Cycloadditions of mesitonitrile oxide with amino- and nitrostilbenes†

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Received (in Cambridge, UK) 30th September 1999, Accepted 2nd June 2000
Published on the Web 19th July 2000

2-Amino, 4-amino- and 2-nitrostilbenes react with mesitonitrile oxide affording the 5-substituted phenyldihydroisoxazole as the more abundant regioisomer, while 3-amino and 3-, 4-nitro derivatives give comparable amounts of the two regioisomers. Reactions of 2-acylamino derivatives show a lower regioselectivity and furthermore no solvent effect was found for the regiochemistry of 2-aminostilbene and its *N*-acetyl derivative. These experimental results indicate that reactions of 2-aminostilbene and its *N*-acyl derivatives are not governed by hydrogen bonding or steric effects. They are not explainable by the frontier molecular orbital theory, but semiempirical PM3 calculations performed on regioisomeric transition structures gave values of regioisomeric ratios well in accord with those experimentally observed.

Introduction

Recently, we have focused on the role that hydrogen bonding plays in the cycloadditions of nitrile oxides. Cyclic dipolarophiles containing a hydroxy or amino group in a suitable position with respect to the unsaturation show an enhanced dipolarophilic activity[1,2] and/or site-,[3–5] regio- and stereoselectivity[6–13] in their reactions with nitrile oxides. This control can be attributed to a coordination of the hydrogen atom of the dipolarophile with the oxygen atom of the 1,3-dipole, which can assist the cycloaddition by reducing the energy of the transition state.[11,14] Such an effect, however, is very modest in acyclic dipolarophiles.[15,16]

Within our studies on the synthetic applications of nitrile oxide cycloadditions,[17] we have found that the dipolarophilic activity of the cyano group in 2-acylamino[1] and 2-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, respectively, and in all these cases the reactivity of the cyano group is remarkably dependent on the solvent, in accordance with a hydrogen bonding involvement. Contrary to our expectations, the cyano group of 3-aminopropenenitriles[3,4] is more reactive than the olefinic double bond towards nitrile oxides and it exclusively reacts with benzonitrile oxide in 2-amino-3-cyano-4,5-dihydro pentatomic heterocycles.[5] Recently, furthermore, we have shown that the regioselectivity of the reaction between mesitonitrile oxide (**1**) (Scheme 1) and 2-hydroxystilbene (**2**) achieves the regioisomeric ratio of 5:1 in favour of the 5-(2-hydroxyphenyl) substituted isomer according to a directed hydrogen bonding model, while for the reactions of the 4-hydroxy- and 4-methoxystilbene, which show a 2:1 ratio between the 5- and 4-regioisomer, an electron-donor effect has been suggested.[6]

As an extension of this line of research and particularly in the search for other acyclic dipolarophiles which add to nitrile oxides under the control of favourable hydrogen bonding effects, we have investigated the reactions of **1** with the *trans*-forms of 2- (**3**), 3- (**4**) and 4-aminostilbene (**5**) and those of **1** with the *N*-acetyl (**6**) and *N*-4-tolylsulfonyl substituted derivative (**7**). Furthermore, seeking to support this hydrogen bonding model, we have carried out a series of competitive experiments between **3** and each one of its 3- and 4-isomers (**4** and **5**), *N*-acyl derivatives (**6** and **7**) and **2**, and we have carried out solvent effect studies on the reactions of **3** and **6** in the presence of **2** and *trans*-stilbene.

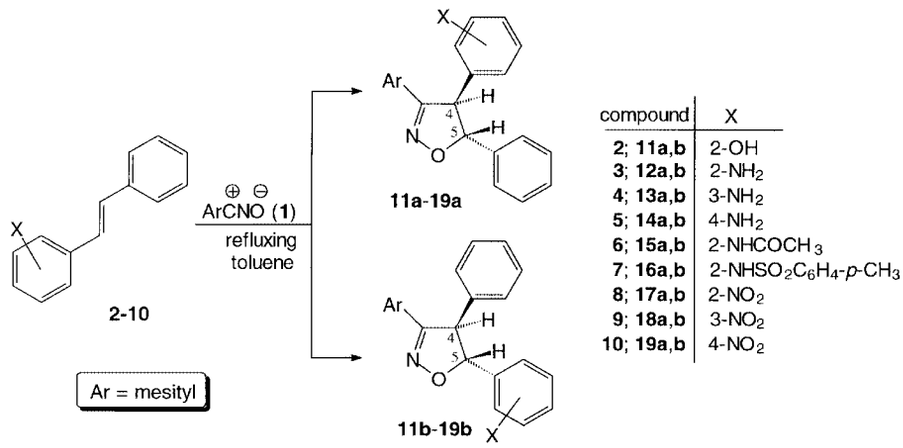
Contrary to our expectations, however, these competitive experiments and solvent effect studies have not supported the directed hydrogen bonding model and so we have also investigated the reactions of **1** with 2- (**8**), 3- (**9**) and 4-nitrostilbene (**10**) in search of electronic or steric effects. Here we report the results of this study, which are also discussed in the light of the frontier molecular orbital (FMO) theory.[18] Furthermore, for the reaction of **3**, which is the simplest structure among those examined able to form an intermolecular hydrogen bond between the aminic hydrogen atom and the dipolar oxygen atom, we have tried to determine the transition state geometry through semiempirical PM3[19] and AM1[20] calculations.

Results and discussion

The reaction of **1** with **2**–**10** in a 1:2 ratio under refluxing toluene until the 1,3-dipole was consumed, gave a mixture of the two dihydroisoxazole regioisomers (**11a,b**–**19a,b**), whose ratios and global yields are reported in Table 1. As is evident from Table 1, all 2-substituted stilbenes afforded the 5-substituted phenyl regioisomer as the major product. In particular, the 2-aminostilbene **3** shows a regioselectivity (**12a**:**12b** = 14:86) which is similar to that of **2** (**11a**:**11b** = 16:84) and **6** (**15a**:**15b** = 17:83) and slightly higher than that of **7** (**16a**:**16b** = 27:73). On the contrary, *N*-acyl and *N*-tosyl derivatives **6** and **7** were expected to be more regioselective on the

† PM3 and AM1 calculations of total energies and *z*-matrices for transition states **12**–**19** are available as electronic supplementary information. For direct electronic access, see http://www.rsc.org/suppdata/p2/a9/a907861d/

DOI: 10.1039/a907861d



Scheme 1

Table 1 Regioisomeric ratios[a] and global yields[b] of dihydroisoxazoles **11a,b**–**19a,b**

Starting substituted stilbenes	Dihyhdroisoxazole regioisomers	Ratios (%)	Overall yields (%)
2 (2-OH)	**11a** + **11b**	16:84	90
3 (2-NH_2)	**12a** + **12b**	14:86	89
4 (3-NH_2)	**13a** + **13b**	51:49	88
5 (4-NH_2)	**14a** + **14b**	33:67	89
6 (2-NHAc)	**15a** + **15b**	17:83	84
7 (2-NHTs)	**16a** + **16b**	27:73	82
8 (2-NO_2)	**17a** + **17b**	30:70	86
9 (3-NO_2)	**18a** + **18b**	44:56	84
10 (4-NO_2)	**19a** + **19b**	49:51	85

[a] Determined by integration of the two methine doublets in the ^{1}H NMR spectra of the crude reaction mixture performed in toluene; the maximum deviation from the average of triplicate runs was ±0.3%. [b] Isolated yields based on the 1,3-dipole.

Table 2 Relative rates of stilbenes **2**, **4**–**10** to that of **3** in mesitonitrile oxide cycloadditions[a]

2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0.73	1	0.22	0.32	0.66	0.52	1.7	2.5	1.5

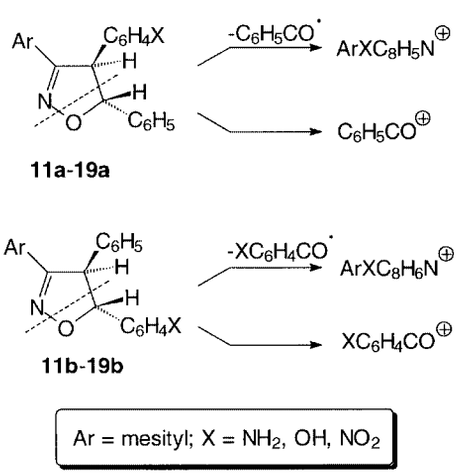
[a] All reactions were carried out by allowing a solution to react containing 1 mol of any reagent in toluene at rt until the 1,3-dipole was consumed (*ca.* 2 days); the solvent then was removed under reduced pressure and the residue was subjected to ^{1}H NMR analysis in DMSO-d_6 solution. Yields were determined by the integration of H-4 and H-5 protons of each product in the crude ^{1}H NMR. The maximum deviation from the average of duplicate runs was ±0.3%.

basis of the anticipated formation of the hydrogen bond between the dipolarophile amino group and the dipole oxygen atom. The reactions of **4**, **9** and **10** were found not to be regioselective with the products being formed in approximately equal amounts, while in the reactions of **5** and **8** a regioselectivity of 33 to 67 and of 30 to 70 in favour of the 5-substituted phenyl regioisomer was obtained. The regioselectivity observed in the case of **5** is probably attributable to an electron-donor effect, as was proposed for 4-hydroxy- and 4-methoxystilbenes,[6] while steric effects can be invoked for 2-nitrostilbene **8**.

The regioisomeric ratios of Table 1 were supported by the results of competitive experiments carried out by refluxing a toluene solution of 1 mmol of each compound **1**, **3** and **2** or **4**–**10** until the 1,3-dipole was consumed. In accordance with the small effect of phenyl substituents on the rate of cycloaddition reactions, these competitive experiments provide an evaluation of the relative cycloaddition constants which falls within one power of ten (Table 2). From Table 2, the 2-aminostilbene **3** is slightly more reactive than its isomers **4** and **5** and its *N*-acyl and *N*-tosyl derivatives **6** and **7**, but slightly less reactive than the nitro-derivatives **8**–**10**. The competition of **3** with **2** for mesitonitrile oxide was particularly diagnostic for ascertaining the absence of hydrogen bonding involvement, yielding a value of 0.73.

Furthermore, solvent effect studies performed by analysing the crude ^{1}H NMR spectra of reactions of **1** with **3** or **6** carried out in the presence of (*E*)-stilbene (0.15 mmol of any reagent) at room temperature in benzene-d_6, dimethylformamide-d_6, dimethyl sulfoxide-d_6 and deuterochloroform until the 1,3-dipole was consumed, have shown that the reactions under examination do not undergo any substantial variations upon changing the solvent. Finally, the contextual ^{1}H NMR monitoring of the reactions of **3** in benzene-d_6 and dimethyl sulfoxide-d_6 (four measurements in two days) has shown that cycloaddition products are kinetically controlled as in most nitrile oxide cycloadditions.[21]

The two regioisomers, which in some cases were not easily separated and required repeated flash-chromatography to isolate small quantities of a pure sample, were unequivocally distinct by means of mass spectrometry. Upon electron impact, the 4- and 5-regioisomers undergo, among others, two important diagnostic fragmentation reactions originating directly from molecular ions,[22] which afford typical fragmentation ions corresponding to the benzoyl ion or substituted benzoyl ions and those deriving from the loss of the benzoyl radical or substituted benzoyl radicals (Scheme 2). Typically, the presence of



Scheme 2

the benzoyl ion in the mass spectra indicates that the unsubstituted phenyl is attached at the 5-position of the dihydroisoxazole ring.

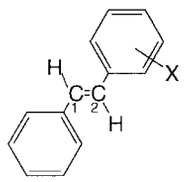
The assigned structures were also supported by the relative chemical shifts of the dihydroisoxazole 4- and 5-protons and carbon atoms in their ^{1}H and ^{13}C NMR spectra, respectively. The major isomers **11b**–**19b** exhibit two closely spaced doublets in their ^{1}H NMR spectra, but two widely spaced signals in their ^{13}C NMR spectra (see Experimental). On the contrary, an inverse pattern of signals appears in the ^{1}H and ^{13}C NMR of the two *N*-acyl derivatives **15** and **16**. In the amino and nitro derivatives the H^4 and H^5 coupling constants are larger for the more abundant regioisomer, but they are minor in the case of **15** and **16**.

Dihydroisoxazoles **15a**,**b** and **16a**,**b** were identified by comparison of their IR and NMR spectra with those of samples obtained starting from **12a**,**b** by treatment with acetyl and toluene-4-sulfonyl chloride. Initially, the highest regioselectivity found for **3** with respect to those of **4** and **5** has led us to think that the reaction of **3** with **1** also depended on hydrogen bonding effects, but this hypothesis was not supported by the minor regioselectivity observed for *N*-acyl and *N*-tosyl derivatives, which present more acid aminic protons. Generally, the strength of the hydrogen bonding parallels the acidity of the NH bonds.[1,13,23] Since, furthermore, for the most bulky amides **6** and **7** steric effects could not be taken into consideration, because these show a more minor regioselectivity than **3**, likewise secondary cyanamides,[16g] we have tried to rationalize the observed regiochemistry of our cycloadditions by means of the FMO theory.[18]

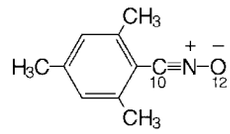
Because of the large size of the systems under study, the geometry optimization of each one was performed at the PM3 level of theory.[19] Using the obtained eigenvalues (Table 3) it was determined that the reaction was LUMO dipole–HOMO dipolarophile controlled for compounds **2**–**6** and HOMO dipole–LUMO dipolarophile controlled for compounds **8**–**10**, while for compound **7** the HOMO dipole–LUMO dipolarophile gap was nearly the same as the LUMO dipole–HOMO dipolarophile one. Furthermore, the energy-gap in the interactions of compounds **2**–**6** is larger than the energy-gap in the interactions of compounds **8**–**10**. This trend is in line with the observed faster cycloaddition rates of **8**–**10** with respect to those of **2**–**7**, even if there is not a direct correlation among the energy-gaps and relative rates within the group of **8**–**10**.

In spite of this and because of the nearly similar coefficients at the carbon and the oxygen atoms of the LUMO in the 1,3-dipole, the FMO approach cannot be unambiguously used to assign the regiochemistry for compounds **2**–**7**; while it predicts the formation of the 4-substituted phenyl regioisomer for compounds **8**–**10**, contrary to our experimental results. However, although the FMO theory has enjoyed considerable success in rationalizing the regiochemistry of Diels–Alder reactions, in many cases it has been inadequate for the treatment of 1,3-dipolar cycloadditions.[18] In the simple FMO theory, this is due to the disregard of steric and electrostatic effects as well as the effects of the interactions of other high-energy filled orbitals with low-energy unfilled orbitals (secondary orbital interactions).

The failure of FMO theory to correctly predict the regiochemical course of cycloadditions of **1** with substituted stilbenes **2**–**10** led us to perform semiempirical PM3[19] and AM1[20] calculations to examine the regioisomeric transition states. Previously, in the case of the cycloaddition of **2** to **1**, semiempirical AM1 calculations supported the **11a**:**11b** = 1:5 regioisomeric ratio as a consequence of a directed hydrogen bond model between the phenolic hydrogen atom of the dipolarophile and the 1,3-dipolar oxygen atom.[6] As for the transition states of the reaction of **2** with **1**, transition states of reactions of **3**–**10** with **1** were reached through several steps. The first optimization was carried out though the TS keyword, maintaining the distances between the atoms involved in the reaction pathway fixed to 2 Å. In the second calculation such distances were also optimized and finally a full geometry optimization was carried out.



2-10



1

Table 3 HOMO and LUMO energies (eV) and orbital coefficients of stilbenes **2**–**10** and nitrile oxide **1**

Compd.	X	Orbital	*E*/eV	Orb. Coeff. 1	Orb. Coeff. 2
2	2-OH	HOMO	−8.74	0.34	0.35
		LUMO	−0.41	0.38	−0.42
3	2-NH_2	HOMO	−8.30	0.35	0.29
		LUMO	−0.58	0.39	−0.40
4	3-NH_2	HOMO	−8.49	0.31	0.29
		LUMO	−0.58	0.40	−0.40
5	4-NH_2	HOMO	−8.19	0.36	0.28
		LUMO	−0.54	0.39	−0.39
6	2-NHAc	HOMO	−8.41	0.35	0.28
		LUMO	−0.70	0.40	−0.40
7	2-NHTs	HOMO	−8.49	0.38	0.35
		LUMO	−0.81	0.16	−0.14
8	2-NO_2	HOMO	−9.01	0.36	0.44
		LUMO	−1.36	0.36	−0.22
9	3-NO_2	HOMO	−9.09	0.38	0.43
		LUMO	−1.24	0.31	−0.24
10	4-NO_2	HOMO	−9.21	0.36	0.44
		LUMO	−1.50	0.37	−0.25
		Orbital	*E*/eV	Orb. Coeff. 10	Orb. Coeff. 12
1		HOMO	−9.01	0.28	−0.33
		LUMO	−0.26	0.21	0.20

The authenticity of transition states was ascertained by the presence of only one negative force constant, characteristic of these systems through the frequency calculation. We have examined different TS conformation structures by imposing a 30° step variation of the phenyl substituted ring and in the case of compounds **12**–**14**, we have also examined the inversion at the pyramidalized amine moiety. In this last case, we have registered an average increment of 1.22 kcal mol^{-1} for 5-substituted phenyl regioisomers and of 0.78 kcal mol^{-1} for 4-substituted phenyl regioisomers.

In any case the TS structures involve an interaction of out-of-plane orbitals belonging to the HOMO or LUMO of the dipole and dipolarophile system, as expected for this type of reaction. The analyses of C^1–C^2 and C^3–C^4 bond lengths, in all minor energy TS conformers, show an average length of 2.1267 Å for the C^1–C^2 bond and of 2.0913 Å for the C^3–C^4 bond in the case of 4-substituted phenyl regioisomers, whereas for the 5-substituted phenyl regioisomers the averages are 2.10923 and 2.10515 Å, respectively (Fig. 1).

The values of the regioisomeric ratio, calculated by the Boltzman equation, in accord with the difference in formation enthalpies ($\Delta\Delta H_f$TS) of regioisomeric transition states, agree sufficiently with the experimentally observed ones for PM3 (Table 4) and AM1 calculations (Table 5). Although AM1 results, on the whole, parallel the PM3 ones, the PM3 method seems to give a better description of all the systems under study, whilst AM1 results differ from PM3 ones in correctly predicting the observed regioisomeric ratio in the 2-nitro derivative.

Based on PM3 results, the following conclusions were drawn. The C^1–C^2 and C^3–O^4 bond lengths, nearly equal to each other

Table 4 ΔH_f of the transition states of the two regioisomers **12a**–**19a** and **12b**–**19b** obtained by PM3 calculations

Compd.	X	ΔH_f regioisomer **a**	ΔH_f regioisomer **b**	Calculated	Found
12	2-NH_2	127.91	127.05	**12a**:**12b** = 1:3.4	**12a**:**12b** = 1:6.14
13	3-NH_2	126.64	126.73	**13a**:**13b** = 1.1:1	**13a**:**13b** = 1:0.96
14	4-NH_2	126.66	126.32	**14a**:**14b** = 1:1.6	**14a**:**14b** = 1:2.03
15	2-NHAc	87.40	86.94	**15a**:**15b** = 1:1.9	**15a**:**15b** = 1:4.88
16	2-NHTs	83.70	83.00	**16a**:**16b** = 1:2.7	**16a**:**16b** = 1:2.70
17	2-NO_2	123.66	123.14	**17a**:**17b** = 1:2.1	**17a**:**17b** = 1:2.33
18	3-NO_2	119.28	118.80	**18a**:**18b** = 1:2.0	**18a**:**18b** = 1:1.27
19	4-NO_2	118.60	118.98	**19a**:**19b** = 1.7:1	**19a**:**19b** = 1:1.04

Table 5 ΔH_f of the transition states of the two regioisomers **12a**–**19a** and **12b**–**19b** obtained by AM1 calculations

Compd.	X	ΔH_f regioisomer **a**	ΔH_f regioisomer **b**	Calculated	Found
12	2-NH_2	126.09	122.14	**12a**:**12b** = 1:278	**12a**:**12b** = 1:6.14
13	3-NH_2	124.59	124.97	**13a**:**13b** = 1.7:1	**13a**:**13b** = 1:0.96
14	4-NH_2	124.39	123.39	**14a**:**14b** = 1:4.1	**14a**:**14b** = 1:2.03
15	2-NHAc	90.94	87.44	**15a**:**15b** = 1:146	**15a**:**15b** = 1:4.88
16	2-NHTs	85.51	83.75	**16a**:**16b** = 1:12	**16a**:**16b** = 1:2.70
17	2-NO_2	131.04	133.14	**17a**:**17b** = 20:1	**17a**:**17b** = 1:2.33
18	3-NO_2	128.60	128.63	**18a**:**18b** = 1:1	**18a**:**18b** = 1:1.27
19	4-NO_2	128.38	129.22	**19a**:**19b** = 3.3:1	**19a**:**19b** = 1:1.04

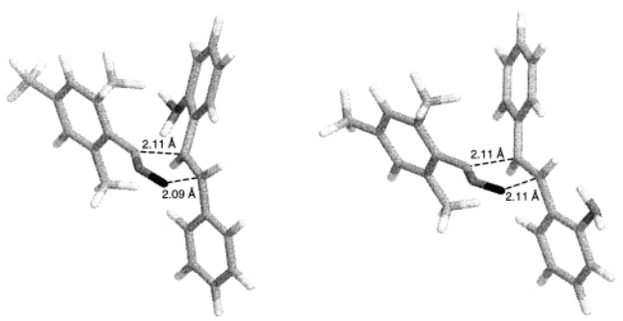


Fig. 1 TS structures of **3** as representative structures for the cycloaddition processes.

and of the same order found in other simpler transition states involving the nitrile oxide framework, are consistent for the synchronicity of the process. Moreover, the synchronicity of the transition states is in agreement with a poor steric effect and the regiochemistry of the process does not appear to be controlled by the hydrogen-bond formation either in the transition state or in the ground-state structures, but is probably controlled by other factors such as, for example, secondary orbital and/or van der Waals interactions.

Conclusion

Compounds **3** and **8** react with **1** affording the 5-substituted phenyl dihydroisoxazole as the predominant regioisomer with respect to their isomers **4**, **5**, **9** and **10**. Derivatives **6** and **7** show a minor regioselectivity and no solvent effect has been found for the reactions of **3** and **6**. Furthermore, compound **3** is more regioselective than **8** for which the involvement of a hydrogen bond was proved.[6] These experimental results indicate that the reactions of **3**, **6** and **7** are not governed by hydrogen bonding effects or by steric effects. The attempt to rationalize the results by the FMO approach failed, but semiempirical PM3 calculations performed on regioisomeric transition structures gave values of regioisomeric ratios sufficiently in accord with those experimentally observed. Therefore the regiochemistry of these process appears to be governed by secondary orbital and/or van der Waals interactions.

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. ^{1}H and ^{13}C NMR spectra were recorded on Varian instruments at 200 and 500 MHz (^{1}H) and at 50 and 125 MHz (^{13}C) using tetramethylsilane as internal standard and deuterochloroform 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 (**1**)[24] and (*E*)-2-hydroxystilbene (**2**)[25] were prepared following literature methods. 2- (**8**),[26] 3- (**9**)[27] and 4-Nitro-(*E*)-stilbene (**10**)[28] were prepared by the Wittig reaction starting from triphenylbenzylphosphonium chloride and the appropriate nitrobenzaldehyde in an alkaline medium. These were obtained in the *trans*-form by isomerization of the *cis*-form with selenium at the fusion temperature. 2- (**3**),[26] 3- (**4**)[27] and 4-Amino-(*E*)-stilbene (**5**)[28] were synthesized from the corresponding nitro compounds by reduction with stannous chloride. 2-Acetylamino- (**6**)[29] and 2-(4-tolylsulfonylamino)-stilbene (**7**) were obtained by acylation of 2-aminostilbene with acetyl and 4-tolylsulfonyl chloride, respectively. (*E*)-Stilbene was purchased from Aldrich Co.

Eluents used in chromatography were reagent grade. Solvents for competitive experiments were dried following literature procedures.[30] The identification of samples deriving from different experiments was made by superimposable IR spectra.

Reactions

Cycloaddition reactions of (*E*)-stilbene and its 2-hydroxy derivative (2) with mesitonitrile oxide (1). A solution of stilbene (4 mmol) and mesitonitrile oxide (**1**) (2 mmol) in toluene (30 ml) was refluxed until the 1,3-dipole was consumed (*ca*. 24 h). The reaction mixtures were then worked up and cycloadducts were identified as in the previous work.[6]

Cycloaddition reactions of substituted stilbenes (2–10) with mesitonitrile oxide (1). A solution of the substituted stilbene (**2**–**10**) (4 mmol) and mesitonitrile oxide (**1**) (2 mmol) in toluene (30 ml) was refluxed until the 1,3-dipole was consumed (*ca*. 24 h). After removing the solvent under reduced pressure, an aliquot of the crude mixture was taken and used to determine the regioisomeric ratio, the remaining aliquot was chromato-

graphed under a nitrogen atmosphere to give the two cycloadducts as a mixture, which was then subjected to flash-chromatography in order to separate the two components. In some cases the separation of the two regioisomers or the isolation of the minor regioisomer required repeated flash-chromatography.

Products

3-Mesityl-4-(2-aminophenyl)-5-phenyl-4,5-dihydroisoxazole (12a). 12% yield, mp 189–191 °C (from ethyl acetate) (Found: C, 80.91; H, 6.75; N, 7.88. $C_{24}H_{24}N_2O$ requires: C, 80.87; H, 6.79; N, 7.86%); ν_{max} (KBr)/cm^{-1} 3400 br, 3340 br; δ_H (DMSO-d_6) 1.99 (s, 6H), 2.14 (s, 3H), 4.62 (d, 1H, J = 4.7 Hz), 4.80 (br s, 2H), 6.25 (d, 1H, J = 4.7 Hz), 6.55–6.79 (m, 2H), 6.97–7.30 (m, 9H); δ_C (DMSO-d_6) 19.34, 20.11, 62.17, 85.94, 116.17, 116.64, 122.00, 123.24, 126.32, 127.53, 127.81, 128.35, 128.66, 136.54, 136.91, 138.01, 145.73, 159.64; *m*/*z* 356 ($M^{+\bullet}$), 250, 211, 195, 161, 145, 105.

3-Mesityl-4-phenyl-5-(2-aminophenyl)-4,5-dihydroisoxazole (12b). 77% yield, mp 192–193 °C (from ethyl acetate) (Found: C, 80.85; H, 6.80; N, 7.87. $C_{24}H_{24}N_2O$ requires: C, 80.87; H, 6.79; N, 7.86%); ν_{max} (KBr)/cm^{-1} 3440 br, 3362 br; δ_H (DMSO-d_6) 2.08 (s, 6H), 2.20 (s, 3H), 4.74 (d, 1H, J = 7.3 Hz), 5.02 (br s, 2H), 6.05 (d, 1H, J = 7.3 Hz), 6.71–6.82 (m, 2H), 7.10–7.33 (m, 9H); δ_C (DMSO-d_6) 19.52, 20.47, 63.83, 84.97, 116.12, 116.83, 122.47, 123.90, 126.26, 127.57, 127.99, 128.33, 128.60, 132.70, 136.50, 136.83, 137.24, 145.63, 159.52; *m*/*z* 356 ($M^{+\bullet}$), 235, 211, 195, 161, 145.

3-Mesityl-4-(3-aminophenyl)-5-phenyl-4,5-dihydroisoxazole (13a). 45% yield, mp 194–196 °C (from ethyl acetate) (Found: C, 80.90; H, 6.76; N, 7.89. $C_{24}H_{24}N_2O$ requires: C, 80.87; H, 6.79; N, 7.86%); ν_{max} (KBr)/cm^{-1} 3466 br, 3342 br; δ_H (DMSO-d_6) 2.02 (s, 6H), 2.25 (s, 3H), 4.25 (d, 1H, J = 6.6 Hz), 5.32 (br s, 2H), 5.77 (d, 1H, J = 6.6 Hz), 6.42 (s, 1H), 6.48 (s, 1H), 6.94–7.52 (m, 9H); δ_C (DMSO-d_6) 19.75, 20.55, 64.96, 88.29, 114.63, 114.82, 126.37, 127.29, 127.70, 127.92, 128.34, 128.73, 129.16, 135.35, 137.17, 138.10, 145.17, 158.79; *m*/*z* 356 ($M^{+\bullet}$), 250, 211, 195, 161, 141, 105.

3-Mesityl-4-phenyl-5-(3-aminophenyl)-4,5-dihydroisoxazole (13b). 43% yield, mp 191–192 °C (from ethyl acetate) (Found: C, 80.85; H, 6.81; N, 7.87. $C_{24}H_{24}N_2O$ requires: C, 80.87; H, 6.79; N, 7.86%); ν_{max} (KBr)/cm^{-1} 3442 br, 3352 br; δ_H (DMSO-d_6) 2.00 (s, 6H), 2.34 (s, 3H), 4.64 (d, 1H, J = 7.2 Hz), 5.28 (br s, 2H), 5.28 (d, 1H, J = 7.2 Hz), 6.32 (s, 1H), 6.56 (s, 1H), 6.85–7.48 (m, 9H); δ_C (DMSO-d_6) 19.43, 20.12, 66.32, 85.46, 114.65, 116.87, 125.72, 126.45, 127.66, 127.95, 128.29, 128.71, 129.10, 135.30, 136.59, 138.04, 145.81, 159.21; *m*/*z* 356 ($M^{+\bullet}$), 235, 211, 195, 161, 145.

3-Mesityl-4-(4-aminophenyl)-5-phenyl-4,5-dihydroisoxazole (14a). 30% yield, mp 198–200 °C (from ethyl acetate) (Found: C, 80.84; H, 6.77; N, 7.89. $C_{24}H_{24}N_2O$ requires: C, 80.87; H, 6.79; N, 7.86%); ν_{max} (KBr)/cm^{-1} 3432 br, 3380 br; δ_H (DMSO-d_6) 1.99 (s, 3H), 2.16 (s, 6H), 4.47 (d, 1H, J = 5.2 Hz), 5.20 (br s, 2H), 5.87 (d, 1H, J = 5.2 Hz), 6.77 (s, 1H), 6.87 (s, 1H), 7.10–7.62 (m, 9H); δ_C (DMSO-d_6) 19.75, 20.52, 64.42, 88.24, 117.57, 126.47, 127.94, 128.33, 128.59, 132.93, 134.89, 135.30, 136.97, 138.77, 145.40, 158.98; *m*/*z* 356 ($M^{+\bullet}$), 250, 211, 195, 161, 145, 105.

3-Mesityl-4-phenyl-5-(4-aminophenyl)-4,5-dihydroisoxazole (14b). 59% yield, mp 201–203 °C (from ethyl acetate) (Found: C, 80.86; H, 6.75; N, 7.87. $C_{24}H_{24}N_2O$ requires: C, 80.87; H, 6.79; N, 7.86%); ν_{max} (KBr)/cm^{-1} 3446 br, 3368 br; δ_H (DMSO-d_6) 1.96 (s, 6H), 2.16 (s, 3H), 4.47 (d, 1H, J = 5.2 Hz), 5.07 (br s, 2H), 5.87 (d, 1H, J = 5.2 Hz), 6.55 (s, 1H), 6.59 (s, 1H), 7.04–7.72 (m, 9H); δ_C (DMSO-d_6) 19.77, 20.50, 62.94, 83.98, 117.02, 126.45, 127.66, 127.96, 128.29, 128.71, 132.80, 134.78, 135.30, 136.59, 138.04, 145.65, 158.73; *m*/*z* 356 ($M^{+\bullet}$), 235, 211, 195, 161, 145.

***N*-[2-(3-Mesityl-5-phenyl-4,5-dihydroisoxazol-4-yl)phenyl]-acetamide (15a).** 15% yield, mp 194–195 °C (from ethyl acetate) (Found: C, 78.38; H, 6.61; N, 7.05. $C_{26}H_{26}N_2O_2$ requires: C, 78.36; H, 6.58; N, 7.03%); ν_{max} (KBr)/cm^{-1} 3240 br, 3190 br; δ_H (DMSO-d_6) 1.99 (s, 6H), 2.18 (s, 6H), 5.00 (d, 1H, J = 3.2 Hz), 5.99 (d, 1H, J = 3.2 Hz), 6.38 (s, 2H), 7.41–7.97 (m, 10H); δ_C (DMSO-d_6) 19.44, 20.03, 20.49, 21.20, 64.97, 84.81, 116.42, 116.78, 120.83, 125.46, 127.56, 128.07, 128.67, 129.23, 136.55, 137.79, 138.17, 158.20, 174.45; *m*/*z* 398 ($M^{+\bullet}$), 383, 355, 341, 161, 145, 105.

***N*-[2-(3-Mesityl-4-phenyl-4,5-dihydroisoxazol-5-yl)phenyl]-acetamide (15b).** 69% yield, mp 190–191 °C (from ethyl acetate) (Found: C, 78.34; H, 6.59; N, 7.04. $C_{26}H_{26}N_2O_2$ requires: C, 78.36; H, 6.58; N, 7.03%); ν_{max} (KBr)/cm^{-1} 3214 br, 3188 br; δ_H (DMSO-d_6) 2.04 (s, 6H), 2.20 (s, 6H), 4.30 (d, 1H, J = 3.6 Hz), 6.16 (d, 1H, J = 3.3 Hz), 6.38 (s, 2H), 7.31–8.00 (m, 10H); δ_C (DMSO-d_6) 19.22, 20.15, 20.51, 21.52, 58.81, 87.01, 116.34, 116.83, 120.64, 124.40, 124.53, 125.40, 126.30, 126.65, 127.40, 127.79, 128.15, 128.32, 128.69, 132.28, 134.40, 135.53, 136.43, 137.25, 137.41, 158.89, 174.32; *m*/*z* 398 ($M^{+\bullet}$), 383, 355, 341, 235, 161, 145.

***N*-[2-(3-Mesityl-5-phenyl-4,5-dihydroisoxazol-4-yl)phenyl]-toluene-4-sulfonamide (16a).** 22% yield, mp 197–199 °C (from ethyl acetate) (Found: C, 72.94; H, 5.93; N, 5.51; S, 6.27. $C_{31}H_{30}N_2O_3S$ requires: C, 72.91; H, 5.92; N, 5.49; S, 6.28%); ν_{max} (KBr)/cm^{-1} 3238 br, 1364, 1156; δ_H (DMSO-d_6) 1.90 (s, 6H), 2.14 (s, 3H), 2.37 (s, 3H), 4.74 (d, 1H, J = 2.9 Hz), 5.55 (d, 1H, J = 2.9 Hz), 6.68–6.74 (m, 3H), 7.20–7.35 (m, 9H), 7.50–7.57 (m, 3H), 9.60 (br s, 1H); δ_C (DMSO-d_6) 19.09, 20.48, 20.96, 64.50, 84.14, 124.34, 126.12, 126.69, 126.71, 126.75, 126.91, 127.03, 127.52, 127.65, 128.35, 128.61, 129.66, 133.35, 136.53, 137.23, 138.27, 143.15, 158.68; *m*/*z* 510 ($M^{+\bullet}$), 495, 365, 355, 105.

***N*-[2-(3-Mesityl-4-phenyl-4,5-dihydroisoxazol-5-yl)phenyl]-toluene-4-sulfonamide (16b).** 60% yield, mp 221–223 °C (from ethyl acetate) (Found: C, 72.95; H, 5.90; N, 5.51; S, 6.27. $C_{31}H_{30}N_2O_3S$ requires: C, 72.91; H, 5.92; N, 5.49; S, 6.28%); ν_{max} (KBr)/cm^{-1} 3234 br, 1360, 1156; δ_H (DMSO-d_6) 2.02 (s, 6H), 2.19 (s, 3H), 2.39 (s, 3H), 4.53 (d, 1H, J = 3.3 Hz), 6.36 (d, 1H, J = 3.3 Hz), 6.70–6.73 (m, 3H), 7.12–7.38 (m, 9H), 7.42–7.57 (m, 3H), 9.64 (br s, 1H); δ_C (DMSO-d_6) 19.33, 20.56, 20.96, 58.48, 87.56, 124.42, 126.48, 126.89, 127.19, 127.62, 127.96, 128.27, 128.45, 129.34, 129.49, 133.47, 133.80, 136.68, 137.02, 137.19, 137.91, 143.09, 158.69; *m*/*z* 510 ($M^{+\bullet}$), 495, 365, 355, 235.

3-Mesityl-4-(2-nitrophenyl)-5-phenyl-4,5-dihydroisoxazole (17a). 26% yield, mp 187–188 °C (from ethyl acetate) (Found: C, 74.62; H, 5.73; N, 7.28. $C_{24}H_{22}N_2O_3$ requires: C, 74.59; H, 5.74; N, 7.25%); ν_{max} (KBr) cm^{-1} 1529, 1351; δ_H (DMSO-d_6) 1.97 (s, 3H), 2.15 (s, 3H), 2.35 (s, 3H), 4.60 (d, 1H, J = 3.2 Hz), 6.48 (d, 1H, J = 3.2 Hz), 6.68 (s, 1H), 6.84 (s, 1H), 7.28–8.21 (m, 9H); δ_C (DMSO-d_6) 19.13, 20.39, 62.22, 85.33, 123.35, 124.67, 125.52, 127.59, 129.49, 130.72, 133.49, 134.49, 136.55, 137.95, 138.57, 148.52, 159.48; *m*/*z* 386 ($M^{+\bullet}$), 371, 356, 241, 105.

3-Mesityl-4-phenyl-5-(2-nitrophenyl)-4,5-dihydroisoxazole (17b). 60% yield, mp 192–193 °C (from ethyl acetate) (Found: C, 74.55; H, 5.76; N, 7.21. $C_{24}H_{22}N_2O_3$ requires: C, 74.59; H, 5.74; N, 7.25%); ν_{max} (KBr)/cm^{-1} 1525, 1349; (DMSO-d_6) 1.96 (s, 3H), 2.11 (s, 3H), 2.19 (s, 3H), 5.27 (d, 1H, J = 4.4 Hz), 6.20 (d, 1H, J = 4.4 Hz), 6.71 (s, 1H), 6.96 (s, 1H), 7.29–8.10 (m, 9H); δ_C (DMSO-d_6) 19.06, 20.25, 59.05, 87.41, 123.57, 124.17,

125.11, 125.58, 127.58, 129.69, 132.29, 134.11, 134.79, 136.74, 137.97, 138.29, 148.30, 159.18; *m/z* 386 ($M^{+\cdot}$), 371, 356, 241, 235.

3-Mesityl-4-(3-nitrophenyl)-5-phenyl-4,5-dihydroisoxazole (18a). 37% yield, mp 184–186 °C (from ethyl acetate) (Found: C, 74.61; H, 5.73; N, 7.29. $C_{24}H_{22}N_2O_3$ requires: C, 74.59; H, 5.74; N, 7.25%); ν_{max} (KBr)/cm^{-1} 1522, 1342; (DMSO-d_6) 1.97 (s, 3H), 2.19 (s, 3H), 2.21 (s, 3H), 4.78 (d, 1H, J = 5.2 Hz), 6.22 (d, 1H, J = 5.2 Hz), 6.72 (s, 1H), 6.74 (s, 1H), 7.08–8.37 (m, 9H); δ_C (DMSO-d_6) 19.43, 20.97, 64.20, 86.20, 123.10, 125.14, 126.87, 127.80, 128.66, 128.92, 129.88, 132.80, 133.84, 135.82, 136.93, 138.88, 143.40, 158.96; *m/z* 386 ($M^{+\cdot}$), 371, 356, 241, 105.

3-Mesityl-4-phenyl-5-(3-nitrophenyl)-4,5-dihydroisoxazole (18b). 47% yield, mp 186–188 °C (from ethyl acetate) (Found: C, 74.52; H, 5.76; N, 7.29. $C_{24}H_{22}N_2O_3$ requires: C, 74.59; H, 5.74; N, 7.25%); ν_{max} (KBr)/cm^{-1} 1518, 1340; (DMSO-d_6) 1.87 (s, 3H), 1.96 (s, 3H), 2.19 (s, 3H), 5.00 (d, 1H, J = 6.0 Hz), 6.08 (d, 1H, J = 6.0 Hz), 6.72 (s, 1H), 6.74 (s, 1H), 7.21–8.30 (m, 9H); δ_C (DMSO-d_6) 19.45, 20.98, 63.48, 87.90, 123.08, 125.13, 126.05, 126.79, 127.80, 128.26, 128.90, 129.12, 129.86, 132.23, 133.84, 136.91, 143.32, 158.96; *m/z* 386 ($M^{+\cdot}$), 371, 356, 241, 235.

3-Mesityl-4-(4-nitrophenyl)-5-phenyl-4,5-dihydroisoxazole (19a). 42% yield, mp 197–199 °C (from ethyl acetate) (Found: C, 74.57; H, 5.75; N, 7.23. $C_{24}H_{22}N_2O_3$ requires: C, 74.59; H, 5.74; N, 7.25%); ν_{max} (KBr)/cm^{-1} 1522, 1342; (DMSO-d_6) 1.92 (s, 3H), 2.18 (s, 3H), 2.25 (s, 3H), 4.71 (d, 1H, J = 5.8 Hz), 6.57 (d, 1H, J = 5.8 Hz), 6.74 (s, 1H), 6.76 (s, 1H), 7.38–8.30 (m, 9H); δ_C (DMSO-d_6) 19.57, 20.95, 64.10, 86.50, 123.68, 124.24, 125.83, 126.89, 127.29, 127.84, 128.23, 128.49, 128.84, 133.42, 136.64, 138.42, 148.23, 158.81; *m/z* 386 ($M^{+\cdot}$), 371, 356, 241, 105.

3-Mesityl-4-phenyl-5-(4-nitrophenyl)-4,5-dihydroisoxazole (19b). 43% yield, mp 199–200 °C (from ethyl acetate) (Found: C, 74.61; H, 5.73; N, 7.29. $C_{24}H_{22}N_2O_3$ requires: C, 74.59; H, 5.74; N, 7.25%); ν_{max} (KBr)/cm^{-1} 1524, 1348; (DMSO-d_6) 1.84 (s, 3H), 2.13 (s, 3H), 2.21 (s, 3H), 4.95 (d, 1H, J = 6.5 Hz), 6.10 (d, 1H, J = 6.5 Hz), 6.68 (s, 1H), 6.71 (s, 1H), 7.28–8.26 (m, 9H); δ_C (DMSO-d_6) 19.45, 20.96, 63.94, 87.75, 123.82, 124.02, 125.71, 126.34, 127.12, 127.86, 128.38, 128.70, 129.39, 133.23, 136.48, 138.29, 148.13, 158.62; *m/z* 386 ($M^{+\cdot}$), 371, 356, 241, 235.

Acylation of cycloadducts 12a,b

A solution of cycloadducts **12a**,**b** (1 mmol) in pyridine (30 ml) was heated at 90 °C with the acetyl or toluene-4-sulfonyl chloride (1.2 mmol) to give quantitatively **15a**,**b** and **16a**,**b** which were recovered by removal of the solvent and crystallization of the residue. Products **15a**,**b** and **16a**,**b** were identical to samples obtained by reactions of acylamino derivatives **6** and **7** with **1**.

Method of calculations

The calculations were performed by means of the semiempirical PM3[19] and AM1[20] methods available in the MOPAC version 6.0 computation package distributed by QCPE.

Acknowledgements

The authors are grateful to the Italian M.U.R.S.T. for financial support.

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