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STERIC EFFECTS ON REGIOSELECTIVITY IN 1.3-DIPOLAR CYCLOADDITION OF C,N-DIALKYL NITRONES WITH ACCEPTOR-SUBSTITUTED ALKYNES

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Abstract: The 1.3 dipolar cycloaddition of alkynes **4-6** with acyclic nitrones **1-3**, **23** and **24** as well as with cyclic nitrones **27** is studied. As was found for the reaction of the aldonitrones **1-3** an increased portion of 5-regioisomers is formed with increasing steric demand of either of the two substituents, the C-alkyl substituent R^2 and the N-alkyl substituent R^1. Thus the conclusion is drawn that cycloaddition of **1-3** proceeds not only via transition states arising from Z-nitrones but also via transition states developing from E-nitrones, although in the ground-state the Z-isomer is favored to a considerable extent. In this context steric destabilization of the transition states is discussed qualitatively.

INTRODUCTION

In the 1.3-dipolar cycloaddition of nitrones with asymmetrically substituted alkenes or alkynes regioisomers can be formed[1]. The regioselectivity of this reaction is affected by several factors as is discussed in a number of recent publications[1,2,3]. In spite of the complexity of the factors the regioselectivity of this reaction is in accord with predictions based on the simple Frontier Molecular Orbital method (FMO) in many cases. This is true, in particular, if the cycloaddition of a number of related nitrones with the same dipolarophile or of related dipolarophiles with the same nitrone is considered[4]. In general, it can be stated that related to a given pair of nitrone and dipolarophile, formation of 4-substituted cycloadducts is increased by making either the nitrone more electron-rich or the dipolarophile more electron-deficient. In contrast, an increased portion of 5-substituted cycloadducts will be formed with more electron deficient nitrones or more electron-rich dipolarophiles.

However, these electronic effects can be modified by steric effects[5]. The goal of our work was to study such steric effects in cycloadditions of various C,N-dialkyl-substituted nitrones with acceptor-substituted alkynes[6].

Since it is assumed that acyclic nitrones can react either as Z-isomers or as E-isomers[1,7] we were anxious to study in particular this aspect. For comparison cycloadditions of cyclic nitrones were included in our program. Finally, we calculated the differences of the ground state energies between the Z-isomer and the E-isomer of some nitrones to get a more qualitative idea of the energy differences of the transition states derived from the Z-nitrones and the E-nitrones.

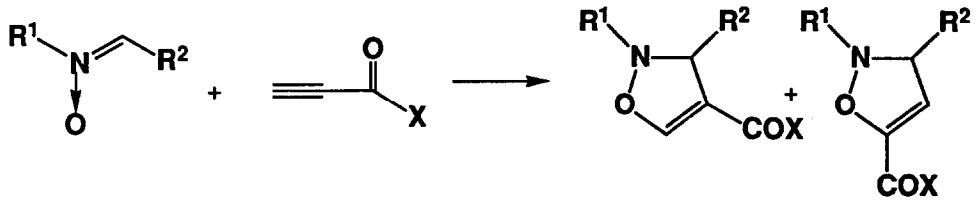
RESULTS

A. Aldonitrones

Reaction of nitrones **1-3** with alkynes **4-6** in diethyl ether or dichloromethane at room temperature afforded generally mixtures of the 4-regioisomers **7-14** and the 5-regioisomers **15-22**, respectively. Only

nitrone **3c** yielded the 5-substituted cycloadducts **17c** and **22c** without formation of the corresponding 4-isomers. No change in the ratio of the regioisomers was observed over a longer period of time in solution.

The compounds decomposed on the attempt of chromatographic separation as well as on storage without solvent[8,9]. Thus the mixtures of the regioisomers were characterized by their ^1H and ^{13}C NMR spectra. The product ratios 4-regioisomer/5-regioisomer estimated from the integrals of the ^1H NMR signals are given in Table 1.



1 - 3 **4 - 6** **7 - 14** **15 - 22**

	R^1
1	Me
2	i-Pr
3	t-Bu

	X
4	OMe
5	O tBu
6	Me

	R^2
a	Et
b	i-Pr
c	t-Bu
d	Me

	R^1	X	
7, 15	Me	OMe	a, b, c
8, 16	i-Pr	OMe	a, b, c
9, 17	t-Bu	OMe	a, b, c [a], d
10, 18	Me	O tBu	b
11, 19	t-Bu	O tBu	b
12, 20	Me	Me	b, c
13, 21	i-Pr	Me	b, c
14, 22	t-Bu	Me	b, c [b]

a) **9c** was not formed

b) **14c** was not formed

The ^1H NMR spectra of the 4-substituted 4-isoxazolines **7-14** show characteristic singlet signals at 7.3-7.5 ppm (5-H), whereas for the 5-substituted 4-isoxazolines **15-22** doublet signals at 5.6-5.8 ppm (J = 2.9-3.2 Hz) (4-H) were observed.

Table 1. Product ratios 4-regioisomer/5-regioisomer

	R^2	7/15	8/16	9/17[a)]	10/18	11/19	12/20	13/21	14/22
a	Et	9:1	1:1	1:2.3	-	-	-	-	-
b	iPr	1.9:1	1:2	1:4	2:1	1:11	1:2	1:4	1:4
c	tBu	1:1.3	1:2.5	only **17**	-	-	1:5	1:13	only **22**
d	Me	-	-	1:1.5	-	-	-	-	-

a) **9/17** for R^2 = H: 1:2.3 (ref.[10])

The ^{13}C NMR spectra reveal the following characteristic signals:

Compounds **7-11**: 106.1-108.8 ppm (s, C-4); 151.7-154.4 ppm (d, J = 190-195 Hz, C-5).
12-14: 118.2-120.3 ppm (s, C-4); 153.8-155.5 ppm (d, J = 190-195 Hz, C-5).
15-19: 107.3-110.5 ppm (d, J = 168-182 Hz, C-4); 142.1-147.5 ppm (s, C-5).
20-22: 106.7-108.5 ppm (d, J = 168-180 Hz, C-4); 151.0-153.5 ppm (s, C-5).

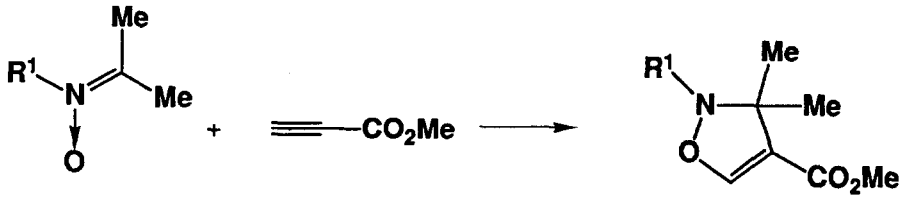
Reaction of 0.1 mol of nitrone **1b** and 0.1 mol of nitrone **3b** with 0.1 mol of methyl propiolate **4** was performed as a competition experiment. The corresponding cycloadducts were formed in the ratio as follows: **7b**:**15b**:**9b**:**17b** = 13:7:2:8. That means the 4-substituted 2-methyl-4-isoxazoline **7b** was formed approximately 6.5 times as fast as the corresponding 2-tert-butyl compound **9b**, whereas the formation of the 5-substituted 4-isoxazolines **15b** and **17b** occurs with the same rate at first approximation.
In Table 2 the energy differences between the Z-isomers and the E-isomers of various nitrones calculated by MNDO are given. Whereas for the N-methylnitrone **1a** the energy gap is rather small, the differences for the N-tert butylnitrones **3** are much higher.

Table 2. MNDO-Calculations of the energy differences between Z- and E-isomers of nitrones in kcal/mol.

	R^2	1(R^1=Me)	2(R^1=iPr)	3(R^1=tBu)
a	Et	1.83	2.80	7.19
c	tBu	4.89	5.29	17.67

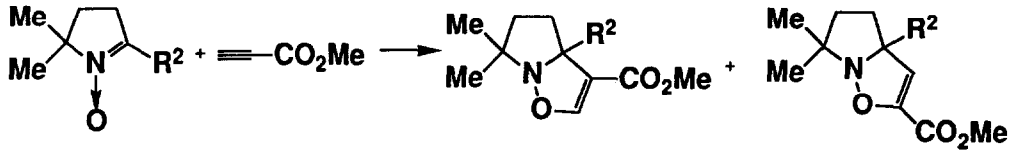
B. Ketonitrones

Reaction of ketonitrones **23** and **24** with methyl propiolate **4** afforded in either case only the 4-substituted 4-isoxazolines **25** and **26**, respectively. Likewise, only **28a** is formed from the reaction of **4**



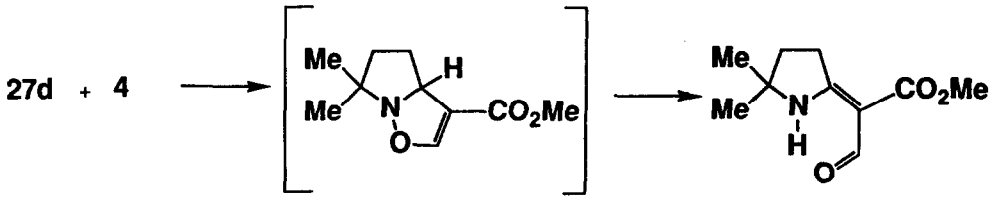
23,24 **4** **25,26**

	R^1
23,25	Me
24,26	i-Pr



27 **4** **28** **29**

	R^2	**28 : 29**
a	Me	only **28**
b	i-Pr	**3 : 1**
c	t-Bu	**1 : 2**
d	H	see text



27d + 4 **28d** **30**

with the cyclic ketonitrone **27a**. In contrast with **27a**, nitrones **27b** and **27c** yielded mixtures of both of the regioisomers **28b** and **29b** or **28c** and **29c**, respectively, the portion of **29c** being increased relative to **29b**. Reaction of **27d**, however, furnished solely compound **30**, which is obviously formed by rearrangement of the unstable product **28d**[11].

DISCUSSION

Since within the series of the aldonitrones **1-3** on one hand, and of the ketonitrones **23**, **24** and **27** on the other hand, the changes in electronic effects should be small, differences in the ratio of the regioisomers should reflect steric effects[12].

A. Steric effect of substituent R^2

a. Ketonitrones. Ketonitrones are relatively electron-rich, thus in cycloaddition with the electron-poor propiolates the HOMO (nitrone) - LUMO (propiolate) interaction is so strongly dominant that the electronic effects clearly favor the formation of 4-substituted regioisomers. For this reason only the 4-regioisomers **25**, **26** and **28** are formed in the reaction of **4** with nitrones **23**, **24** and **27a** (R^2 = Me), respectively. Steric effects by larger substituents R^2 at the α carbon atom, however, should favor formation of the 5-substituted 4-isoxazolines, because in the transition states (TS) of the reactions leading to the 4-regioisomers destabilization due to the steric interaction between the CR^2 moiety and the CO_2Me group would be much stronger compared to the interaction between H and CO_2R in the TS for the 5-regioisomers. On the other hand, destabilization by corresponding interactions with the oxygen atom of the nitrone should be neglectibly small.

In fact, increasing size of substituent R^2 in **27b** (R^2 = iPr) and **27c** (R^2 = tBu) leads to competitive formation of the 5-regioisomers **29b** and **29c**, respectively. When R^2 is tert-butyl the steric effect even overcomes the electronic effect, thus the 5-regioisomer is formed as main product. Clearly, these results reflect the influence of the steric effect of alkyl substituents at the α-position of the nitrone on the nitrone alkyne cycloaddition.

b. Aldonitrones. This steric effect is also observed in the reation of aldonitrones **1-3** with propiolate **4** and with 3-butyn-2-one **6** on changing substituent R^2 from ethyl (**a**) via isopropyl (**b**) to tert-butyl (**c**) or from isopropyl to tert-butyl, respectively. In every case the portion of the 5-regioisomer rises with increasing steric demand of substituent R^2.

Since aldonitrones are less electron-rich than ketonitrones the HOMO(nitrone)-LUMO(alkyne) interaction, favoring formation of 4-substituted products, is decreased. Thus the portion of the 5-regioisomer is considerably higher in the cycloadduct pairs **9b/17b** and **9c/17c** compared to **28b/29b** and **28c/29c**, respectively[13].

B. Steric effect of substituent R^1

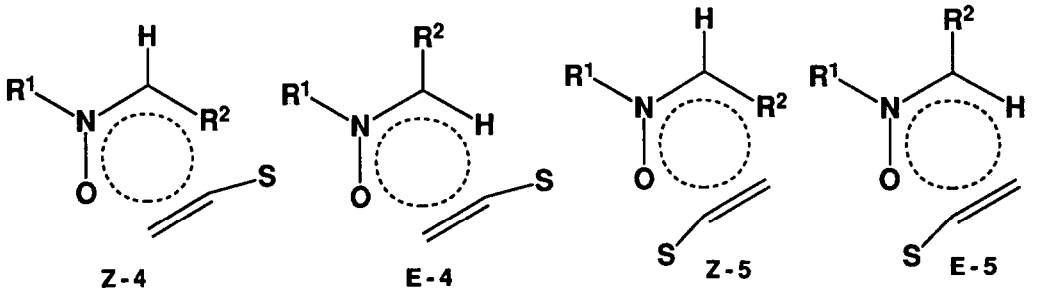
As already mentioned the electronic effects should not change very much, if the N-alkyl substituent R^1 is changed as in the series of nitrones **1** to **3**. Consequently, the changes in product ratios found for the reactions of nitrones **1** (R^1 = Me), **2** (R^1 = iPr) and **3** (R^1 = tBu) with the dipolarophiles must be of different origin.

a. Z- and E-nitrones - the Curtin-Hammett Principle. In principle, nitrones can exist either as Z-isomers or as E-isomers[14]. In cycloaddition with mono-substituted alkynes both isomers would afford the same products, either the 4-substituted or the 5-substituted 4-isoxazolines, depending only on the direction of alkyne approach.

In fact, E-aldonitrones are far less stable then Z-aldonitrones (see Table 2). Thus with a very few exceptions the portion of E-isomers in equilibrium with Z-isomers is so small that it cannot be detected by NMR spectroscopy[14]. Nevertheless, cycloaddition via E-isomers must be considered for the following reason.

In contrast to C-arylnitrones C-alkylnitrones with primary or secondary alkyl substituents R^2 at the α-carbon atom can form N-hydroxy-enamine tautomers[15] and hence facile isomerization of Z- and E-isomers via these tautomers should be possible. If, however, the interconversion of the isomers is fast compared to the following reaction steps, according to the Curtin-Hammett Principle the position of the equilibrium between Z- and E-nitrone does not play any role for the reaction rate[16]. That means the crucial point for the product ratio of the kinetically-controlled reaction is only the relative height of the transition states derived from the Z- and the E-isomer.

For this reason the four transition states Z-4, E-4, Z-5 and E-5 arising from the Z- and the E-nitrone by attack of the alkyne to give either the 4- or the 5-substituted 4-isoxazoline, respectively, must be considered. As a consequence, the *4-substituted cycloadduct will be formed preferentically if one of the two transition-states Z-4 or E-4 is lower in energy than Z-5 and E-5, and vice versa.* Therefore, the ratio of the two regioisomeric products depends on the electronic effect as well as on the sum of the steric destabilization interactions at the Z-side and the E-side of the individual transition states.



b. Steric interactions in the transition states. To substantiate the importance of the steric interactions in the transition states for the regioselectivity of the nitrone-alkyne cycloaddition the following points are emphasized.

1. In the reaction of **1a** (R^1 = Me, R^2 = Et) with **4** transition state **E-4** is obviously the most favorable one, due to better electronic stabilization compared to **Z-5** and **E-5** and smaller steric destabilization compared to **Z-4** (**E-4**: Z-side: H - CO_2Me, E-side: Me - Et. - **Z-4**: Z-side: Et - CO_2Me, E-side: Me - H).

The relative small steric interaction between methyl and ethyl group is also reflected by the small difference for the ground state energies of the Z- and E-isomers of nitrone **1a** (see Table 2).

2. For reaction of **3a** (R^1 = tBu, R^2 = Et) with **4** transition states **E-4** and **E-5** are unfavorable due to the increased steric interaction on the E-side (tBu - Et, compare also the differences for the ground-state energies of Z- and E-isomer of **3a** in Table 2). As a result of the destabilization of **Z-4** by the steric interaction at the Z-side (Et - CO_2Me) **Z-5** is the one of lowest energy. Thus the electronic effect which would favour the formation of the 4-regioisomer is overcome by the steric effect.
3. Since for reaction of **4** with **1a** and **3a** the steric interactions in the transition state **Z-4** do not differ much (E-side: Me - H vs. tBu - H), the different outcome of the reactions confirms that **1a** reacts mainly via transition state **E-4**.
4. The result that formation of **7b** (from **1b** and **4**, R^1 = Me) takes place about 6.5 times faster than formation of **9b** (from **3b** and **4**, R^1 = tBu) is in accord with a preferred reaction path via transition-state **E-4** for **1b**, in contrast to **3b**, which mainly reacts via **Z-4**. On the other hand, the 5-substituted products **15b** and **17b**, assumed to arise via **Z-5**, are formed with approximately the same rate.
5. Reaction via transition states **E-4** and **Z-5** seems to be the reason that with **1b** (R^1 = Me) the produced ratio (**7b/15b** and **10b/18b**) is nearly unchanged when instead of methyl propiolate **4** tert-butyl propiolate **5** is used as dipolarophile. In contrast, with **3b** (R^1 = t-Bu) reacting mainly via **Z-4** and **Z-5** the portion of the 4-isomer **11b** is clearly diminished with tert-butyl propiolate **5**.
6. Due to a stronger steric effect of the COMe group in 3-butyn-2-one **6** compared to the COOMe group in methyl propiolate **4** the portion of the 4-substituted products is diminished in the cycloadducts with 3-butyn-2-one. Thus it is indicated that in this particular case the effect caused by the change of steric interactions is stronger than the effect caused by the change in electronic conditions, because the latter should operate in the opposite direction due to the lower lying LUMO.
7. In general, with increasing steric interactions between R^1 and R^2 the Z-transition states, in particular **Z-5**, become more favorable, with the result that an increased portion of 5-substituted cycloadduct is formed. An extreme situation arises for **3c** (R^1 = R^2 = tBu) which yields only 5-substituted products.

EXPERIMENTAL PART

Elemental analyses were performed by the division Routine-Analytik, Fachbereich Chemie, University of Marburg.- Spectra were recorded with following instruments: NMR: Bruker AC 300. ^1H NMR 300 MHz, ^{13}C NMR 75 MHz. Solvent $CDCl_3$ with tetramethylsilane as internal standard, if not otherwise quoted. - MS: Varian CH7 (EI) and 711 (FD). - IR: Beckman IR-33 and Bruker IFS 88.

The MNDO calculations (Table 2) were carried out using the program version SCAMP[25], a modified scalar MOPAC package.

A. *Preparation of the nitrones*

A mixture of 0.005 mol of N-alkylhydroxylamine, 0.005 mol of aldehyde and 5 g of $MgSO_4$ in 60 ml chloroform was stirred for

12 h at room temperature. After filtration the solution was evaporated to afford the nitrone.

N-Methyl-(2-methylpropylidene)amine N-oxide **(1b)**: Colourless oil in 90% yield. MS (FD): m/e = 101 (100%, M^+). ^1H NMR:δ = 0.8 (dd, 7.8 and 2.8 Hz, 6H), 2.8 (m, 1H), 3.4 (s, 3H), 6.3 (d, 7.8 Hz, 1H). - ^{13}C NMR ($CDCl_3$): δ = 19.6 (2q, iPr), 23.0 (d, iPr), 52.3 (q, Me), 146.3 (d, CH=N).

N-Methyl-(2.2-dimethylpropylidene)amine N-oxide **(1c)**: Light yellow oil in 73% yield. MS (FD): m/e = 115 (100%, M^+). ^1H NMR: δ = 0.88 (s, tBu), 3.40 (s, Me), 6.23 (s, CH=N). - ^{13}C NMR: δ = 25.9 (q, tBu), 32.6 (s, tBu), 53.6(q, Me), 146.3 (d, CH=N).

N-Isopropyl-(2-methylpropylidene)amine N-oxide **(2b)**: Yellow oil in 80% yield. MS (EI): m/e = 129 (13%, M^+). ^1H NMR: δ = 0.90 (d, 4.4Hz, iPr), 1.20 (d, 4.4 Hz, iPr), 2.99 (m, 4.4 Hz, iPr), 3.81 (m, 4.4 Hz, iPr), 6.41.(d, 7.0 Hz, CHN). - ^{13}C NMR: δ = 18.7 (q, iPr), 20.4 (q, iPr), 25.4 (d, iPr), 65.8 (d, iPr), 142.1 (d, CH=N).

N-Isopropyl-(2.2-dimethylpropylidene)amine N-oxide **(2c)**: Light yellow oil in 75% yield. MS (EI): m/e = 143 (2.5%, M^+). ^1H NMR: δ = 1.19 (s, tBu), 1.30 (d, 6.5 Hz, iPr), 3.90 (sept, 6.5 Hz, iPr), 6.44 s, CH=N). - ^{13}C NMR: δ = 20.9 (q, tBu), 26.2 (q, iPr), 32.5 (s, tBu), 67.0 (d, iPr), 142.0 (d, CH=N).

N-tert-Butyl-(2.2-dimethylpropylidene)amine N-oxide **(3c)**: 6.0 g (0.07 Mol) of pivaldehyde, 4.45 g (0.05 mol) of N-tert-butylhydroxylamine and molecular sieves (2 g) were stirred at room temperature for 15 hours. The mixture was treated with 50 ml of dichlorodimethane, the molecular sieves were separated by filtration. After evaporation the colourless oil was dissolved in a small portion of n-hexane and stored at -18°C until crystallization occurred. Colourless crystals, 70% yield, m.p. 84°C.

$C_9H_{19}NO$ (157.3) Calcd C 68.74 H 12.18 N 8.90 Found C 68.54 H 12.43 N 8.80.- MS (FD): m/e = 157 (5.5%, M^+). - ^1H NMR: δ = 1.2 (s, tBu), 1.3 (s, tBu), 6.5 (s, CH=N). - ^{13}C NMR: δ = 26.2 (q, tBu), 28.3 (q, tBu), 32.5 (s, tBu), 69.6 (s, tBu), 139.7 (d, CH=N).

N-Isopropyl-(methylethylidene)amine N-oxide **(24)**: was prepared in analogy to the procedure described for **23**[17]. - ^1H NMR (C_6D_6): 1.17 (d, 6.6 Hz, iPr), 1.37 (s, Me), 1.93 (s, Me)[18], 3.9 (sept, 6.6 Hz, iPr).

5.5-Dimethyl-1-hydroxy-2-isopropylpyrrolidine: A solution of 5.5-dimethyl-1-pyrroline-1-oxide[19] (10 g, 0.09 mol) in 30 ml of anhydrous diethyl ether was added to an ethereal solution of an equimolar portion of isopropylmagnesium bromide. The mixture was heated under reflux for 30 minutes. After addition of an aqueous solution of ammonium chloride the ether layer was separated, dried over $MgSO_4$ and fractionally distillated to give the hydroxylamine. Colourless solid, 72% yield, m.p. 32-34°C.

$C_9H_{19}NO$ (157.3) Calcd C 68.74 H 12.18 N 8.90 Found C 67.33, H 11.86, N 8.64. - MS (EI): m/e = 157 (10%, M^+). - ^1H NMR: δ = 0.87 (d, 6.7 Hz, iPr), 0.94 (d, 6.1 Hz, iPr), 1.03 (s, Me), 1.16 (s, Me), 1.3-1.9 (m, 5H, $2CH_2$ + iPr), 2.82 (m, 2-H). - ^{13}C NMR: δ = 16.6 (q, iPr), 18.3 (q, iPr), 19.9 and 34.7 (2t,C-3 and C-4), 20.1 and 27.2 (2s, Me), 29.9 (d, iPr), 63.7 (s, C-5), 69.0 (d, C-2).

5.5-Dimethyl-2-isopropyl-1-pyrroline N-oxide **(27b)** was prepared by aerial oxidation of the hydroxylamine in aqueous ethanol containing copper acetate and ammonia. Colourless oil, 53% yield. MS (FD): m/e = 155 (100%, M^+). - ^1H NMR: δ = 1.02 (d, iPr), 1.32 (2s, Me), 1.89 (t, 7.4 Hz, 2H, 4-H), 2.46 (t, 7.4 Hz, 2H, 3-H), 3.22 (m, iPr). - ^{13}C NMR: δ = 17.6 (q, iPr), 23.5 (t, C-4), 24.8 (q, 2Me), 25.2 (d, iPr), 31.6 (t, C-3), 73.0 (s, C-5), 148.1 (s, C-2).

2-tert-Butyl-5.5-dimethyl-1-hydroxypyrrolidine was prepared as described for the 2-isopropyl compound. Colourless solid, 67% yield, m.p. 42°C. MS (EI): m/e = 171 (2.5%, M^+). - ^1H NMR: δ = 0.89 (s, tBu), 1.05 (s, Me), 1.13 (s, Me), 1.4-1.8 (m, 4H), 2.73 (dd, 7.4 and 5.1 Hz, 2-H). - ^{13}C NMR: δ = 18.2 (q, Me), 21.9 and 35.2 (2t, C-3 and C-4), 26.8 (q, tBu), 27.3 (q, Me), 33.9 (s, tBu), 64.4 (s, C-5), 72.5 (d, C-2).

2-tert-Butyl-5.5-dimethyl-1-pyrroline N-oxide **(27c)** was prepared as described for **27b**. Colourless solid, 65% yield m.p. 72°C.

$C_{10}H_{19}NO$ (169.3) Calcd C 70.96 H 11.32 N 8.27 Found C 70.80 H 11.13 N 8.27. - MS (FD): m/e = 169 (100%, M^+). - ^1H NMR: δ = 1.3 (s, tBu), 1.36 (s, 2Me), 1.92 (t, 7.5 Hz, 2H, 4-H), 2.61 (t, 7.5 Hz, 2H, 3-H). - ^{13}C NMR: δ = 25.1 (q, 2Me), 25.3 (q, tBu), 26.3 (t, C-4), 30.1 (t, C-3), 31.6 (s, tBu), 74.1 (s, C-5), 148.6 (s, C-2).

B. Formation of the cycloadducts[20]

Procedure A: To a solution of 0.01 mol of nitrone in 5 ml of anhydrous diethyl ether a solution of 0.01 mol of alkyne of ether (5 ml) was added at 0°C under an argon atmosphere. Then the solution was stirred at room temperature for 12 hours. After evaporation unreacted educts were removed under vacuum (0.1 Torr) at room temperature. Procedure B: To a solution of 0.005 mol of nitrone in 5 ml of dichlorodimethane a solution of 0.005 mol of alkyne was added in the same solvent at 10°C. The reaction mixture was stirred for 12 to 24 hours. (In some special cases reaction time was considerably longer.) Subsequently the solvent was removed and the residue was washed with 1.5 ml of cold ether and dried under vacuum.

3-Ethyl-4-methoxycarbonyl-2-methyl-4-isoxazoline (7a) and *3-ethyl-5-methoxycarbonyl-2-methyl-4-isoxazoline* (15a): Procedure A from **1a**[21] and **4**. Light yellow oil, 68% yield, product ratio 9:1. Decomposed within 2 days.

$C_8H_{13}NO_3$ (171.1) Calcd C 56.11 H 7.60 N 8.18 Found C 55.43 H 7.71 N 8.28. - MS (FD): m/e = 171 (100%, M^+). - IR (neat): 1720, 1650 cm^{-1}.

3-Isopropyl-4-methoxycarbonyl-2-methyl-4-isoxazoline (7b) and *3-isopropyl-5-methoxycarbonyl-2-methyl-4-isoxazoline* (15b): Procedure A from **1b** and **4**. Light yellow oil, 82% yield, product ratio 1.9:1.

$C_9H_{15}NO_3$ (185.2) Calcd C 58.36 H 8.16 N 7.56 Found C 57.60 H 7.27 N 7.42. - MS (EI): m/e = 185 (13%, M^+). - IR (neat): 1740-1700 cm^{-1}.

3-tert-Butyl-4-methoxycarbonyl-2-methyl-4-isoxazoline (7c) and *3-tert-butyl-5-methoxycarbonyl-2-methyl-4-isoxazoline* (15c): Procedure B from **1c** and **4**. Orange oil, 62% yield, product ratio 1:1.3. - MS(FD): m/e = 199 (100%, M^+),- IR (neat): 1740, 1625 cm^{-1}

3-Ethyl-2-isopropyl-4-methoxycarbonyl-4-isoxazoline (8a) and *3-ethyl-2-isopropyl-5-methoxycarbonyl-4-isoxazoline* (16a): Procedure A from **2a**[21] and **4**. Light yellow oil, 87% yield, product ratio 1:1. - MS (EI): m/e = 199 (24%, M^+). IR (neat): 1740, 1700, 1640 cm^{-1}.

2,3-Diisopropyl-4-methoxycarbonyl-4-isoxazoline (8b) and *2,3-diisopropyl-5-methoxycarbonyl-4-isoxazoline* (16b): Procedure B from **2b** and **4**, red oil, 65% yield, product ratio 1:2. MS (EI): m/e = 213 (1.5%, M^+). - IR (neat): 1740, 1700, 1650, 1640 cm^{-1}.

3-tert-Butyl-2-isopropyl-4-methoxycarbonyl-4-isoxazoline (8c) and *3-tert-butyl-2-isopropyl-5-methoxycarbonyl-4-isoxazoline* (16c): Procedure B from **2c** and **4**, red oil, 64% yield, product ratio 1:2.5. - MS (FD): m/e = 227 (33%, M^+). - IR (neat): 1750, 1640 cm^{-1}.

2-tert-Butyl-3-ethyl-4-methoxycarbonyl-4-isoxazoline (9a) and *2-tert-butyl-3-ethyl-5-methoxycarbonyl-4-isoxazoline* (17a): Procedure A from **3a**[21] and **4**, yellow oil, 70% yield, product ratio 1:2.3.- MS (FD): m/e = 213 (100%, M^+).- IR (neat): 1750, 1720, 1650 cm^{-1}.

2-tert-Butyl-3-isopropyl-4-methoxycarbonyl-4-isoxazoline (9b) and *2-tert-butyl-3-isopropyl-5-methoxycarbonyl-4-isoxazoline* (17b): Procedure A from **3b**[22] and **4**, yellow oil, 81% yield, product ratio 1:4. - MS (EI): m/e = 227 (26%, M^+).- IR (neat): 1740 (broad), 1630.

2,3-Di-tert-butyl-5-methoxycarbonyl-4-isoxazoline (17c): Procedure A from **3c** and **4**; reaction time 3 days, colourless solid, 69% yield, m.p. 63°C (from n-hexane).

$C_{13}H_{23}NO_3$ (241.3) Calcd C 64.64 H 9.67 N 5.80 Found C 64.33 H 9.76 N 5.76. - MS (EI): m/e = 241 (4%, M^+). - IR (KBr): 1740,1640 cm^{-1}.

2-tert-Butyl-3-methyl-4-methoxycarbonyl-4-isoxazoline (9d) and *2-tert-butyl-3-methyl-5-methoxycarbonyl-4-isoxazoline* (17d): Procedure A from **3d**[23] and **4**, yellow oil, 75% yield, product ratio: 1:1.5. - MS (EI): m/e = 199 (55%, M^+). - IR (neat): 1740, 1710, 1640 cm^{-1}.

4-tert-Butoxycarbonyl-3-isopropyl-2-methyl-isoxazoline (10b) and *5-tert-butoxycarbonyl-3-isopropyl-2-methyl-isoxazoline* (18b): Procedure B from **1b** and **5**, reaction time 5 days, red oil, 51% yield, product ratio 2:1.

4-tert-Butoxycarbonyl-2-tert-butyl-3-isopropyl-4-isoxazoline (11b) and *5-tert-butoxycarbonyl-2-tert-butyl-3-isopropyl-4-isoxazoline* (19b): Procedure B from **3b**[22] and **5**, reaction time 5 days, red oil, 45% yield, product ratio 1:11.

4-Acetyl-3-isopropyl-2-methyl-4-isoxazoline (12b) and *5-acetyl-3-isopropyl-2-methyl-4-isoxazoline* (20b): Procedure B from **1b** and **6**, red oil, 72% yield, product ratio 1:2. - MS (FD): m/e = 169 (2%, M^+). - IR (neat): 1700, 1690, 1630, 1620 cm^{-1}.

4-Acetyl-3-tert-butyl-2-methyl-4-isoxazoline (12c) and *5-acetyl-3-tert-butyl-2-methyl-4-isoxazoline* (20c): Procedure B from **1c** and **6**, red oil, 65% yield, product ratio 1:5. - MS (FD): m/e = 183 (31%, M^+). - IR (neat): 1715, 1630 cm^{-1}.

4-Acetyl-2,3-diisopropyl-4-isoxazoline (13b) and *5-acetyl-2,3-diisopropyl-4-isoxazoline* (21b): Procedure B from **2b** and **6**, red oil, 72% yield, product ratio 1:4. - MS (FD): m/e = 197 (36%, M^+). - IR (neat): 1710, 1700, 1630, 1620 cm^{-1}.

4-Acetyl-3-tert-butyl-2-isopropyl-4-isoxazoline (13c) and *5-acetyl-3-tert-butyl-2-isopropyl-4-isoxazoline* (21c): Procedure B from **2c** and **6**, red oil, 70% yield, product ratio 1:13. - MS (FD): m/e = 211 (41%, M^+). - IR (neat): 1695, 1620 cm^{-1}.

4-Acetyl-2-tert-butyl-3-isopropyl-4-isoxazoline (14b) and *5-acetyl-2-tert-butyl-3-isopropyl-4-isoxazoline* (22b): Procedure B from **3b**[22] and **6**, red oil, 71% yield, product ratio 1:14. - MS (EI): m/e = (11%, M^+). - IR (neat): 1690, 1630 cm^{-1}.

5-Acetyl-2,3-di-tert-butyl-4-isoxazoline (22c): Procedure B from **3c** and **6**, reaction time three days, orange-yellow oil. - MS (FD): m/e = 125 (11%, M^+). - IR (neat): 1695, 1640 cm^{-1}.

Table 3. ^{1}H NMR data of the 4-substituted 4-isoxazolines. Chemical shifts in ppm, solvent $CDCl_3$.

	3-H	5-H(s)	-CO-X(s)	R^1 a)			R^2 b)		
7a[c]	3.7 m	7.3	3.6	2.7			0.9		1.55
7b	3.75 d	7.4	3.72	2.8			0.85-0.95		2.0
7c	3.42 d[d]	7.29 d[d]	3.59	2.50			0.76		
8a[c]	4.01 m	7.4	3.65	1.1[f]		3.0	0.9		1.5
8b	4.02 m	7.39	3.71	1.09	1.13	3.18	0.83	1.08	1.96
8c	3.81 d[d]	7.44 d[d]	3.71	1.14		2.95	0.87		
9a[c]	4.2 m	7.4	3.7	1.0			0.8		1.4
9b[c]	4.05 m	7.4	3.62	1.0			0.8		1.8
9d	4.3 qd[d]	7.3 d[d]	3.62	1.05			1.2		
10b	3.69 dd[d]	7.25 d[d]	1.49	2.79			0.84	0.92	2.0
11b	4.06 dd[d]	7.31 d[d]	e)	e)			e)		e)
12b	3.61 d	7.27	2.07	2.56			0.56	0.68	1.82
12c	3.64 s	7.42	2.25	2.64			0.78		
13b	4.03 m	7.38	2.19	1.08		3.07	0.71	1.37	1.89
13c	e)	7.46 d[d]	2.22	e)			0.77		
14b	4.14 dd[d]	7.44 d[d]	2.17	0.98			0.71		e)
25	-	7.25	3.64	2.68			1.30[g]		
26	-	7.29	3.62	1.11		3.31	1.41[g]		
28a	-	7.3	3.6	h)			1.5		
28b	-	7.37	3.7	i)			0.89	0.94	1.9-2.3
28c	-	7.41	3.69	k)			0.92		

a) s (3H) for Me - 1d (6H) or 2d (3H) + m (1H) for iPr - s (9H) for tBu

b) t (3H) + m (2H) for Et (**a**) - 1d (6H) or 2d (3H) + m (1H) for iPr (**b**) - s (9H) for tBu (**c**) - d (3H) for Me (**d**)

c) in $CDCl_3/(CD_3)_2CO$

d) long range coupling between 3-H and 5-H: 0.7 - 1.5 Hz

e) the signal is too weak to be detected beside the signals of the 5-regioisomer

f) broadened

g) s (6H)

h) 1.13 + 1.18 (2s, Me), 1.6 (m, 2H), 1.82 (m, 1H), 2.2 (m, H)

i) 1.16 + 1.23 (2s, Me), 1.61 (t, 2H), 1.9 - 2.3 (m, 2H)

k) 1.10 + 1.25 (2s, Me), 1.40 - 2.30 (m, 4H)

4-Methoxycarbonyl-5,8,8-trimethyl-2-oxa-1-azabicyclo[3.3]octene-3 (**28a**): Procedure A from **27a**[24] and **4**, yellow oil, 95% yield. - MS(FD): m/e = 211 (100%, M^+). - IR (neat): 1710, 1640 cm^{-1}.

5-Isopropyl-4-methoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3.3]octene-3 (**28b**) and ***5-isopropyl-3-methoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3.3]octene-3*** (**29b**): Procedure A from **27b** and **4**, reaction time three days, yellow oil 98% yield, product ratio 3:1.

$C_{13}H_{21}NO_3$ (239.3) Calcd C 65.25 H 8.84 N 5.85 Found C 65.13 H 8.95 N 5.92. - MS (FD): m/e = 239 (100%, M^+). - IR (neat): 1710, 1630 cm^{-1}.

Table 4. ^{1}H NMR data of the 5-substituted 4-isoxazolines. Chemical shifts in ppm, solvent $CDCl_3$.

	3-H	4-H(d)	-CO-X(s)	R$^{1\,a)}$			R$^{2\,b)}$		
15a[c)]	d)	5.7	d)	d)			d)		
15b	3.50 dd	5.8	3.82	2.8[e)]			0.85-0.95		1.75
15c	3.29 d	5.65	3.68	2.67			0.77		
16a[c)]	4.01 m	5.8	3.75	1.1		3.0	0.9		1.5
16b	3.77 dd	5.77	3.80	1.09	1.12	3.02	0.90	0.91	1.69
16c	3.63 d	5.78	3.82	1.09		2.93	0.88		
17a[c)]	4.1 dt	5.8	3.8	1.1			0.9		1.5
17b[c)]	3.9 dd	5.7	3.7	1.1			0.85		1.55
17c	3.7 d	5.8	3.8	1.0			0.9		
17d[c)]	4.22 dq	5.7	3.7	1.05			1.3		
18b	3.47 dd	5.64	1.52	2.79			0.90	0.92	1.72
19b	3.93 dd	5.60	1.51	1.09			0.91	0.92	1.59
20b	3.32 dd	5.55	2.11	2.56			0.69	0.70	1.53
20c	3.36 d	5.64	2.26	2.70			0.82		
21b	3.69 dd	5.65	2.23	1.02	1.03	2.92	0.83	0.84	1.63
21c	3.57 d	5.67	2.25	1.02	1.06	2.79	0.81		
22b	3.90 dd	5.62	2.22	1.0			0.83		1.54
22c	3.69 dd	5.67	2.26	1.09			0.81		
29b	-	5.66	3.81	f)			0.89	0.94	1.9-2.3
29c	-	5.76	3.88	g)			0.92		

a) s (3H) for Me - 1d (6H) or 2d (3H) + m (1H) for iPr - s (9H) for tBu

b) t (3H) + m (2H) for Et (**a**) - 1d (6H) or 2d (3H) + m (1H) for iPr (**b**) - s (9H) for tBu (**c**)

c) in $CDCl_3/(CD_3)_2CO$

d) the signal is too weak to be detected beside the signals of the 4-regioisomer

e) broadened

f) 1.16 + 1.23 (2s, Me), 1.61 (t, 2H), 1.9 -2.3 (m, 2H)

g) 1.16 + 1.23 (2s, Me), 1.4 -2.3 (m, 4H)

5-t-Butyl-4-methoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3.3]octene-3 (**28c**) and ***5-butyl-3-methoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3.3]octene-3*** (**29c**): Procedure A from **27c** and **4**, reaction time seven days, brown oil, 58% yield, product ratio 1:2.

$C_{14}H_{23}NO_3$ (253.3) Calcd C 66.37 H 9.15 N 5.53 Found C 66.19 H 9.18 N 5.71. - MS (FD): m/e = 253 (19%, M^+). - IR (neat): 1750, 1620 cm^{-1}.

5,5-Dimethyl-2-[(-methoxycarbonyl-2-oxo-)ethylidene]pyrrolidine (**30**): Procedure A from **27d**[19], yellow solid, 27% yield, m.p. 95°C (from diethyl ether).

$C_{10}H_{15}NO_2$ (197.2) Calcd C 60.84 H 7.66 N 7.09 Found C 60.81 H 7.52 N 6.92. - MS (FD): m/e = 197 (63%, M^+). - IR (KBr): 3200, 2990, 1680, 1630 cm^{-1}. - ^{1}H NMR: δ = 1.4 (s, 2Me), 1.9 (t, 7.7 Hz, 2H, CH_2), 3.3 (t, 7.7 Hz, 2H, CH_2), 3.7 (s, OMe), 9.8 (s, CHO), 11.3 (s, broad, NH). - ^{13}C NMR: δ = 28.4 (q, 2Me), 34.2 (t, CH_2), 34.9 (t, CH_2), 50.6 (t, OMe), 63.8 (s, $\underline{C}(CH_3)_2$), 97.5 (s, =$\underline{C}$-CO, Me), 168.1 (s, N-C=), 172.9 (s, $\underline{C}O_2Me$), 189.7 (d, 176.8 Hz, CH=O).

Table 5. ^{13}C NMR data of the 4-substituted 4-isoxazolines[a]. Chemical shifts in ppm, solvent $CDCl_3$.

	C-3(d)	C-4(s)	C-5(d)	C=O(s)	CO-X[b]		R^1[c]			R^2[d]		
7a	71.5	108.7	152.3	164.3	50.9		47.7			9.3		27.0
7b	65.8	107.0	152.6	164.7	52.3		48.0			16.4-19.1		30.8
7c	78.4	106.1	153.6	165.4	51.2		48.0			25.7		36.1
8a	65.4	108.6	152.9	164.1	50.8		19.5		57.8	9.8		27.6
8b	69.4	107.9	153.5	164.5	51.0		19.1	19.6	58.5	15.9	17.6	31.1
8c	72.4	107.0	154.4	165.1	51.0		17.8	19.7	57.4	25.7		35.8
9a	62.2	108.8	153.3	164.3	50.9		24.8		60.3	9.0		28.4
9b	e)	108.7	153.9	e)	e)		e)			e)		
9d	65.8	110.5	153.1	164.4	50.8		25.7		60.0	27.9		
10b	75.7	108.8	151.7	163.8	28.3	67.1	48.8			15.9	19.1	30.9
12b	75.2	118.2	153.8	189.4	30.0		48.7			15.4	19.0	30.0
12c	77.8	117.8	154.5	192.9	27.5		48.0			25.8		36.1
13b	69.2	119.6	154.6	192.1	27.1		19.2	19.5	58.6	15.9	17.7	30.5
14b	57.7	120.3	155.5	191.5	e)		28.0		60.7	e)		
25	67.3[f]	114.0	153.2	164.3	50.9		38.9			23.5[g]		
26	67.2[f]	115.1	152.9	164.1	50.8		21.2		52.7	24.1[g]		
28a	75.0	112.3	153.2	164.1	50.9		h)			27.6		
28b	80.5	110.6	154.0	164.3	50.8		i)			22.4	28.1	35.8
28c	81.9	109.9	155.0	164.7	50.7		k)			25.2		38.4

a) ^{13}C signals of **11b** and **13c** are too weak to be detected beside the signals of the 5-regioisomers

b) q for OMe or Me - q + s for OtBu

c) q for Me - 1 or 2 q + d for iPr - q + s for tBu

d) q + t for Et (**a**) - 2q + 1d for iPr (**b**) - q + s for tBu (**c**) - q for Me (**d**)

e) the signal is to weak to be detected beside the signals of the 5-regioisomer

f) singlet

g) 2 Me groups

h) 23.6 + 28.7 (2q, Me), 69.6 (s, tert C), 36.2 + 36.6 (2t, CH_2)

i) 22.4 + 28.1 (2q, Me), 69.0 (s, tert C), 31.7 + 36.8 (2t, CH_2)

k) 21.9 + 28.2 (2q, Me), 68.4 (s, tert C), 29.8 + 36.4 (2t, CH_2)

4-Methoxycarbonyl-2,2,3-trimethyl-4-isoxazoline (**25**) and ***3,3-dimethyl-2-isopropyl-4-methoxycarbonyl-4-isoxazoline*** (**26**) were detected by NMR spectroscopy (see Tables 3 and 5). To a solution of 2.2 mmol of **23**[17] or **24**, respectively, in 3 mL of $CDCl_3$ 2.2 mmol of methyl propiolate (**4**) were added. The spectra were taken after 24 hours. **25** and **26** had formed in 100% yield. However, the products were only stable in solution. Evaporation of the solvent was immediately followed by decomposition of the products.

In a competition experiment 0.1 mol of nitrone **1b** and 0.1 mol of nitrone **3b** were brought to reaction with 0.1 mol of methyl propiolate **4** in the usual way according to procedure B. The portions of products **7b**:**15b**:**9b**:**17b** were estimated to be in the ratio 13:7:2:8 from the integrals of their 3-H signals.

Table 6. ^{13}C NMR data of the 5-substituted 4-isoxazolines. Chemical shifts in ppm, solvent $CDCl_3$.

	C-3(d)	C-4(d)	C-5(s)	C=O(s)	CO-X[a]		R^1[b]			R^2[c]		
15a	d)	109.8	144.5	d)	d)		d)			d)		
15b	65.8	108.0	144.8	159.7	52.9		48.8			16.4-19.1		33.2
15c	83.0	107.3	144.9	159.6	52.2		48.8			25.5		35.4
16a	68.6	110.3	145.0	159.3	51.8		19.5		57.3	9.8		29.3
16b	73.3	109.0	142.1	159.4	52.0		18.4	19.4	58.0	17.8	17.9	33.8
16c	76.8	108.4	145.8	159.4	51.9		16.8	19.9	58.8	25.4		35.2
17a	65.5	110.5	145.3	159.3	52.0		24.8		60.3	10.0		30.7
17b	69.6	109.0	146.3	159.2	51.9		24.7		60.0	17.3	18.5	34.3
17c	72.5	109.3	146.6	159.5	51.7		25.4		60.7	24.9		34.5
17d	65.8	112.2	145.3	159.4	52.1		25.7		60.0	28.0		
18b	77.3	106.9	146.1	158.5	28.1	67.1	48.1			18.2	18.5	33.3
19b	69.9	107.5	147.5	158.2	28.1	67.1	24.9		60.4	17.7	18.9	34.5
20b	79.2	108.1	151.0	189.4	27.0		47.8			18.0	18.2	33.1
20c	83.0	106.7	151.5	189.6	27.2		48.8			25.5		35.4
21b	73.5	108.1	152.2	189.4	27.2		18.5	19.5	58.0	17.9	18.0	33.8
21c	76.8	107.7	152.5	189.4	27.2		16.9	20.0	58.8	25.6		35.2
22b	69.9	108.3	153.0	189.2	27.3		25.0		60.4	17.6	18.8	34.6
22c	72.6	108.5	153.5	189.3	27.4		26.0		60.7	25.4		35.7
29b	84.3	111.7	145.7	159.3	51.9		e)			17.0	18.9	38.6
29c	85.1	113.7	145.4	159.3	51.8		f)			24.8		37.4

a) q for OMe or Me - q + s for OtBu

b) q for Me - 1 or 2q + d for iPr - q + s for tBu

c) q + t for Et (**a**) - 2q + 1d for iPr (**b**) - q + s for tBu (**c**) - q for Me (**d**)

d) the signal is too weak to be detected beside the signals of the 4-regioisomer

e) 22.7 + 27.9 (2q, Me), 69.2 (s, tert, C), 33.6 + 36.1 (2t, CH_2)

f) 21.8 + 28.4 (2q, Me), 69.0 (s, tert, C), 29.8 + 36.4 (2t, CH_2)

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