CYCLOADDITIONS OF MESITONITRILE OXIDE WITH HYDROXY- AND METHOXY-SUBSTITUTED STILBENES. A DIRECTING HYDROGEN BONDING MODEL

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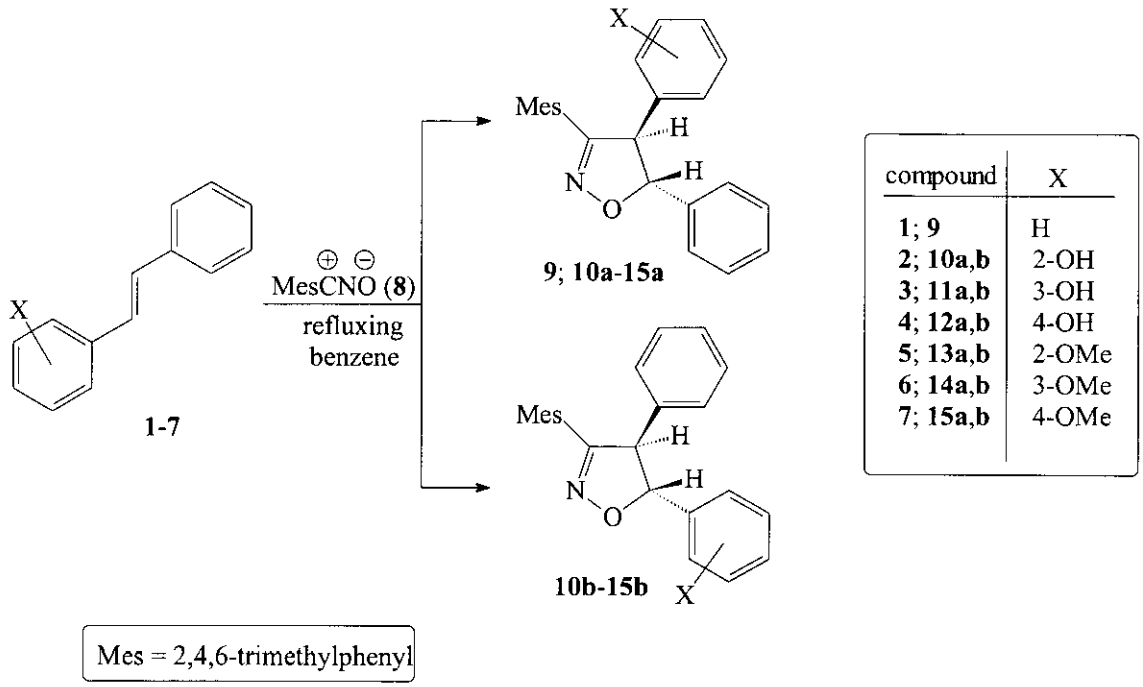
Abstract - The regioselectivity of the reaction of mesitonitrile oxide with *o*-hydroxystilbene in favour of the 5-(2-hydroxyphenyl) isomer (regioisomeric ratio 5:1) is accounted by a directing hydrogen bonding model, while for reactions of the *p*-hydroxy- and *p*-methoxystilbene which show a 2:1 ratio between the 5- and 4-regioisomer, an electron-donor effect is invoked. These phenomena of regioselectivity are supported by semiempirical AM1 calculations.

The reactivity, as well as the site-, regio- and stereoselectivity, of nitrile oxide cycloadditions can be controlled by favourable hydrogen bonding effects.[1-11] Cyclic dipolarophiles containing a hydroxyl or amino group, in a suitable position with respect to the unsaturation show an enhanced dipolarophilic activity[1,2] and/or a site-,[3-5] regio- and stereoselectivity.[6-12] This control can be attributable to a coordination of the hydrogen atom of the dipolarophile with the oxygen atom of the 1,3-dipole and it can assist the cycloaddition by reducing the energy of the transition state.[11] Such an effect, however, is very modest in acyclic dipolarophiles.[12-14]

Within our studies on synthetic applications of nitrile oxide cycloadditions,[5, 15] we have shown that the dipolarophilic activity of nitrile function in *o*-cyanoaniline,[1] *o*-cyanophenol[2] and β-enamino nitriles[3-5] is enhanced by hydrogen bonding effect. The cyano group in *o*-acylamino[1] and *o*-hydroxy[2] substituted benzonitrile is activated in the reaction with benzonitrile oxide, but its reactivity is depressed to normal values in *N*- and *O*-methyl derivatives. In all these cases the reactivity of the cyano group is remarkably dependent by the solvent. Contrary to the expectations, the cyano group of β-enamino nitriles is more reactive than the olefinic double bond towards nitrile oxides[3,5] and it exclusively reacts with benzonitrile oxide in heterocyclic β-enamino nitriles.[4]

As extension of this line of research we have investigated reactions of *o*- (**2**), *m*- (**3**) and *p*-hydroxystilbene (**4**) and their *O*-methyl derivatives (**5-7**, respectively) in the *trans* form with mesitonitrile

oxide (**8**) (Scheme 1). We have also compared the reactivity and regiochemistry of **2** with that of its isomers, *O*-methyl derivatives and *trans*-stilbene (**1**) by means of competitive experiments with the aim of verifying the possibility of a rationalization of their reactivity and regiochemistry by an accelerative and/or directive hydrogen bonding model.



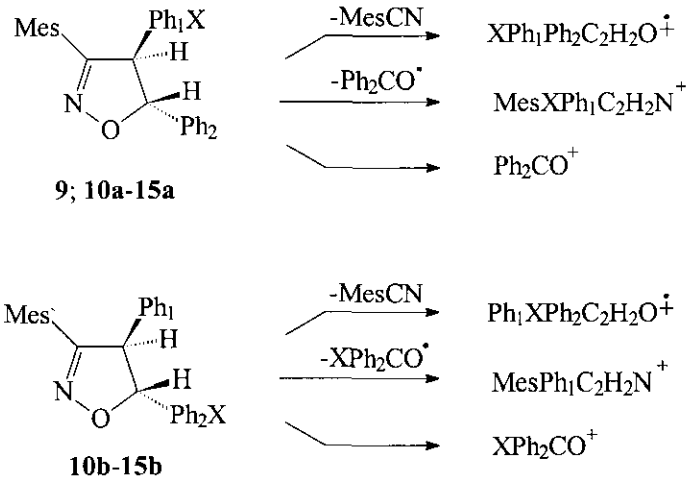
Scheme 1

Here we report the results of this study and we discuss them in terms of steric, electronic and hydrogen bonding effects. For the reaction of **2,** furthermore, which is the sole structure among those examined able to form an intermolecular hydrogen bonding between the hydroxylic hydrogen atom and the dipolar oxygen atom, we tried to determine the transition state geometry through semiempirical AM1 calculations.

RESULTS AND DISCUSSION

Reactions of two equivalents of **2-4** with one equivalent of **8** under refluxing benzene until the 1,3-dipole was consumed, gave a mixture of 4-(hydroxy substituted phenyl)-5-phenyl-4,5-dihydroisoxazoles (**10a-12a**) and its regioisomers (**10b-12b**) in the ratio 1:5, 1:1 and 1:2, respectively, while those with **5-7** gave

the corresponding dihydroisoxazoles (**13a-15a**) and (**13b-15b**) in the ratio of 1:1, 1:1 and 1:2, respectively (Scheme 1). The yield of **10a,b**, based on the consumed 1,3-dipole, was of 92% and it was *ca.* 1.5 times higher than that of **11a,b-15a,b**. The two regioisomers, which in some cases were not easily separated requiring repeated flash chromatographies to isolate small quantities of a pure sample, were unequivocally distinct by means of MS spectra and their assignments were supported by their ^{13}C NMR spectra. The most important fragmentation reactions upon electron impact of the 4- and 5-regioisomer are shown in Scheme 2. Three typical fragment ions, all originating directly from molecular ions,[16] are the radical ion corresponding to the loss of mesitonitrile, the ion corresponding to the loss of substituted or not benzoyl radical and the substituted or not benzoyl ion.



Scheme 2

While ^{1}H NMR spectra showed classical chemical shifts and coupling constants,[17] which were not diagnostic for the identification of two regioisomers, in ^{13}C NMR spectra chemical shifts of the two C-4 and C-5 carbon atoms appeared clearly distinct in comparison to those of the reference stilbene. The signal of the carbon atom to which the hydroxy or methoxy substituted phenyl ring is bonded, was always shifted upfield with respect to that of stilbene owing to the electron richest phenyl ring which increases the electron density of that carbon atom. This effect is greater in the case of *o*-, smaller in *p*- and finally nearly null in *m*-substituted stilbenes (Table 1).

Table 1. ^{13}C NMR Chemical shifts of C-4 and C-5 carbon atoms of dihydroisoxazoles (**9**, **10a,b-15a,b**).

	C-4	C-5		C-4	C-5
9	64.73	87.89			
10a	57.80	87.72	**10b**	64.11	84.31
11a	63.84	87.88	**11b**	64.85	87.11
12a	60.80	87.38	**12b**	64.31	86.43
13a	58.09	86.76	**13b**	64.43	84.35
14a	63.71	87.82	**14b**	64.85	86.74
15a	60.10	88.04	**15b**	64.41	86.01

Results on the reactivity and regiochemistry of the above reactions were confirmed by competitive experiments carried out by refluxing a benzene solution of **2** and one of its isomers (**3**, **4**) or its *O*-methyl derivatives (**5-7**) with **8** until the 1,3-dipole was consumed. Competition experiments allowed also to determine that **2** is *ca.* 2.5 times higher reactive than stilbene (**1**) and moreover they showed that the reaction of **2** is moderately dependent on the solvent used, while reactions of **3-7** do not undergo any variation changing the solvent at room temperature. The ratio of *ca.* 1.5 in yields of **10a,b** and **11a,b-15a,b** and in particular the regioisomeric ratio **10a**:**10b** of 1:5 observed in benzene, are maintained in chloroform, but the yield ratio diminished to 1 and 0.9 and the regioisomeric ratio reduced to 1:1.5 and 1:1 in dimethyl sulfoxide and dimethyl formamide, respectively.

By considering that **1**, **3** and **4** are planar, or anyhow with small phenyl ring oscillations (energy variation lower to 0.2 Kcal/mol), but that only the 4-hydroxy group of **4** is directly conjugated with the olefinic double bond, the lowest regioisomeric ratio **12a**:**12b** of 1:2 in comparison to that of **11a**:**11b** (1:1) is attributable to the electron-donor effect of 4-hydroxy group which polarizes the olefinic double bond. This observed regiochemistry is satisfactorily accounted by FMO treatment.[18] As it can be seen in Figure 1 and Table 2, which report orbital energies and coefficients of stilbenes (**1-7**) and mesitonitrile oxide (**8**) determined by using the AM1 method, all reactions of stilbenes (**1-7**) with the 1,3-dipole are controlled by the $HOMO_{dipolarophile}$- $LUMO_{1,3\text{-}dipole}$ interaction which contains the most polarized HOMO in the case of the *p*-hydroxystilbene. This interaction favours the 5-regioisomer (**12b**) since the electrophilic carbon terminus of the nitrile oxide (largest LUMO coefficient) becomes bonded to the more nucleophilic C-2 carbon atom (largest HOMO coefficient). Stilbenes (**6**) and (**7**) behave exactly in the same manner as **3** and **4**.

Figure 1. FMO energies of stilbenes (**1**-**7**) and mesitonitrile oxide (**8**) calculated by the AM1 method.

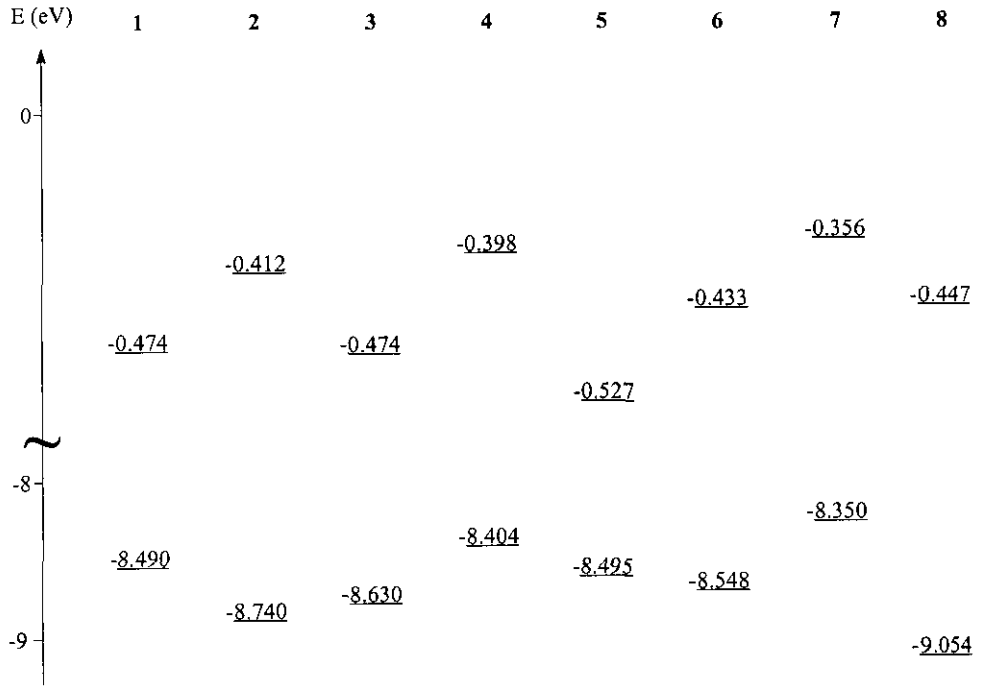
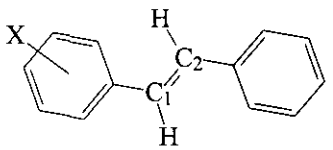
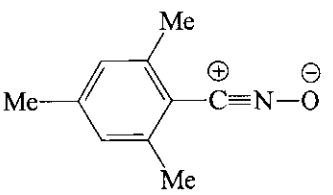


Table 2. Orbital coefficients of C-1 and C-2 carbon atoms of hydroxy and methoxy substituted stilbenes (**2**-**7**) and carbon atom and oxygen atom of mesitonitrile oxide (**8**).



	X	LUMO		HOMO	
		C-1	C-2	C-1	C-2
2	2-OH	0.422	-0.379	0.344	0.346
3	3-OH	0.388	-0.396	0.373	0.375
4	4-OH	0.385	-0.385	0.351	0.392
5	2-OMe	0.395	-0.398	0.375	0.384
6	3-OMe	0.378	-0.402	0.390	0.393
7	4-OMe	0.389	-0.383	0.343	0.390



LUMO		HOMO	
C	O	C	O
0.225	-0.211	0.312	-0.438

Furthermore, Figure 1 and Table 2 show that energies and coefficients of FMO do not support the reactivity of **2** in comparison to those of **3**-**7** and particularly its observed regioisomeric ratio **10a**:**10b** (1:5). It must be considered that **2** and **5** are not planar because of steric effects between the *o*-substituent

in the phenyl ring and the olefinic hydrogen atom and therefore the electronic effect of the hydroxy or methoxy group can not fully manifest on the C=C double bond. A steric effect of the hydroxy group could be invoked in the case of **2**, but also **5** would manifest the same effect and this would not be sensitive to the solvent effect which is not strong, but it is significant. These considerations induced us to hypothesize the occurrence of an intermolecular hydrogen bond which assists the cycloaddition reaction in directing the attack of nitrile oxide to form the prevailing 5-(2-hydroxyphenyl)-4-phenyl-4,5-dihydroisoxazole (**10b**).

To prove this supposition we tried to determine the transition state geometry of the reaction of **2** with **8** through quantomechanical calculations, which, owing to the remarkable molecular dimensions, were performed at semiempirical level. In particular, the AM1 method,[19] available in the MOPAC version 6.0 computational package distributed by QCPE,[20] was adopted.

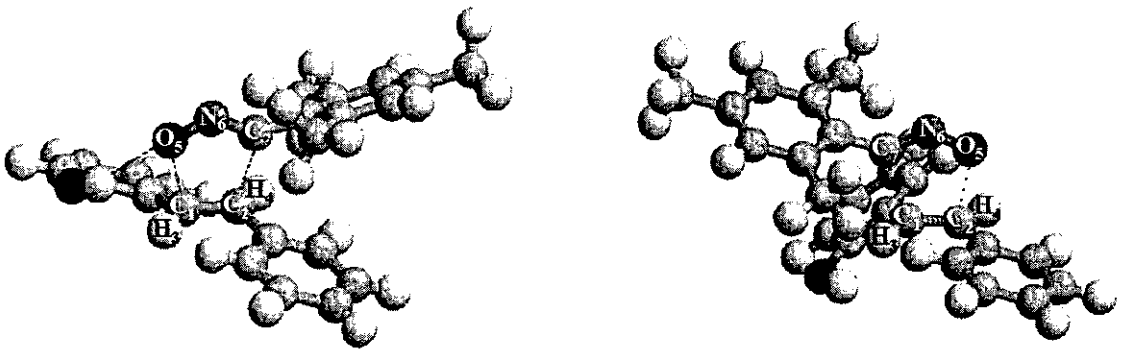
The transition states were reached through several calculation steps. The first optimization was carried out through the NLLSQ keyword maintaining the distances between the atoms involved in the reaction pathway fixed to 2 Å. In the second calculation also such distances were optimized and finally a full geometry optimization, with the PRECISE and GNORM = 0.01 keywords was carried out.

Two possible transition states were located for the reaction of **2** with **8**, corresponding to the two possible reaction attaches:

a) the dipolar oxygen atom is attached at the olefinic C_1 carbon atom [$\mathbf{TS_1}$, Figure 2, a)];

b) the dipolar oxygen atom is attached at the olefinic C_2 carbon atom [$\mathbf{TS_2}$, Figure 2, b)].

Figure 2. Transition states ($\mathbf{TS_1}$ and $\mathbf{TS_2}$) for the reaction of **2** with **8**.



a) TS_1 b) TS_2

Their most relevant geometrical parameters and formation enthalpies (ΔH_f) are collected in Table 3, from which the following remarks are noteworthy.

Table 3. Optimized geometrical parameters of the two possible transition states, TS_1 and TS_2, and related products obtained by the semiempirical AM1 method (distance in Å, angles in degrees).

	TS_1	Product		TS_2	Product
r(C-1--C-2)	1.398	1.558	r(C-1--C-2)	1.400	1.555
r(C-1--H-3)	1.106	1.123	r(C-1--H-3)	1.104	1.124
r(C-2--H-4)	1.107	1.124	r(C-2--H-4)	1.107	1.121
r(C-1--HOPh)	1.454	1.491	r(C-1--HOPh)	1.463	1.487
r(C-2--Ph)	1.463	1.487	r(C-2--Ph)	1.456	1.490
r(C-1--O-5)	2.093	1.480	r(C-2--O-5)	2.072	1.486
r(O-5--N-6)	1.205	1.316	r(O-5--N-6)	1.203	1.312
r(N-6--C-7)	1.261	1.318	r(N-6--C-7)	1.260	1.319
r(C-2--C-7)	2.097	1.536	r(C-1--C-7)	2.116	1.536
r(C-7--Me_3Ph)	1.429	1.462	r(C-7--Me_3Ph)	1.432	1.462
ϑ(C-1--C-2--H-4)	119.3	110.3	ϑ(C-1--C-2--H-4)	118.6	113.4
ϑ(C-1--C-2--C-7)	102.5	100.5	ϑ(C-2--C-1--C-7)	102.7	100.3
ϑ(C-1--C-2--Ph)	120.3	113.0	ϑ(C-1--C-2--Ph)	124.5	113.5
ϑ(C-2--C-1--H3)	118.8	112.4	ϑ(C-2--C-1--H-3)	118.6	109.1
ϑ(C-2--C-1--O-5)	99.9	103.4	ϑ(C-1--C-2--O-5)	99.8	103.6
ϑ(C-2--C-1--HOPh)	123.5	112.9	ϑ(C-2--C-1--HOPh)	118.9	113.9
ϑ(C-1--O-5--N-6)	105.6	112.4	ϑ(C-2--O-5--N-6)	106.0	112.1
ϑ(O-5--N-6--C-7)	128.8	111.7	ϑ(O-5--N-6--C-7)	130.0	112.1
ϑ(N-6--C-7--C-2)	102.6	111.9	ϑ(N-6--C-7--C-1)	100.8	111.7
ϑ(N-6--C-7--Me_3Ph)	141.3	119.9	ϑ(N-6--C-7--Me_3Ph)	139.7	126.2
ω(HOPh)	-164.4	-122.5	ω(HOPh)	138.5	139.8
ω(Ph)	145.5	131.3	ω(Ph)	160.5	60.3
ω(Me_3Ph)	70.2	71.3	ω(Me_3Ph)	75.2	71.7
ω(HOPh--C-2--C-1--Ph)	-152.5	-120.0	ω(HOPh--C-1--C-2--Ph)	-152.2	-123.8
ω(H-3--C-1--C-2--H-4)	165.1	129.2	ω(H-3--C-1--C-2--H-4)	163.4	127.2
ΔHf (Kcal/mol)	80.86	34.28	ΔHf (Kcal/mol)	84.47	34.77

a) The C-1ONC-7C-2 ring is practically planar and about 50° tilted with respect to the paper sheet plane. The C-1--O-5 and C-2--C-7 bond lengths are nearly equal to each other and of the same order found in other simpler transition states involving the nitrile oxide framework. All the phenyl rings are rotated to minimize repulsive interactions between non bonded atoms. In particular, the framework torsion angle [ω(HOPh)] of the hydroxy substituted phenyl ring is -164.4° and the hydroxy group is oriented in such a way that oxygen and hydrogen atoms are separated by 2.889 and 2.224 Å, respectively, from the oxygen atom. Since the van der Waals radius of the oxygen atom is 1.52 Å and that of the hydrogen atom is 1.20

Å,[21] the O···O and H···O distances obtained from calculations are shorter than the sum of the related radii and allow hydrogen bonding interactions, which are responsible for the TS_1 transition state stabilization. If the hydroxyl group is rotated by 180°, the new transition state, after optimization, is 2.26 Kcal/mol less stable than TS_1: this value can be assumed as a rough estimate of the hydrogen bond strength.

b) In the TS_2 transition state the C-1C-2O-5N-6C-7 ring is nearly perpendicular to the sheet of paper plane (81.6°) and all phenyl rings are rotated, as in the previous case. However the torsion angle around the phenyl-carbon atom bond is 138.5° and in such position the hydroxyl group is too distant from the nitrile oxide oxygen atom to allow the formation of the hydrogen bridge. From the energetic point of view, the energy of TS_2 is 3.64 Kcal/mol higher than that of TS_1, therefore, on the ground of the Boltzman equation, TS_1 should be the only transition state present during the reaction time, even if quantitative considerations on ΔE coming from semiempirical approaches are to be taken with some caution. Looking at Figure 2 it could seem that remarkable steric effects are present in TS_2, owing that two phenyl rings are oriented in the same space region. Comparison of optimized geometrical parameters do not evidence significant structural differences attributable to different steric hindrance in the two cases. On the contrary, it is noteworthy that the stability difference between the two transition states is of the same order of the hydrogen bond energy estimate which can be therefore considered to be responsible for the different reactivity of *o*-hydroxystilbene with respect to the *o*-methoxystilbene.

The above transition state characteristics are evident also in two different compounds expected from TS_1 and TS_2, which, however, are nearly isoenergetic.

In conclusions, the 5:1 regioisomeric ratio in favour of 5-(2-hydroxyphenyl) substituted isomer observed in the reaction of **2** with **8** is accounted for by a directing hydrogen bond model between the phenolic hydrogen atom of dipolarophile and the 1,3-dipolar oxygen atom, while that one of 2:1 in favour of 5-(4-hydroxyphenyl) and 5-(4-methoxyphenyl) substituted isomer in reactions of **4** and **7** is accounted for by an electron-donor effect. Semiempirical AM1 calculations support these two favourable effects. In agreement with our expectations and AM1 calculations no regioselectivity is observed in reactions of **3**, **5** and **6**.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 281 spectrophotometer using potassium bromide discs. ^1H and ^{13}C NMR Spectra were recorded on a Bruker W P 80 spectrometer using tetramethylsilane as internal standard and deutero-chloroform or dimethyl sulfoxide-d_6 as solvents. Elemental analyses were performed on a Carlo Erba Elemental Analyser 1106. Thin layer chromatography was performed on Merck silica gel 60-F_{254} precoated aluminium

plates and gravity- and flash-chromatography were performed on Merck silica gel 60 by using mixtures of cyclohexane-ethyl acetate as eluents.

Starting materials. Mesitonitrile oxide[22] were prepared following a literature method. *O*-,[23] *m*- and *p*-hydroxy[24] and *o*-, *m*- and *p*-methoxy[25] substituted *trans*-stilbenes were prepared by the method of Wittig starting from triphenylbenzylphosphonium salts and the appropriate aromatic aldehydes in alkaline medium. *Trans*-stilbene was purchased from Aldrich Co.

Cycloaddition reactions of unsubstituted or hydroxy and methoxy substituted stilbene (**1-7**) *with mesitonitrile oxide* (**8**). A solution of not or hydroxy- or methoxy-substituted stilbene (**1-7**) (2 mmol) and mesitonitrile oxide (**8**) (1 mmol) in benzene (30 mL) was refluxed until the 1,3-dipole was consumed (*ca.* 24 h). After removing the solvent, the reaction mixture was chromatographed under a nitrogen pressure to give the two cycloadducts in mixture, which was then subjected to flash-chromatography in order to separate the two components. In some cases the separation required several flash-chromatographies.

3-Mesityl-4,5-diphenyl-4,5-dihydroisoxazole (**9**): 89 % yield, mp 107-108 °C from ethyl acetate (Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.39; H, 6.72; N, 4.05); ν_{max} (KBr) 1610 cm^{-1}; δ_H (DMSO-d_6) 1.93 (s, 6H), 2.15 (s, 3H), 4.70 (d, 1H, J = 7.2 Hz), 5.98 (d, 1H, J = 7.2 Hz), 6.76 (s, 2H), 7.38-7.44 (m, 10H); δ_C (DMSO-d_6) 19.60, 20.53, 64.73, 87.89, 125.66, 127.75, 127.91, 128.16, 128.31, 128.42, 128.69, 128.74, 139.39, 145.10, 158.74; MS: m/z 341 (M^+), 236, 196, 105.

3-Mesityl-4-(2-hydroxyphenyl)-5-phenyl-4,5-dihydroisoxazole (**10a**): 18 % yield, mp 140-141 °C from ethyl acetate (Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.69; H, 6.43; N, 3.89); ν_{max} (KBr) 3360br, 1590 cm^{-1}; δ_H (DMSO-d_6) 2.03 (s, 6H), 2.14 (s, 3H), 5.16 (d, 1H, J = 7.3 Hz), 5.85 (d, 1H, J = 7.3 Hz), 6.64-7.40 (m, 11H), 9.52 (s, 1H); δ_C (DMSO-d_6) 19.63, 20.47, 57.80, 87.72, 115.13, 119.29, 122.89, 125.12, 125.48, 128.00, 128.26, 128.63, 136.65, 137.74, 154.53, 158.59; MS: m/z 357 (M^+), 252, 212, 105.

3-Mesityl-4-phenyl-5-(2-hydroxyphenyl)-4,5-dihydroisoxazole (**10b**): 74 % yield, mp 162-163 °C from ethyl acetate (Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.58; H, 6.51; N, 3.99); ν_{max} (KBr) 3360br, 1600 cm^{-1}; δ_H (DMSO-d_6) 1.83 (s, 6H), 2.14 (s, 3H), 4.52 (d, 1H, J = 5.0 Hz), 6.03 (d, 1H, J = 5.0 Hz), 6.74-7.35 (m, 11H), 9.73 (s, 1H); δ_C (DMSO-d_6) 19.26, 20.47, 64.11, 84.31, 115.32, 116.74, 125.91, 126.48, 127.53, 128.59, 128.82, 136.56, 137.83, 154.24, 158.73; MS: m/z 357 (M^+), 236, 212, 121.

3-Mesityl-4-(3-hydroxyphenyl)-5-phenyl-4,5-dihydroisoxazole (**11a**): 32 % yield, mp 131-132 °C from ethyl acetate (Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.61; H, 6.55; N, 3.95); ν_{max} (KBr) 3360br, 1600 cm^{-1}; δ_H (DMSO-d_6) 1.87 (s, 6H), 2.42 (s, 3H), 4.64 (d, 1H, J = 7.6 Hz), 5.87 (d, 1H, J = 7.6 Hz), 6.37-7.35 (m, 11H), 9.58 (s, 1H); δ_C (DMSO-d_6) 19.47, 20.51, 63.84, 87.88, 110.28, 113.06, 114.86, 118.44, 125.56, 126.46, 127.56, 127.88, 128.13, 128.22, 128.30, 128.65, 129.60,136.61, 138.32, 140.40, 157.64, 158.68; MS: m/z 357 (M^+), 252, 212, 105.

3-Mesityl-4-phenyl-5-(3-hydroxyphenyl)-4,5-dihydroisoxazole (**11b**): 32 % yield, mp 145-146 °C from ethyl acetate (Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.71; H, 6.62; N, 4.01); ν_{max} (KBr) 3360br, 1590 cm^{-1}; δ_H (DMSO-d_6) 1.95 (s, 6H), 2.36 (s, 3H), 4.57 (d, 1H, J = 4.6 Hz), 5.87 (d, 1H, J = 4.6 Hz), 6.72-7.61 (m, 11H), 9.63 (s, 1H); δ_C (DMSO-d_6) 19.32, 20.21, 64.85, 87.11, 112.23, 114.65, 116.00, 126.36, 127.12, 127.34, 127.60, 127.66, 128.38, 128.58, 127.60, 127.66, 136.17, 138.04, 140.85, 157.41, 158.84; MS: m/z 357 (M^+), 236, 212, 121.

3-Mesityl-4-(4-hydroxyphenyl)-5-phenyl-4,5-dihydroisoxazole (**12a**): 24 % yield, mp 176-177 °C from ethyl acetate (Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.58; H, 6.43; N, 3.87); ν_{max} (KBr) 3360br, 1610 cm^{-1}; δ_H (DMSO-d_6) 2.07 (s, 6H), 2.42 (s, 3H), 4.84 (d, 1H, J = 7.6 Hz), 5.71 (d, 1H, J = 7.6 Hz), 6.81-6.92 (m, 7H),7.28-7.35 (m, 4H), 9.62 (s, 1H); δ_C (DMSO-d_6) 19.50, 20.40, 60.80, 87.38, 126.65, 128.39, 128.40, 129.02,138.21, 157.63, 158.47; MS: m/z 357 (M^+), 252, 212, 105.

3-Mesityl-4-phenyl-5-(4-hydroxyphenyl)-4,5-dihydroisoxazole (**12b**): 48 % yield, mp 181-182 °C from ethyl acetate (Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.63; H, 6.55; N, 3.94); ν_{max} (KBr) 3360br, 1630 cm^{-1}; δ_H (DMSO-d_6) 1.99 (s, 6H), 2.15 (s, 3H), 4.70 (d, 1H, J = 7.9 Hz), 5.82 (d, 1H, J = 7.9 Hz), 6.77-6.82 (m, 4H), 7.24-7.28 (m, 7H), 9.54 (s, 1H); δ_C (DMSO-d_6) 19.73, 20.52, 64.31, 86.34, 115.36, 125.05, 127.34, 127.60, 127.93, 128.37, 128.66, 129.85, 136.55, 136.79, 137.97, 157.40, 158.82; MS: m/z 357 (M^+), 236, 212, 121.

3-Mesityl-4-(2-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (**13a**): 34 % yield, mp 122-123 °C from ethyl acetate (Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.80; H, 6.81; N, 3.74); ν_{max} (KBr) 1605, 1240, 1020 cm^{-1}; δ_H (DMSO-d_6) 1.96 (s, 6H), 2.14 (s, 3H), 3.69 (s, 3H), 5.11 (d, 1H, J = 7.2 Hz), 5.94 (d, 1H, J = 7.2 Hz), 6.74 -7.45 (m, 11H); δ_C (DMSO-d_6) 19.44, 20.49, 55.20, 58.09, 86.76, 111.36, 120.83, 125.46, 127.56, 128.07, 128.29, 128.67, 129.23, 136.55, 137.79, 156.32, 158.20; MS: m/z 371 (M^+), 264, 226, 105.

3-Mesityl-4-phenyl-5-(2-methoxyphenyl)-4,5-dihydroisoxazole (**13b**): 34 % yield, mp 150-151 °C from ethyl acetate (Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.85; H, 6.75; N, 3.81); ν_{max} (KBr) 1610, 1250, 1040 cm^{-1}; δ_H (DMSO-d_6) 1.82 (s, 6H), 2.18 (s, 3H), 3.72 (s, 3H), 4.47 (d, 1H, J = 4.0 Hz), 6.00 (d, 1H, J = 4.0 Hz), 6.69-7.26 (m, 11H); δ_C (DMSO-d_6) 19.68, 20.95, 64.43, 84.35, 110.35, 120.51, 126.11, 127.48, 127.67, 128.46, 128.62, 128.84, 129.10, 137.14, 138.32, 156.15, 158.53; MS: m/z 371 (M^+), 236, 226, 119.

3-Mesityl-4-(3-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (**14a**): 33 % yield, mp 137-138 °C from ethyl acetate (Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.89; H, 6.81; N, 3.72); ν_{max} (KBr) 1600, 1250, 1030 cm^{-1}; δ_H (DMSO-d_6) 1.94 (s, 6H), 2.12 (s, 3H), 3.65 (s, 3H), 4.71 (d, 1H, J = 6.7 Hz), 5.94 (d, 1H, J = 6.7 Hz), 6.76-7.41 (m, 11H); δ_C (DMSO-d_6) 19.75, 20.16, 64.71, 87.82, 116.70, 118.50, 124.17, 131.60, 132.75, 133.26, 133.42, 142.10, 158.69, 159.34; MS: m/z 371 (M^+), 264, 226, 105.

3-Mesityl-4-phenyl-5-(3-methoxyphenyl)-4,5-dihydroisoxazole (**14b**): 33 % yield, mp 142-143 °C from ethyl acetate (Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.75; H, 6.83; N, 3.81); ν_{max} (KBr) 1600, 1250, 1030 cm^{-1}; δ_H (DMSO-d_6) 1.99 (s, 6H), 2.12 (s, 3H), 3.70 (s, 3H), 4.71 (d, 1H, J = 6.7 Hz), 5.95 (d, 1H, J = 6.7 Hz), 6.79-7.41 (m, 11H); δ_C (DMSO-d_6 19.57, 20.25, 64.85, 88.04, 111.36, 120.21, 120.83, 124.46, 124.93 125.46, 127.56, 128.18, 128.30, 128.67, 128.71, 136.55, 137.79, 138.01, 140.94, 156.32, 158.20; MS: m/z 371 (M^+), 236, 226, 119.

3-Mesityl-4-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (**15a**): 23 % yield, mp 166-167 °C from ethyl acetate (Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.64; H, 6.75; N, 3.72); ν_{max} (KBr) 1610, 1260, 1010 cm^{-1}; δ_H (DMSO-d_6) 1.97 (s, 6H), 2.12 (s, 3H), 3.68 (s, 3H), 4.66 (d, 1H, J = 7.2 Hz), 5.87 (d, 1H, J = 7.2 Hz), 6.76-7.43 (m, 11H); δ_C (DMSO-d_6) 19.19, 20.49, 54.97, 64.10, 88.04, 114.02, 127.22, 127.63, 127.91, 128.08, 128.36, 128.66, 129.04, 136.75, 140.30, 158.73, 158.99; MS: m/z 371 (M^+), 264, 226, 105.

3-Mesityl-4-phenyl-5-(4-methoxyphenyl)-4,5-dihydroisoxazole (**15b**): 46 % yield, mp 179-180 °C from ethyl acetate (Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.78; H, 6.82; N, 3.81); ν_{max} (KBr) 1590, 1250, 1030 cm^{-1}; δ_H (DMSO-d_6) 1.98 (s, 6H), 2.14 (s, 3H), 3.75 (s, 3H), 4.70 (d, 1H, J = 7.6 Hz), 5.88 (d, 1H, J = 7.6 Hz), 6.76-7.40 (m, 11H); δ_C (DMSO-d_6) 19.70, 20.52, 55.11, 64.41, 88.01,

114.02, 127.27, 127.65, 127.93, 128.37, 128.68, 131.72, 136.56, 136.72, 138.02, 158.53, 159.16; MS: m/z 371 (M^+), 236, 226, 119.

Competition experiments. For competitive experiments of **2** in the presence of **3-7**, and of **5** in the presence of **6**, **7**, a solution of **8** (1 mmol), **2** (1 mmol) and the substituted stilbene (1 mmol) in benzene (10 mL) was refluxed until the 1,3-dipole was consumed.

For the solvent effect, a solution of **8** (1 mmol), **2** (1 mmol) and the substituted stilbene (1 mmol) in the appropriate solvent (deuterated benzene, chloroform, dimethyl sulfoxide and dimethylformamide) (1 mL) was allowed to react at rt until the 1,3-dipole was consumed.

Yields and regioisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. The maximum deviation from the average of triplicate runs was ± 0.2%.

Method of calculation. The MOPAC computation package, distributed by QCPE (Quantum Chemistry Program Exchange), allows to perform quantomechanical calculations by means of MINDO/3, MNDO, AM1 and PM3 semiempirical methods. AM1 and PM3 are evolutions of the MNDO approach, from which differ mainly for the parameterization techniques. Moreover, extra terms, which define spherical Gaussian function, were added to reduce the excessive core-core repulsions in the region outside bonding distances and less than the van der Waals distances. Such corrections have improved the quality of the results of both methods because they are now able to describe hydrogen bonding, even if the energy of the hydrogen bridges is still underestimated with respect to the values coming from *ab initio* methods. On the other hand, they are by far much less time consuming than *ab initio* calculations and allow to handle very big molecules.

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