1,3-CYCLOADDITION OF BENZONITRILE OXIDES TO DIAZEPINES.I. 1-ETHOXYCARBONYL-5-METHYL-1,2-DIAZEPINE

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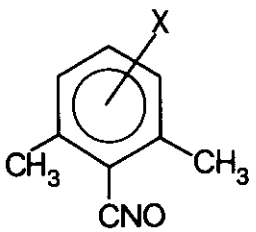
Abstract - Stable aryl nitrile oxides (**1a-e**) and 1-ethoxycarbonyl-5-methyl-1,2-diazepine (**2**) undergo 1,3-cycloaddition reactions to give isomeric 1,2,4-oxadiazole (**3**), 4,5-dihydroisoxazole (**4**) and isoxazole (**5**) derivatives, the first one being in any case the most abundant product. Overall kinetics were measured at temperatures in the range 50-90°C, in 1,1,2,2-tetrachloroethane and mixtures of the latter with DMF; rate coefficients for the parallel reactions were, thus, obtained. Substituent and solvent effects are discussed.

The [3+2] cycloaddition of benzonitrile oxides to CC and CN unsaturated bonds was previously investigated, such bonds being separately present on different molecules[1,2] or in competition on the same dipolarophile, as in

the case of β-cinnamonitriles[3] and 1,4-diaryl-1-aza-1,3-butadienes.[4] In order to study further cases of such competition between C=C and C=N bonds, diazepines appear to be interesting dipolarophiles. In the present study, the stable nitrile oxides (**1a-e**) and 1-ethoxycarbonyl-5-methyl-1,2-diazepine (**2**) were considered. On the basis of literature [5,6] and of our previous experience,[3,4] the C=N bond was expected to be the preferred site of cycloaddition.



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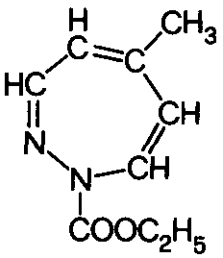
a : X = 4-OCH_3
b : 4-CH_3
c : H
d : 4-Br
e : 3,5-Cl_2-4-CH_3



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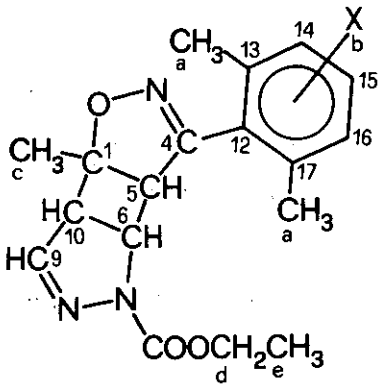
RESULTS

Preparation and separation of products

Excess amounts of diazepine (**2**), synthesized from the corresponding pyridinium ylide by a photochemical rearrangement,[7] were treated with nitrile oxides (**1a-e**) in chloroform at 50-60°C, usually obtaining mixtures of three products. Analogous mixtures were obtained in the conditions of kinetic runs, i.e. in 1,1,2,2-tetrachloroethane (TCE) or in TCE-DMF mixed solvents, at temperatures in the range 50-90°C.

Chromatographic separation, followed by elemental, spectral and crystallographical analysis, evidenced that the main product (ca. 80%) in



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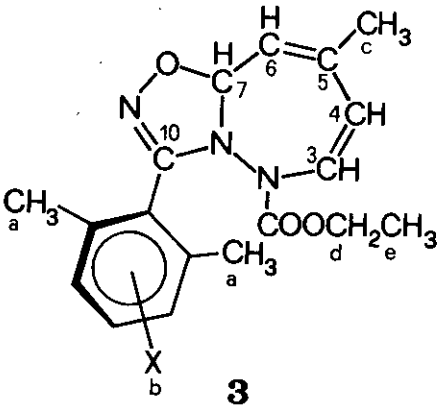

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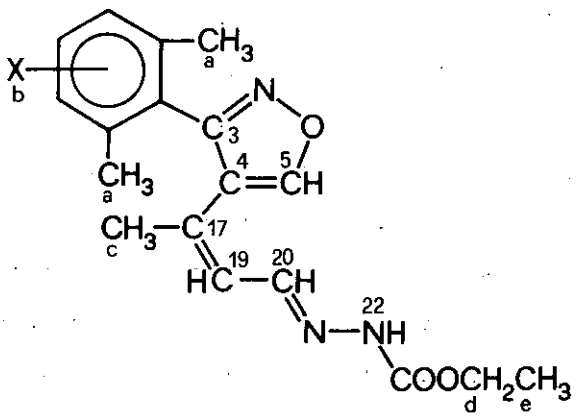

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any case belongs to the class of 2-ethoxycarbonyl-5-methyl-10-aryl-1,2,9-triaza-8-oxabicyclo[5.3.0^{1,7}]-3,5,9-decatrienes (**3**), while minor products were identified as 1-methyl-4-aryl-7-ethoxycarbonyl-3,7,8-triaza-2-oxatricyclo[3.3.0^{1,5}0^{6,10}]-3,8-decadienes (**4**) and 3-aryl-4-[(1Z,3E)-5-ethoxycarbonyl-1-methyl-4,5-diaza-1,3-pentadienyl]isoxazoles (**5**). The 1Z, 3E configuration of the latter compounds was assigned as a result of XRD

analysis of **5e**. The relative abundance of adducts (**3**), (**4**) and (**5**) was roughly (80-85):(5-10):(5-15). This was determined by quantitative hplc analysis of reaction mixtures obtained in the same conditions of the kinetic runs, in reactions carried out to complete conversion of the aryl nitrile oxide: overall yields were in the range 80-96% and no other product was ever observed; therefore, reaction selectivities were calculated by a normalization procedure.

Analytical and spectroscopic properties

Elemental analyses and mp's of cycloadducts are collected in Table 1. Nmr spectra are presented in Tables 2-5. Among the adducts (**3**), (**4**) and (**5**), only **3b** has been already described.[8]

Our assignment of nmr bands having δ-value of ca. 5.7 and 6.0 ppm (Table 2) differs from that of Streith et al.[8] since a complete series of double resonance experiments on the cycloadduct (**3b**) showed a coupling between a methyl proton and the proton whose resonance occurred at 6.04 ppm; this is therefore assigned to proton 6.

The same criteria were obviously used to assign nmr signals corresponding to H-6 and H-7 for the other members of the **3**-series. Among the cycloadducts investigated in this work the adducts (**3**) show up a magnetic nonequivalence of the arylic methyl resonances as it can be seen in Table 2. A similar observation can be possibly extended to the aromatic proton signals, though the effect seems much weaker as indicated by a signal broadening. No attempt was made to further associate the two signals to the respective methyls. In Table 3 (cycloadducts (**4**)) it can be noticed that the chemical shifts of protons H-5, H-6 and H-10 (3.7 - 4.7 ppm) agree with their bonding to saturated C-atoms; even better evidence comes from the ^{13}C-nmr spectra (Table 4), where the chemical shifts of C-5, C-6 and C-10 are in the range 55-66 ppm.

Table 1 - Analytical Data of Cycloadducts

Adduct	mp °C	Formula	Elemental analysis (%)[a] C	H	N
3a[b]	145	$C_{19}H_{23}N_3O_4$	63.7	6.4	11.6
5a	205			c	
			(63.9)	(6.5)	(11.8)
3b	136[d]		66.7	6.8	12.1
4b	157.5	$C_{19}H_{23}N_3O_3$	66.8	6.9	12.5
5b	217.5		66.6	6.6	12.2
			(66.9)	(6.8)	(12.3)
3c	131.5		66.2	6.6	12.5
4c	158	$C_{18}H_{21}N_3O_3$	65.8	6.4	12.6
5c	197		65.9	6.3	12.7
			(66.0)	(6.5)	(12.8)
3d	155		53.4	5.2	10.2
4d	178.5	$C_{18}H_{20}N_3O_3Br$	53.0	5.1	10.5
5d	191.5		53.3	5.2	10.4
			(53.2)	(5.0)	(10.3)
3e	160		55.5	5.3	10.1
4e	211.5	$C_{19}H_{21}N_3O_3Cl_2$	55.4	5.2	10.4
5e	224		55.9	5.0	10.1
			(55.6)	(5.2)	(10.2)

a) Calculated values, for the isomers, in parentheses.

b) The compound (**4a**) was not isolated.

c) The results for C,H,N were always low probably due to incomplete combustion, but the theoretical atomic ratio was observed.

d) lit.(ref.8), mp 122°C

Table 2 - ^{1}H-Nmr spectra of adducts **3**($CDCl_3$)*

Adduct	**3a**	**3b**	**3c**	**3d**	**3e**
X	4-OMe	4-Me	H	4-Br	4-Me-3,5-Cl_2
H_3** (d)	6.46	6.47	6.45	6.48	6.49
H_4** (d)	5.19	5.12	5.12	5.13	5.13
H_6** (m)	6.04	6.04	6.06	6.06	6.06
H_7** (m)	5.75	5.75	5.75	5.73	5.73
$H_{(Ar)}$	6.58(s_b)	6.86(s_b)	7.03(d)	7.21(s_b)	=
a (s)	2.33	2.28	2.26	2.24	2.26
a' (s)	2.34	2.33	2.37	2.36	2.36
b	3.78(s)	2.23(s)	7.21(t)	=	2.56(s)
c** (m)	1.94	1.94	1.93	1.94	1.93
d** (q)	4.19	4.20	4.20	4.20	4.18
e (t)	1.28	1.28	1.26	1.27	1.27

*δppm; internal standard TMS.

**3a:$J_{3,4}$=9.0 Hz; $J_{6,7}$=0.5 Hz; $J_{6,c}$=1.5 Hz; $J_{7,c}$=0.5 Hz; $J_{d,e}$=6,9 Hz;

3b: $J_{3,4}$=9.0 Hz; $J_{6,7}$=0.5 Hz; $J_{6,c}$=1.5 Hz; $J_{7,c}$=0.5 Hz; $J_{d,e}$=6.9 Hz;

3c: $J_{3,4}$ =9.0 Hz; $J_{d,e}$ =6.3 Hz;

3e: $J_{3,4}$ =9.0 Hz; $J_{d,e}$ =6.9 Hz.

Finally, reaction products (**5**) show, in their ^{1}H-nmr spectra (Table 5), proton chemical shifts in agreement with an extensive system of conjugated double bonds, with a high δ-value of H-5, due to its position in the isoxazole ring.

Table 3 - ^{1}H-Nmr spectra of adducts **4**($CDCl_3$)*

Adduct		**4b**	**4c**	**4d**	**4e**
X		4-Me	H	4-Br	4-Me-3,5-Cl_2
H_9	(d)	6.99	7.05	6.93	6.99
H_{10}	(m)	3.78	3.80	3.70	3.70
H_5**	(d)	4.67	4.68	4.60	4.67
H_6	(m)	4.27	4.27	4.23	4.28
$H_{(Ar)}$		6.89(s)	7.08(d)	7.20(s)	=
a,a'	(s)	2.29	2.32	2.25	2.34
b		2.27(s)	7.20(t)	=	2.52(s)
c	(s)	1.55	1.58	1.52	1.57
d**	(m)	4.10	4.10	4.20	4.10
e	(m)	0.90	0.90	0.80	0.80

* δ ppm; internal standard TMS.

** **4b**: $J_{(9,5)}$=1.2 Hz; $J_{(10,5)}$=2.0 Hz; $J_{(5,6)}$=8.0 Hz; $J_{(d,e)}$=6.6 Hz;
4e: $J_{(5,6)}$=6.9 Hz

The occurrence of an exchangeable proton (NH) has been evidentiated by comparison of the nmr spectra of the adducts (**5b**) and (**5d**) in $CDCl_3$ with and without added D_2O and then extended to the other members of the series.

Crystallographic analysis.

For the three compounds, (**3b**), (**4c**) and (**5e**), the crystal data and diffraction intensities were measured on a CAD-4 single-crystal diffracto-

Table 4 - ^{13}C-Nmr spectra of cycloadducts **4***

Atom	ADDUCT 4b	4c	4d	4e
C_1	89.8	89.8	89.8	89.9
C_4	151.9	151.9	151.9	151.9
C_5	55.1	55.2	55.2	54.8
C_6	62.3	63.6	62.5	62.4
C_9	145.0	144.8	144.8	144.7
C_{10}	64.9	65.6	64.6	65.3
C_{12}	124.5	123.3	123.3	127.5
$C_{13,17}$	136.3	129.5	130.9	133.8
$C_{14,16}$	128.8	126.7	126.7	133.0
C_{15}	138.9	138.7	138.7	135.8
$CH_3(13,17)$	20.1	20.1	20.0	18.8
$CH_3(15)$	21.0	=	=	19.2
$CH_3(1)$	19.1	19.2	19.1	19.0
$-CH_2-$	59.2	59.5	59.2	59.2
$-CH_3$	13.8	16.6	14.0	13.9
C=O	157.1	157.0	156.1	156.4

*δ ppm; $CDCl_3$; internal standard TMS.

meter using a MoKα radiation. The structures were solved by direct methods and refined by means of the NRCVAX system of programs.[9]
The identification of the atoms on the resulting E-maps was straightforward for the main and expected product (**3b**).

Table 5 -^{1}H-Nmr spectra of adducts **5***

Adduct		**5a**	**5b**	**5c**	**5d**	**5e**
X		4-OMe	4-Me	H	4-Br	4-Me-3,5-Cl_2
H_5	(s)	8.63	8.44	8.58	8.46	8.48
H_{22}	(s)	8.30	7.88	8.02	7.98	8.09
H_{19}**	(m)	6.29	6.34	6.12	6.38	6.70
H_{20}**	(d)	7.53	7.62	7.62	7.55	7.55
H_{Ar}		6.58(s)	6.92(s)	7.10(m)	7.28(s)	=
a ,a'	(s)	2.08	2.06	2.06	2.07	2.10
b		3.74(s)	2.31(s)	7.23(m)	=	2.56(s)
c	(d)	1.63	1.73	1.70	1.71	1.72
d**	(q)	4.17	4.20	4.23	4.27	4.26
e	(t)	1.22	1.30	1.22	1.30	1.29

*$CDCl_3$; δ ppm ; internal standard TMS.

** **5b**: $J_{19,c}$ =1.2Hz; $J_{19,20}$=9.3Hz; $J_{d,e}$=6.6Hz

5c: $J_{19,20}$ =9.9Hz; $J_{d,e}$ =9.0Hz;

5d: $J_{19,20}$ =10.7Hz; $J_{d,e}$ =7.0Hz;

5e: $J_{19,c}$=1.5Hz; $J_{19,20}$ =8.7Hz; $J_{d,e}$ =6.6Hz.

All the (non-hydrogen) atoms for **4c**, and all but the two chlorine atoms for **5e** were initially considered as carbon atoms; their identity was assessed during the refinement, on the basis of values obtained for bond distances and isotropic thermal factors. All the three structures seem to be more or less affected by disorder. In compounds (**3b**) and (**4c**) one or more atoms in the side chain are split over different orientations. In

compound (**5e**) a very high thermal factor has been found for the terminal carbon atoms in the same chain. Moreover, in **5e** the packing of molecules leaves channels, running through the crystal, along which a residual electron density gives a clue for the presence of disordered molecules of solvent (possibly ethyl acetate).

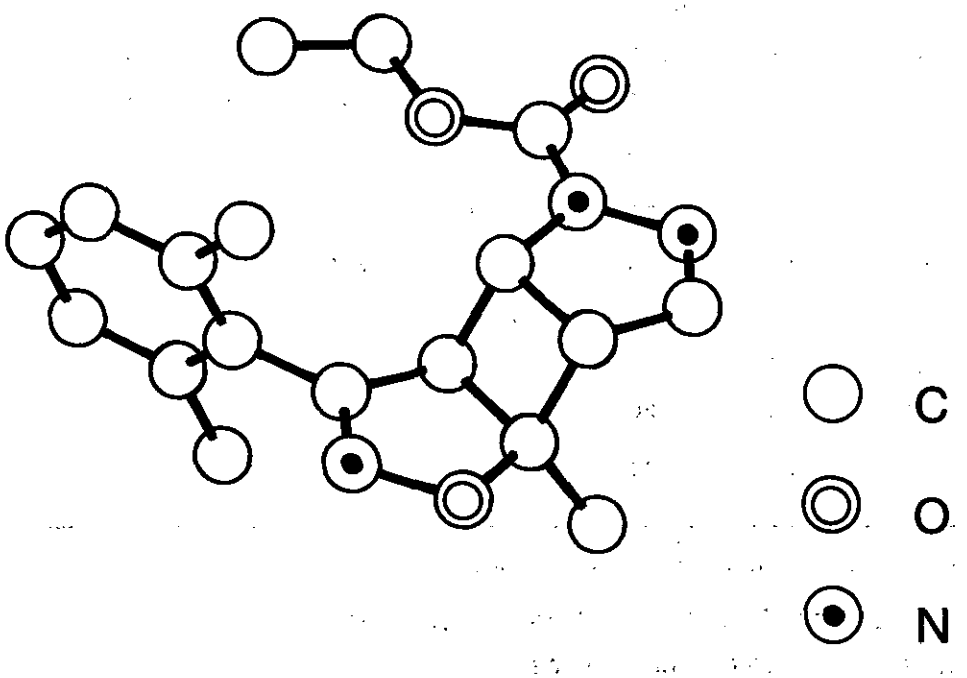


Figure 1- Crystal structure of compound (**4c**). In the side chain, for the sake of clarity, only the atoms having the highest site occupation factor are shown.

Current R values at this point of the refinement are 0.08 for **3b**, 0.07 for **4c** and 0.15 for **5e** (not considering the solvent contributions), over about 1600, 2300 and 1800 observed reflections, respectively. Models for the types of disorder encountered are being considered; final results will be reported elsewhere.

XRD analysis confirmed the expected structure of the main cycloadduct (**3**). As to the minor products (**4**) and (**5**), their structure was largely

unexpected, but in agreement with their nmr spectra. A ball-and-stick representation of **4c** and **5e** is given in Figures 1 and 2.

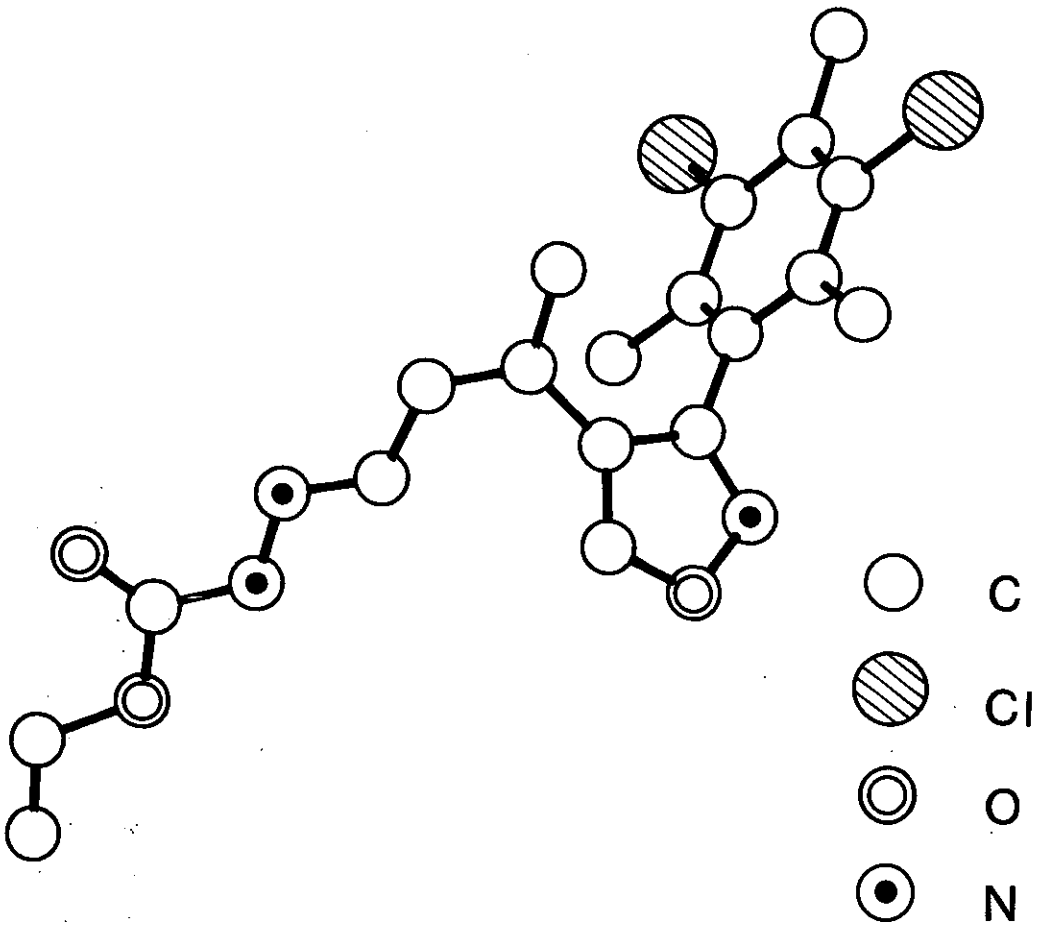


Figure 2 - Crystal structure of compound (**5e**)

Kinetic measurements

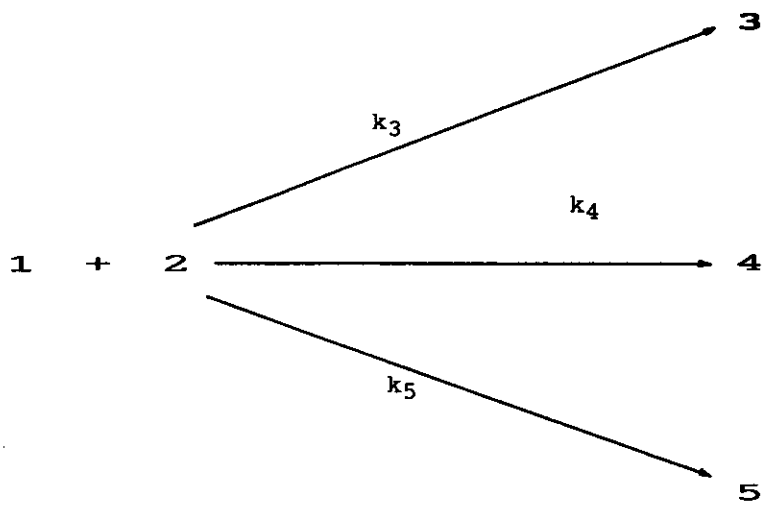
Kinetic runs were followed by ir analysis, on a band typical of nitrile oxides (**1**), to measure the overall rate coefficient. Concomitant hplc determinations of the product fractions gave the results shown in Table 6.

Table 6 - Reaction Products of types (3), (4) and (5) as determined by hplc after complete reaction

ArCNO	Solvent*	T(°C)	Molecular Fraction of Products 3	4	5
1a	TCE	70	0.83 ± 0.01	=	0.17 ± 0.01
1b	TCE	50	0.84 ± 0.00	0.113 ± 0.014	0.051 ± 0.013
	TCE	60	0.84 ± 0.04	0.095 ± 0.007	0.067 ± 0.030
	TCE	70	0.80 ± 0.00	0.075 ± 0.015	0.126 ± 0.015
	TCE/DMF(A)		0.82 ± 0.00	0.055 ± 0.000	0.133 ±.0.003
	TCE/DMF(B)		0.80 ± 0.02	0.068 ± 0.025	0.132 ± 0.004
	TCE/DMF(C)		0.79 ± 0.02	0.067 ± 0.002	0.144 ± 0.027
	TCE	80	0.80 ± 0.01	0.092 ± 0.004	0.109 ± 0.003
1c	TCE	60	0.84 ± 0.00	0.075 ± 0.004	0.083 ± 0.006
	TCE	70	0.83 ± 0.01	0.082 ± 0.015	0.093 ± 0.014
	TCE	80	0.82 ± 0.02	0.085 ± 0.007	0.097 ± 0.015
	TCE	90	0.81 ± 0.01	0.075 ± 0.011	0.115 ± 0.005
1d	TCE	60	0.85 ± 0.01	0.062 ± 0.009	0.090 ± 0.005
	TCE	70	0.85 ± 0.00	0.061 ± 0.006	0.093 ± 0.003
	TCE/DMF(A)		0.79 ± 0.02	0.061 ± 0.016	0.153 ± 0.038
	TCE/DMF(B)		0.79 ± 0.02	0.056 ± 0.004	0.149 ± 0.020
	TCE/DMF(C)		0.80 ± 0.02	0.051 ± 0.003	0.149 ± 0.026
	TCE	80	0.82 ± 0.03	0.053 ± 0.004	0.125 ± 0.029
	TCE	90	0.82 ± 0.04	0.049 ± 0.004	0.129 ± 0.035
1e	TCE	50	0.84 ± 0.01	0.069 ± 0.007	0.091 ± 0.014
	TCE	60	0.85 ± 0.02	0.059 ± 0.022	0.092 ± 0.014
	TCE	70	0.81 ± 0.02	0.073 ± 0.021	0.114 ± 0.009
	TCE/DMF(A)		0.83 ± 0.00	0.059 ± 0.003	0.108 ± 0.000
	TCE/DMF(B)		0.82 ± 0.03	0.065 ± 0.025	0.111 ± 0.011
	TCE/DMF(C)		0.82 ± 0.02	0.065 ± 0.001	0.114 ± 0.014
	TCE	80	0.85 ± 0.03	0.041 ± 0.008	0.110 ± 0.019
	TCE	90	0.85 ± 0.03	0.064 ± 0.026	0.084 ± 0.007

*TCE=1,1,2,2-tetrachloroethane; DMF= N,N-dimethylformamide; (A), (B) and (C) indicate solvent mixtures with 10%, 20% and 30% by volume of DMF, respectively.

Results were interpreted by the following reaction scheme:



The overall coefficient (k) was then split into values of k_3, k_4 and k_5. Rate coefficients for reactions at 70°C (the only temperature at which several solvents have been used) are gathered in Table 7. Other rate coefficients are in Table 8. Having determined kinetic coefficients at three to five different temperatures for each reaction, activation parameters could be evaluated by the Arrhenius and Eyring equations, obtaining activation energies (ΔE_a) and activation entropies ($\Delta S^{\neq}$), as shown in Table 9.

DISCUSSION

There is evidence of three (occasionally only two) parallel reactions of [3+2] cycloaddition:

(i) addition of nitrile oxide (**1**) to the C=N bond of diazepine (**2**) to give products (**3**);

(ii) addition of **1** to **2** with concomitant [2+2] cycloaddition within the dipolarophile, giving rise to products (**4**);

(iii) addition of **1** to the CH=CH bond of **2**, with opening of the diazepine ring and proton shift from a Carbon to a Nitrogen atom, to give adducts (**5**).

In no case cycloaddition of **1** to the $CH=C-CH_3$ of **2** has been observed. Probably this attack is sterically hindered.

Kinetic effects of substituents in **1** can be judged by examining Table 7. In any case, the slight rate-enhancing effect of electron-withdrawing substituents X in **1** is apparent: if the comparison is limited to compounds (**1b**), (**1d**) and (**1e**) (X = 4-CH_3, 4-Br, 3,5-Cl_2-4-CH_3, respectively) ρ-values between +0.4 and + 0.6 can be found. However, when a larger spectrum of substituents has been tested (in solvent TCE), V-shaped Hammett plots were found, with a minimum rate coefficient for X = H, the reaction being accelerated also by electron-releasing substituents on the nitrile oxide.

A similar situation was previously found for cycloadditions to both CC and CN unsaturated bonds,[3,4] and discussed in terms of a LUMO (dipole)-controlled reaction that can become, in the presence of electron-releasing X substituents, a HOMO (dipole)-controlled one.[3]

All reactions are positively affected (Table 7) by enhancing the solvent polarity with increasing amounts of DMF. By mixing to pure TCE (Dielectric constant D = 8.08) increasing amounts of DMF (D = 36.71), the relative permittivities of the mixed solvents, calculated on the ideal assumption of a linear combination of the constants of pure solvents, based on their volume fraction in the mixture, increase along the series as follows: 8.08, 10.94, 13.81, 16.69. Since the accelerating effect is of a general nature, i.e. product selectivities are scarcely affected, it could be a solvent effect on the stability of the reactants; otherwise, three transition states of a similarly polar nature should be envisaged.

Table 7 - Kinetic runs at 70.0°C for reaction of aryl nitrile oxides (**1**) with diazepine (**2**)

ArCNO	k	Kinetic coefficients/ $10^{-4}dm^3mol^{-1}s^{-1}$ k_3	k_4	k_5
		Solvent[a] : TCE		
1a	1.72 ± 0.10	1.43 ± 0.09		0.29 ± 0.02
1b	1.82 ± 0.04	1.45 ± 0.03	0.14 ± 0.03	0.23 ± 0.03
1c	1.57 ± 0.03	1.30 ± 0.03	0.13 ± 0.02	0.15 ± 0.02
1d	2.73 ± 0.17	2.31 ± 0.14	0.17 ± 0.02	0.25 ± 0.02
1e	3.92 ± 0.07	3.19 ± 0.08	0.29 ± 0.08	0.44 ± 0.03
		Solvent[a]: TCE/DMF (A)		
1b	1.90 ± 0.01	1.55 ± 0.01	0.10 ± 0.00	0.25 ± 0.01
1d	2.99 ± 0.18	2.35 ± 0.16	0.19 ± 0.05	0.46 ± 0.12
1e	4.63 ± 0.08	3.86 ± 0.20	0.27 ± 0.01	0.50 ± 0.01
		Solvent[a]: TCE/DMF (B)		
1b	2.12 ± 0.05	1.70 ± 0.06	0.14 ± 0.05	0.28 ± 0.01
1d	3.36 ± 0.02	2.67 ± 0.08	0.19 ± 0.01	0.50 ± 0.07
1e	6.14 ± 0.02	5.06 ± 0.19	0.40 ± 0.15	0.68 ± 0.07
		Solvent[a]: TCE/DMF (C)		
1b	2.72 ± 0.05	2.15 ± 0.07	0.18 ± 0.01	0.39 ± 0.07
1d	3.83 ± 0.11	3.06 ± 0.13	0.20 ± 0.01	0.57 ± 0.10
1e	6.72 ± 0.16	5.52 ± 0.17	0.43 ± 0.01	0.76 ± 0.10

[a]TCE = 1,1,2,2-tetrachloroethane; DMF = N,N-dimethylformamide; (A), (B) and (C) indicate solvent mixtures with 10%, 20% and 30% by volume of DMF, respectively.

Table 8 - Kinetic runs at temperatures other than 70.0°C in TCE[a]

		Kinetic coefficients / $10^{-4}dm^3mol^{-1}s^{-1}$			
ArCNO	T(°C)	k	k_3	k_4	k_5
1b	50	0.41 ± 0.00	0.34 ± 0.00	0.046 ± 0.006	0.021 ± 0.005
	60	0.86 ± 0.01	0.72 ± 0.03	b	b
	80	3.49 ± 0.03	2.79 ± 0.04	0.32 ± 0.02	0.38 ± 0.01
1c	60	0.83 ± 0.01	0.70 ± 0.01	0.062 ± 0.003	0.069 ± 0.005
	80	2.94 ± 0.08	2.41 ± 0.09	0.25 ± 0.02	0.28 ± 0.05
	90	5.98 ± 0.08	4.85 ± 0.10	0.45 ± 0.06	0.68 ± 0.03
1d	60	1.30 ± 0.04	1.10 ± 0.03	0.080 ± 0.010	0.12 ± 0.01
	80	5.26 ± 0.09	4.32 ± 0.16	0.28 ± 0.02	0.66 ± 0.15
	90	8.55 ± 0.21	7.03 ± 0.42	0.42 ± 0.03	1.11 ± 0.30
1e	50	0.77 ± 0.03	0.65 ± 0.03	0.053 ± 0.006	0.070 ± 0.012
	60	1.87 ± 0.05	1.59 ± 0.05	0.11 ± 0.04	0.17 ± 0.03
	80	7.76 ± 0.27	6.59 ± 0.31	0.32 ± 0.06	0.85 ± 0.15
	90	14.78 ± 0.08	12.58 ± 0.48	b	b

[a]TCE = 1,1,2,2-tetrachloroethane; (b) only the main coefficient (k_3) was considered reliable in this case, due to large uncertainty in the determination of S_4 or S_5.

Recently, it has been reported that a [4+2] cycloaddition (Diels-Alder reaction) in Et_2O can be strongly accelerated by $LiClO_4$.[10] A few tests were made on the reaction of **1e** + **2** at 70.0°C, in a solvent containing TCE, DMF and Et_2O in ratios 6:2:2 by volume, with dissolved $LiClO_4$ (0.8 mol l^{-1}). The product distribution (fractions: **3e**, 0.82; **4e**, 0.064;

5e, 0.115) was quite similar to the one reported in Table 6 for a run on solvent TCE/DMF (B) (ratio 8:2), in the absence of both Et_2O and $LiClO_4$. Results for the various kinetic coefficients were (in TCE/DMF (B) [Table 7] , in TCE/DMF/Et_2O without $LiClO_4$, in TCE/DMF/Et_2O with $LiClO_4$): k_3, 5.06 ± 0.19, 4.83 ± 0.35, 4.39 ± 0.13, k_4, 0.40 ±0.15, 0.41 ± 0.10, 0.34 ± 0.04; k_5, 0.68 ± 0.07, 0.55 ± 0.04, 0.61 ± 0.09. Within experimental error, $LiClO_4$ shows no kinetic effect in the present case.

Table 9 - Values of activation energy (ΔE_a) and activation entropy ($\Delta S^{\neq}$) from rate coefficients k_3, k_4 and k_5 for reactions of nitrile oxides (**1b-e**) with diazepine (**2**) in TCE

ArCNO	ΔE_a (KJ/mol)			$\Delta S^{\neq}$(J/molK)		
	3	**4**	**5**	**3**	**4**	**5**
1b	66.5±0.2	59.4±8.4	95.1±14.2	-134±1	-173±38	-69±65
1c	64.6±2.5	66.3±1.2	75.8±4.1	-141±11	-155± 5	-126±1
1d	62.4±2.9	55.4±4.3	77.5±5.1	-143±14	-186±20	-116±23
1e	71.8±1.2	60.5±10.8	80.3±3.2	-112±6	-168±49	-104±15

Activation parameters (Table 9) belong to two different classes of precision: on one side, k_3 coefficients give reliable values of ΔE_a and $\Delta S^{\neq}$, affected by small standard deviations; on the other side, k_4 and k_5 coefficients give less reliable values. This can be attributed to the absolute error in the product fractions (hplc analysis) being propagated to the determinations of the kinetic coefficients, and particularly of k_4

and k_5 in terms of relative error, due to the small value of these coefficients. Besides, in the case of **1b** + **2**, only three temperature values have been considered for the Arrhenius-Eyring correlation of k_4 and k_5.

As to the mechanism of the reactions, one can suggest a concerted cycloaddition for the formation of adducts (**3**), by analogy with similar cases, by considering the slight effects of substituent and solvent polarity and because the activation entropy has large negative values.

The reaction giving rise to products (**4**) could, in principle, be a multistage process with an initial isomerization of diazepine (**2**) to the corresponding 2,3-diazabicyclo[3.2.0]heptadiene, followed by attack of nitrile oxide (**1**) to the newly formed C=C double bond. However such isomerization was described by Streith et al.[11] as a photochemical reaction requiring a long reaction time for low yields; as a matter of fact, no evidence for the formation of such by-product was observed in the conditions of our photochemical synthesis of **2**; moreover, the reaction product was carefully purified in order to isolate diazepine (**2**). On the other hand, in the conditions of 1,3-cycloaddition, no photochemical reaction could have taken place. A thermal process giving rise to **4** could be a two-step cycloaddition, the first step being an electrophilic attack of the nitrile oxide carbon onto atom C-6 of **2** ; however, the transition state along the path to the corresponding dipolar intermediate should be polar enough to be revealed by substituent and solvent effects which have not been found. Actually, k_4 coefficients depend on substituent and solvent effects approximately in the same way as k_3 coefficients. Tentatively, a radical process could be suggested.

The formation of adducts (**5**) can be rationalized as a concerted cycloaddition of **1** to the CH=CH bond of **2**, followed by a rearrangement, favoured by the aromatic nature of the resulting π-system.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded with a Varian VXR-300 spectrometer (Me_4Si as internal standard, $CDCl_3$ as the solvent). Reagent grade reagents and solvents were used.

Materials.

Aryl nitrile oxides (**1a-e**) were obtained as previously described.[12] The diazepine (**2**) was prepared starting from 1-ethoxycarbonylimino-4-methylpyridinium ylide obtained by reaction of γ-picoline with hydroxylamine-O-sulfonic acid and ethyl chloroformate as described.[7] A solution of the pyridinium ylide in acetone was irradiated under nitrogen and internal cooling to 10 - 15°C, with a 125 W high pressure mercury lamp (volume 500 ml). The solution was then concentrated in vacuo and purified by silica gel chromatography (petroleum ether (bp 40-70°C) and ethyl acetate (70:30, v/v) as eluant). The product was then crystallized from petroleum ether. Yield 75%, mp 53°C (lit.,[7] mp 51 -53 °C).

General procedure for the reaction of compounds (1a-e) with the diazepine (2).

A solution of **1** (0.01 mol) and **2** (3.6 g, 0.02 mol) in chloroform (50 ml) was kept at 50 - 60 °C for 48 h. The solvent was evaporated under reduced pressure and the residue was fractionated by flash chromatography on a Merck silica gel (230-400 mesh) column of 40 cm length and 2.5 cm internal diameter, eluting initially with a mixture of petroleum ether and ethyl acetate (85:15,v/v) to obtain the cycloadduct (**3**) and the diazepine in excess. Successively the separation was continued eluting with a mixture of petroleum ether and ethyl acetate (70:30, v/v) and the

cycloadducts (**4**) and (**5**) were obtained. The adducts were initially recrystallized from petroleum ether and ethyl acetate. Samples of some of these products were used for X-ray diffraction. Cycloadducts (**4**) and (**5**) were later recrystallized from ethanol, giving rise to microcrystalline powders.

The analytical data and nmr spectra of the cycloaddition products are collected in Tables 1 - 5.

The thermal stability of the diazepine (**2**) in the reaction conditions was controlled by tlc and hplc analyses. The latter were performed using an ordinary phase Spheris - Sorb 5S-Amino column, of 25 cm length and 4.6 mm i.d., employing a mixture of n-hexane and ethyl acetate (75:25, v/v) as eluant.

The diazepine was also unchanged after irradiation, at 20°C, for ca. 100 h, with a 125 W high pressure mercury lamp.

Reaction selectivities.

Besides the excess of diazepine (**2**), the analysis revealed the occurrence of compounds (**3**), (**4**) and (**5**). Only in the case of reaction of aryl nitrile oxide (**1a**) we were not able to isolate the compound (**4a**). The compounds were determined in the reaction mixtures, after reaction for ca. 10 half lives (solvent, temperature and reactant concentrations as in the kinetic runs) followed by dilution with chloroform, using reversed-phase hplc analysis.

A column RSilC$_{18}$ Alltech (length 25 cm, i.d. 4.6 mm) was employed. The eluant (1 cm^3 min^{-1}) was usually a mixture methanol-water (water content in the range 16- 27%, v/v) and the uv detector was positioned at 243 nm.

All determinations were carried out on the basis of calibration plots on the pure compounds. 5-(4-Chlorophenyl)tetrazole was used as a reference. At least duplicated analyses were carried out and the results averaged.

Selectivity values S_3, S_4 and S_5 were obtained from the molar concentrations C_3, C_4 and C_5 since $S_3 = C_3/(C_3+C_4+C_5)$; $S_4 = C_4/(C_3+C_4+C_5)$; $S_5 = C_5/(C_3+C_4+C_5)$.

Kinetics

The reactions were carried out in a thermostatted 0.5 mm sodium chloride cell (Beckmann FH-01 variable temperature cell) positioned in a ir spectrophotometer. The temperature was kept constant to within ± 0.2°C. Quantitative analyses were made of the band at 2280 - 2300 cm^{-1}, typical of nitrile oxides (**1**). The concentration of the latter was ca. 0.02 mol dm^{-3} while for diazepine (**2**) was in the range 0.13 - 0.54 mol dm^{-3}. Absorbance values were obtained from the peak heights and the concentration read from calibration plots. Kinetic runs were carried out for up to one to two half-lives and results interpreted by the equation for second order reactions [equation (1)]:

$$\ln (C_2/C_1) = (C_2^\circ - C_1^\circ)\, kt + \text{constant} \qquad (1)$$

The overall kinetic coefficients k were then split into k_3, k_4 and k_5 parameters on the basis of the selectivity values S_3, S_4 and S_5, since for parallel reactions of the same order :

$$k_3 = kS_3 \qquad k_4 = kS_4 \qquad k_5 = kS_5$$

Duplicate kinetic runs were always carried out with good reproducibility.

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