DOI: 10.1002/ejoc.201101615

1,2,4-Oxadiazole 4-Oxides as Nitrones in 1,3-Dipolar Cycloaddition Reactions to Vinyl Ethers

Paolo Quadrelli,*[a] Fabio Lunghi,[a] Bruna Bovio,[a] William Gautschi,[a] and Pierluigi Caramella*[a]

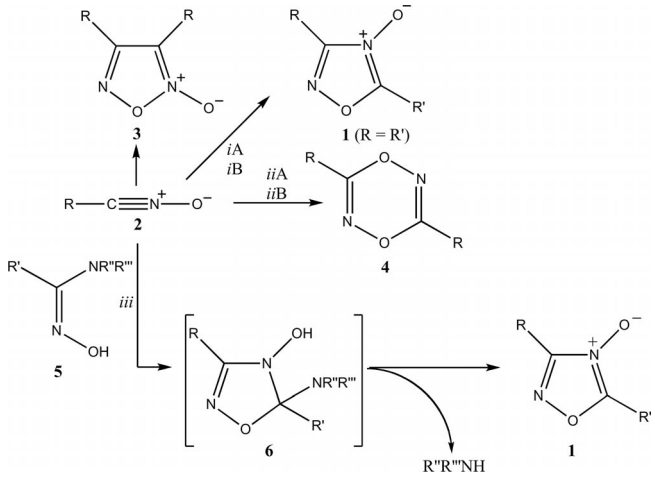
Keywords: Heterocycles / Nitrones / Vinyl ethers / Cycloaddition / Synthesis design

1,2,4-Oxadiazole 4-oxides display nitronic reactivity and selectivities identical to those of *N*-methyl-*C*-phenyl nitrone, which is a typical acyclic nitrone, affording comparable amounts of *endo*- and *exo*-5-alkoxyisoxazolidines. The *exo* stereoisomers undergo an easy rearrangement under the reaction conditions to yield oxadiazolinic esters. The structures of the adducts have been confirmed by X-ray structures and spectroscopic data. A donor *p*-methoxyphenyl at the nitronic carbon slows down the cycloaddition rate, while an acceptor *p*-nitrophenyl retards the rearrangement of the *exo* adduct.

Introduction

1,2,4-Oxadiazole 4-oxides **1** are a family of heterocyclic N-oxides that were prepared for the first time by Wieland and Bauer in 1906.[1] These compounds remained largely a chemical curiosity until very recently when further studies on their synthesis and reactivity widened their applications.[2]

These heterocyclic N-oxides have properties that are closely related to the chemistry of nitrile oxides **2**, which were actively studied in the past half century and provided the first access to disubstituted 1,2,4-oxadiazole 4-oxides carrying the same substituents (referred to herein as symmetrical).[3] The dimerization of **2** typically affords furoxans **3** in the absence of special additives. Under acid catalysis [HCl in benzene or BF_3 (0.5 equiv.) in hexane or benzene] or basic catalysis (Me_3N/EtOH), nitrile oxides **2** dimerize into 1,2,4-oxadiazole 4-oxides **1**. Alternatively, under slightly different catalytic conditions (BF_3 excess or pyridine/EtOH), nitrile oxides **2** afford the six-membered dioxadiazines **4** (Scheme 1).[2] However, the more general route to 1,2,4-oxadiazole 4-oxides **1** is based on the nitrile oxide **2** cycloadditions to amidoximes **5**, which afforded, through the labile adducts **6**, either the symmetrical or the asymmetrical ($R \neq R'$) disubstituted 1,2,4-oxadiazole 4-oxides **1** by combining nitrile oxides **2** with amidoximes **5** carrying the same or different substituents in benzene or methanol.[4]



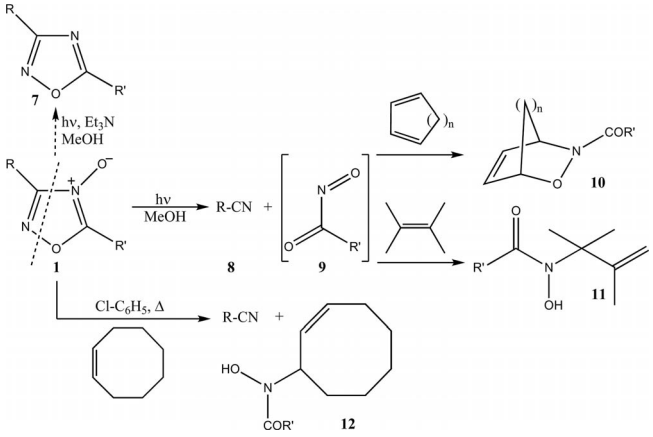
Scheme 1. R and R′ stand for alkyl and/or aryl substituents. Label A after the compound number specifies the diphenyl derivatives described in the text; these were more extensively investigated. (*i*A) BF_3 (0.5 equiv.) in hexane or benzene. (*ii*A) Excess amount of BF_3 in hexane. (*i*B) Me_3N in EtOH. (*ii*B) Pyridine (Py) in EtOH. (*iii*) Benzene or methanol at room temp.

The chemistry of 1,2,4-oxadiazole 4-oxides **1** is related to the fragility of the heterocyclic ring, which undergoes a ready photochemical cycloreversion to nitriles and nitrosocarbonyl intermediates (Scheme 2). Some authors noticed that the 1,2,4-oxadiazole 4-oxides **1** were light sensitive in solution, especially in the presence of triethylamine, and had to be kept in the dark to prevent degradation to the deoxygenated 1,2,4-oxadiazoles **7**, which were always found in old samples of **1**.[5] The 1,2,4-oxadiazole 4-oxides **1** exhibit a low-frequency absorption in the UV spectra at 320–350 nm that is responsible of their photochemical behaviour. When degassed solutions of **1** in methanol were exposed to sunlight or irradiated at 310 nm, smooth cleav-

[a] Dipartimento di Chimica, Università degli Studi di Pavia
Viale Taramelli 12, 27100 Pavia, Italy
Fax: +39-0382-987323
E-mail: paolo.quadrelli@unipv.it
pierluigi.caramella@unipv.it

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101615.

age afforded nitriles **8** and the highly reactive nitrosocarbonyl intermediates **9**, which could be easily and quantitatively trapped in situ with dienes and enes, affording a variety of hetero-Diels–Alder (HDA) adducts, such as **10**, and ene adducts, such as **11**.[6] Nitrosocarbonyls are fleeting intermediates discovered by Kirby in the periodate oxidation of hydroxamic acids and are very reactive dienophiles in HDA cycloadditions.[7] They are also formed in the thermal reversions of the HDA cycloadducts and under these non-oxidative conditions easily enter ene reactions, too.[7b]

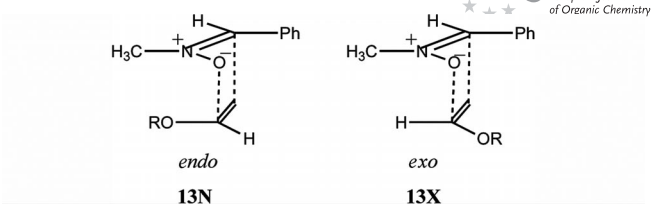


Scheme 2.

The photochemical cleavage of 1,2,4-oxadiazole 4-oxides **1** represents the softest entry to the fleeting nitrosocarbonyl intermediates and allows the study of their chemistry[8] and the intriguing regio- and stereoselectivities of their ene reactions under convenient and simple experimental conditions.[9] Thermal cleavage also occurs, but requires harsher conditions. The 1,2,4-oxadiazole 4-oxides **1** fragment neatly in chlorobenzene (b.p. 132 °C) at reflux. In the presence of an excess of cyclooctene, the ene adducts **12** were obtained in excellent yields (73–87%).[10]

The structure of the 1,2,4-oxadiazole 4-oxides **1** contains a fused nitrone moiety and suggests the possibility of a further reactivity channel of these heterocycles as nitrones. The 1,3-dipolar cycloadditions of nitrones have been extensively investigated[11] and a few cases of nitronic reactivity of heteroaromatic nitrones (pyridine *N*-oxides and benzo derivatives,[12] furoxans[13]) were reported.

Herein, we report evidence of the nitronic reactivity of 3,5-diphenyl-1,2,4-oxadiazole 4-oxide (**1A**) and a few symmetrically or unsymmetrically substituted derivatives in the 1,3-dipolar cycloaddition to ethyl and *n*-butyl vinyl ethers. Somewhat surprisingly, these heterocyclic N-oxides display reactivity and selectivities almost identical to those of *N*-methyl-*C*-phenylnitrone, a typical, well-investigated acyclic nitrone, which affords only 5-alkoxy-substituted isoxazolidines because of the dominating influence of the $HOMO_{(enol\ ether)}$–$LUMO_{(nitrone)}$ interaction and comparable amounts of the two possible stereoisomers, **13N** and **13X**, derived from the *endo* and *exo* approaches.[14]

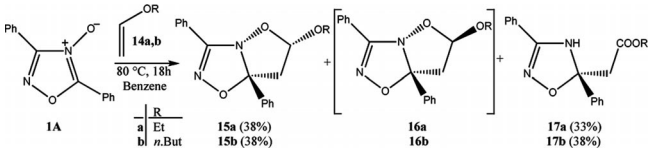


N-Oxide **1A** behaves similarly to *N*-methyl-*C*-phenylnitrone, but one of the stereoisomers undergoes an easy and unexpected rearrangement under the reaction conditions.

Results and Discussion

Cycloadditions of 1A

N-Oxide **1A** reacted smoothly with an excess (10 equiv.) of vinyl ethers **14a**,**b** under the same conditions as those reported for the reaction of *N*-methyl-*C*-phenylnitrone with ethyl vinyl ether (80 °C for 18 h in benzene). After 18 h, the starting *N*-oxide **1A** was fully consumed and chromatographic separation afforded the cycloadducts **15a**,**b** and the esters **17a**,**b** in comparable yields (Scheme 3) along with minor amounts (10%) of 3,5-diphenyl-1,2,4-oxadiazole (**7A**) derived from decomposition/deoxygenation of **1A**.

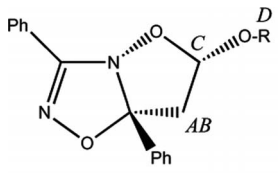


Scheme 3.

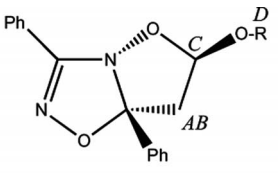
Table 1 gives the relevant ^1H and ^{13}C NMR spectroscopic data that allowed structural assignments. The structures of the (6*S*,7a*R*)-6-alkoxy-3,7a-diphenyl-7,7a-dihydro-6*H*-isoxazolo[2,3-*d*][1,2,4]oxadiazole cycloadducts (**15a** and **15b**; Figure 1) were confirmed by single-crystal analyses, which allowed regio- and stereochemical assignments. In the cycloadducts, the alkoxy substituents are *cis* to the oxadiazolinic rings and derive from *endo* cycloaddition of the heterocyclic nitrone. The bicyclic systems have boat-like shapes with the isoxazolidinic ring adopting an envelope conformation with the flap on the side of the oxadiazolinic ring. In the envelope conformation, the acetalic methine proton is orthogonal to the adjacent *trans*-methylene proton and synperiplanar to the *cis* one (see below). The spectroscopic data of **15a**,**b** are fully consistent with this picture; the acetalic methine is a doublet (J = 5 Hz) because of coupling with the adjacent *cis* protons and no coupling to the adjacent orthogonal *trans* protons is observed.

The spectroscopic data of the (*R*)-alkyl 2-(3,5-diphenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)acetate adducts **17a**,**b** are not consistent with the structure of a primary cycloadduct. The methine proton is missing in the ^1H and ^{13}C NMR

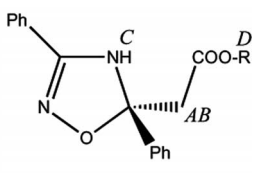
Table 1. Yields, physical constants and relevant NMR spectroscopic data[a] of cycloadducts **15a**,**b** and **16a**,**b** along with the esters **17a**,**b**.



15a,b



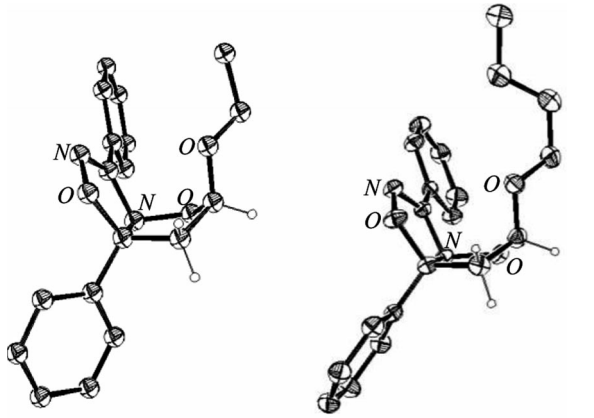
16a,b



17a,b

	Yield	M.p. [°C]	NMR[b]	Atom label			
	[%][b]	Solvent		*A*	*B*	*C*	*D*[c]
R = OEt							
15a	38 [28]	90–92 ethanol	^{1}H	2.95 (dd, 14; 5)	3.19 (d, 14)	5.38 (d, 5)	3.31 (m)
			^{13}C	51.9	51.9	104.4	63.7
16a	0 [15]	80 (dec.) ethanol	^{1}H	2.94 (dd, 14; 3)	3.34 (dd, 14; 5)	5.47 (dd, 5; 3)	3.62, 3.96 (m)
			^{13}C	51.3	51.3	108.0	64.1
17a	33 [22]	97–102 ethanol	^{1}H	3.25 (d, 15)	3.25 (d, 15)	6.32 (br. s)	4.09 (q)
			^{13}C	43.4	43.4	/	61.0
R = O*n*Bu							
15b	38 [28]	88–90 ethanol	^{1}H	2.94 (dd, 14; 5)	3.18 (d, 14)	5.36 (d, 5)	3.23 (m)
			^{13}C	51.5	51.5	104.3	67.9
16b	0 [17]	82 (dec.) ethanol	^{1}H	2.92 (dd, 14; 3)	3.24 (dd, 14; 5)	5.45 (dd, 5; 3)	3.49, 3.58 (m)
			^{13}C	51.4	51.4	102.7	64.9
17b	38 [22]	82–85 ethanol	^{1}H	3.33 (d, 15)	3.33 (d, 15)	6.42 (br. s)	4.12 (q)
			^{13}C	43.4	43.4	/	69.4

[a] δ, $CDCl_3$; multiplicities and coupling constants (*J* in Hz) are given in parentheses. [b] The yields after 10 h at 80 °C are given in square brackets. [c] OCH_2 moiety of OR substituent.



15a **15b**

Figure 1. ORTEP plots of cycloadducts **15a** and **15b** with atom labelling (ellipsoids at the 25% probability level). Hydrogen atoms are omitted for clarity, except for those of the isoxazolidinic ring.

spectra and the methylene protons appear as an AB system with no coupling to adjacent protons. Moreover, a broad NH signal at δ = 6.3–6.4 ppm is present in the ^{1}H NMR spectra, while the OCH_2 protons of the ethyl and *n*-butyl substituents are deshielded by 0.8 ppm and fall in the typical region of ester derivatives. Accordingly, the IR spectra of **17a** show an ester absorption at 1734 cm^{-1} and an NH absorption at 3212 cm^{-1}. Isomer **17b** gives similar absorptions. The spectroscopic data are consistent with the rearranged structures given for **17a**,**b**.

The Labile *exo* Cycloadducts

Because the *cis endo* adducts **15a** are thermally stable under the reaction conditions, the likely origin of the rearranged adducts **17a**,**b** is their formation from the labile and missing (6*R*,7a*R*)-6-alkoxy-3,7a-diphenyl-7,7a-dihydro-6*H*-isoxazolo[2,3-*d*][1,2,4]oxadiazole adducts (**16a**,**b**). Control experiments on samples withdrawn from the reaction mixture of **1A** and **14a** at the beginning of the experiment (Δ, 1 h) showed the doublet for the acetalic proton of **15a** at δ = 5.38 ppm along with a dd of comparable intensity at δ = 5.47 ppm that was attributed to the acetalic proton of the missing primary cycloadduct **16a**. The ratio **15/16** steadily increases with time and reaches 1.7:1 after heating for 10 h. By interrupting the reaction after heating for 10 h, chromatographic separation afforded a sample of **16a** in a 15% yield along with unreacted **1A** (20%), **15a** (28%) and **17a** (22%). Operating in the same way for the reaction of **1A** with **14b**, the primary adduct **16b** could be similarly isolated. Control experiments showed that the primary adducts **16a**,**b** rearranged quantitatively to **17a**,**b** under these reaction conditions (benzene, Δ, 18 h).

The spectroscopic data for the labile cycloadducts **16a**,**b** are similar to those of **15a**,**b**. The only noteworthy difference is the multiplicity of the methine protons, which appear as doublets in **15a**,**b** and double doublets in **16a**,**b**. B3LYP/6-31G* calculations[15] on the model methyl derivatives **15c** and **16c** (R = OMe) show a change in the conformations of the adducts, which account for the observed trend (Figure 2).

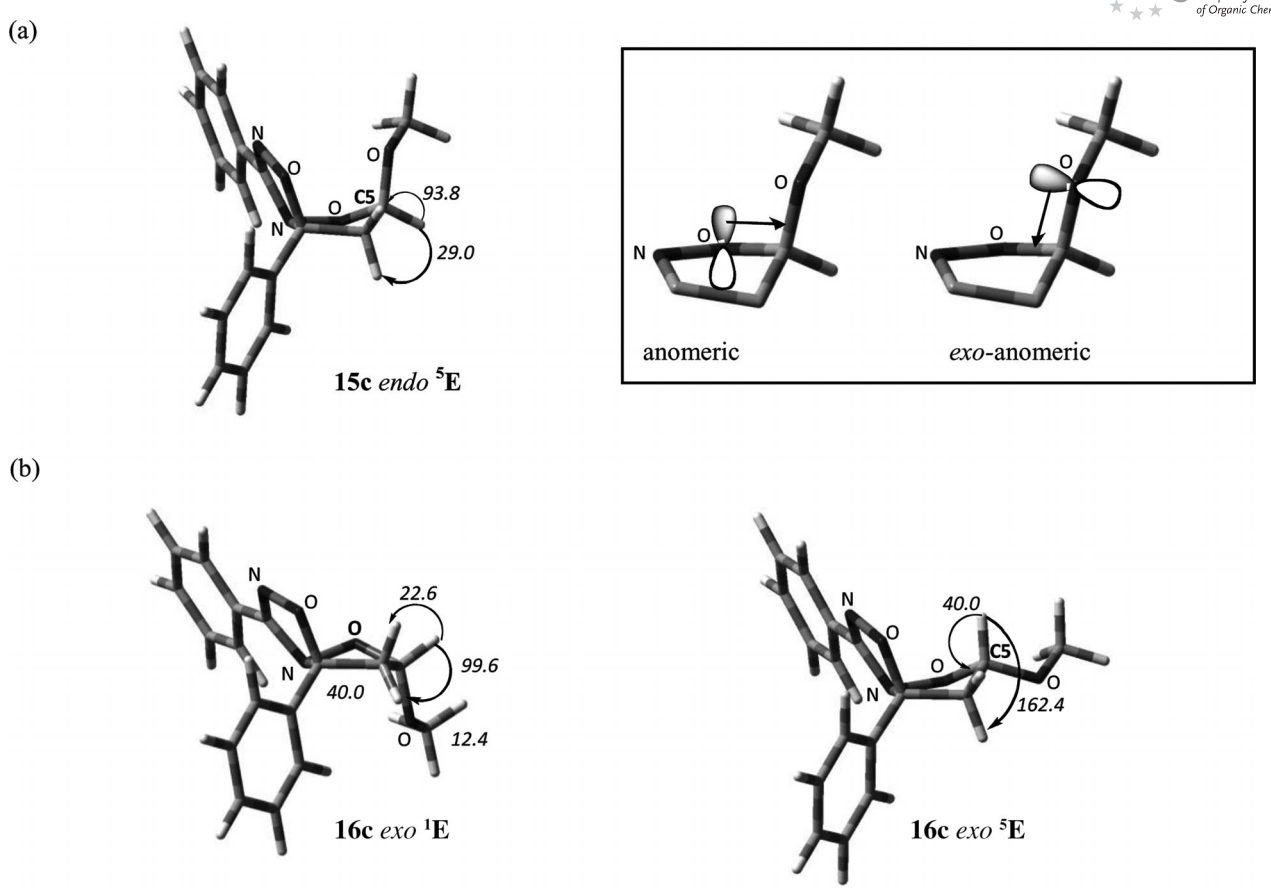


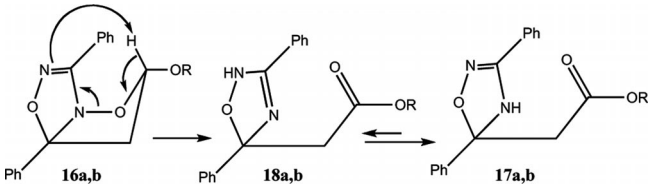
Figure 2. The lowest energy conformers of methoxy derivatives **15c** (a) and **16c** (b). Bold symbols indicate the atoms residing on the flap of the isoxazolidinic envelope. Curved arrows specify the dihedral angles in degrees between the acetalic methine and the adjacent methylene protons. The inset shows the almost parallel alignments (arrows) of the π-type p_z lone pairs with the adjacent C–O bond of **15c** involved in the anomeric and *exo* anomeric effects.

Figure 2a shows the boat-like conformer of the lowest energy *endo* adduct **15c** and labelled ^{5}**E** to indicate the envelope conformation of the isoxazolidinic ring with the isoxazolidinic C-5 on the flap above the envelope plane; conformer ^{5}**E** is essentially identical to the X-ray structures of **15a**,**b** and the dihedral angles between the methine and methylene protons are specified beside the curved arrows. This conformation lies in a deep minimum and other conformers are too high in energy (by more than 3 kcal mol^{-1}) to contribute to the coupling constants. The remarkable stability of the lowest energy conformer ^{5}**E** can be ascribed to anomeric and *exo* anomeric effects,[16] which involve the stabilizing interactions of the π-type p_z lone pairs of the ring and chain oxygen atoms with the neighbouring σ* C–O bonds, as depicted in the inset of Figure 2. The almost parallel alignments of the p_z lone pairs with the adjacent σ* C–O bonds constrain the exocyclic methoxy group in an axial position and the O–R bond in a *gauche* relationship to the C–O bond of the envelope.

Figure 2b shows the two lowest energy conformers of the *exo* adduct **16c**. The preferred conformer is ^{1}**E**, in which the flap of the isoxazolidinic envelope involves the ring oxygen atom and the bicyclic system is twisted, and a boat-like conformer ^{5}**E** lies at slightly higher energy. The free energy difference is 1.1 kcal mol^{-1} and corresponds to a 86:14 ratio of the conformers. The boat-like conformation is usually preferred in similar bicyclic systems. Fusion of cyclopentane to an isoxazolinic ring[17] or similar rings[18] favour boat-like conformations because of the relief of non-bonded interactions between the heterocyclic ring and the substituents on the adjacent cyclopentane carbon atoms. In the case of **15c**, the conformational preference for the boat is relieved by anomeric and *exo* anomeric effects, which efficiently stabilize conformer ^{1}**E**, whereas the boat-like conformer ^{5}**E** maintains only the *exo* anomeric stabilization. In the more abundant conformer ^{1}**E**, the methine and adjacent *trans*-methylene proton are still almost orthogonal, whereas in the minor conformer ^{5}**E** they are in an antiperiplanar arrangement and contribute to the larger *trans* coupling constants of **16a**,**b** as a weighted average of the couplings of the two conformers.

In the labile *exo* cycloadducts **16a**,**b**, the methine protons face the –O–N=C(Ph) moiety of the oxadiazolinic ring and this proximity could induce easy thermal rearrangements. A likely mechanism for the rearrangement is the retro-ene reaction depicted in Scheme 4 to yield the tautomers **18a**,**b**

of the ester **17a**,**b**. The driving force of the reaction can be attributed to the cleavage of a weak N–O bond and the formation of a strong C=O bond.

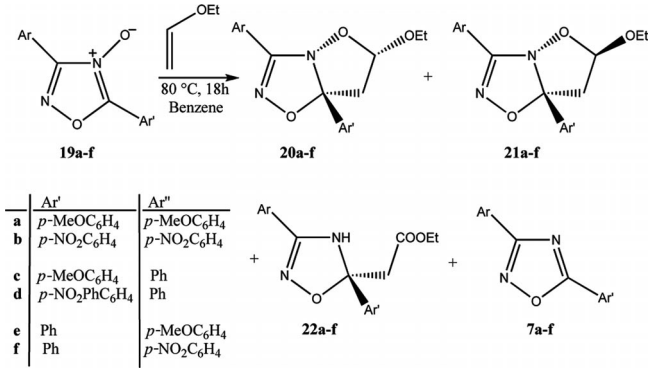


Scheme 4.

Retro-ene reactions have broad applications in synthesis.[19] The best-known retro-ene reaction is perhaps the ready thermal decarboxylation of β-keto acids, which affords CO_2 and the enol tautomer of the ketone. Other useful retro-ene reactions are known and include various related elimination reactions, such as the Cope elimination of N-oxides and sulfoxide and selenoxide eliminations.

Other Cycloadditions

To ascertain the possible role of the substituents of 1,2,4-oxadiazole 4-oxides on the reaction outcome in cycloadditions to vinyl ethyl ether, we have briefly examined the reactions of the symmetrical 1,2,4-oxadiazole 4-oxides **19a**,**b** with *p*-methoxyphenyl and *p*-nitrophenyl groups as donor and acceptor aryls, respectively. We have also tested the reactions of a few unsymmetrical 1,2,4-oxadiazole-4-oxides **19c**,**d** and **19e**,**f**, in which donor and acceptor aryls replace the phenyls in the 3- and 5-positions, respectively (Scheme 5).



Scheme 5.

The cycloadditions were performed under the same conditions already described and the reaction mixtures were submitted to chromatographic separation to afford products **20**–**22** in variable amounts along with the deoxygenated oxadiazoles **7a**–**f**. The structures of the isolated adducts were determined by spectroscopic characterization and were similar to those of adducts **15**–**18** already described; Table 2 reports the product distributions.

Table 2. Yields of products in the cycloadditions of **19a**–**f** to vinyl ethyl ether.

	3-Ar	5-Ar′	Yield [%]				
			20	**21**	**22**	**7**	**20/21 + 22**
19a	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	6	–	10	60	0.6
19b	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	39	10	24	15	1.15
19c	*p*-$MeOC_6H_4$	Ph	28	–	14	20	2
19d	*p*-$NO_2C_6H_4$	Ph	36	–	24	15	1.5
19e	Ph	*p*-$MeOC_6H_4$	12	–	10	65	1.2
19f	Ph	*p*-$NO_2C_6H_4$	29	8	7	20	1.93

The most striking features of Table 2 are the low yields of adducts **20** and **22** in the reactions of the 5-(*p*-methoxyphenyl) derivatives **19a**,**e**, which afford mainly the oxadiazoles **7a**,**e**, and the presence of significant amounts of the unrearranged adducts **21** in the case of the 5-(*p*-nitrophenyl) derivatives **19b**,**f**. The low yields of adducts in the reactions of **19a**,**e**, in which the donor aryl group is attached to the nitronic carbon atom, can be attributed to a decrease of the cycloaddition rate with respect to deoxygenation because the 5-donor aryl should decrease the electrophilicity of the nitronic carbon atom and then influence the $HOMO_{(enol\ ether)}$–$LUMO_{(nitrone)}$ interaction. The effect of the 5-acceptor aryl in the case of **19b**,**f** instead indicates a decrease in the rearrangement rate of adducts **21b**,**f**; this is presumably of inductive origin.

The stereoselectivity of the cycloadditions is also affected by the aryl substituents, as shown by the last column of Table 2, which gives the *endo*/*exo* ratios as **20**/(**21** + **22**). In all cases, comparable amounts of *endo* and *exo* products are formed and the stereoselectivity ranges from 2:1 to 1:2.

In summary, 1,2,4-oxadiazole 4-oxides (**1**) easily enter 1,3-dipolar cycloadditions with enol ethers under conditions similar to those of *N*-methyl-*C*-phenylnitrone. Various furoxans **3** similarly enter cycloaddition reactions under slightly more forcing conditions (boiling toluene).[13] This stands in marked contrast to heteroaromatic *N*-oxides derived from pyridine *N*-oxides. In cycloadditions with ethyl crotonate, isoquinoline *N*-oxide and phenanthridine *N*-oxide are less reactive than *N*-methyl-*C*-phenylnitrone by 820- and 420-fold, respectively, and the reduced reactivity may be in part attributed to the loss of aromaticity in the cycloaddition transition state.[12c] The 1,2,4- and 1,2,5-oxadiazoles display, however, reduced aromaticity[20] and the loss of aromaticity in the cycloadditions should become less demanding.

Conclusions

Symmetrical 1,2,4-oxadiazole 4-oxide **1A** underwent smooth 1,3-dipolar cycloaddition reactions with vinyl ethers at 80 °C in benzene to afford *endo* adducts and oxadiazolinic esters, which derived from an easy rearrangement of the *exo* adducts. The labile *exo* cycloadducts could be isolated and the structures of the products were assigned on the basis of the spectroscopic data as well as X-ray analyses. Sizeable substituent effects on the reaction outcome derived

mainly from substitutions at the nitronic carbon atom. Replacement of the phenyl group at the nitronic carbon atom with a *p*-methoxyphenyl group slowed down the cycloaddition rate, whereas an acceptor *p*-nitrophenyl group retarded the rearrangement of the *exo* adducts.

Experimental Section

General: Elemental analyses were performed on a C. Erba 1106 elemental analyzer. IR spectra (Nujol mulls) were recorded on an FTIR Perkin–Elmer RX-1 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 spectrometer in the specified deuterated solvents. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ). Column chromatography and TLC were performed on silica gel 60 (0.063–0.200 mm) (Merck) with cyclohexane/ethyl acetate from 9:1 to 5:5 as the eluant. The identification of samples from different experiments was secured by mixed melting points and superimposable IR spectra.

Materials: 3,5-Diphenyl-1,2,4-oxadiazole 4-oxide (**1A**) and the 1,2,4-oxadiazole 4-oxides **19a**–**f** were prepared according to published procedures.[4b]

Cycloadditions of 1A with Vinyl Ethers 14a,b: *N*-Oxide **1A** (500 mg, 2.1 mmol) was heated along with the vinyl ethers **14a**,**b** (10 equiv.) in closed vessels kept at 80 °C over a 18 h period in stirred solutions in benzene (15 mL), up to complete disappearance of the starting heterocycle. After evaporation of the solvent and excess vinyl ether under reduced pressure, the residues were submitted to column chromatography to isolate the products.

Cycloadduct 15a: 0.25 g (38%). M.p. 90–92 °C from ethanol. IR: $\tilde{\nu}$ = 1654 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.99 (t, J = 7 Hz, 3 H, CH_3), 2.95 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.19 (d, J = 14 Hz, 1 H, HC-H), 3.31 (m, 2 H, O-CH_2), 5.38 (d, J = 5 Hz, 1 H, O-CH-O), 7.49 (m, 6 H, arom.), 7.71 (m, 2 H, arom.), 8.02 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.4, 51.9, 63.7, 104.4, 106.7, 125.4, 125.7, 127.4, 128.4, 128.5, 128.6, 130.7, 139.6, 159.1 ppm. $C_{18}H_{18}N_2O_3$ (310.13): calcd. C 69.66, H 5.85, N 9.03; found C 69.6, H 5.9, N 9.1.

Compound 17a: 0.21 g (33%). M.p. 97–102 °C from ethanol. IR: $\tilde{\nu}$ = 3212 (NH), 1734 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.14 (t, J = 7 Hz, 3 H, CH_3), 3.25 (AB syst., J_{AB} = 15 Hz, 2 H, CH_2), 4.09 (q, 2 H, O-CH_2), 6.32 (s, 1 H, NH), 7.46 (m, 6 H, arom.), 7.65 (m, 2 H, arom.), 7.79 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.8, 43.4, 61.0, 98.1, 125.4, 125.6, 126.4, 128.3, 128.6, 128.7, 130.9, 140.3, 155.6, 170.3 ppm. $C_{18}H_{18}N_2O_3$ (310.13): calcd. C 69.66, H 5.85, N 9.03; found C 69.7, H 5.8, N 9.0.

Upon reducing the reaction time to 10 h, in addition to unreacted **1A** (20%) and the adducts **15a** (28%) and **17a** (22%) previously described, the *exo* adduct **16a** (15%) was isolated and fully characterized. 0.10 g (15%). IR: $\tilde{\nu}$ = 1653 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.33 (t, J = 7 Hz, 3 H, CH_3), 2.94 (dd, J = 14, 3 Hz, 1 H, CH-H), 3.34 (dd, J = 14, 5 Hz, 1 H, HC-H), 3.62 and 3.96 (m, 1 H, 1 H, O-CH_2), 5.47 (dd, J = 5, 3 Hz, 1 H, O-CH-O), 7.45 (m, 6 H, arom.), 7.56 (m, 2 H, arom.), 8.25 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.1, 51.3, 64.1, 108.0, 126.1, 127.5, 128.1, 128.3, 128.6, 128.7, 129.0, 130.9, 158.3 ppm. $C_{18}H_{18}N_2O_3$ (310.13): calcd. C 69.66, H 5.85, N 9.03; found C 69.6, H 5.7, N 9.1.

Cycloadduct 15b: 0.27 g (38%). M.p. 88–90 °C from ethanol. IR: $\tilde{\nu}$ = 1688 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.77 (t, J = 7 Hz, 3 H, CH_3), 1.17 (m, 2 H, CH_2), 1.32 (m, 2 H, CH_2), 2.94 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.18 (d, J = 14 Hz, 1 H, HC-H), 3.23 (m, 2 H, O-CH_2), 5.36 (d, J = 5 Hz, 1 H, O-CH-O), 7.41 (m, 6 H, arom.), 7.71 (m, 2 H, arom.), 8.01 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.3, 18.5, 30.7, 51.5, 67.9, 104.3, 106.3, 125.0, 125.3, 127.1, 128.0, 128.1, 128.2, 130.2, 139.2, 158.4 ppm. $C_{20}H_{22}N_2O_3$ (338.39): calcd. C 70.99, H 6.55, N 8.28; found C 71.0, H 7.0, N 8.1.

Compound 17b: 0.27 g (38%). M.p. 82–85 °C from ethanol. IR: $\tilde{\nu}$ = 3209 (NH), 1736 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.96 (t, J = 7 Hz, 3 H, CH_3), 1.35 (m, 2 H, CH_2), 1.59 (m, 2 H, CH_2), 3.33 (AB syst., J_{AB} = 15 Hz, 2 H, CH_2), 4.12 (m, 2 H, O-CH_2), 6.42 (s, 1 H, NH), 7.59 (m, 6 H, arom.), 7.74 (m, 2 H, arom.), 7.88 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.5, 18.8, 30.2, 43.4, 64.9, 98.1, 125.4, 125.5, 126.4, 128.3, 128.6, 128.7, 130.9, 140.3, 155.6, 170.4 ppm. $C_{20}H_{22}N_2O_3$ (338.39): calcd. C 70.99, H 6.55, N 8.28; found C 70.9, H 6.7, N 8.2.

Upon reducing the reaction time to 10 h, in addition to unreacted **1A** (18%) and the adducts **15b** (30%) and **17b** (20%) previously described, the *exo* adduct **16b** (17%) was isolated and characterized. 0.12 g (17%). IR: $\tilde{\nu}$ = 1652 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.01 (t, J = 7 Hz, 3 H, CH_3), 2.92 (dd, J = 14, 3 Hz, 1 H, CH-H), 3.24 (dd, J = 14, 5 Hz, 1 H, HC-H), 3.49 and 3.58 (m, 1 H, 1 H, O-CH_2), 5.45 (dd, J = 5, 3 Hz, 1 H, O-CH-O), 7.42 (m, 6 H, arom.), 7.70 (m, 2 H, arom.), 8.03 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.4, 51.4, 64.9, 102.7, 125.8, 126.1, 128.1, 128.3, 128.6, 128.7, 129.0, 131.1, 158.5 ppm. $C_{20}H_{22}N_2O_3$ (338.39): calcd. C 70.99, H 6.55, N 8.28; found C 71.0, H 6.6, N 8.3.

Cycloadditions of 19a–f with Ethyl Vinyl Ether: 3,5-Aryl-1,2,4-oxadiazole 4-oxides **19a**–**f** (500 mg) were heated with ethyl vinyl ether (10 equiv.) in closed vessels kept at 80 °C over a 18 h period in stirred solutions in benzene (15 mL). After evaporation of the solvent and excess vinyl ether under reduced pressure, the residues were submitted to column chromatography to isolate the products.

Cycloadduct 20a: 0.04 g (6%). Thick oil. IR: $\tilde{\nu}$ = 1660 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.99 (t, J = 7 Hz, 3 H, CH_3), 2.93 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.13 (d, J = 14 Hz, 1 H, HC-H), 3.30 (q, 2 H, O-CH_2), 3.83 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.35 (d, J = 5 Hz, 1 H, O-CH-O), 6.99 (m, 4 H, arom.), 7.58 (m, 2 H, arom.), 7.94 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.4, 51.7, 55.2, 63.7, 104.4, 106.2, 113.5, 113.7, 113.9, 118.2, 126.8, 129.0, 131.8, 159.7, 161.4 ppm. $C_{20}H_{22}N_2O_5$ (370.40): calcd. C 64.85, H 5.99, N 7.56; found C 64.8, H 6.0, N 7.5.

Compound 22a: 0.06 g (10%). oil. IR: $\tilde{\nu}$ = 3329 (NH), 1731 (C=O), 1686 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.14 (t, J = 7 Hz, 3 H, CH_3), 3.19 (AB syst., J = 16 Hz, 1 H, CH_2), 3.80 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.06 (q, 2 H, O-CH_2), 6.28 (s, 1 H, NH), 6.93 (m, 2 H, arom.), 6.99 (m, 2 H, arom.), 7.56 (m, 2 H, arom.), 7.69 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.9, 43.2, 55.2, 55.3, 60.9, 97.7, 107.7, 113.5, 113.7, 114.0, 117.7, 127.1, 127.9, 132.6, 159.8, 161.5, 170.4 ppm. $C_{20}H_{22}N_2O_5$ (370.40): calcd. C 64.85, H 5.99, N 7.56; found C 65.0, H 6.0, N 7.6.

Cycloadduct 20b: 0.24 g (39%). Thick oil. IR: $\tilde{\nu}$ = 1605 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.97 (t, J = 7 Hz, 3 H, CH_3), 2.91 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.30 (m, 2 H, O-CH_2), 3.22 (d, J = 14 Hz, 1 H, HC-H), 5.44 (d, J = 5 Hz, 1 H, O-CH-O), 7.87 (m, 2 H, arom.), 8.18 (m, 2 H, arom.), 8.31 (m,

4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.3, 52.0, 64.2, 104.6, 107.2, 123.9, 124.0, 126.5, 128.2, 131.1, 145.7, 148.1, 149.0, 157.8 ppm. $C_{18}H_{16}N_4O_7$ (400.34): calcd. C 54.00, H 4.03, N 13.99; found C 54.1, H 4.0, N 13.5.

Cycloadduct 21b: 0.06 g (10%). M.p. 115–117 °C from ethanol. IR: $\tilde{\nu}$ = 1609 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.35 (t, J = 7 Hz, 3 H, CH_3), 2.94 (dd, J = 14, 2 Hz, 1 H, CH-H), 3.38 (dd, J = 14, 5 Hz, 1 H, HC-H), 3.65 and 3.98 (m, 2 H, O-CH_2), 5.49 (dd, J = 5, 2 Hz, 1 H, O-CH-O), 8.00 (m, 2 H, arom.), 8.12 (m, 2 H, arom.), 8.30 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.0, 51.6, 64.2, 102.4, 108.4, 123.7, 123.9, 127.3, 128.3, 131.1, 144.5, 148.3, 149.1, 156.9 ppm. $C_{18}H_{16}N_4O_7$ (400.34): calcd. C 54.00, H 4.03, N 13.99; found C 54.0, H 4.1, N 13.8.

Compound 22b: 0.15 g (24%). oil. IR: $\tilde{\nu}$ = 1654 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.19 (t, J = 7 Hz, 3 H, CH_3), 3.25 (AB syst., J = 16 Hz, 1 H, CH_2), 4.12 (q, 2 H, O-CH_2), 6.52 (s, 1 H, NH), 7.84 (m, 2 H, arom.), 7.94 (m, 2 H, arom.), 8.32 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.8, 43.4, 61.7, 98.2, 123.7, 124.0, 126.7, 127.4, 130.8, 147.2, 148.1, 149.1, 154.1, 169.7 ppm. $C_{18}H_{16}N_4O_7$ (400.34): calcd. C 54.00, H 4.03, N 13.99; found C 54.1, H 4.2, N 13.9.

Cycloadduct 20c: 0.18 g (28%). M.p. 88–90 °C from ethanol. IR: $\tilde{\nu}$ = 1610 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.00 (t, J = 7 Hz, 3 H, CH_3), 2.93 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.16 (d, J = 14 Hz, 1 H, HC-H), 3.30 (m, 2 H, O-CH_2), 3.88 (m, 3 H, OCH_3), 5.36 (d, J = 5 Hz, 1 H, O-CH-O), 6.98 (m, 2 H, arom.), 7.41 (m, 3 H, arom.), 7.68 (m, 2 H, arom.), 7.94 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.4, 52.0, 55.3, 63.7, 104.3, 106.3, 113.9, 118.1, 125.4, 128.5, 128.6, 129.1, 139.7, 158.8, 161.4 ppm. $C_{19}H_{20}N_2O_4$ (340.37): calcd. C 67.04, H 5.92, N 8.23; found C 67.0, H 6.0, N 8.2.

Compound 22c: 0.09 g (14%). M.p. 98–102 °C from ethanol. IR: $\tilde{\nu}$ = 3252 (NH), 1732 (C=O), 1614 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.12 (t, J = 7 Hz, 3 H, CH_3), 3.21 (AB syst., J = 17 Hz, 1 H, CH_2), 3.83 (s, 3 H, O-CH_3), 4.05 (q, 2 H, O-CH_2), 6.33 (s, 1 H, NH), 6.93 (m, 2 H, arom.), 7.38 (m, 3 H, arom.), 7.66 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.8, 43.5, 55.3, 61.0, 97.8, 108.3, 113.8, 117.7, 125.5, 127.3, 128.0, 128.3, 128.6, 130.2, 140.6, 155.4, 170.2 ppm. $C_{19}H_{20}N_2O_4$ (340.37): calcd. C 67.04, H 5.92, N 8.23; found C 67.1, H 5.9, N 8.3.

Cycloadduct 20d: 0.23 g (36%). M.p. 97–99 °C from ethanol. IR: $\tilde{\nu}$ = 1654 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.98 (t, J = 7 Hz, 3 H, CH_3), 2.97 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.21 (d, J = 14 Hz, 1 H, HC-H), 3.31 (m, 2 H, O-CH_2), 5.40 (d, J = 5 Hz, 1 H, O-CH-O), 7.41 (m, 3 H, arom.), 7.68 (m, 2 H, arom.), 8.19 (m, 2 H, arom.), 8.33 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.4, 51.9, 63.9, 104.6, 108.0, 123.8, 125.2, 128.1, 128.6, 128.9, 131.8, 138.8, 148.8, 157.7 ppm. $C_{18}H_{17}N_3O_5$ (355.34): calcd. C 60.84, H 4.82, N 11.83; found C 60.8, H 4.8, N 11.5.

Compound 22d: 0.15 g (24%). M.p. 203–205 °C from ethanol. IR: $\tilde{\nu}$ = 1611 (C=N), 1736 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.16 (t, J = 7 Hz, 3 H, CH_3), 3.24 (AB syst., 1 H, CH_2), 4.09 (q, 2 H, O-CH_2), 6.43 (s, 1 H, NH), 7.40 (m, 3 H, arom.), 7.64 (m, 2 H, arom.), 7.95 (m, 2 H, arom.), 8.31 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.8, 43.5, 61.3, 99.1, 125.4, 127.3, 128.5, 129.0, 131.4, 133.1, 140.1, 149.0, 154.1, 170.1 ppm. $C_{18}H_{17}N_3O_5$ (355.34): calcd. C 60.84, H 4.82, N 11.83; found C 60.7, H 4.7, N 11.8.

Cycloadduct 20e: 0.08 g (12%). M.p. 96–99 °C from ethanol. IR: $\tilde{\nu}$ = 1609 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.98 (t, J = 7 Hz, 3 H, CH_3), 2.95 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.15 (d, J = 14 Hz, 1 H, HC-H), 3.29 (m, 2 H, O-CH_2), 3.84 (m, 3 H, OCH_3), 5.36 (d, J = 5 Hz, 1 H, O-CH-O), 6.95 (m, 2 H, arom.), 7.47 (m, 3 H, arom.), 7.60 (m, 2 H, arom.), 7.99 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.3, 51.6, 55.2, 63.7, 104.4, 107.9, 113.5, 113.8, 114.4, 126.8, 127.4, 128.1, 128.4, 128.7, 128.8, 129.2, 130.0, 130.6, 132.8, 159.1 ppm. $C_{19}H_{20}N_2O_4$ (340.37): calcd. C 67.04, H 5.92, N 8.23; found C 67.1, H 5.9, N 8.4.

Compound 22e: 0.06 g (10%). M.p. 165–168 °C from ethanol. IR: $\tilde{\nu}$ = 1613 (C=N), 1739 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17 (t, J = 7 Hz, 3 H, CH_3), 3.23 (AB syst., 1 H, CH_2), 3.83 (s, 3 H, OCH_3), 4.08 (q, 2 H, O-CH_2), 6.29 (s, 1 H, NH), 6.93 (m, 2 H, arom.), 7.47 (m, 3 H, arom.), 7.58 (m, 2 H, arom.), 7.78 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.9, 43.0, 55.2, 61.0, 113.6, 114.4, 125.4, 126.3, 127.1, 127.4, 128.7, 130.0, 130.8 155.6, 159.9, 170.4 ppm. $C_{19}H_{20}N_2O_4$ (340.37): calcd. C 67.04, H 5.92, N 8.23; found C 67.0, H 6.0, N 8.2.

Cycloadduct 20f: 0.18 g (29%). M.p. 113–116 °C from ethanol. IR: $\tilde{\nu}$ = 1601 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.98 (t, J = 7 Hz, 3 H, CH_3), 2.87 (dd, J = 14, 5 Hz, 1 H, CH-H), 3.21 (d, J = 14 Hz, 1 H, HC-H), 3.29 (m, 2 H, O-CH_2), 5.41 (d, J = 5 Hz, 1 H, O-CH-O), 7.50 (m, 3 H, arom.), 7.88 (m, 2 H, arom.), 7.99 (m, 2 H, arom.), 8.30 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.3, 52.1, 64.0, 104.4, 105.9, 123.8, 125.0, 126.5, 127.5, 128.6, 131.0, 146.5, 148.0, 159.2 ppm. $C_{18}H_{17}N_3O_5$ (355.34): calcd. C 60.84, H 4.82, N 11.83; found C 60.7, H 4.7, N 11.9.

Cycloadduct 21f: 0.05 g (8%). M.p. 82–85 °C from ethanol. IR: $\tilde{\nu}$ = 1608 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.34 (t, J = 7 Hz, 3 H, CH_3), 2.89 (dd, J = 14, 2 Hz, 1 H, CH-H), 3.20 (d, J = 14 Hz, 1 H, HC-H), 3.63 and 3.98 (m, 2 H, O-CH_2), 5.49 (dd, J = 5, 2 Hz, 1 H, O-CH-O), 7.50 (m, 3 H, arom.), 7.94 (m, 2 H, arom.), 7.98 (m, 2 H, arom.), 8.25 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.0, 51.5, 64.0, 102.4, 104.4, 123.5, 123.8, 126.5, 127.4, 127.5, 128.6, 128.7, 128.9, 129.1, 131.0, 131.2, 145.3, 146.5, 158.2 ppm. $C_{18}H_{17}N_3O_5$ (355.34): calcd. C 60.84, H 4.82, N 11.83; found C 60.8, H 4.8, N 11.7.

Compound 22f: 0.04 g (7%). Thick oil. IR: $\tilde{\nu}$ = 3338 (NH), 1730 (C=O), 1602 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.16 (t, J = 7 Hz, 3 H, CH_3), 3.24 (AB syst., 1 H, CH_2), 4.09 (q, 2 H, O-CH_2), 6.45 (s, 1 H, NH), 7.49 (m, 3 H, arom.), 7.84 (m, 2 H, arom.), 7.93 (m, 2 H, arom.), 8.26 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 13.8, 43.5, 61.5, 97.2, 109.1, 123.3, 123.5, 128.5, 129.0, 131.2, 133.3, 147.7, 148.0, 155.6, 169.8 ppm. $C_{18}H_{17}N_3O_5$ (355.34): calcd. C 60.84, H 4.82, N 11.83; found C 60.9, H 4.8, N 11.8.

CCDC-764733 (for **15a**) and -764734 (for **15b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Crystallographic data and bond lengths, angles and torsion angles of cycloadducts **15a** and **15b**. Cartesian coordinates of compounds **15c** and **16c** reported in Figure 2.

Acknowledgments

Financial support by the University of Pavia (Fondo d'Ateneo per la Ricerca, FAR), Ministero dell'Università e della Ricerca (MIUR) (PRIN 2008, CUP F11J10000010001) and EUTICALS

S.p.a. (V. le Milano, 86/88, 26900 Lodi, Italy) is gratefully acknowledged. Thanks are due to Dr. Massimo Boiocchi (Centro Grandi Strumenti, CGS) for X-ray data collection. Allocation of computer time by CINECA (Centro Interuniversitario Nord-Est di Calcolo Automatico) Casalecchio di Reno (Bologna) is also gratefully acknowledged.

[1] H. Wieland, H. Bauer, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1480–1488.
[2] P. Quadrelli, P. Caramella, *Curr. Org. Chem.* **2007**, *11*, 959–986.
[3] P. Caramella, P. Grünanger in *1,3-Dipolar Cycloaddition Chemistry* (Eds.: A. Padwa), Wiley, New York, **1984**, vol. 1, pp. 291–392.
[4] a) P. Caramella, E. Cereda, *Synthesis* **1971**, 433–434; b) P. Quadrelli, A. Gamba Invernizzi, M. Falzoni, P. Caramella, *Tetrahedron* **1997**, *53*, 1787–1796.
[5] a) F. De Sarlo, A. Guarna, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1825–1827; b) P. Quadrelli, M. Mella, P. Caramella, *Tetrahedron Lett.* **1999**, *40*, 797–800.
[6] P. Quadrelli, M. Mella, A. Gamba Invernizzi, P. Caramella, *Tetrahedron* **1999**, *55*, 10497–10510.
[7] a) G. W. Kirby, *Chem. Soc. Rev.* **1977**, *6*, 1–24; b) G. E. Keck, R. R. Webb, J. B. Yates, *Tetrahedron* **1981**, *37*, 4007–4016; c) L. H. Dao, J. M. Dust, D. Mackay, K. N. Watson, *Can. J. Chem.* **1979**, *57*, 1712–1719; d) S. M. Weinreb, R. R. Staib, *Tetrahedron* **1982**, *38*, 3087–3128; e) D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Chemistry*, Academic Press, San Diego, **1987**; f) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1990**; g) J. Streith, A. Defoin, *Synthesis* **1994**, 1107–1117; h) P. F. Vogt, M. J. Miller, *Tetrahedron* **1998**, *54*, 1317–1348.
[8] a) A. D. Cohen, B.-B. Zeng, S. B. King, J. P. Toscano, *J. Am. Chem. Soc.* **2003**, *125*, 1444–1445; b) P. Quadrelli, R. Scrocchi, A. Piccanello, P. Caramella, *J. Comb. Chem.* **2005**, *7*, 887–892.
[9] a) P. Quadrelli, M. Mella, A. Piccanello, S. Romano, P. Caramella, *J. Org. Chem.* **2007**, *72*, 1807–1810; b) P. Quadrelli, S. Romano, A. Piccanello, P. Caramella, *J. Org. Chem.* **2009**, *74*, 2301–2310.
[10] P. Quadrelli, G. Campari, M. Mella, P. Caramella, *Tetrahedron Lett.* **2000**, *41*, 2019–2022.
[11] a) J. J. Tufariello in *1,3-Dipolar Cycloaddition Chemistry* (Eds.: A. Padwa), Wiley, New York, **1984**, vol. 2, pp. 83–168; b) K. B. G. Torsell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, Weinheim, **1988**; c) P. Grünanger, P. Vita-Finzi, *Isoxazoles*, Wiley, New York, **1991**, vol. 49, part 2, pp. 649–778.
[12] a) H. Seidl, R. Huisgen, R. Knorr, *Chem. Ber.* **1969**, *102*, 904–914; b) R. Huisgen, H. Seidl, J. Wulff, *Chem. Ber.* **1969**, *102*, 915–925; c) H. Seidl, R. Huisgen, R. Grashey, *Chem. Ber.* **1969**, *102*, 926–930.
[13] a) T. Shimizu, Y. Hayashi, K. Teramura, *J. Org. Chem.* **1983**, *48*, 3053–3058; b) T. Shimizu, Y. Hayashi, T. Taniguchi, K. Teramura, *Tetrahedron* **1985**, *41*, 727–738.
[14] P. DeShong, C. M. Dicken, R. R. Staib, A. J. Freyer, S. M. Weinreb, *J. Org. Chem.* **1982**, *47*, 4397–4403.
[15] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision B.02, Gaussian, Inc., Pittsburgh, PA, **2003**.
[16] a) W. L. Jorgensen, L. Salem, *The Organic Chemist's Book of Orbitals*, Academic Press, New York, **1973**, pp. 42–43; b) E. Juaristi, G. Cuevas, *Tetrahedron* **1992**, *48*, 5019–5087; c) G. R. J. Tatcher, *The Anomeric Effect and Related Stereoelectronic Effects*, ACS Symposium Series, Washington (DC), **1993**.
[17] P. Quadrelli, R. Scrocchi, P. Caramella, A. Rescifina, A. Piperno, *Tetrahedron* **2004**, *60*, 3643–3651.
[18] a) F. G. Cocu, G. Wolczunowicz, L. Bors, T. Posternak, *Helv. Chim. Acta* **1970**, *53*, 739–749; b) R. Steyn, H. Z. Sable, *Tetrahedron* **1971**, *27*, 4429–4447; c) E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**.
[19] a) G. V. Boyd, *The Chemistry of Double Bonded Functional Groups* (Ed.: S. Patai), Wiley, New York, **1989**, pp. 477–525; b) B. B. Snider, *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 2, pp. 527–561 and vol. 5. pp. 1–27; c) P. C. Astles, S. V. Mortlock, E. J. Thomas, *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**; d) for a concise summary, see: I. Fleming, *Pericyclic Reactions*, Oxford University Press, Oxford, **1999**, pp. 84–87.
[20] A. R. Katritzky, K. Jug, D. C. Onicin, *Chem. Rev.* **2011**, *101*, 1421–1449.

Received: November 8, 2011
Published Online: January 20, 2012

