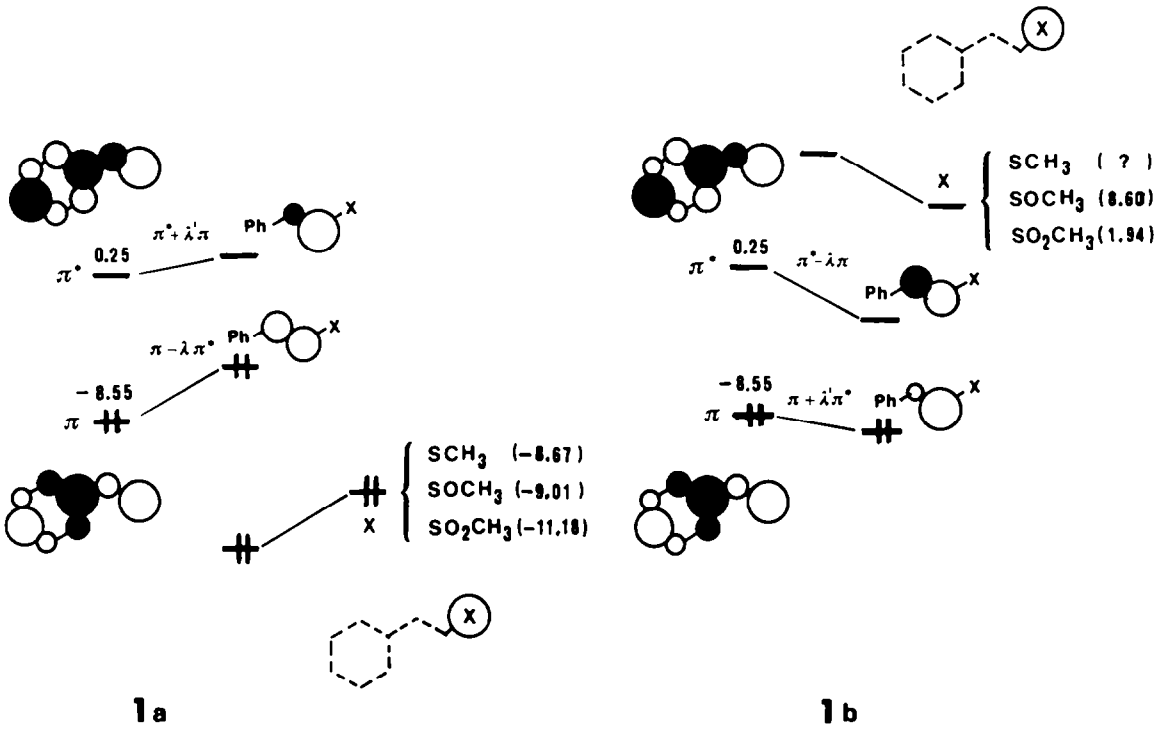


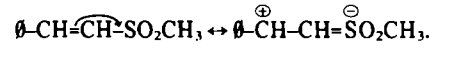
Fig. 1. Occupied orbitals of substituents raise and depolarize styrene HOMO (Fig. 1a) while vacant orbitals lower and depolarize styrene LUMO (Fig. 1b). The orbitals of substituents slightly increase the polarization of the far styrene FO ($\lambda' < \lambda$).

observed in the cyclic dipolarophiles. The attenuation of the effect of the substituent is simply due to the lower overlap between the styrene FOs and the substituent orbitals when the substituents are placed between the omega and ortho position of styrene in building the cycle, in an almost nodal position of the styrene HOMO.

The success of the orbital interaction scheme in accounting for the changes of the shapes of linear and cyclic dipolarophiles supports the idea that the main factors determining the shapes of the FOs are conjugative (mesomeric) effects. On the other hand the changes of the FO energies does not depend simply upon the orbital interactions but allowance has to be made for inductive effects. The lowering of the π levels in vinyl sulfones relatively to the unsubstituted systems has been attributed to the dominance of inductive effects.[38] Thus, the changes of the energies and those of the shapes of the FOs depend on different blends of conjugative and inductive effects.

An evaluation of the relative influence of inductive and conjugative effects in determining the energies and the shapes of the FOs can be made with a stepwise construction of styryl methyl sulfone with the CNDO/2 method, as shown in Fig. 2. Upon attaching the SO_2CH_3 substituent to styrene in a σ fashion, i.e. with the π interactions between styrene and the substituent deleted, the electron withdrawing substituent causes the FOs of styrene to decrease significantly in energy. The polarizations are however only slightly affected; the HOMO polarization is increased and the LUMO polarization decreased as a consequence of the increasing electronegativity of the ω C (static mixing).[36b] The electron drift toward the ω C in the HOMO corresponds to the familiar inductive effect of the sulfonyl group as represented by the arrow in **15**

15 **16**



17

When allowing the π interactions, i.e. in normal calculation, the orbital interactions cause a moderate raising of the HOMO, which mitigates the inductive lowering, and a further lowering of the LUMO, while the polarization of the FOs remarkable decreases. The decrease is quite large in the LUMO, whose polarization almost vanishes. The conjugative effect of the sulfonyl group compensates therefore moderately the HOMO polarization of styrene and almost completely its LUMO polarization. In VB terms, the moderate effect on the HOMO corresponds to the delocalization shown by the arrows of **16** whereas the large effect on LUMO corresponds to the more familiar mesomeric structure **17**. The limiting structures derived from **16** and **17** can be regarded as VB equivalents of the small and large change in the HOMO and LUMO polarization induced by the sulfonyl group, and their influence upon the site of attack of electrophiles and nucleophiles can be assessed through molecular orbital calculations.

The rather unusual, albeit small, ability of the sulfonyl group in polarizing the HOMO toward the β C, as

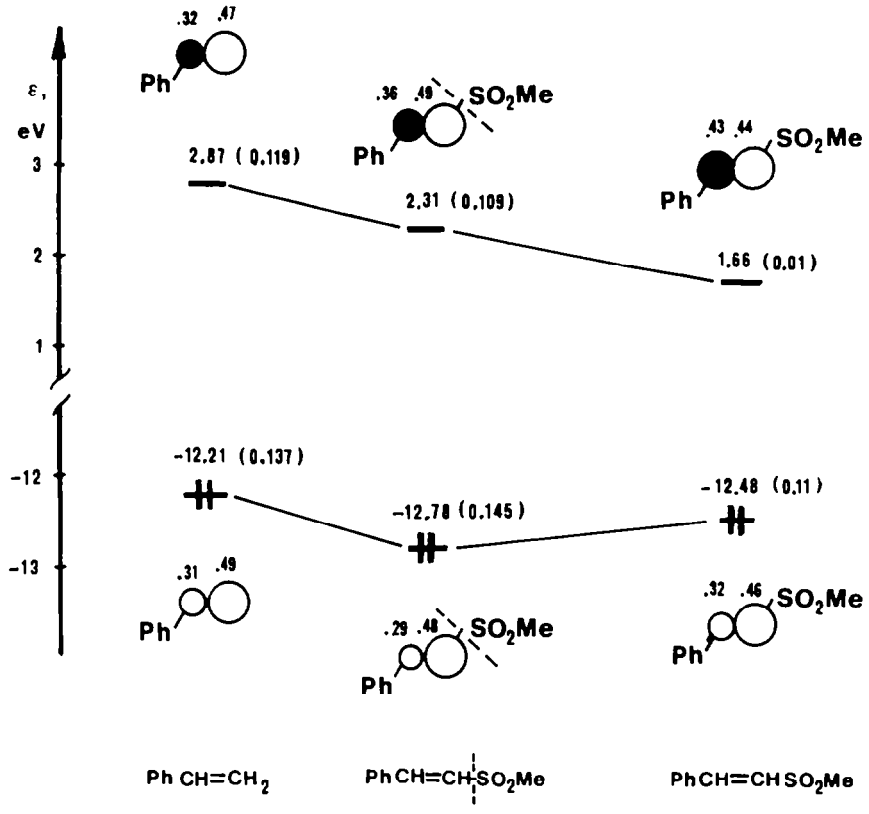
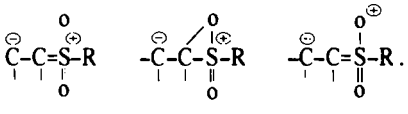


Fig. 2. Stepwise construction of the methyl styryl sulfone FOs from the styrene FOs with the CNDO/2 method. The interruption of π interactions between the fragments (in the middle) is represented by a dashed line. Numbers above the levels are FO energies (eV), while polarizations, defined as in Table 3, are given in parentheses.

represented in **16**, deserves some more comment. Close inspection of the orbitals of the sulfonyl group shows that the drift results mainly as a delocalization of the oxygen lone pairs. The delocalization occurs through hyperconjugative, spyroconjugative and conjugative mechanisms which can be exemplified in VB terms with the limiting structures **18–20** shown below



18 **19** **20**

The polarizing effects of the sulfonyl shows up more clearly in the FOs of the simple vinyl methyl sulfone, which has the anticipated small and high polarizations in HOMO and LUMO, resp., as displayed in Fig. 3. The slight effect on the HOMO is easily overcome even by a moderately donating β-Me substituent. With the heavier conjugating β-phenyl a reversal in both FOs occurs.

Polarization away from the substituent is commonly found in ethylenes carrying acceptor substituents and is important in determining the regioselectivity of cycloadditions.[30,39] In reactions with electrophiles the importance of these slight HOMO polarizations in governing the stability of the carbonium ion intermediates is however easily offset by the more influential inductive component of the acceptors.

The regiochemistry of the cycloadditions of the moderately electrophilic nitrile oxides to the (*E*)-styryl and cyclic dipolarophiles parallels therefore the change in shape of the HOMOs. On going to the more nucleophilic mesitonitrile oxide a shift toward regioisomer II occurs, because of the higher nucleophilicity of the nitrile oxide oxygen which binds to the ω-styrene C possessing the higher coefficient in the LUMO. The same ω site of (*E*)- and (*Z*)-styryl sulfones is preferentially attached by the diazomethane C.[11] Cycloadditions of mesitonitrile oxide to (*Z*)-styryl sulfones show however an opposite shift of regioselectivity, toward regioisomer I (Table 2). The spatial proximity of the phenyl and thio substituents in the (*Z*)-series should affect the geometry of these dipolarophiles, causing, e.g. a twisting of the phenyl out of the plane of the double bond, the adoption of biased conformations for the thio substituents as well as changes in the bond lengths and angles of the double bond. The twisting reduces the interaction of the phenyl with the π bond and can cause a switch of the low LUMO polarization of the styryl sulfones. On the other hand twisting increases the steric hindrance for attack on the adjacent double bond carbon. The LUMO switch and the steric effect could account for the remarkable increase of the regioisomer ratios observed with the nucleophilic, but more steric demanding, mesitonitrile oxide. In diazomethane cycloadditions an approximate cancellation of the two factors should occur.

The change of the FO shapes clarifies the changes of regiochemistry within the vinyl, propenyl and styryl sulfones. The β-alkyl and phenyl substituents cause a reversal of polarization in the HOMO of vinyl sulfones and a reversal of regiochemistry in nitrile oxide cycloadditions. In diazomethane cycloadditions the reversal

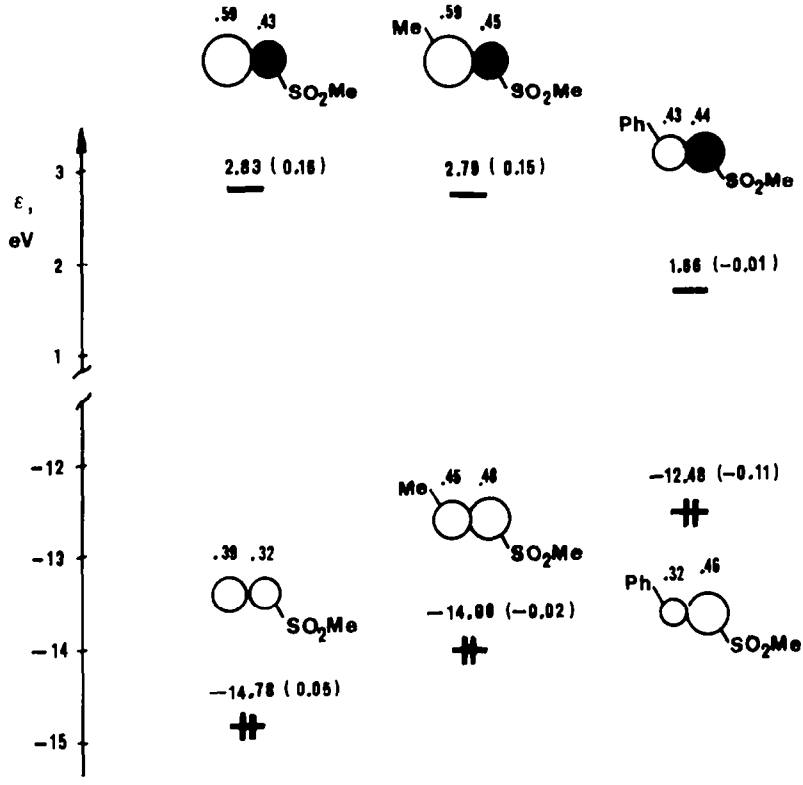


Fig. 3. Frontier orbitals of vinyl, propenyl and styryl methyl sulfones (CNDO/2). Energies (eV) are given above the levels and polarizations, defined as differences between the squares of the coefficients at β- and α-sulfonyl carbons, are given in parentheses.

occurs on going from vinyl and propenyl sulfones to styryl sulfone, since reversal of LUMO polarization is caused by a β phenyl substituent.

Nucleophiles add to the β-sulfonyl C of vinyl and propenyl sulfones and to the same site of styryl sulfones, too.[40] The β orientation is usually attributed to the larger stabilization of anionic centers caused by an adjacent sulfonyl. The β orientation could however reflect the increased influence of closed shell interactions. In nucleophilic additions the HOMO–HOMO destabilizing interactions are not relieved by symmetry[41] and nucleophilic attacks on styryl sulfones should be directed at the β-site, which has a significantly lower coefficient in the HOMO. Interestingly enough, α and β attacks have been observed in the additions of enamines to styryl sulfones.[42] The enamines possess the same allyl anion system of 1,3 dipoles and HOMO–HOMO destabilizations can be relieved in the two-planes approach of the reactants, as in cycloadditions.

CONCLUSIONS

Frontier orbital treatments account for the reactivity and selectivity phenomena, even if in some cases recurse has to be made to other MO interactions as well as to exchange, polarizability, flexibility and electrostatic effects.[43] The present paper shows that the regiochemistry of the cycloadditions to the thio dipolarophiles fits satisfactorily the FO approach and revises previous opinions.[7] The frontier orbitals we have used have been anchored to the orbitals of the fragments, whose IPs and EAs can be reasonably estimated. The trends shown in the calculation are therefore real, although more refined methods may cause some numerical changes.

Care must be indeed exercized when dealing with semiempirical methods to avoid that unadequate parametrization could bury the chemical phenomena under a tumulus of numbers.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra: Perkin Elmer mol. 197 spectrophotometer, Nujol mulls. NMR spectra: Perkin Elmer R 12 spectrometer. Microanalyses were performed by Dr. L. Maggi Dacrema on a Elemental Analyzer mod. 1106 Carlo Erba. Satisfactory analytical data ($\pm$ 0.4% for C, H, N) were obtained for all new compounds. Column chromatography and qualitative tlc: Silica Gel H and GF_{254} (Merck) respectively, eluant cyclohexane AcOEt 9 : 1 to 7 : 3 unless otherwise specified.

Starting and reference materials. The (*E*)- and (*Z*)-methyl styryl sulfides were obtained by the Horner–Wittig reaction on benzaldehyde[44] and by nucleophilic addition of methyl thiol to phenylacetylene,[31] resp. The sulfoxides and sulfones were prepared by oxidation of the sulfides with periodate and H_2O_2, resp.[45,46] The (*Z*)-sulfoxide crystallized from diisopropyl ether-light petroleum, colorless crystals m.p. 32°. (*E*)-phenyl styryl sulfone[47] and (*Z*) n-butyl styryl sulfone[11] were similarly prepared Samples of 3,5-diphenylisoxazole,[47a] 3 - (2,4,6 - trimethylphenyl) - 5 - phenylisoxazole[48] and 3,4 - diphenylisoxazole[49] were obtained according to known procedures.

General cycloaddition procedures. To a stirred, ice cooled soln of benzhydroximic acid chloride and a slight excess of the dipolarophile in anhyd ether, Et_3N (1.1 eq) was added dropwise. After keeping 2 days at r.t., the triethylammonium salt was filtered off and the filtrate was evaporated at reduced pressure.

In cycloadditions with mesitonitrile oxide, a soln of the dipole and the dipolarophile (1.1 eq) was stored at r.t. for 1 month. Evaporation of the solvent left a residue.

Cycloadditions to (E) *and* (Z)*-methyl styryl sulfides.* From 10 g (64 mmoles) benzhydroximic acid chloride and 10 g (66 mmoles) (*E*)-methyl styryl sulfide, 3.2 g of **1a**, soft white needles m.p.

117–119°, were obtained by grinding the residue with diisopropyl ether. Column chromatography of the mother liquors (benzene : cyclohexane 1 : 1 to benzene as eluants) gave, besides dimerization products of BNO, regiosomer **2a** (120 mg, 0.7%), white needles m.p. 125–126° from diisopropyl ether, along with further **1a** (800 mg, 23.2% total yield).

The (*Z*)-sulfide similarly yielded, by fractional crystallization, isoxazoline **5a** (10% yield), white crystals m.p. 141–142° from EtOH.

In cycloaddition of mesitonitrile oxide (5 g, 31 mmoles) to (*E*)-methyl styryl sulfide (7 g, 46 mmoles), 8.7 g (90% yield) of **1b**, white needles from EtOH m.p. 143–5°, were obtained by grinding the residue with light petroleum. The (*Z*)-sulfide similarly yielded, by fractional crystallization, isoxazoline **5b** (16%), white silver needles, m.p. 116–7° from EtOH.

Acidic cleavage of adducts to methyl styryl sulfides. A soln of **1a** or **5a** (100 mg) in HOAc (3 ml) and 50% H_2SO_4 (3 ml) was refluxed for 2 hr. After cooling, the mixture was poured on ice. 3,4-Diphenylisoxazole **3a** was filtered off in almost quantitative yield, identical with an authentic specimen.

Similarly, the adducts of mesitonitrile oxide **1b** and **5b** yielded **3b**, colorless crystals m.p. 118–9° from MeOH (Found: C 82.23%, H 6.59%, N 5.37%; $C_{18}H_{17}NO$ requires C 82.10%, H 6.51%, N 5.32%), NMR ($CDCl_3$) δ 2.02s (6H), 2.32s (3H), 6.94s (2H), 7.28 m (5H) and 8.76s (1H).

Cycloadditions to (E)- *and* (Z)-*methyl styryl sulfoxides.* From 155 mg (1 mmole) benzhydroximic acid chloride and 200 mg (1.2 mmoles) (*E*)-methyl styryl sulfoxide, a mixture of **3a** and **4a** was obtained, in a ratio 45 : 55, as determined by NMR integration of the 5- and 4-isoxazolic protons at 8.5 and 6.9 δ, resp.

Analogously from 161 mg (1 mmole) mesitonitrile oxide and 200 mg (1.2 mmole) (*E*)-sulfoxide, besides some dimesitylurea, a mixture of **3b** and **4b** resulted, in a ratio 79 : 21.

From benzhydroximic acid chloride (1 mmole) and (*Z*)-methyl styryl sulfoxide (1.2 mmole) a mixture of products was formed. The NMR spectrum shows signals attributable (Table 1) to adducts **9a** and **10a** in a ratio 9 : 1. Fractional crystallization afforded the major adduct **9a** (30%), m.p. 80–82° from EtOH.

Mesitonitrile oxide (161 mg, 1 mmole) and (*Z*)-sulfoxide (200 mg, 1.2 mmole) gave a mixture of regioisomers **9b** and **10b** in a ratio 7 : 3. Column chromatography of the mixture afforded adduct **10b** (5%), white crystals from EtOH, m.p. 143–5° and the major adduct **9b** (43%), white crystals m.p. 117–8° from EtOH.

Cycloadditions of (E) *and* (Z)-*methyl styryl sulfones.* From 1.5 g (10 mmole) benzhydroximic acid chloride and 2 g (11 mmole) (*E*)-methyl styryl sulfone, 0.7 g **12a** were obtained by grinding the residue with benzene, white crystals m.p. 148–150° from benzene. Column chromatography of the mother liquors gave, besides the dimerization products of the dipole, further **12a** (36% total yield), regioisomer **11a** (430 mg, 15%), white needles, m.p. 180–1° from EtOH and unreacted sulfone.

When reacted under the standard conditions as above, the (*Z*)-methyl styryl sulfone afforded the *trans*-**12a**, which was separated in a 38% yield grinding the residue with benzene. The NMR spectrum of the mother liquors shows the presence of **3a**. In the absence of bases, i.e. by adding the (*Z*)-sulfone to an etheral soln of preformed BNO,[10] the white crystals of *cis*-**14a**, m.p. 226–8° from CH_3CN, crystallyzed out in a 56% yield. Column chromatography of the mother liquors ($CHCl_3$ as eluant) gave the regioisomeric *cis*-**13a** (16.2%), while crystals from EtOH, m.p. 144–6° and unreacted (*Z*)-sulfone.

In cycloadditions of mesitonitrile oxide (1.06 g, 6.6 mmole) to (*E*)-sulfone (1.2 g, 6.6 mole), 0.43 g (19.5%) of **11b**, m.p. 210–1° from EtOH, were obtained by grinding the residue with EtOH. Column chromatography of the mother liquors gave **12b** (0.33 g, 15%), white needles m.p. 151–2° from EtOH, and unreacted (*E*)-sulfone (0.6 g).

The (*Z*)-sulfone similarly yielded 0.85 g (54%) of *cis*-**14b**, white crystals m.p. 216–7° from CH_3CN, which precipitated from the mixture. The NMR spectrum of the residue of mother liquors shows the presence of the regioisomeric **13b**.

The ratios of regioisomers reported in Table 2 were measured by NMR integration of the signals of the isoxazolinic protons on samples of the cycloaddition mixtures.

Cycloadditions to (E) *phenyl styryl sulfone.* Cycloaddition of BNO to (*E*)-phenyl styryl sulfone (1.1 eq) gave a residue from which **12c**, m.p. 145° from MeOH (lit.[8] 145°) was obtained in a 47% yield by grinding with MeOH. The NMR spectrum of the mother liquors shows signals attributable (Table 1) to regioisomer **11c**. A 84 : 16 ratio of adducts **12c** and **11c** was determined by NMR on a sample of the cycloaddition mixture.

Cycloaddition of mesitonitrile oxide (2 mmole) to (*E*)-phenyl styryl sulfone afforded regioisomers **12d** and **11d** in a 62 : 38 ratio (NMR). Crystallization of the mixtures afforded the major adduct **12d** (0.41 g, 51%), white needles m.p. 156–7° from EtOH.

Cycloadditions to (Z) *n-butyl styryl sulfone.* Cycloaddition of BNO to (*Z*)-n-butyl styryl sulfone under the standard conditions afforded the *trans*-**12e**, colorless crystals from EtOH, m.p. 127° (lit.[8] 127°), in a 45% yield on grinding the residue with EtOH. In the absence of bases, by adding the (*Z*)-sulfone to an ethereal soln of preformed BNO,[10] the *cis*-**14e**, white needles m.p. 166–7° from benzene (lit.[8] 166–7°), crystallized out. The NMR spectrum of the mother liquors indicates the presence of the regioisomer **13e**. A ratio 79 : 21 of the regioisomers **14e** and **13e** was determined on a sample of the cycloaddition mixture by NMR.

Cycloaddition of mesitonitrile oxide (2 mmole) to 2 mmole (*Z*)-n-butyl styryl sulfone in benzene afforded the couple of regioisomers **14d**/**13d** in a 95 : 5 ratio, as measured by NMR integration of the isoxazolinic protons. Crystallization of the mixture afforded the major adduct **14d** (0.54 g, 70%), white crystals m.p. 133–4° from EtOH.

Oxidation of the sulfides. Cycloadduct **1a** (130 mg, 0.5 mmole) was treated with 0.6 mmole *m*-chloroperbenzoic acid in 10 ml CH_2Cl_2. After 1 night at r.t. the mixture was poured into 10% of Na_2SO_3 aq. The soln was extracted with $CHCl_3$, washed with $NaHCO_3$ aq and also with water. The organic layers were dried on Na_2SO_4. Evaporation at reduced pressure gave a residue; crystallization from light petroleum afforded 3,4-diphenylisoxazole in a 63% yield.

Oxidation of cycloadducts **1b** and **2a** similarly afforded 3-mesityl-4-phenyl and 3,5-diphenylisoxazole, resp.

When a CH_2Cl_2 soln of **1a,b** and **2a** was slowly added to a CH_2Cl_2 soln of excess (7 eq) *m*-chloroperbenzoic acid, consistent yields (30–40%) of **11a,b** and **12a** are formed along with isoxazoles. Separation was achieved by column chromatography, where isoxazoles are eluted first.

Oxidation of the *cis*-**5a,b** with a slight excess of peracid (3 eq) afforded in quantitative yields the corresponding **13a,b**. No traces of **3a,b** were detected.

If the oxidation of **5a** and **5b** with *m*-chloroperbenzoic acid was interrupted after 5 min, **9a** and **9b** were obtained along with **13a** and **13b** and separated by column chromatowgraphy, 1 : 1 mixture of cyclohexane and AcOEt serving as eluant.

Epimerization and elimination of the sulfonyl isoxazolines. To a suspension of the *cis*-**14a** (50 mg) in anhyd benzene, 1 ml Et_3N was added. After one night, the soln was evaporated under reduced pressure. NMR spectrum of residue indicated only the presence of the *trans*-**12a**. Similarly, the *cis*-**14b,e,f** afforded quantitatively the *trans*-**12b,e,f**. A similar treatment on the *cis*-**13a,b** caused a quantitative elimination to **3a,b**, resp., as shown by the NMR spectra.

Epimerization of *cis*-**14a,e** occurred also by refluxing their methanolic solns, whereas the regioisomers **13a,e** were recovered unchanged.

The *trans*-**12a–f** are stable toward Et_3N. They undergo elimination by boiling with NaOH in EtOH. An ethanolic soln of **12** (100 mg) and 2 drops of NaOH was refluxed for 2 hr. After evaporation of the solvent, grinding the residue with water afforded 3,5-diphenyl or 3-mesityl-5-phenylisoxazole in almost quantitative yields.

Competitions experiments. BNO (0.1 mmole) was generated in diethyl ether soln at 0° in the presence of (*E*)-methyl styryl sulfide (50 mmole) and styrene (1 mmole). After keeping two days at 0°, the ratio of **1a** and the styrene adduct was determined by the comparison with mixture of known composition and a reactivity ratio 70 ± 10 of styrene and the sulfide was calculated. Competition experiments with (*E*)-methyl styryl sulfoxide and sulfone gave similar values.

Calculations. The calculations were executed with MINDO/3 and CNINDO programs on a CDC 6600 computer available at the University of Catania.

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