Pergamon

Tetrahedron 55 (1999) 7027–7044

TETRAHEDRON

Cycloaddition of Nitrile Oxides to Cyclic and Acyclic α,β-Unsaturated Amides. Frontier Orbital Interactions and an Unexpected Steric Drift Determine Regiochemistry

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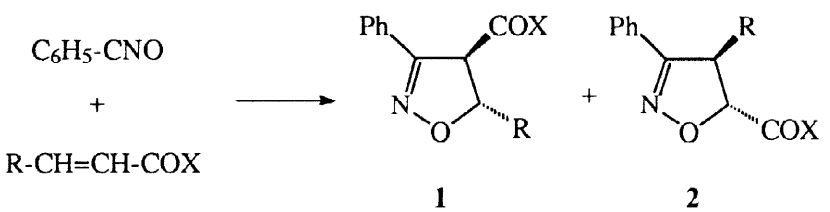
Received 8 February 1999; revised 24 March 1999; accepted 8 April 1999

Abstract: The regiochemistry of the cycloadditions of nitrile oxides to α,β-unsaturated amides is determined by frontier orbital interactions and by a regiochemical drift due to steric effects. Cycloadditions to α,β-unsaturated lactames afford mainly 4-carboxamido-isoxazolines with high regioselectivity. In cycloadditions to acyclic α,β-unsaturated amides the regioselectivity relaxes and finally reverses in the case of *N,N*-disubstituted derivatives, because of the increasing steric congestion at the amine nitrogen.

Keywords:1,3-Dipolar Cycloadditions, Regiochemistry, Isoxazoles, Amides, Steric effects.

A quarter of century ago Huisgen reported a thorough study on the cycloadditions of nitrile oxides to α,β-unsaturated esters,[1] which has remained the obligatory reference and canon for any other regiochemical result in nitrile oxide cycloadditions to α,β-unsaturated compounds.[2] As a typical case benzonitrile oxide (BNO) adds to crotonate and cinnamate esters yielding mixtures of 4- and 5-acyl-isoxazolines **1** and **2** (Scheme 1), where the 4-acyl isomers are the major product (Table 1) in keeping with the preferred binding of the nitrile oxide oxygen, which has the highest *HOMO* coefficient,[3] to the β-carbon of the α,β-unsaturated esters.



1 **2**

Scheme 1

Table 1

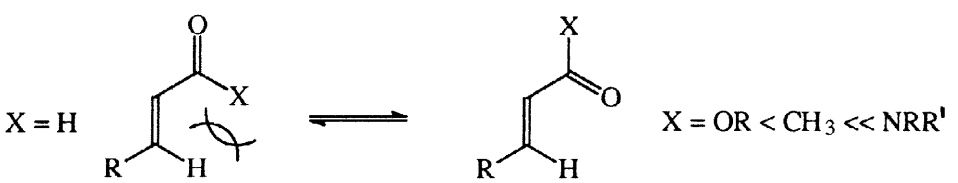
X	R	1 / 2	Ref.
OCH_3	CH_3	66 : 34	1
	C_6H_5	70 : 30	1
H	CH_3	9 : 1	4
	C_6H_5	>9 : 1	5
CH_3	CH_3	50 : 50	6
	C_6H_5	59 : 41	7
$-OCH_2-$		>9 : 1	8
$-CH_2CH_2-$		91 : 9	7

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00331-2

Changes in the carbonyl moiety cause changes in the regiochemistry. Thus, regioselectivity is higher in cycloadditions to α,β-unsaturated aldehydes[4,5] but markedly lower in the case of α,β-unsaturated ketones.[6,7] On the other hand, α,β-unsaturated lactones[8] or cyclic alkenones[7] afford mainly the 4-acyl cycloadducts **1** with high regioselection.

The origin of this perplexing behaviour could not be satisfactorily clarified and a recent review calls for more accurate models of the cycloaddition transition states and reliable calculations as well.[9]

As a matter of fact, a high regioselectivity is observed with aldehydes and cyclic esters or ketones, whose unsaturated systems are held in a transoid arrangement, while selectivity is lower with acyclic esters and even more with ketones. In acyclic α,β-unsaturated carbonyl compounds the conformational equilibrium is determined by the steric interaction between the acyl substituent X and the β-vinylic hydrogen.[10] While the aldehydes adopt mainly the transoid conformation **3**, the esters and even more the ketones prefer the cisoid conformation **4**, which becomes almost exclusive in the case of amides.[11]



3 **4**

A tempting hypothesis is then that the changes in regioselectivity reflect the changes in the conformational equilibrium. While the transoid arrangement gives rise to high regioselective cycloadditions, in keeping with frontier orbital (FO) expectations, the cisoid arrangement apparently is associated with a low regioselection. In the latter case some unidentified factors must tip the balance away from cycloadduct **1** and/or toward cycloadduct **2**.

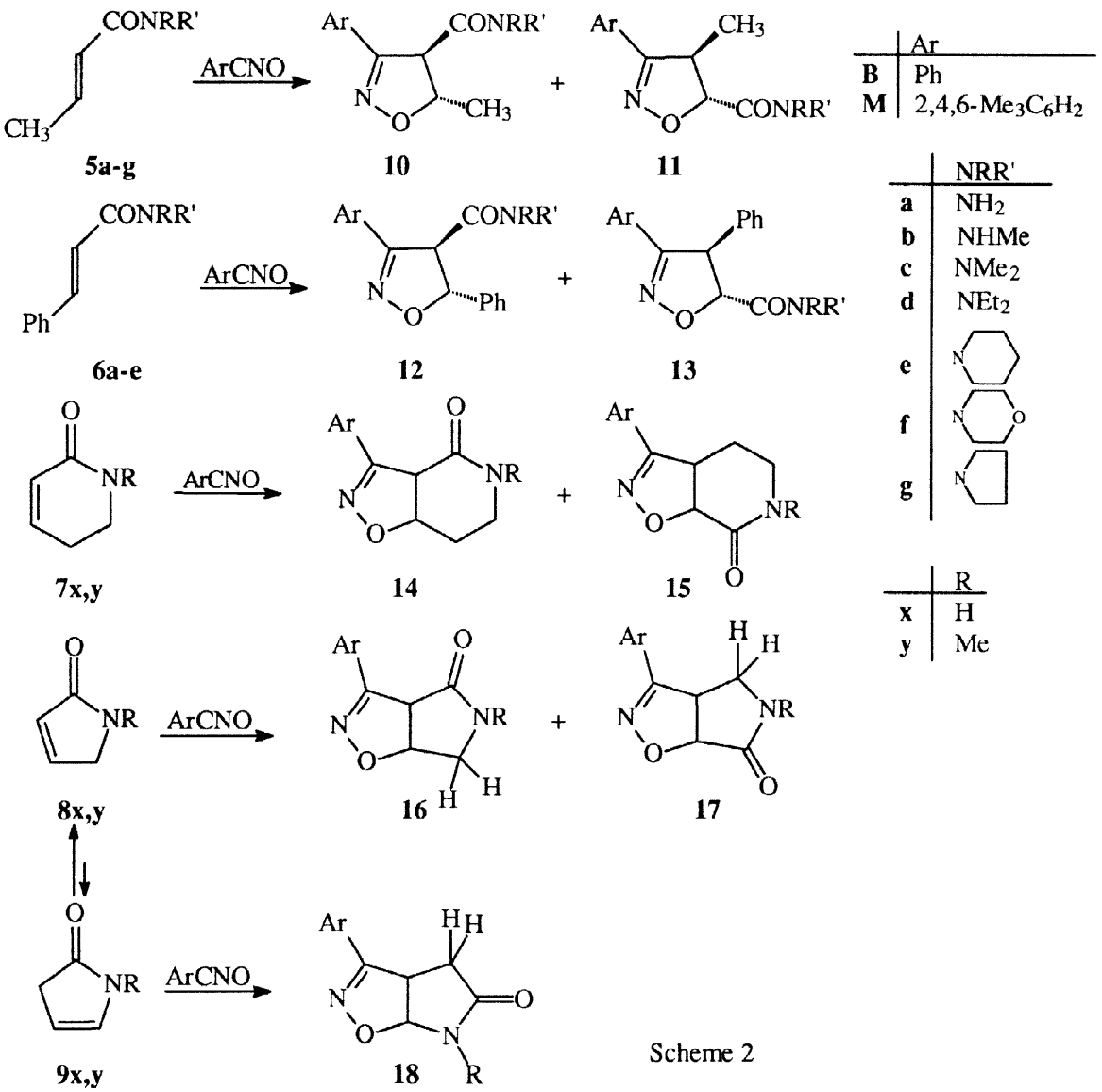
To test this idea we have investigated the cycloadditions to some crotonamides and cinnamamides, which adopt the cisoid conformation, and, for comparison, to a few unsaturated lactams, which are constrained in a transoid conformation.

Recently, several asymmetric Diels-Alder[12] and 1,3-dipolar[13] cycloaddition reactions have been studied with chiral α,β-unsaturated amides derived from chiral amines (pyrrolidines, *Evans* 2-oxazolidinones or *Oppolzer* sultams). Achiral *N*-acryloyl-2-oxazolidinones have also been extensively used in studies devoted to the asymmetric catalysis of cycloadditions, owing to their ready complexation with metal cations and chiral ligands. The major concern in these studies was however the diastereo- and enantio-selectivities related to the asymmetric reaction engineering and the regiochemical issues were not specifically addressed.

Quite recently, after the completion of our work, a related study[14] reported the unusual reversal of regiochemistry in the cycloadditions of nitrile oxides to tertiary crotonamides and cinnamamides, which overlaps in part with our own results.

Results

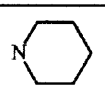
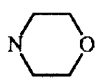
We have studied the cycloadditions of BNO and mesitonitrile oxide (MNO) to the variously substituted crotonamides **5a-g**, cinnamamides **6a-e** and the six- and five-membered unsaturated lactams **7x,y** and **8x,y** (Scheme 2). Cycloadditions have been performed in benzene at r.t. by generating BNO *in situ* from benzhydroximoyl chloride and a stoichiometric amount of triethylamine or by addition of the stable MNO to a benzene solution containing a slight excess (1.2-1.5 equiv) of the dipolarophiles.



Scheme 2

The pairs of cycloadducts **10/11**, **12/13**, **14/15** and **16/17** are usually formed in fair yields (Table 2) and have been separated by column chromatography. The regioisomer ratios have been determined by integration of the signals of the regioisomeric adducts in the nmr spectra of the crude mixtures and correspond closely to those obtained in the separations.

Table 2. Ratios of the 4-acyl / 5-acyl regioisomers (reaction yields) in cycloadditions of BNO and MNO to α,β-unsaturated amides.

		Crotonamides, **10 / 11**		Cinnamamides, **12 / 13**	
	NRR'	BNO	MNO	BNO	MNO
a	NH_2	56:44 (49)	69:31 (42)	72:28 (52)	35:65 (50)
b	NHMe	55:45 (57)	65:35 (51)	66:34 (49)	33:67 (53)
c	NMe_2	15:85 (76)	37:63 (90)	24:76 (81)	20:80 (80)
d	NEt_2	12:88 (61)	24:76 (88)	20:80 (66)	12:88 (68)
e		18:82 (70)	41:59 (87)	27:73 (67)	23:77 (71)
f		17:83 (82)	46:54 (81)		
g		20:80 (70)	47:53 (80)		

		5,6-Dihydropyridin-2-ones, **14 / 15**		3-Pyrrolin-2-ones, **16 / 17**	
	NR	BNO	MNO	BNO	MNO
x	NH	>95:5 (51)	>95:5 (62)	91:9 (43)	95:5 (48)
y	NMe	90:10 (61)	90:10 (70)	95:5 (54)	91:9 (64)

The structure assignment to the cycloadducts relies upon the nmr spectra and is based on the multiplicity of the high- and low-field signals of the 4- and 5-isoxazoline hydrogens. In the case of the cinnamamide regioisomers **12** and **13**, assignment is based on the larger separation of the signals of the isoxazoline 4- and 5- of the 4-acyl regioisomers **12**, owing to the larger deshielding by the phenyl substituent.[1]

In the case of pyrrolinones **8x,y**, the cycloadducts **18** derived from the tautomers **9x,y**[15] have also been isolated in moderate yields. The structures of adducts **18x,y** follows from their nmr spectra, which are similar to those of cycloadducts **17** but show more deshielded signals for the isoxazoline 5-H, because of the adjacent nitrogen, as well as more shielded signal for CH_2 in the range typical for CH_2 α to a carbonyl.

Discussion

The regiochemistry of the cycloadditions to the α,β-unsaturated amides changes widely. The regioselection is high with the unsaturated lactams but decreases somewhat in the case of crotonamide and its *N*-methyl derivative and finally reverses in the case of *N,N*-disubstituted derivatives. The dimethylamino, piperidino, morpholino and pyrrolidino derivatives show very similar regioisomer ratios, in spite of the difference in basicity of the amine moieties, while the reversal is invariably more consistent in the case of the more congested diethylamino derivative.

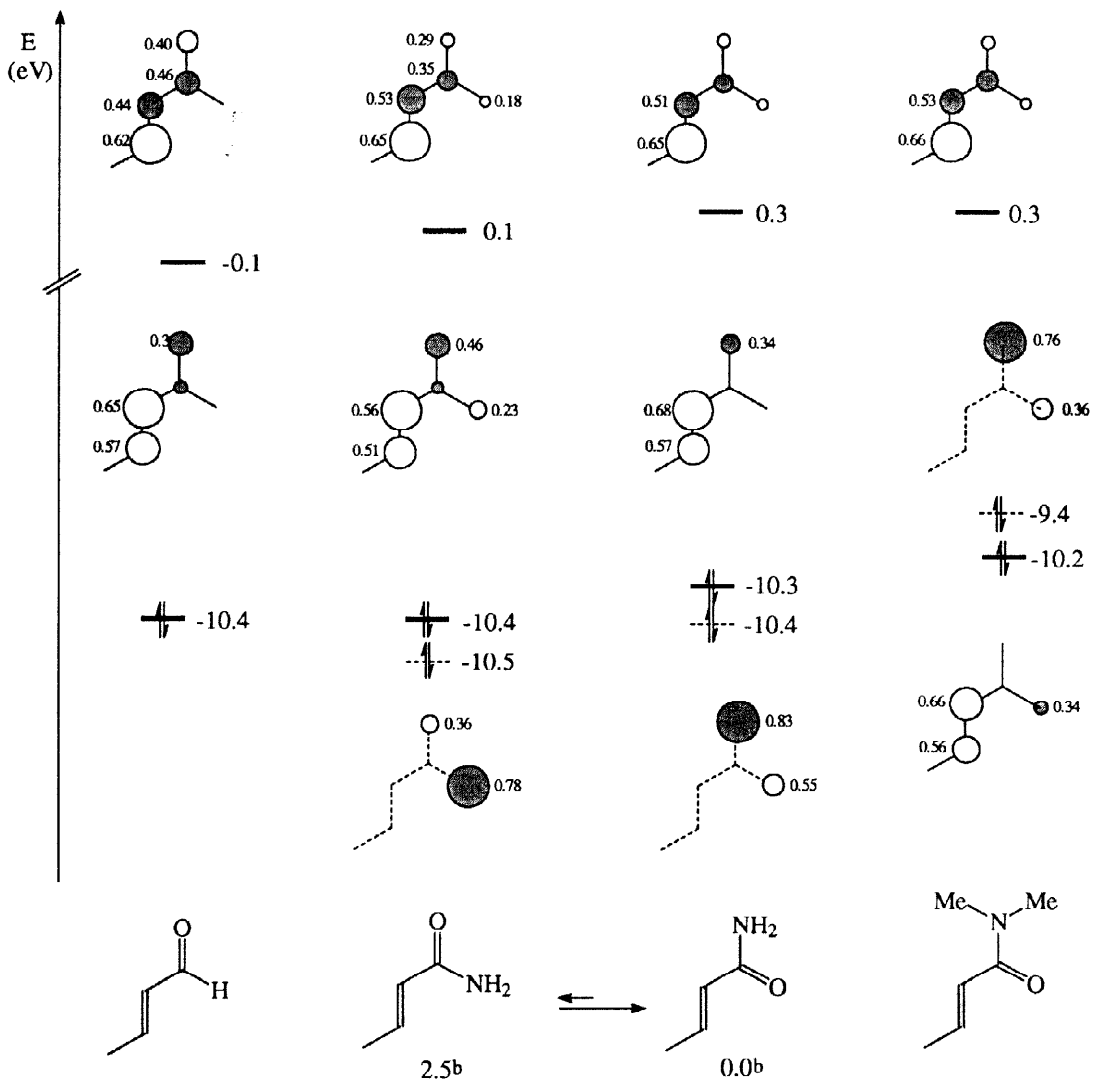
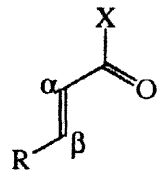
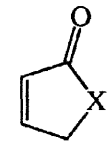


Figure 1. Frontier orbital[a] of the transoid and cisoid conformers of crotonamide along with those of the more stable conformers of crotonaldehyde (left) and *N,N*-dimethyl crotonamide (right). Dashed levels indicate high-lying orbitals mainly localized on the carboxamide moiety.

(a). Shapes and energies from AM1 calculations for AM1 optimized geometries. Numbers near the lobes represent the p_z AO coefficients and numbers near the levels are the energies of the orbitals in eV. (b). Relative energies of the conformers in kJ mol^{-1}.

Table 3. AM1 eigenvectors and eigenvalues for the FOs of some representative crotonic and cinnamic derivatives and cyclic dipolarophiles.[a]





	HOMO				LUMO			
X	C_α	C_β	ε(ev)	P^b	C_α	C_β	ε(ev)	P^b
Crotonic derivatives, R = CH_3								
H	0.67	0.57	-10.38	-0.12	0.43	-0.63	-0.04	0.21
CH_3	0.67	0.57	-10.31	-0.12	0.42	-0.62	0.05	0.21
OCH_3	0.67	0.57	-10.51	-0.12	0.48	-0.65	0.00	0.19
NH_2	0.67	0.57	-10.30	-0.12	0.51	-0.66	0.30	0.18
NMe_2	0.66	0.56	-10.24	-0.12	0.50	-0.66	0.32	0.19
Cyclic dipolarophiles								
CH_2	0.64	0.57	-10.40	-0.08	0.45	-0.62	-0.04	0.18
O	0.57	0.48	-10.88	-0.09	0.54	-0.66	-0.41	0.14
NCH_3	0.66	0.63	-10.66	-0.04	0.55	-0.65	0.06	0.12
$NHCH_2$	0.61	0.55	-10.47	-0.07	0.53	-0.64	0.12	0.13
Cinnamic derivatives, R = C_6H_5								
H	0.48	0.28	-9.34	-0.15	0.42	-0.45	-0.71	0.03
CH_3	0.48	0.29	-9.29	-0.15	0.42	-0.44	-0.64	0.02
OCH_3	0.47	0.27	-9.40	-0.15	0.44	-0.45	-0.71	0.01
NH_2	0.48	0.29	-9.28	-0.15	0.44	-0.42	-0.53	-0.02

a) AM1 optimized geometries.
b) Polarization of the orbitals defined as $C_\beta^2 - C_\alpha^2$.

The FOs of the unsaturated amides remain almost unaffected by *N*-substitution or conformational change. Figure 1 displays the AM1[16] FOs of the cisoid and the more stable transoid conformer of crotonamide along with the FOs of the more stable conformers of crotonaldehyde (transoid) and *N,N*-dimethylamino crotonamide (cisoid). As shown in Figure 1 the shape of the FOs of crotonaldehyde, with moderate *HOMO* polarization toward the α-carbon and a high *LUMO* polarization toward the β-carbon, is essentially retained in the π and π* orbitals of the unsaturated amides. The shape of the FOs does not change sizeably upon changes in the X substituent in the crotonic derivatives (Table 3), in keeping with the modest influence of the acyl substituents on

the conjugation of the carbonyl and the C=C bond in cross-conjugated systems.[17] Therefore a high regioselection should occur in cycloadditions with nitrile oxides, since the two FO interactions favor the same 4-acyl regioisomers (Figure 2). This is indeed what is observed in the case of crotonaldehyde and the unsaturated lactams. Why does then regioselection diminish in cycloadditions to crotonamide and *N*-methyl crotonamide and reverse after *N,N*-disubstitution?

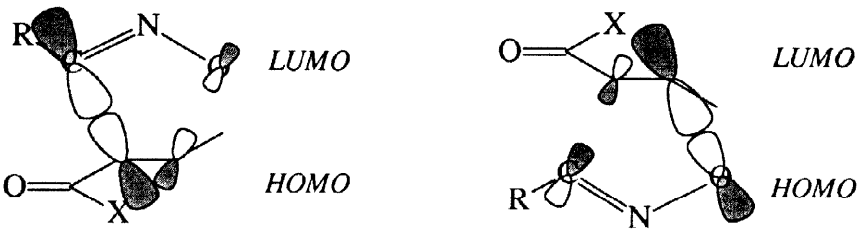
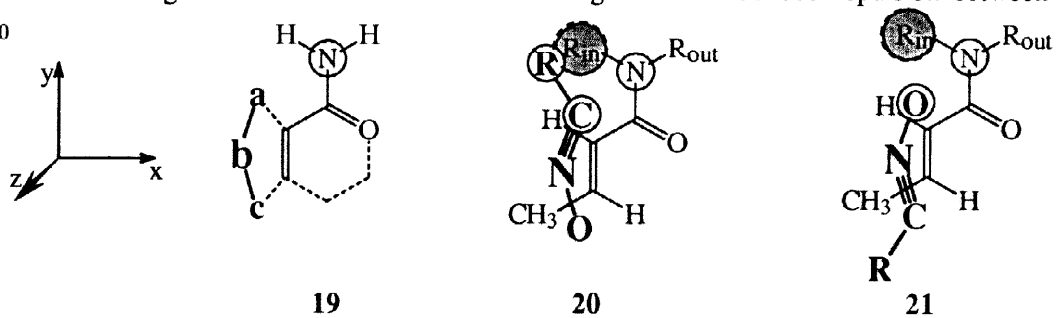


Figure 2

Repulsive interactions in cycloadditions to cisoid crotonamides.

In the case of crotonamides the $\pi_{C=C}$ orbital is close in energy to the lone pair (l.p.) orbital of the amide nitrogen which is mainly localized at nitrogen.[18] This l.p. orbital is depicted in the dashed formulae in Figure 1 and is the *SHOMO* in crotonamide itself and the *HOMO* in *N,N*-dimethylcrotonamide, owing to its raising upon *N,N*-disubstitution. In the transoid conformation of crotonamide this l.p. orbital is located rather away from the direction of attack and should not interfere with the cycloaddition to the C=C bond. In the cisoid conformation, however, the l.p. is closer to the plane of attack, in a position, sketched in **19**, which reminds the familiar ortho-effect in aromatic derivatives and causes steric hindrance by increasing the destabilizing filled orbital interactions between the addends.[19] In the cycloaddition of nitrile oxides steric hindrance should be greater in the approach **20** rather than in the regioisomeric one **21** because of the greater non-bonded repulsion between the atoms encircled.[20]

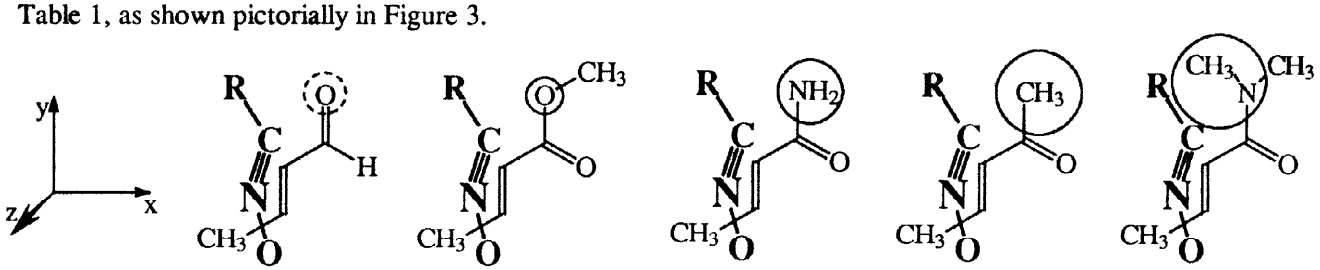


19 **20** **21**

The decrease of regioselection in cycloaddition to crotonamide can then be attributed to the larger steric hindrance in the approach **20**, which slows down the formation of the 4-acyl cycloadduct **10**. On going to *N*-methyl crotonamide the regioselection remains essentially unchanged because of the strong preference of the *N*-methyl substituent for the conformation cisoid to the carbonyl,[21] in the position R_{out} of **20**, away from the plane of attack. On the other hand, in *N,N*-disubstituted crotonamides one of the *N*-substituents occupies the position R_{in}, shown in **20** as a shaded circle, causing additional hindrance and reversal of regioselection.

A regiochemical drift due to steric hindrance.

As discussed above, the regiochemistry of the nitrile oxide cycloadditions to crotonamides is determined by frontier orbital interactions, which act in a rather constant fashion, as well as by an additional steric hindrance, which causes a variable regiochemical drift toward the 5-acyl cycloadducts **11**. The model works successfully in rationalizing the perplexing changes of regioselectivity observed in cycloadditions to the crotonoyl derivatives of Table 1, as shown pictorially in Figure 3.



Ratio[a] ($\Delta\Delta G^{\neq}$)[b]	9:1 (5.44)	66:34 (1.63)	56:44 (0.59)	50:50 (0.0)	15:85(-4.31)
Drift[c]	0.0	3.81	4.85	5.44	9.75
A values[d]		3.35	5.44	7.53	8.79

Figure 3. Variable steric hindrance in cycloadditions to crotonic derivatives.The size of the circles represents the steric hindrance of the crotonoyl substituents.
(a). The ratios refer to the regioisomers of Table 1. (b). Free energy differences between the two regioisomeric transition states, kJ mol^{-1}, from the relation $\Delta\Delta G^{\neq} = RTln(ratio)$. (c). Decrease of $\Delta\Delta G^{\neq}$ relative to the first entry. (d). The A values of X substituents are taken from ref. 22, kJ mol^{-1}.

In Figure 3 the regioisomeric ratios and the free energy differences between the two regioisomeric transition states ($\Delta\Delta G^{\neq}$) are given along with the drift, defined as the decrease of $\Delta\Delta G^{\neq}$ relative to the first entry. As a measure of the steric hindrance of the acyl substituent X, we have reported in Figure 3 the A values of the substituent X in cyclohexane derivatives.[22] The A values are derived from the conformational equilibrium of X-substituted cyclohexanes and are a measure of the destabilization of the axial conformer due to the steric interaction of the substituent X with the two syn 1,3-diaxial hydrogens on the ring. The similar magnitude and fair correspondence between the drift and A values is impressive in spite of the different origin of the two steric parameters. The dashed circle in the first formula of Figure 3 shows the conceivable hindrance due to the carbonyl oxygen in the transoid arrangement typical of cyclic dipolarophiles and the aldehyde. Hindrance is presumably low in this case, since the oxygen p_z orbital is involved and localized in the carbonyl π bond.

Cinnamamides.

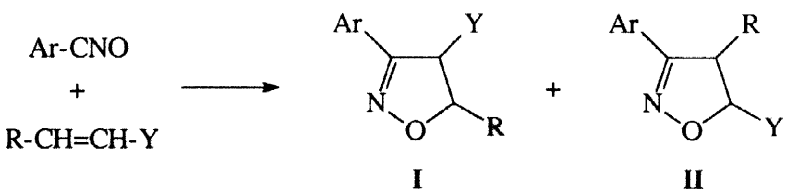
In cycloadditions to cinnamamides regiochemistry follows the main trends described for crotonamides. However, some noteworthy and meaningful differences become evident after perusal of the ratios of Table 2 and comparison with the FOs of Table 3. The most striking difference is the variable response of α,β-unsaturated amides in BNO and MNO cycloadditions. When comparing the cycloadditions of the two nitrile oxides to the

same unsaturated amide, MNO consistently affords slightly higher proportions of the 4-acyl crotonamide adducts **10** but sizeably lower proportions of the 4-acyl cinnamamide adducts **12**.

The FOs nicely account for these intriguing changes. The FOs of the cinnamic derivatives (Table 3) are "compressed" and show higher *HOMO*s and lower *LUMO*s with respect to crotonic derivatives because of the phenyl conjugation.[3] The *HOMO*s retain the "styrenic" polarization toward the carbon α to the carbonyl while the *LUMO*s are essentially unpolarized owing to the interactions with vacant orbitals of phenyl and $\pi^*_{C=O}$.[23,24] In cycloadditions to crotonamides both FO interactions favour the same 4-acyl regioisomer (Figure 2). On going from BNO to the more nucleophilic[2] MNO the regioselective weakening associated with the decrease of the *HOMO*(dipolarophile) - *LUMO*(dipole) interaction is more than compensated by the increase of the other interaction, owing to the high *LUMO* polarization of the crotonic dipolarophiles. In cycloadditions to cinnamamides no such a compensation is possible because of the unpolarized shape of the cinnamamide *LUMO*s.

Available examples on this effect in cinnamic derivatives are gathered in Table 4,[1,7,24,25] along with the case of benzofuran[26] and benzothiophene[27] where the regiochemical effects of the two FOs interactions are opposite and regioselection reverses. In the case of cinnamamide, methyl styryl sulfone and benzyliden acetone the reversal can be attributed to the additional action of the steric drift.

Table 4. Ratio of regioisomers in cycloadditions of BNO and MNO to cinnamic derivatives.



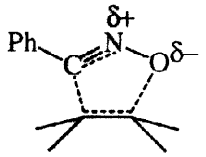
I II

R	Y	BNO I/II	MNO I/II	Ref.
C_6H_5	SO_2Ph	84:16	62:38	24
C_6H_5	CN	76:24	56:44	25
C_6H_5	$COOCH_3$	70:30	52:48[a]	1
C_6H_5	$CONH_2$	72:28	35:65	a
C_6H_5	SO_2CH_3	71:29	43:57	24
C_6H_5	$COCH_3$	59:41	20:80	7
-*o*.C_6H_4-O		70:30	26:74	26
-*o*.C_6H_4-S		70:30	26:74	27

(a). Present work.

With regard to MNO another subtle question deserves mention. According to the transition state (TS) model **20**, on going from BNO to MNO, steric hindrance should increase, because of the bulkier 2,4,6-trimethylphenyl substituent of MNO, and consequently a larger steric drift should be observed. The columns of Table 2

show exactly the opposite: on going from the primary amides to the *N,N*-diethyl derivatives the spread of the ratios is larger with BNO than with MNO. The observed behaviour is consistent with the view[2] of a change in the TS structures in BNO and MNO cycloadditions, as depicted in **22** and **23**.



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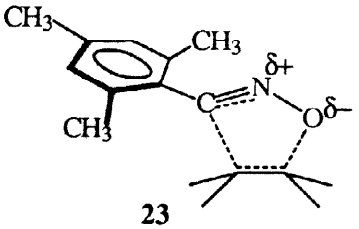


23

Available evidence suggests[2] that the higher nucleophilicity of MNO derives in part from electronic factors (FO energies and coefficients), but also from a distortion of the transition structure to the more open TS **23**, which minimizes the steric interactions between the addends as well as the steric drift discussed above.

Conclusions

In cycloadditions of nitrile oxides to crotonic and cinnamic derivatives we have identified a steric factor which has a remarkable influence in determining the regiochemistry. The steric effect modifies the result of FO interactions causing a regiochemical drift toward the 5-acyl cycloadducts. The drift is proportional to the steric hindrance of the crotonoyl and cinnamoyl substituent and is especially evident in the case of tertiary amides, as independently shown by Weidner-Wells.[14] We have worked out a model of the cycloaddition transition state which accounts for the puzzling changes in regiochemistry of crotonic, cinnamic and related cyclic derivatives and is amenable to further experimental verification, by proper choice of the dipolarophiles.

Steric effects are important in determining the reactivity of nitrile oxide cycloadditions and manifest for instance in the well-known decrease in reactivity with alkyl substitution on ethylene, in spite of the favourable electronic (frontier) effects.[2] In cycloadditions to monosubstituted ethylenes steric effects dominate the regiochemistry and the 5-substituted isoxazolines are formed almost exclusively. In this case the two ends of the double bond are sterically very different and cause a large regiochemical drift toward the 5-substituted cycloadducts.[28]

In the 1,2-disubstituted ethylenes the steric effects of the two substituents compensate each other somewhat. In cycloadditions to crotonic and cinnamic derivatives the changes of steric hindrance at the carbonyl moiety manifest however rather clearly because of the almost invariant FO control of regiochemistry with these dipolarophiles.

Experimental

All mps are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. ^{1}H-NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ) and coupling constants are in Hertz (Hz): b, broad; s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Ir spectra (nujol mulls) were recordered on an FT-IR Perkin-Elmer Paragon 1000 spectrophotometer and absorbtions (ν) are in cm^{-1}. Column chromatography and tlc: silica gel H60 and GF_{254} (Merck) respectively, eluant cyclohexane/ethyl acetate 9:1 to ethyl acetate. The identification of samples from different experiments was secured by mixed mps and superimposable ir spectra.

Starting and reference materials. Benzhydroximoyl chloride was obtained by treatment of benzaldoxime with sodium hypochlorite[29] and mesitonitrile oxide by oxidation of 2,4,6-trimethylbenzaldoxime with bromine.[30]

Cinnamamide **6a** is commercially available (Aldrich). Crotonamide **5d** and cinnamamides **6c-e** were obtained by acylation of the amines with crotonoyl and cinnamoyl chlorides in anhydrous benzene.[31] Crotonamides **5a** mp 158 °C,[32] **5b** mp 67-69 °C,[33] **5c** oil bp 91 °C/14 mmHg,[34] **5e** oil bp 160 °C/30 mmHg,[35] **5f** oil bp 112-114 °C/5 mmHg,[36] **5g** oil bp 75-78 °C/0.4 mmHg,[37] and cinnamamide **6b** mp 111 °C[38] were similarly prepared in fair yields.

The lactam **7x**, 5,6-dihydro-2-(1H)-pyridinone, was prepared by condensation of vinylacrylic acid with concentrated ammonium hydroxide.[39] The *N*-methyl derivative **7y** was obtained from 3-phenylthio-1-methyl-2-piperidone[40] by periodate oxidation[41] and thermolysis of the crude sulfoxide (C_6H_6, Δ 5 h). Column chromatography afforded 1-methyl-5,6-dihydro-2-pyridinone **7y** in a 73% yield, oil bp 130 °C (bath)/0.1 mmHg.[42] Pyrrolinones **8x,y** were prepared by oxidation of pyrrole and *N*-methylpyrrole with H_2O_2.[15]

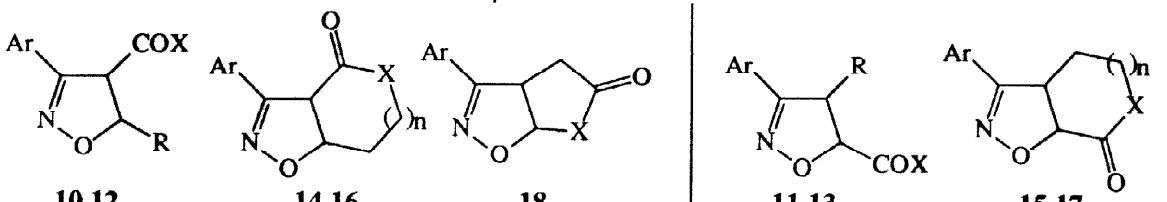
General procedure for the cycloadditions of BNO to the α,β-unsaturated amides. To a stirred solution of benzhydroximoyl chloride (5 g, 32 mmol) and amides (40 mmol) in anhydrous benzene (100 ml), 1.1 equiv. of triethylamine in the same solvent (20 ml) were added over a 0.5 h period. After keeping the reaction mixture two days at room temperature, triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure leaving a residue which was separated by column chromatography. In the case of primary and secondary amides a part of the cycloadducts separates along with triethylamine hydrochloride and, after washing with water, was chromatographed.

General procedure for the cycloadditions of MNO to the α,β-unsaturated amides. A solution of mesitonitrile oxide (1.6 g, 10 mmol) and amides (15 mmol) in anhydrous benzene (100 ml) was stirred 3 weeks at r.t.. After removal of the solvent the mixtures were separated by column chromatography.

*Cycloadducts **10-17***. The yields and the ratios of the regioisomeric cycloadducts **10-17** are reported in Table 2, the physical data in Table 5, the spectroscopic data in Table 6 (adducts to crotonamides **10** and **11**), Table 7 (adducts to cinnamamides **12** and **13**), Table 8 (adducts to unsaturated lactams **14-17**) and the analytical data in Table 9.

*Cycloadducts **18***. In cycloadditions to pyrrolin-2-ones column chromatography afforded the adducts **16** and **17** along with adducts **18**. The physical data of adducts **18** are included in Table 5 and the spectroscopic data in Table 8. **18Bx**: 21%, (found: C, 65.37; H, 5.02; N, 13.76%; $C_{11}H_{10}N_2O_2$ requires: C, 65.33; H, 4.98; N, 13.86%). **18By**: 18%, (found: C, 66.63; H, 5.65; N, 12.91%; $C_{12}H_{12}N_2O_2$ requires: C, 66.65; H, 5.59; N, 12.96%). **18Mx**: 5%, (found: C, 68.78; H, 6.65; N, 13.01%; $C_{14}H_{16}N_2O_2$ requires: C, 68.83; H, 6.60; N, 13.10%). **18My**: 13%. The adduct is eluted with the major adduct **16My**. Crystallization from benzene/ligroin

Table 5. Physical data, mp (°C) and crystallization solvent[a] of cycloadducts **10 – 18** to α,β-unsaturated amides.



10,12 **14,16** **18** **11,13** **15,17**

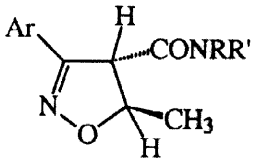
X	Ar = C_6H_5	Ar = Mes	Ar = C_6H_5	Ar = Mes
Crotonamides, R = CH_3	**10**		**11**	
a NH_2	207-208 A	196-197 T	151-152 T	187-188 B/L
b NHMe	192-193 T	159-161 I	160-161 C	85-86 L
c NMe_2	116-117 C	85-86 L	55-56 L	94-95 P
d NEt_2	110-111 C	56-58 P	53-55 P	84-85 E/W
e Piperidino	119-120 I	116-117 L	Oil	139 E/W
f Morpholino	154-155 E	92-93 B/L	107-108 B/L	Oil
g Pyrrolidino	141-142 E/W	83-84 P/B	115-116 C	139-140 L
Cinnamamides, R = C_6H_5	**12**		**13**	
a NH_2	196-197 B	214-215 L	230-231 A	199-200 L
b NHMe	204 B	189-190 P	121-122 B	132-133 B/L
c NMe_2	148-149 E/W	-[b]	93-94 L	124-125 M
d NEt_2	99-100[c] C	-[b]	118[d] C	111-112 L
e Piperidino	115-116 C	122-4 L	129-130 L	157-158 E/W
Dihydropyridin-2-ones, (n=1)	**14**		**15**	
x NH	155-156 B/L	163-164 B/L		
y NMe	132-133 B/L	166-167 B/L	105 B/L	163-164 B/L
Pyrrolin-2-ones, (n=0)	**16**		**17**	
x NH	161 B/L	151-152 B	164-165 E	207-208 L
y NMe	124-125 E	153-154 B/L	169-170 C	144 C
	18			
x NH	159 E	222-223 B/L		
y NMe	103-104 L	-[e]		

(a). A, AcOEt; B, Benzene; C, Cyclohexane; E, Ethanol; L, Ligroin; I, Isopropylether; M, Methanol; P, Petrol Ether; T, Toluene; W, Water. (b). Not isolated in pure form. On crystallization it accumulates in the mother liquors of the major adduct **13M**. (c). ref. [14] mp 94-96 °C. (d) ref. [14] mp 118-119 °C. (e). Inseparable from **16My**. On crystallization it accumulates in the mother liquors.

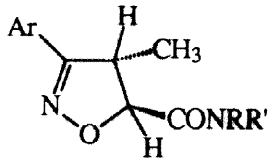
afforded the pure adduct **16My** while **18My** concentrates in the mother liquors of crystallization.

Cycloaddition of MNO to methyl cinnamate. A solution of mesitonitrile oxide (1.6 g, 10 mmol) and methyl cinnamate (2.4 g, 15 mol) in anhydrous benzene (100 ml) was kept at r.t. for 3 weeks. After removal of the solvent, the mixture was separated by column chromatography affording, besides methyl cinnamate, methyl

Table 6. Spectroscopic data of adducts to crotonamides **10** and **11**.



10

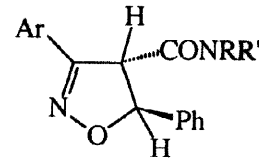


11

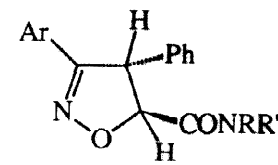
NRR'	H_5	H_4	CH_3[a]	J_{4-5}	Other	$\nu_{C=O}$ (ν_{NH})
Regioisomer 10B, Ar = Ph						
a NH_2[b]	4.80 dq	4.15 d	1.35	7.2	7.3, 7.95 bs (NH_2)	1665 (3420,3180)
b NHMe	4.95 dq	3.95 d	1.40	4.0	5.7 b (NH),2.75 d (MeN)[c]	1645 (3310)
e NMe_2	4.95 dq	4.40 d	1.55	7.0	3.2, 3.0 s (Me_2N)	1640
d NEt_2	4.90 dq	4.30 d	1.52	7.2		1631
e Piperidino	4.90 dq	4.40 d	1.50	7.0		1630
f Morpholino	4.95 dq	4.35 d	1.50	7.5		1640
g Pyrrolidino	4.95 dq	4.25 d	1.50	7.2		1640
Regioisomers 10M, Ar = Mes						
a NH_2[b]	4.90 dq	3.9 d	1.40	8.3	7. 0, 7.45 bs (NH_2)	1695 (3350,3160)
b NHMe	5.30 dq	3.70 d	1.50	7.5	5.1 b (NH),2.68 d (MeN)[c]	1670(3390)
e NMe_2	5.35 dq	4.18 d	1.45	7.0	2.45, 2.85 s (Me_2N)	1640
d NEt_2	5.35 dq	4.10 d	1.48	7.5		1640
e Piperidino	5.41 dq	4.18 d	1.47	7.2		1640
f Morpholino	5.45 dq	4.10 d	1.52	7.5		1650
g Pyrrolidino	5.38 dq	4.01 d	1.48	7.0		1645
Regioisomers 11B, Ar = Ph						
a NH_2[b]	4.65 d	4.05 dq	1.25	4.2	7.4, 7.6 bs (NH_2)	1665 (3420,3180)
b NHMe	4.70 d	4.10 dq	1.45	3.5	6.75 b (NH),2.8 d (MeN)[c]	1655 (3310)
e NMe_2	4.95 d	4.60 dq	1.35	5.1	3.2, 3.0 s (Me_2N)	1650
d NEt_2	4.90 d	4.60 dq	1.35	5.5		1640
e Piperidino	4.95 d	4.60 dq	1.35	5.5		1640
f Morpholino	4.91 d	4.60 dq	1.35	5.6		1645
g Pyrrolidino	4.85 d	4.50 dq	1.35	4.9		1650
Regioisomers 11M, Ar = Mes						
a NH_2[b]	4.65 d	3.70 dq	1.15	6.0	7.45, 7.65 bs (NH_2)	1695 (3420,3190)
b NHMe	4.65d	3.75 dq	1.25	4.5	6.7 b (NH),2.85 (MeN)[c]	1658 (3328)
e NMe_2	4.90 d	4.40 dq	1.15	7.5	3.25, 3.05 s (Me_2N)	1640
d NEt_2	4.85 d	4.35 dq	1.15	7.5		1640
e Piperidino	4.85 d	4.40 dq	1.12	8.2		1650
f Morpholino	4.87 d	4.41 dq	1.17	8.0		1650
g Pyrrolidino	4.80 d	4.32 dq	1.15	7.0		1645

(a). Doublet, $J_{5\text{-}Me}$ ~6-6.5 Hz in regioisomer **10**, ~7-7.5 Hz in **11**. (b). DMSO. (c) J_{NHMe} = 5 Hz.

Table 7. Spectroscopic data of adducts to cinnamamides **12** and **13**.



12



13

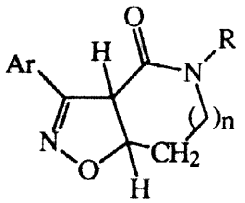
NRR'	H_5	H_4	J_{4-5}	Other	$\nu_{C=O}$ (ν_{NH})
Regioisomers **12B**, Ar = Ph					
a NH_2[a]	5.74 d	4.59 d	7.2	8.0, 7.4 bs (NH_2)	1671 (3406,3170)
b NHMe	5.92 d	4.29 d	4.5	5.3 b (NH),2.82 d (MeN)[b]	1646 (3257)
c NMe_2	5.72 d	4.78 d	8.5	2.95, 3.13 s (Me_2N)	1647
d NEt_2	5.71 d	4.63 d	9.0		1627
e Piperidino	5.70 d	4.78 d	8.3		1630
Regioisomers **12M**, Ar = Mes					
a NH_2	6.25 d	4.15 d	7.5	5.0; 5.25 bs (NH_2)	1648 (3413,3187)
b NHMe	6.25 d	4.01 d	8.2	5.0 bs (NH), 2.7 (MeN)[b]	1645 (3314)
c NMe_2	6.35 d	4.55 d	8.5	2.95 s (Me_2N)	c
d NEt_2	6.25 d	4.45 d	8.5		c
e Piperidino	6.35 d	4.55 d	7.9		1645
Regioisomers **13B**, Ar = Ph					
a NH_2[a]	5.15 d	4.88 d	3.2	5.6, 6.8 bs (NH_2)	1680 (3450, 3150)
b NHMe	5.15 d	4.88 d	3.5	6.85 b (NH),2.88 d (MeN)[b]	1674(3372)
c NMe_2	5.68 d	5.15 d	5.5	3.0, 3.15 s (Me_2N)	1664
d NEt_2	5.68 d	5.12 d	5.2		1645
e Piperidino	5.70 d	5.15 d	5.8		1645
Regioisomers **13M**, Ar = Mes					
a NH_2	5.25 d	4.85 d	3.2	5.6, 7.0 bs (NH_2)	1671 (3430,3170)
b NHMe	5.25 d	4.80 d	2.9	7.05 b (NH), 2.95 d (MeN)[b]	1655 (3398)
c NMe_2	5.52 d	5.48 d	5.2	3.05, 3.28 s (Me_2N)	1655
d NEt_2	5.52 d	5.45 d	5.2		1633
e Piperidino	5.55 d	5.45 d	5.8		1655

(a). DMSO. (b).J_{NHMe}= 5Hz. (c).Not isolated in pure form.

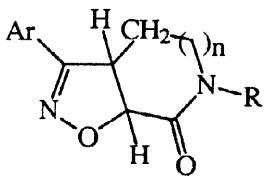
3-(2,4,6-trimethylphenyl)-5-phenyl-2-isoxazoline-4-carboxylate, 1.48 g (46%), mp 129 °C from methanol (lit. [1], 124-126 °C) and methyl 3-(2,4,6-trimethylphenyl)-4-phenyl-2-isoxazoline-5-carboxylate, 1.36 g (42%), mp 125 °C from ethanol/water (found C, 74.19; H, 6.58; N, 4.23%; $C_{20}H_{21}NO_3$ requires: C, 74.28; H, 6.55; N, 4.33%).

Acknowledgements: Financial support by CNR and MURST is gratefully acknowledged.

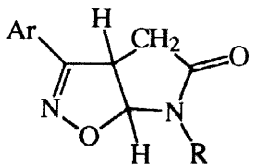
Table 8. Spectroscopic data of adducts to α,β-unsaturated lactams **14-18**.



14,16



15,17



18

Ar	R	H-5	H-4	$J_{4,5}$	CH_2	$J_{5(4)\text{-}CH2}$	Other	$\nu_{C=O}$ (ν_{NH})
Dihydropyridin-2-ones, n = 1								
Regioisomers **14**								
C_6H_5	H	5.18 dt	4.52 d	10.2	2.1 m	3.2	6.5 b (NH)	1663 (3210)
C_6H_5	CH_3	5.11 dt	4.51 d	10.0	2.1 m	3.0	2.95 s (NCH_3)	1640
Mes	H	5.18 dt	4.27 d	10.5	2.1 m	3.5	6.4 b (NH)	1670 (3200)
Mes	CH_3	5.14 dt	4.30 d	10.8	2.1 m	3.2	2.94 s (NCH_3)	1653
Regioisomers **15**								
C_6H_5	CH_3	5.01 d	4.09 dt	10.0	2.0 m	6.3	3.03 s (NCH_3)	1660
Mes	CH_3	5.02 d	3.90 dt	10.0	1.9 m	6.5	3.10 s (NCH_3)	1658
Pyrrolin-2-ones, n = 0								
Regioisomers **16**								
C_6H_5	H	5.52 ddd	4.41 d	9.2	3.8 m	6.0; 1.5	6.3 b (NH)	1704 (3204)
C_6H_5	CH_3	5.53 ddd	4.45 d	9.3	3.8 m	6.0; 1.2	2.85 s (NCH_3)	1691
Mes	H	5.52 ddd	4.20 d	9.5	3.7 m	6.2; 1.8	6.5 b (NH)	1700 (3200)
Mes	CH_3	5.45 ddd	4.25 d	9.5	3.8 m	6.2; 1.8	2.89 s (NCH_3)	1697
Regioisomers **17**								
C_6H_5	H	5.25 d	4.55 ddd	10	3.7 m	8.0; 1.5	6.4 b (NH)	1680 (3250)
C_6H_5	CH_3	5.35 d	4.45 ddd	10.2	3.7 m	8.0; 2.1	2.9 s (NCH_3)	1682
Mes	H	5.25 d	4.3 ddd	9.5	3.4 m	7.5; 1.2	6.05 b (NH)	1702 (3200)
Mes	CH_3	5.28 d	4.22 ddd	9.5	3.4 m	7.5; 1.2	2.9 s (NCH_3)	1702
Adducts **18**								
C_6H_5	H	6.12 d	4.45 ddd	7.8	2.7 m	10.2; 2.8	6.7 b (NH)	1694 (3180)
C_6H_5	CH_3	5.95 d	4.25 ddd	7.8	2.8 m	10.0; 2.5	3.0 s (NCH_3)	1691
Mes	H	6.15 d	4.2 ddd	7.0	2.4 m	10.0; 2.0	6.25 b (NH)	1681 (3223)
Mes	CH_3	5.95 d	4.12 ddd	7.1	2.4 m	9.5; 1.8	3.0 s (NCH_3)	1691

Table 9: Analytical data of cycloadducts **10-17**.

		Calc, %			Found, %			Found, %		
		C	H	N	C	H	N	C	H	N
Crotonamides					**10-B**			**11-B**		
a	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.62	5.84	13.66	64.78	5.99	13.49
b	$C_{12}H_{14}N_2O_2$	66.03	6.47	12.84	65.91	6.49	12.88	66.12	6.40	12.96
c	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.26	6.80	12.17	67.34	7.05	12.01
d	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76	69.11	7.99	10.72	69.14	7.65	10.85
e	$C_{16}H_{20}N_2O_2$	70.56	7.40	10.29	70.61	7.46	10.21	70.54	7.47	10.38
f	$C_{15}H_{18}N_2O_3$	65.67	6.61	10.21	65.69	6.53	10.13	65.73	6.54	10.32
g	$C_{15}H_{18}N_2O_2$	69.74	7.02	10.85	69.66	7.12	10.91	69.75	7.15	10.97
					10-M			**11-M**		
a	$C_{14}H_{18}N_2O_2$	68.27	7.37	11.37	68.29	7.46	11.31	68.12	7.45	11.39
b	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76	69.21	7.86	10.70	69.18	7.58	10.76
c	$C_{16}H_{22}N_2O_2$	70.04	8.08	10.21	70.05	8.18	10.30	70.09	7.97	10.20
d	$C_{18}H_{26}N_2O_2$	71.49	8.67	9.26	71.54	8.78	9.26	71.55	8.64	9.29
e	$C_{19}H_{26}N_2O_2$	72.58	8.34	8.91	72.65	8.38	9.01	72.48	8.43	8.88
f	$C_{18}H_{24}N_2O_3$	68.33	7.65	8.85	68.23	7.66	8.79	68.36	7.65	8.97
g	$C_{18}H_{24}N_2O_2$	71.97	8.05	9.33	71.89	7.99	9.37	71.84	8.01	9.23
Cinnamamides					**12-B**			**13-B**		
a	$C_{16}H_{14}N_2O_2$	72.16	5.30	10.52	72.09	5.33	10.34	72.06	5.34	10.56
b	$C_{17}H_{16}N_2O_2$	72.84	5.75	9.99	72.75	5.77	9.92	72.78	5.65	10.02
c	$C_{18}H_{18}N_2O_2$	73.45	6.16	9.52	73.34	6.11	9.65	73.47	6.03	9.43
e	$C_{21}H_{22}N_2O_2$	75.42	6.63	8.38	75.34	6.55	8.32	75.51	6.76	8.40
					12-M			**13-M**		
a	$C_{19}H_{20}N_2O_2$	74.00	6.54	9.09	73.87	6.58	9.18	74.10	6.55	9.16
b	$C_{20}H_{22}N_2O_2$	74.51	6.88	8.69	74.44	6.77	8.63	74.56	6.94	8.77
c	$C_{21}H_{24}N_2O_2$	74.97	7.19	8.33				75.01	7.24	8.30
d	$C_{23}H_{28}N_2O_2$	75.79	7.74	7.69				75.88	7.77	7.61
e	$C_{24}H_{28}N_2O_2$	76.56	7.50	7.44	76.55	7.57	7.32	76.51	7.48	7.49
Dihydropyridin-2-ones					**14-B**			**15-B**		
x	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.96	66.55	5.53	12.90			
y	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	67.86	6.23	12.21	67.77	6.19	12.11
					14-M			**15-M**		
x	$C_{15}H_{18}N_2O_2$	69.74	7.02	10.85	69.68	7.05	10.90			
y	$C_{16}H_{20}N_2O_2$	70.56	7.40	10.29	70.51	7.47	10.25	70.49	7.35	10.32
Pirrolin-2-ones					**16-B**			**17-B**		
x	$C_{11}H_{10}N_2O_2$	65.33	4.98	13.86	65.39	4.95	13.81	65.41	4.96	13.80
y	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.96	66.75	5.63	12.89	66.59	5.55	12.90
					16-M			**17-M**		
x	$C_{14}H_{16}N_2O_2$	68.83	6.60	13.10	68.91	6.58	13.15	68.78	6.61	13.13
y	$C_{15}H_{18}N_2O_2$	69.74	7.02	10.85	69.80	7.07	10.80	69.70	7.05	10.91

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