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1,3-Cycloaddition of Benzonitrile Oxides to Diazepines.II. 1-Ethoxycarbonyl-4-methyl- and 6-methyl-1,2-diazepine

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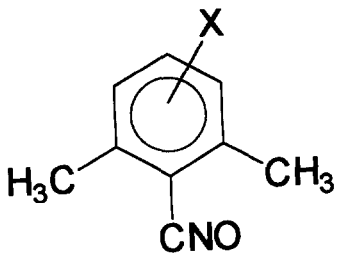
Abstract - Stable arylnitrile oxides (**1b-e**) and 1-ethoxycarbonyl-4-methyl and 6-methyl-1,2-diazepines (**2f** and **2h**) undergo 1,3-cycloaddition reactions to give 1,2,4-oxadiazole derivatives (**3**) as the most abundant products. Secondary products of the class of isoxazoles (**5** or **8**) and 4,5-dihydroisoxazoles (**6** or **7**) were also identified. Overall kinetics were measured at 70.0°C, in mixtures of 1,1,2,2-tetrachloroethane and DMF, rate coefficients for the parallel reactions were obtained. Substituent and solvent effects are discussed

Being interested in the [3+2] cycloaddition of benzonitrile oxides to CC and CN unsaturated bonds, we started investigating 1,2-diazepines as dipolarophiles. The general system under consideration is that of the stable nitrile oxides (**1a-e**) and the methyl substituted 1-ethoxycarbonyl-1,2-diazepines (**2f-h**)

The results of a study on the reaction of **1a-e** with **2g** were previously reported [1] Isomeric 1,2,4-oxadiazole (**3**), 4,5-dihydroisoxazole (**4**) and isoxazole (**5**) derivatives were found as products, the first one being in any case the most abundant

In the present work, some of the same nitrile oxides were made to react with other diazepines (**2f** and **2h**), in order to check the influence of the position of the methyl group on the nature of the products and on the rate of their formation.

In agreement with the literature reports that in case of competition between C=C and C=N bonds the preferred site of cycloaddition is the latter,[1] the main product of every reaction was found again to be of type **3** However, significant differences were found as to secondary products



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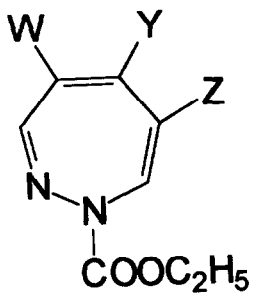
a X = 4-OCH_3
b 4-CH_3
c H
d 4-Br
e 3,5-Cl_2-4-CH_3



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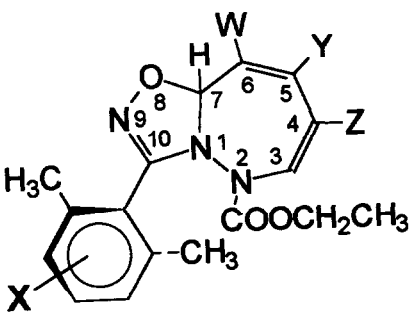
	W	Y	Z
f	CH_3	H	H
g	H	CH_3	H
h	H	H	CH_3



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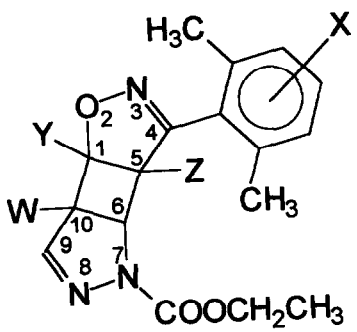

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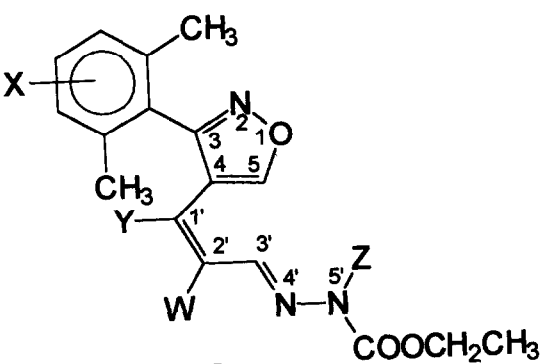

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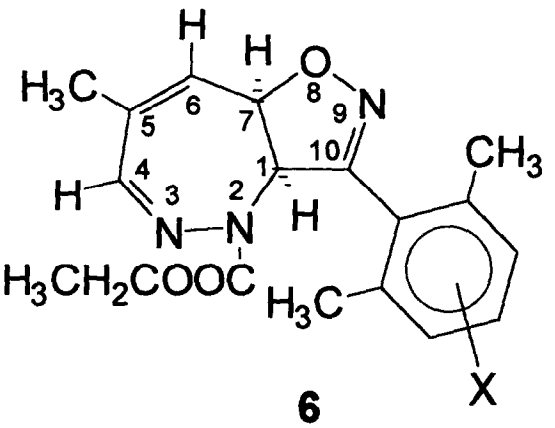
RESULTS

Preparation and separation of products

Excess amounts of diazepine (**2f** or **2h**) were treated with nitrile oxides (**1b-e**) in chloroform at 50-60°C or in the mixed solvents of the kinetic runs, *i.e* 1,1,2,2,-tetrachloroethane (TCE) + DMF, at 70°C

Chromatographic separation, followed by elemental and spectral analysis, evidenced that in the case of diazepine **2f**, the main product (*ca.* 80%) belongs to the class of 2-ethoxycarbonyl-6-methyl-10-aryl-1,2,9-triaza-8-oxabicyclo[5.3 $0^{1,7}$]-3,5,9-decatrienes (from **3bf** to **3ef**). The identification of other products was not pursued in the case of **1c+2f**, in the other cases, secondary products were identified as 3-aryl-4-[(1*Z*,3*E*)-5-ethoxycarbonyl-2-methyl-4,5-diaza-1,3-pentadienyl]isoxazoles (**5df** and **5ef**) and 2-ethoxycarbonyl-5-methyl-10-aryl-2,3,9-triaza-8-oxabicyclo[5 3 $0^{1,7}$]-3,5,9-decatrienes (**6bf** and **6ef**) The 1*Z*, 3*E* configuration of **5df** and **5ef** was assigned because of their strict analogy with **5eg**, for which such configuration resulted from XRD analysis [1]



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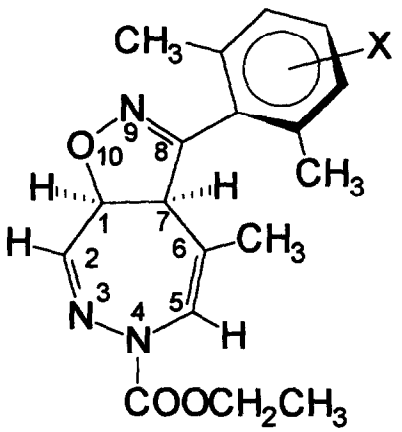
Analogous separation and analyses evidenced that in the case of diazepine (**2h**), tested in the reaction with **1b** and **1e**, the main product (*ca.* 50%) was a 4-methyl-substituted derivative of type **3**, *i.e* **3bh** and **3eh**, respectively A few minor products were detected by HPLC, but in each case only two of them were isolated in a pure form. They were identified as 4-ethoxycarbonyl-6-methyl-8-aryl-3,4,9-triaza-10-oxabicyclo[5.3.$0^{1,7}$]-2,5,8-decatrienes (**7bh** and **7eh**) and 4-ethoxycarbonyl-6-methyl-10-aryl-3,4,9-triaza-8-oxabicyclo[5.3.$0^{1,7}$]-2,5,7,9-decatetraenes (**8bh** and **8eh**).

Melting points and elemental analyses of cycloadducts are collected in Table 1. For NMR and Mass Spectra, see Experimental.



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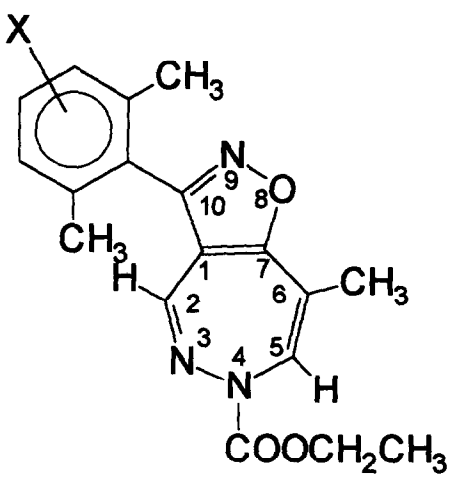

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Kinetic measurements

Kinetic runs were carried out at 70 0°C They were followed by IR analysis, on the band at 2280-2300 cm^{-1}, typical of nitrile oxides (1), to measure the overall rate coefficient TCE and TCE-DMF mixtures were chosen as solvents, in order to compare the present measurements with previous ones on diazepine **2g** [1]

However, in pure TCE IR bands of unknown secondary products were interfering with the analysis, since this did not happen after addition of a polar solvent, e g MeOH or DMF, kinetic runs were carried out only in TCE-DMF mixtures HPLC determinations of the

Table 1- Analytical Data of Cycloadducts[a].

Adduct	mp°C	Formula	C%	H%	N%
3bf	152[b]		66.6	6.7	12.4
3bh	125[b]		66 6	6.6	12.1
6bf	138[b]		66 6	6 7	12 1
7bh	165[b]		66 7	6 7	12 0
		$C_{19}H_{23}N_3O_3$	(66.9	6 8	12 3)
3cf	135[b]		66.3	6 4	12.7
		$C_{18}H_{21}N_3O_3$	(66 0	6 5	12.8)
3df	125[c]		53.0	4 9	10.6
5df	211[b]		53.0	4 9	10.1
		$C_{18}H_{20}N_3O_3Br$	(53 2	5.0	10.3)
3ef	178[b]		55.4	5.2	10.4
3eh	162.5[b]		55 5	5 3	10 1
5ef	234[b]		55 4	5.1	10 2
6ef	171 5[b]		55.5	5 3	10 3
7eh	201[b]		55 4	5.2	10.1
		$C_{19}H_{21}N_3O_3Cl_2$	(55 6	5.2	10 2)
8bh	183[c]		67.1	6.3	12.1
		$C_{19}H_{21}N_3O_3$	(67 2	6.2	12 4)
8eh	121[d]		55 9	4 8	10.3
		$C_{19}H_{19}N_3O_3Cl_2$	(55 9	4.7	10 3)

[a] Required values in parentheses [b] from ethanol. [c] from petroleum ether [d] from cyclohexane

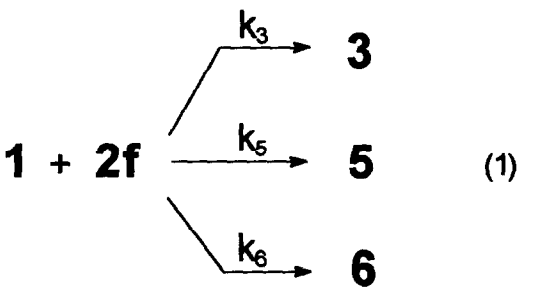
product fractions, accompanying the kinetic measurements, gave the results of Tables 2 and 3.

The product molar fractions were calculated neglecting any unidentified minor product In order to evaluate the weight of the secondary products that have been neglected, it can be mentioned that the overall yields of identified products at complete conversion of the aryl nitrile oxide were in the range 80-96% in the case of diazepine **2g**,[1] 80-94% for **2f**, 63-71% for **2h**

Table 2 - Reaction Products of type **3**, **5** and **6** as determined by HPLC, after complete reaction, at 70 0°C.

Solvent TCE/DMF	ArCNO	Diazepine	Molecular Fraction of Products 3	5	6
0 90 0 10	**1b**	**2f**	0 88±0 00		0 12±0.00
0 84 0.16			0.83±0.03		0 17±0 03
0 70 0 30			0 86±0 01		0 14±0 01
0 50 0 50			0.84±0.01		0.16±0 01
0 90 0 10	**1d**	**2f**	0.82±0 01	0.18±0 01	
0.84·0 16			0 85±0 03	0 15±0 03	
0 70 0 30			0 84±0 01	0 16±0.01	
0 50 0 50			0.84±0 01	0 16±0 01	
0 90 0 10	**1e**	**2f**	0 81±0 00	0.038±0 001	0 15±0 00
0 84 0 16			0 81±0 00	0.038±0.003	0 15±0.00
0 70 0 30			0 82±0.00	0 034±0.002	0.14±0.00
0 50 0 50			0.83±0 00	0 033±0 002	0.14±0.01

Results were interpreted by the following schemes of parallel reactions:



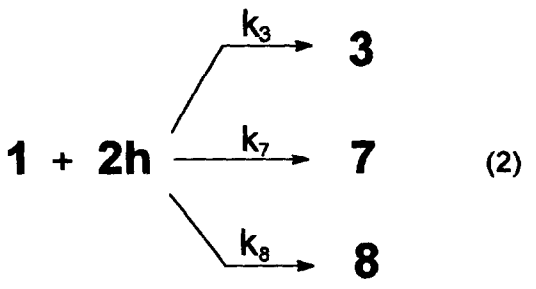


Table 3 - Reaction Products of type **3**, **7** and **8** as determined by HPLC analysis after complete reaction at 70 0°C

Solvent TCE/DMF	ArCNO	Diazepine	Molecular Fraction of Products 3	7	8
0 84 0 16	**1b**	**2h**	0 50±0 05	0 14±0 01	0 31±0 00
0.70 0.30			0 55±0 02	0.15±0 01	0 30±0 02
0 77 0 23			0.54±0 00	0 14±0.00	0 32±0 00
0.50 0 50			0 55±0 03	0 17±0 01	0 28±0 03
0 90 0 10	**1e**	**2h**	0 51±0 04	0 10±0 01	0 39±0 05
0 84 0 16			0 54±0 03	0.093±0 011	0 37±0.03
0 70.0.30			0.56±0.04	0.091±0 012	0 35±0.04
0 50.0 50			0 60±0 02	0 11±0 01	0.29±0 01

In the case of scheme (1), sometimes only two out of three reactions were detected

The overall coefficient (k) was split into the appropriate values of parallel reaction coefficients, as shown in Table 4

DISCUSSION

Formulae of type **3** were assigned to the main products because their spectral properties are analogous to those of the main derivatives from **2g** , one of which (**3bg**) had the structure determined by XRD [1] ^{1}H-NMR spectra are similar, in particular, it can be noticed that the signal assigned to H-7 appears at δ 5.93-5 99 for compounds from **3bf** to **3ef**, at δ 6 12-6 16 for **3bh** and **3eh**, at δ 5 73-5 75 for compounds from **3ag** to **3eg**.[1] Mass spectra have an interesting common feature, showing evidence of retrocycloaddition: the most abundant peak (m/z = 180) always corresponds to the diazepine (**2**), and in addition there are minor peaks corresponding to the mass of nitrile oxides (**1**) or close to it (- H or - 2H) For sake of comparison, the mass spectrum of **3eg** has been recorded, finding the same feature

Also derivatives of type **5** showed analogies to a series of compounds already described and in particular to one of them (**5eg**), whose structure was determined by XRD [1] An important characteristic of these derivatives is the high δ-value of H-5 : **5df**, 8 67, **5ef**, 8 68; for the previous series, δ-values from 8 44 to 8 63 had been recorded for compounds from **5ag** to **5eg**.[1] Moreover, in all these cases, an exchangeable proton (NH) was evidentiated by addition of D_2O. Interestingly, **5df** and **5ef**, as well as the five analogous compounds described,[1] have a m p >190°C

As to derivatives **6**, **7** and **8**, the molecular peaks in their mass spectra and the elemental analyses indicate that they are cycloadducts, either as such (**6** and **7**) or dehydrogenated (**8**)

Table 4 - Kineticc coefficients at 70 0°C

Solvent TCE/DMF	10^4k	10^4k_3	10^4k_5	10^4k_6
		$l\ mol^{-1}s^{-1}$		
Reaction **1b** + **2f**				
0.84:0 16	1 91±0 01	1 59±0 07		0 32±0.03
0 70 0 30	2 36±0 00	2 02±0.02		0.34±0 02
0 50 0 50	2 96±0 02	2 50±0 02		0.46±0.02
Reaction **1d** + **2f**				
0 90 0 10	2 21±0 05	1 82±0 05	0 39±0 03	
0 84 0 16	2 62±0 04	2 23±0 08	0 38±0 07	
0 70 0 30	3 03±0 15	2 53±0 12	0 50±0 03	
0 50 0 50	3 56±0 03	3 00±0 05	0 56±0 05	
Reaction **1e** + **2f**				
0 90 0 10	4 38±0 04	3 57±0.04	0 17±0 00	0.64±0 02
0 84 0 16	4 88±0 05	3 97±0 04	0.18±0 01	0.72±0 01
0 70 0 30	5 70±0 16	4 68±0 13	0 19±0 07	0 82±0.03
0 50.0 50	6 61±0.02	5.46±0 06	0 22±0.02	0 93±0 07
Solvent TCE/MF	10^4k	10^4k_3	10^4k_7	10^4k_8
		$l\ mol^{-1}s^{-1}$		
Reaction **1b** + **2h**				
0 70 0 30	3 05±0 04	1 69±0 07	0 46±0.03	0 92 ±0 07
0.50 0 50	3 95±0 03	2 18±0 13	0 66±0 06	1.10±0.11
Reaction **1e** + **2h**				
0 90 0 10	6 25±0 03	3 19±0 26	0 64±0 07	2 41±0 33
0 84 0 16	7 30±0 33	3 95±0 27	0 68±0 09	2 67±0.23
0 70 0 30	8 60±0 43	4 78±0 41	0 78±0 11	3.04±0 39
0 50 0 50	11 6±0 7	6 99±0 51	1 23±0.19	3.35±0 27

The structure assignment to derivatives **6** rests on spectral evidence a comparison of ^{1}H-NMR spectra of **6bf**, **6ef**, and **2f** shows that the region interested to the cycloaddition is the CH=CH bond of the diazepine Signals from HC=N and CH_3-C=C are scarcely affected, while the other protons on the diazepine ring undergo significant chemical shift changes from **2f** to **6**

	HC=C(CH_3)	δ = 6.31 dd (**2f**);	7.00 d (**6bf**);	7.04 d (**6ef**);
HC=C(H), then	HC - C(H)	5 67 t;	4.60 dd,	4 53 dd;
	HC - N	6.16 d;	4.25 d;	4.19 d.

The larger δ-value for the second of these protons, when compared with the third one, in the adducts, indicates a cycloaddition with the orientation corresponding to products **6**, since in isoxazolines a proton at C_5 absorbs at a lower field than a proton at C_4.[2] Therefore, besides the main cycloaddition of **1** to the C=N bond of **2f**, secondary additions occur at the CH=CH bond, to give, according to the orientation, either derivatives **5**, with opening of the diazepine ring and proton shift from a carbon to a nitrogen atom, or derivatives **6** Both by-products were obtained from the reaction of **1e**.

Different secondary products were identified after reaction of **2h**. The spectral evidence in favour of structure **7** is mainly from ^{1}H-NMR. When comparing the spectra of **7bh**, **7eh**, and **2h**, one finds that among the diazepine protons only signals from H-C=N are not affected Changes from **2h** to **7** are as follows:

HC=C(H), then	HC - C(H)	δ = 6.29 dd (**2h**),	5 40 dd (**7bh**);	5 41 dd (**7eh**),
	HC - C(CH_3)	6.52 d;	4 35 d;	4.38 d;
	CH_3-C=C	1.83 d,	1.31 s;	1.34 s;
	HC = C(CH_3)	6.02 s,	6.85 s;	6.91 s

Such changes are in agreement with cycloaddition at the CH=CH bond, with the orientation indicated in the formula scheme of **7**. The aryl ring was drawn rotated out of the isoxazolinic plane because the adducts **7** show up a magnetic nonequivalence of the arylic methyl resonances This position of the ring causes, *inter alia*, magnetic effects on the CH_3 at C_6 and on H-5, as evidenced by the δ–values listed above. Mass spectra of derivatives **6** and **7** show some analogy in their fragmentation pathway· in all four cases, an intense peak corresponding to the mass of the diazepine (m/z = 180), has been found, the most abundant, or at least an intense, peak had m/z = 95 (M - CO_2 - C_2H_6 - HCN - ArCN).

Derivatives **8** show up their nature of dehydrogenated cycloadducts with a system of conjugated double bonds, because they present a light absorption band shifted towards the visible (yellow colour) and the appropriate signals in the ^{13}C-NMR spectrum, when available (**8eh**), as compared with a case without dehydrogenation (**7eh**) In the ^{1}H-NMR spectra of **8bh** and **8eh**, as compared with **2h** and also with cycloadduct **3bh** and **3eh**, the region CH_3C=CH is scarcely affected, proving that the cycloaddition has taken place on the CH=CH bond Furthermore, the absence of magnetic effects of the aryl ring on the CH_3-C=CH region in derivatives **8** evidences that the orientation of the cycloaddition is different from that of adducts **7**. It can be noticed that in derivatives **8** the aryl ring is freely rotating (as confirmed by molecular models), so that *ortho* -CH_3 groups are equivalent in NMR spectra

Mass spectra show a high stability of the derivatives **8**, at variance with other cycloadducts the molecular peak is the most abundant one, for both **8bh** and **8eh** On the

other hand, in these mass spectra there are scarce analogies with those of derivatives **6** and **7**, where the diazepine ring is substantially unaltered

As a conclusion, also in the case of **2h** the main cycloaddition of **1** occurs at the C=N bond, while secondary products so far evidenced derive from attack at the CH=CH bond, to give, according to the orientation, either derivatives **7** or **8**, the latter with loss of two H atoms at the site of attack

In no case attack of **1** to the other CC double bond ($CH=C-CH_3$) was observed, probably because such a cycloaddition is sterically hindered

Kinetic effects of the different position of the methyl group on the diazepine (**2**) can be mainly judged considering the common reaction giving rise to **3**. Data in Table 4 (for **2f** and **2h**) and in a previous paper (for **2g**) show that cycloadditions of **1b** and **1e** in the same mixed solvents occur with similar rates at 70°C Values of 10^4k_3 ($l\ mol^{-1}s^{-1}$) available for the three diazepines are for **1b** in TCE/DMF (70 30), 2 02 (+ **2f**), 2.15 (+**2g**), 1.69 (+**2h**), for **1e** in TCE/DMF (90·10), 3 57 (+**2f**), 3.86 (+ **2g**), 3 19 (+ **2h**), for **1e** in TCE/DMF (70:30), 4 68 (+ **2f**), 5 52 (+ **2g**), 4 78 (+ **2h**) Further examination of these coefficients shows that the reaction of **1** with **2g** is slightly faster than the one with **2f** or **2h**, possibly because in **2g** (Y = CH_3) the position of the methyl group better favours the polarization of the C=N bond In every case shown in Table 4 and in the previous work,[1] the enhanced polarity of the solvent, due to addition of DMF, slightly favours this cycloaddition, as well as the other ones

Since rate coefficients for comparable reactions are available for two or three nitrile oxides (**1b** and/or **1d**, besides **1e**), the kinetic effects of substituents in **1** can be judged it appears that there is a slight rate-enhancing effect of electron-withdrawing substituents on the main cycloaddition, corresponding to a positive ρ-value, although small (<1), both for diazepine **2f** and for **2h** This agrees with previous observations about **2g**.[1] As to the secondary reactions, in every case kinetic measurements are available for only two nitrile oxides (**1b** or **1d**, besides **1e**) more often, the most reactive nitrile oxide is **1e**, again pointing to a positive ρ value, however in the reaction of diazepine **2f** that gives rise to products of type **5**, the contrary is true It may be remarked that this result (*i.e.* a ρ value <0) was not obtained in the case of diazepine **2g** [1]

In the case of the reaction **1e** + **2h**, kinetic runs were carried out at 70.0°C in a TCE/MeOH (70.30 v/v) solvent, without and with addition of $LiClO_4$, which has been reported to accelerate a Diels-Alder reaction [3] Within experimental error, both the effect of replacing DMF by MeOH and the effect of adding 0 9 or 1 4 mol l^{-1} $LiClO_4$ were not significant both selectivities and rates were scarcely affected

EXPERIMENTAL

Melting points are uncorrected. ^1H- and ^{13}C-NMR spectra were recorded with a Varian VXR-300 spectrometer (Me_4Si as internal standard, $CDCl_3$ as the solvent). Mass spectra were recorded, at 70 eV, with a HP 5989 A mass spectrometer, using the DIP (direct insertion probe) method. Reagent grade reagents and solvents were used

Materials

Aryl nitrile oxides **1** were obtained as previously described.[4] The diazepines (**2f**,**2h**) were prepared starting from 1-ethoxycarbonylimino-3-methyl-pyridinium ylide obtained by reaction of β-picoline with hydroxylamine-*O*-sulfonic acid and ethyl chloroformate as described [5]

A solution of pyridinium ylide (7 g, 0 039 mol) in acetone (500 ml) was irradiated under nitrogen and internal cooling to 10-15°C, with a 125 W high pressure lamp The solution was then concentrated *in vacuo*, and the reaction mixture was separated, by flash chromatography on silicic acid prepared by the following procedure a column of Merck silica gel of 50 cm length and 3 5 cm i d. was treated twice with aqueous sulphuric acid (0 36 mol l^{-1}) and then washed twice with water (200 ml) and successively eluted twice with 200 ml of ethanol, ethyl acetate, petroleum ether - ethylacetate, and finally with a mixture of petroleum ether (bp 40-70°C)-ethyl acetate (0.9 0 1,v/v) By applying at the column top a pressure of 0 7 bar, the mixture of the diazepines (**2f**) and (**2h**) was fractionated with petroleum ether-ethylacetate (0 9·0.1, v/v) as eluant Fractions (15 ml) were collected and controlled by TLC, the diazepines (**2f**) and (**2h**) were then obtained, as yellow oils, in the ratio 0 6 0 4 Their purity was controlled by HPLC analysis, 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 Their ^{1}H-NMR spectra, although already published,[6] were recorded again, with the following results.

^{1}H-NMR (δ ppm) **2f** 7 26 (1H, s, H-3), 6 30 (1H, dd, H-5), 6.15 (1H, d, H-7), 5 67 (1H, t, H-6), 4 31(2H, q, -CH_2-), 1.94 (3H, unresolved d, CH_3 in C-4), 1 35 (3H, t, -CH_3);

2h 7 42 (1H, d, H-3), 6 52 (1H, d, H-5), 6 29 (1H, dd, H-4), 6 02 (1H, s, H-7), 4 30 (2H, q, -CH_2), 1.83 (3H, d, CH_3 in C-6), 1.34 (3H, t, -CH_3)

General procedure for the reaction of the aryl nitrile oxides (1) with the diazepines (2).

A solution of **1** (2 3 g, 0 01 mol) and **2** (3.65 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 (0 9:0.1,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 (0.7 0 3,v/v) and the other cycloadducts were obtained The cycloadducts were obtained as white crystals unless otherwise indicated

From the reaction of several aryl nitrile oxides (**1**) with the diazepine (**2f**) the products listed below have been obtained .

Reaction 1b + 2f:

2-Ethoxycarbonyl-6-methyl-10-(2,4,6-trimethylphenyl)-1,2,9-triaza-8-oxabicyclo[5.3.0^{1,7}]-3,5,9-decatriene (**3bf**) ^{1}H-NMR (δ ppm)· 6.84 (2H, s, H_{ar}), 6.37 (1H, d, H-3), 5 93 (1H, s,

H-7), 5 82 (1H, d, H-5), 5 23 (1H, t, H-4), 2.33 (3H, s, *para* CH_3), 2 26 and 2.21 (6H, s, *ortho* CH_3), 2.00 (3H, s, CH_3 in C-6), 4.19 (2H, q, $-CH_2$), 1.26 (3H, t, $-CH_3$)
Mass spectrum m/z(%). 341(M^+, 27.1), 210(2.95); 181(13 5); 180(100); 160(13.3), 159(18.5); 146(23.4); 145(36 8); 144(15.8), 131(18.0); 130(57 7), 121(21 5), 115(9 0), 110(65 9); 109(12.9), 108(75.8), 107(12.5); 103(12 9), 96(12 7), 95(62.5), 94(34.0); 93(17 1), 92(20 5), 91(16 2); 81(38 5), 80(41 2); 78(12 5), 77(20.2); 67(22.8), 65(27 0), 58(24.3); 53(25.8), 43(89 0)

2-Ethoxycarbonyl-5-methyl-10-(2,4,6-trimethylphenyl)-2,3,9-triaza-8-oxabicyclo-[5.3.0^{1,7}]-3,5,9-decatriene (**6bf**) ^{1}H-NMR(δ ppm). 7.50 (1H, s, H-4), 7 00 (1H, d, H-6), 6.88 (2H, s, H_{ar}), 4 60 (1H, dd, H-7), 4 25 (1H, d, H-1), 2 29 (3H, s, *para* CH_3), 2.19 (6H, s, *ortho* CH_3), 1.78 (3H, s, CH_3 in C-5), 4 35 (2H, q, $-CH_2$-), 1 38 (3H, s, $-CH_3$). ^{13}C-NMR (δ ppm). 162 5 (C-4), 158 8 (C=O), 143 8 (C-10), 135 (C-14), 130 (C-5), 129 8 (C-12, C-16), 128 5 (C-13, C-15), 100 8 (C-6), 88.5 (C-1), 64 2 (C-7), 59.3 ($-CH_2$), 19.9 (CH_3 in C-5), 19 0 (*para* CH_3), 18 2 (*ortho* CH_3), 14 4 (CH_3)
Mass spectrum m/z(%) 341(M^+, 16 3), 284(8.4), 252(3.4), 181(11.0); 180(75 3); 167(54.6), 161(38 5), 146(10 7), 145(27 9); 144(11 9), 134(11 6), 132(9.8), 131(9 6), 130(52 7), 129(9 1), 128(9 2), 123(12.6), 121(17 7), 117(14.2), 116(10.3), 115(20.5); 109(10.8), 108(49 5), 107(17 8), 105(12 4); 103(15 1); 96(12 1); 95(88 2); 94(9 2), 91(38 2), 81(100), 80(46 3), 79(16 8), 78(15 2), 77(27.3), 68(10 7), 65(17.2); 63(12 4), 54(18 3), 53(32 8), 52(24 2), 51(29 7), 50(12 4), 43(40 4), 42(9 6), 41(26 1), 39(42 0)

Reaction 1c + 2f :

2-Ethoxycarbonyl-6-methyl-10-(2,6-dimethylphenyl)-1,2,9-triaza-8-oxabicyclo[5.3.0^{1,7}]-3,5,9-decatriene (**3cf**): ^{1}H-NMR (δ ppm) 7 18 (1H, t, H_{ar}), 7 03 (2H, m, H_{ar}), 6 37 (1H, d, H-3), 5 96 (1H, s, H-7), 5 83 (1H, d, H-5), 5 24 (1H, t, H-4), 2 39 and 2 26 (6H, s, *ortho* CH_3), 2 01 (3H, s, CH_3 in C-6), 4 19 (2H, q, $-CH_2$), 1 26 (H, t, CH_3)
Mass spectrum. m/z(%) 327(M^+, 42 4), 310(2 4); 254(3 8); 240(4 3); 239(21.2), 227(2.1); 223(2 2), 211(3.2), 209(3 1), 197(2 8), 196(5.0), 182(7 9), 181(16 3), 180(100); 146(10.6); 145(20 5), 132(17 4), 131(14 3), 130(16 2), 121(19 4), 117(12 3), 116(16.8), 110(66 6); 108(62 5), 107(11 8), 103(11 1), 95(39 7), 94(34 1); 93(18 0), 92(21 3); 91(10 1); 82(10.8); 81(34 1), 80(29 9), 79(9 9), 78(12 9), 77(20 9), 67(22 9), 66(13 0), 65(22.9), 53(19.3), 51(12 5), 44(16 8), 43(11 6), 41(41 6), 39(38 7)

Reaction 1d +2f :

2-Ethoxycarbonyl-6-methyl-10-(4-bromo-2,6-dimethylphenyl)-1,2,9-triaza-8-oxabicyclo-[5.3.0^{1,7}]-3,5,9-decatriene (**3df**) ^{1}H-NMR (δ ppm) 7 21 (2H, s, H_{ar}), 6 38 (1H, d, H-3), 5 94 (1H, s, H-7), 5 82 (1H, d, H-5), 5 24 (1H, t, H-4), 2.37 and 2 24 (6H, s, *ortho* CH_3), 2 00 (3H, s, CH_3 in C-6), 4 18 (2H, q, $-CH_2$-), 1 26 (3H, t, $-CH_3$)
Mass spectrum m/z(%) 407(M^+, 7 6), 319(3 4), 227(9 5), 210(6 9); 180(100), 153(3 6),

130(18 3), 121(19 0); 110(92.8); 108(73.9); 103(14.8); 95(55 4); 94(43.0); 81(36.1); 67(37.6), 53(24 1); 41(50.5)

3-(4-Bromo-2,6-dimethylphenyl)-4-[(1Z,3E)-5-ethoxycarbonyl-2-methyl-4,5-diaza-1,3-pentadienyl]isoxazole (**5df**): ^{1}H-NMR (δ ppm): 8.67 (1H, s, H-5), 8 30 (1H, s, NH), 8.06 (1H, s, H-3'), 7.30 (2H, s, H_{ar}), 5 84 (1H, s, H-1'), 2.05 (6H, s, *ortho* CH_3), 2.00 (3H, s, CH_3 in C-2'), 4.28 (2H, q, -CH_2), 1.33 (3H, t, -CH_3).
Mass spectrum: m/z(%) 407,405(M^+, 47.4), 392(29 3); 390(100), 389(16 0); 388(73 7); 362(14.3), 344(17.1), 342(10.8), 319(12 8); 318(22 3), 317(14.8); 316(19.3), 305(11.7), 304(31.9); 303(43 5), 302(36.6); 301(40 6), 299(16.8), 291(14 7), 290(20.7); 289(34.8); 288(19.7); 287(27 7); 276(31.7); 275(21.4); 274(33 3), 273(14.4); 238(12.8), 223(13.1), 222(10.4); 211(16.0), 210(32.9), 209(35.3), 208(13 0); 196(11 1); 195(36.7), 194(21.4), 181(12.9), 180(13 2), 130(17.4), 104(24.1); 103(28 3); 95(11.3); 78(25.2), 77(32.3); 65(17 5), 63(13 7); 53(15 4), 52(13 2); 51(19.8), 45(15.0); 44(97 0), 41(18.5); 39(38 5)

Reaction 1e + 2f :

2-Ethoxycarbonyl-6-methyl-10-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,9-triaza-8-oxa-bicyclo[5.3.0^{1,7}]-3,5,9-decatriene (**3ef**): ^{1}H-NMR (δ ppm) 6.44 (1H, d, H-3), 5 99 (1H, s, H-7), 5.87 (1H, d, H-5), 5.26 (1H, t, H-4), 2.55 (3H, s, *para* CH_3), 2.41 and 2.29 (6H, s, *ortho* CH_3), 2.03 (3H, s, CH_3 in C-6), 4.23 (2H, q, -CH_2), 1 30 (3H, t,-CH_3).
Mass spectrum m/z(%) 409(M^+, 12 3), 321(4 6); 230(5.3), 229(8.4); 228(6.1); 227(9.9); 216(4 8), 215(5.1); 214(9.0), 213(6.5), 212(4.0), 202(3.9); 193(6.9); 192(4.6); 180(100), 178(15 9), 149(12.1), 140(6.9), 121(17 8); 115(18.6); 110(79 1); 108(55.9), 95(64 0), 92(26.7), 81(33 3), 80(34.5), 67(37 8); 53(25 9); 41(64 7), 39(53 3).

3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4-[(1Z,3E)-5-ethoxycarbonyl-2-methyl-4,5-diaza-1,3-pentadienyl]isoxazole (**5ef**): ^{1}H-NMR (δ ppm): 8.68 (1H, s, H-5), 8.04 (1H, s, NH), 7.98 (1H, s, H-3'), 5.82 (1H, s, H-1'), 2.58 (3H, s, *para* CH_3), 2.09 (6H, s, *ortho* CH_3), 2 01 (3H, s, CH_3 in C-2'), 4 28 (2H, q, -CH_2-), 1.33 (3H, t,-CH_3).
Mass spectrum m/z(%): 409(M^+, 9.4), 394(16.6); 392(16 0); 320(5.0), 305(5.7); 303(5 3), 293(6 9), 280(10 7); 278(15.6), 243(13.2), 180(22 9); 178(13 8), 167(13.0); 166(12 9), 149(15 8), 123(17 0), 117(13 2), 116(19.4), 115(44 3), 108(26.4); 96(10.6), 95(100), 94(13 2), 83(17 9), 81(26 5), 80(28 5); 77(14 8); 65(20 2); 51(19 7), 43(19 3), 41(43 1), 39(48 5)

2-Ethoxycarbonyl-5-methyl-10-(3,5-dichloro-2,4,6-trimethylphenyl)-2,3,9-triaza-8-oxabi-cyclo[5.3.0^{1,7}]-3,5,9-decatriene (**6ef**). ^{1}H-NMR (δ ppm). 7.49 (1H, s, H-4), 7.04 (1H, d, H-6), 4.53 (1H, dd, H-7), 4.19 (1H, d, H-1), 2.54 (3H, s, *para* CH_3), 2 24 and 2.19 (6H, s, *ortho* CH_3), 1.74 (3H, s, CH_3 in C-5), 4.37 (2H, q,-CH_2-), 1.39 (3H, t, -CH_3). ^{13}C-NMR (δ ppm) 162 6 (C-4), 158.8 (C=O), 143 8 (C-10), 135.0 (C-14), 130.0 (C-5), 129 8 (C-13, C-

15), 128 5 (C-12, C-16), 123 0 (C-11), 100.8 (C-6), 88 5 (C-1), 64.7 (C-7), 59 3 (CH_2), 19 9 (CH_3 in C-5), 19 0 (*para* CH_3), 18 2 (*ortho* CH_3), 14 4(-CH_3)
Mass spectrum m/z (%) 409(M^+, 4.0), 215(10 2), 213(14 5), 180(67 4), 178(29 4), 167(59.1), 149(52 6); 141(17 3), 123(19 0), 121(15.3), 115(21.2), 108(37 0), 95(100), 83(34 8), 81(68 3), 77(12 9), 65(7 0); 57(19.9), 53(15 6), 43(50 1), 41(19 7), 39(18 4).

From the reaction of aryl nitrile oxides (**1b** and **1e**) and the diazepine (**2h**) the following products have been obtained

2-Ethoxycarbonyl-4-methyl-10-(2,4,6-trimethylphenyl)-1,2,9-triaza-8-oxabicyclo-[5.3.0^{1,7}]-3,5,9-decatriene (**3bh**) ^{1}H-NMR (δ ppm) 6 86 (2H, s, H_{ar}), 6 24 (1H, s, H-3), 6 12 (1H, s_b, H-7), 5 93 (2H, dd, H-5 and H-6, $J_{5,6}$ = 12 Hz), 2 31 (3H, s, *para* CH_3), 2 28 and 2 21 (6H, s, *ortho* CH_3), 1 78 (3H, d, CH_3 in C-4), 4 20 (2H, q, -CH_2-), 1 28 (3H, t, -CH_3)
Mass spectrum. m/z (%) 341(M^+, 12 6), 253(3 7), 237(3 1), 225(2 4); 207(4 2), 180(100); 161(13 9), 160(13 1), 159(14 5), 146(21 6), 145(25 7), 144(13 0), 130(38 8); 121(25.2), 110(74 6), 108(77 4), 95(41 6), 94(54 9), 91(28.1), 81(61 5), 80(54 0); 65(29 2); 41(69 2)

4-Ethoxycarbonyl-6-methyl-8-(2,4,6-trimethylphenyl)-3,4,9-triaza-10-oxabicyclo-[5.3.0^{1,7}]-2,5,8-decatriene (**7bh**) ^{1}H-NMR (δ ppm) 7 43 (1H, d, H-2), 6 88 (2H, s, H_{ar}), 6.85 (1H, s, H-5), 5 40 (1H, dd, H-1), 4 35 (1H, d, H-7), 2.28 (3H, s, *para* CH_3), 2.21 and 2.13 (6H, s, *ortho* CH_3), 1 31 (3H, s, CH_3 in C-6), 4 34 (2H, q, -CH_2-), 1 35 (3H, t, -CH_3)
Mass spectrum m/z(%) 341(M^+, 22 7); 284(8.1); 241(2 6), 240(3 3), 181(6 5), 180(42 9), 167(27.6), 145(19 3), 130(36 0), 123(13 2), 108(23 2); 95(100), 91(10 2), 81(18 0), 80(16 2), 77(13 0), 68(11 4), 65(12 1), 53(11 9), 51(10.0), 43(16.6), 41(25 2); 39(32.1)

4-Ethoxycarbonyl-6-methyl-10-(2,4,6-trimethylphenyl)-3,4,9-triaza-8-oxabicyclo-[5 3 0^{1,7}]-2,5,7,9-*decatetraene* (**8bh**) yellow crystals; ^{1}H-NMR (δ ppm) 7 42 (1H, s, H-2), 6 94 (2H, s, H_{ar}); 6 33 (1H, s, H-5), 2 31 (3H, s, *para* CH_3); 2 17 (3H, d, CH_3 in C-6), 2.11 (6H, s, *ortho* CH_3), 4 34 (2H, q, -CH_2-), 1 34 (3H, t,-CH_3)
Mass spectrum m/z(%) 339(M^+, 100), 293(2 5), 284(31 8), 267(12.5); 266(21 8), 252(14 5), 250(8 4), 239(17 9); 238(51 4), 223(13 3); 212(24 6), 211(9.4), 197(12 2), 185(15 6), 184(6 2); 170(26 9), 157(12 9); 156(8.2), 155(8 1), 144(14 1), 130(13 5); 128(13 0), 119(59 5), 117(22 0), 115(22 2); 110(17 2), 103(22 4), 91(78.7), 79(15 4), 77(41 8), 65(25 7), 53(38 0), 44(15 4)

2-Ethoxycarbonyl-4-methyl-10-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,9-triaza-8-oxabicyclo[5.3.0^{1,7}]-3,5,9-decatriene (**3eh**) ^{1}H-NMR (δ ppm) 6 31 (1H, s, H-3), 6.16 (1H, s_b, H-7), 5 95 (2H, dd, H-5 and H-6, $J_{5,6}$= 12 Hz), 2.54 (3H, s, *para* CH_3), 2 37 and 2 32 (6H, s, *ortho* CH_3), 1 82 (3H, d, CH_3 in C-4), 4.20 (2H, q, -CH_2-), 1 27 (3H, t, -CH_3)
Mass spectrum m/z(%) 409(M^+, 3 3); 230(2 8), 229(4 8), 228(3 6), 227(4 4); 216(4 0), 215(5 5), 214(7 8), 213(7 9), 212(3 2), 193(4 9), 181(12 2); 180(100), 178(18.8); 168(6 7), 149(17 1), 140(10 2), 123(17 1); 121(21 6), 115(22.0); 110(67 4), 108(63 3), 95(66 9),

94(49 6), 93(19.2), 92(19 2), 81(53 6), 80(44 6), 77(17 7); 67(32.4), 66(21 5), 65(35 8); 53(33 4), 41(78 8), 39(73 3)

4-Ethoxycarbonyl-6-methyl-8-(3,5-dichloro-2,4,6-trimethylphenyl)-3,4,9-triaza-10-oxabicyclo[5.3.0^{1,7}]-2,5,8-decatriene (**7eh**) ^{1}H-NMR (δ ppm) 7 41 (1H, d, H-2), 6.91 (1H, s, H-5), 5 41 (1H, d, H-1), 4 38 (1H, d, H-7), 2 55 (3H, s, *para* CH_3), 2 29 and 2 20 (6H, s, *ortho* CH_3), 1 34 (3H, s, CH_3 in C-6), 4 36 (2H, q, -CH_2), 1 38 (3H, t, -CH_3)
^{13}C-NMR (δ ppm): 161 1 (C-2), 156 1 (C=O), 154 2 (C-8), 136.2 (C-14), 134 0 (C-13, C-15), 132.0 (C-5), 128 0 (C-12, C-16), 126 4 (C-11), 110 8 (C-6), 78 6 (C-7), 64 0 (C-1), 57.8 (-CH_2), 22 2 (*para* CH_3), 19.1 (*ortho* CH_3), 18 4 (CH_3 in C-6), 14 3 (-CH_3).
Mass spectrum m/z (%) 409(M$^+$, 7 4), 322(3 1), 320(3 8), 213(6 7), 180(40 0), 178(15 7), 167(35 5), 149(17 6), 123(14 5), 121(9 0), 115(14 5), 108(23 7), 95(100); 81(16 9); 80(17 2), 77(6 7), 68(10 2), 65(6.8), 53(11 6), 41(22 7), 39(21 1)

4-Ethoxycarbonyl-6-methyl-10-(3,5-dichloro-2,4,6-trimethylphenyl)-3,4,9-triaza-8-oxabicyclo[5.3.0^{1,7}]-2,5,7,9-decatetraene (**8eh**) yellow crystals, ^{1}H-NMR (δ ppm) 7 41 (1H, s, H-2), 6.37 (1H, s, H-5), 2.58 (3H, s, *para* CH_3), 2 18 (6H, s, *ortho* CH_3), 2 18 (3H, s, CH_3 in C-6), 4 32 (2H, q, -CH_2), 1 36 (3H, t, -CH_3) ^{13}C-NMR (δ ppm) 172 3 (C-5), 159 8 (C=O), 154 5 (C-10), 151 7 (C-2), 136 7 (C-14), 134 0 (C-6), 133 9 (C-7), 131 7 (C-13, C-15), 125 2 (C-12, C-16), 120 2 (C-11), 114 5 (C-1), 63 2 (-CH_2), 19 1 (*para* CH_3), 18 7 (*ortho* CH_3), 14 5 (CH_3 in C-6), 14 2 (-CH_3).
Mass spectrum m/z (%) 407(M$^+$, 99 8), 352(35 2), 334(27 3), 308(40 0), 307(20 7), 306(47 5), 301(10 1), 300(17 6); 299(20 0), 282(12 5), 280(17.8), 273(40 6), 272(26 1), 271(59 6), 265(12 5), 252(9 7); 253(15 0); 245(19 8), 240(15 9), 238(22 9), 225(9 2), 214(13 6); 203(15 8), 202(15 8), 187(15 6); 178(19 4), 167(15 2), 152(25 5), 151(22 2), 149(40.6), 128(20 9), 117(42 2), 116(57 0), 115(100); 110(30 3), 94(49 2), 83(27 4); 77(14 3), 67(12 2); 65(28 4), 53(52 3), 51(20 5), 39(67 3), 36(31.2)

Reaction selectivities.

Besides the excess of diazepine, the analysis revealed the occurrence of the cycloadducts above described. The adducts were determined in the reaction mixtures, after reaction for *ca.* 10 half-lives of the nitrile oxide (0.02 mol l^{-1}) with the diazepine (**2f** or **2h**) (0 2-0 5 mol l^{-1}), in solvent mixtures containing 1,1,2,2-tetrachloroethane (TCE) and *N,N*-dimethylformamide (DMF) in the ratio (v/v) 0.90·0.10, 0.84·0.16, 0 70:0.30 and 0 50·0 50, respectively. The samples were diluted with chloroform and analyzed by 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 were obtained from the molar concentrations since

$S_3=C_3/(C_3+C_5+C_6)$, $S_5=C_5/(C_3+C_5+C_6)$ and $S_6=C_6/(C_3+C_5+C_6)$ for the reaction **1e+2f;**
$S_3=C_3/(C_3+C_7+C_8)$, $S_7=C_7/(C_3+C_7+C_8)$, $S_8=C_8/(C_3+C_7+C_8)$ for the reactions **1b+2h** and **1e + 2h,**
$S_3 = C_3/(C_3+C_5)$ and $S_5 = C_5/(C_3+C_5)$ for the reaction **1d + 2f,**
$S_3 = C_3/(C_3+C_6)$ and $S_6 = C_6/(C_3+C_6)$ for the reaction **1b + 2f**

Kinetics

The reactions were carried out in a thermostatted 0 5mm sodium chloride cell (Beckmann FH-01 variable temperature cell) in a IR spectrophotometer The temperature was kept constant to within ±0.2 °C Quantitative analyses were made of the band typical of nitrile oxides (**1**) The concentration of the latter was *ca.* 0 02 mol l^{-1} while for diazepine(**2**) was in the range 0 2-0.5 mol l^{-1} Absorbance values were obtained from the peak heights and the concentration read from calibration plots. Kinetic runs were carried out for up to two half-lives and results interpreted by the equation for second order reactions [equation (3)]:

$$\ln (c_2/c_1) = (c_2^\circ - c_1^\circ)kt + \text{constant} \qquad (3)$$

The overall kinetic coefficients k were then split into k_3, k_5, and k_6 or into k_3, k_7, and k_8 parameters on the basis of the selectivity values S_3, S_5, and S_6 for the reactions **1 + 2f,** and S_3, S_7, and S_8 for the reactions **1 + 2h,** since for parallel reactions of the same order

$$k_3 = kS_3, \quad k_5 = kS_5, \quad k_6 = kS_6, \quad \text{and}$$
$$k_3 = kS_3; \quad k_7 = kS_7, \quad k_8 = kS_8 \qquad (4)$$

in the two cases, respectively
Duplicate kinetic runs were always carried out with good reproducibility

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