1,3-Cycloaddition of Substituted Benzonitrile Oxides to Aliphatic Nitriles. The Kinetic Effect of Substituents

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A previous study of the reaction of aromatic nitrile oxides with simple aliphatic nitriles, with the formation of 3,5-disubstituted 1,2,4-oxadiazoles, has been extended to a larger number of nitrile oxides. Sixteen new oxadiazole derivatives have been prepared and characterized. Cycloaddition rates have been measured in the temperature range from 50 to 80°. When considering the effect of substituents on the aromatic ring, roughly V-shaped Hammett plots have been obtained, as already observed for other concerted 1,3-cycloadditions.

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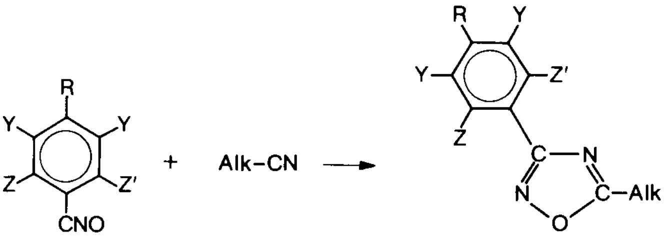
It has been known for a long time that nitrile oxides are able to give 1,3-cycloaddition to aromatic nitriles [1] and in particular cases (activation by electronegative substituents or by a Lewis acid catalyst) to aliphatic nitriles too [2]. More recently it has been reported that even the uncatalysed cycloaddition of aromatic nitrile oxides to simple aliphatic nitriles is possible, using the nitriles in large excess, *i.e.* as both reagents and solvents [3]. In all cases, 3,5-disubstituted 1,2,4-oxadiazoles were obtained; hence the cycloaddition represents a useful synthesis of these compounds.

Further investigation of the reaction with simple aliphatic nitriles, using a larger number of nitrile oxides, seemed appropriate both for the preparation of new 1,2,4-oxadiazolic derivatives and in order to assess the kinetic effect of substituents on the benzene ring. A too limited set of nitrile oxides had been considered in the previous research [3] for an adequate evaluation of such an effect. Furthermore, one of the nitrile oxides then employed, thought to be pure **1a**, was not so. 4-Methoxy-2,6-dimethylbenzaldehyde, a precursor of **1a**, had been prepared by a method [4] which actually gives a mixture of that aldehyde with its isomer 2-methoxy-4,6-dimethylbenzaldehyde, so that the resulting nitrile oxide was **1a** mixed with **1f**. Since separation of the two aldehydes has been later effected [5], nitrile oxides **1a** and **1f**, separately prepared, were made available for a correct study of their reactivity.



1 2 3

	Z	Z'	Y	R		Alk
(a)	CH_3	CH_3	H	OCH_3	(r)	CH_3
(b)	CH_3	CH_3	H	CH_3	(s)	CH_3CH_2
(c)	CH_3	CH_3	H	H	(t)	$(CH_3)_2CH$
(d)	CH_3	CH_3	H	Br	(u)	$CH_3CH_2CH_2$
(e)	CH_3	CH_3	Cl	CH_3		
(f)	CH_3	OCH_3	H	CH_3		

The reaction of nitrile oxides **1** with nitriles **2**, giving rise to 1,2,4-oxadiazoles **3**, is here considered.

Results and Discussion.

Reactions of **1a**, **1c**, **1d**, and **1f**, carried out in excess nitrile at temperatures in the range 50-80°, gave new cycloadducts. Although some products had a difficult combustion, elemental analyses were on the whole satisfactory (Table 1).

Mass spectra were obtained for **3ar**, **3cs**, **3dt**, and **3fu**. In the region of the molecular peak, which was always present, the most intense peaks were as follows (m/e values and assignment):

	$[M\text{-}CH_3]^+$	$[M\text{-}C_2H_5]^+$	$[M\text{-}AlkCN]^+$	$[M\text{-}(Alk\text{-}H)CO]^+$	$[M\text{-}AlkCO]^+$
3ar	203	—	—	176	175
3cs	—	173	147	146	145
3dt	—	—	225-227	224-226	—
3fu	231	—	177	—	175

Two fragmentation pathways of the oxadiazole ring were thus evidenced, one breaking 1-2 and 4-5 bonds, as previously observed [3], the other one leading to a retro-1,3-cycloaddition [6].

The ^1H-nmr spectra corresponding to the expected structure **3** were obtained for all new cycloadducts. Ranges of chemical shifts, listed in Table 2, refer in each case to a set of four compounds. Chemical shifts of alkyl protons are in agreement with those of previous adducts, confirming the structure of 1,2,4-oxadiazole derivatives.

The uv spectra of the new cycloadducts, besides strong

Table 1

Analytical Data of New Cycloadducts **3**

Adduct	Mp (°C)	N_D	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
ar	71		$C_{12}H_{14}N_2O_2$	66.0	6.5	12.8	65.7	6.6	12.5
as		1.5520 [a]	$C_{13}H_{16}N_2O_2$	67.2	7.0	12.1	67.2	7.1	11.8
at		1.5376 [b]	$C_{14}H_{18}N_2O_2$	68.3	7.4	11.4	68.6	7.0	11.3
au		1.5490 [a]	$C_{14}H_{18}N_2O_2$	68.3	7.4	11.4	68.0	7.4	11.2
cr		1.5562 [c]	$C_{11}H_{12}N_2O$	70.2	6.4	14.9	70.5	6.4	14.8
cs		1.5420 [a]	$C_{12}H_{14}N_2O$	71.3	7.0	13.9	71.5	7.2	13.7
ct		1.5280 [d]	$C_{13}H_{16}N_2O$	72.2	7.5	13.0	72.4	7.5	13.0
cu		1.5340 [d]	$C_{13}H_{16}N_2O$	72.2	7.5	13.0	72.3	7.8	13.1
dr	67		$C_{11}H_{11}BrN_2O$	49.4	4.2	10.5	49.5	4.2	10.1
ds		1.5704 [d]	$C_{12}H_{13}BrN_2O$	51.2	4.7	10.0	51.1	4.8	9.7
dt	48		$C_{13}H_{15}BrN_2O$	52.9	5.1	9.5	53.0	5.3	9.2
du		1.5682 [d]	$C_{13}H_{15}BrN_2O$	52.9	5.1	9.5	52.7	5.1	9.3
fr	49		$C_{12}H_{14}N_2O_2$	66.0	6.5	12.8	65.7	6.5	12.9
fs	73		$C_{13}H_{16}N_2O_2$	67.2	7.0	12.1	67.3	7.1	11.9
ft	128		$C_{14}H_{18}N_2O_2$	68.3	7.4	11.4	[e]	[e]	[e]
fu		1.5416 [a]	$C_{14}H_{18}N_2O_2$	68.3	7.4	11.4	68.1	7.3	11.2

[a] At 22°. [b] At 23.5°. [c] At 17°. [d] At 26°. [e] The results for C, H, and N were always low, probably due to incomplete combustion, but in all cases (5 different samples) the theoretical atomic ratio 14:18:2 was observed.

Table 2

Summary of ^{1}H-NMR Spectra of New Cycloadducts **3** (δ ppm)

	Alkyl groups		
	CH_3	CH_2	CH
(r)	2.62-2.66 s	—	—
(s)	1.40-1.42 t	2.95-2.96 q	—
(t)	1.44-1.46 d	—	3.26-3.31 m
(u)	1.02-1.04 t	1.90-1.95 m 2.89-2.94 t	—

	Aromatic moiety			
	arom. H	(substituent)	*ortho*	*para*
(a)	6.62-6.64 s	(CH_3)	2.18-2.19 s	—
		(OCH_3)	—	3.73-3.78 s
(c)	7.10-7.15 m	(CH_3)	2.19-2.20 s	—
(d)	7.27-7.28 s	(CH_3)	2.17-2.18 s	—
(f)	6.65-6.67 s	(CH_3)	2.15-2.16 s	2.32-2.34 s
		(OCH_3)	3.72-3.74 s	—

Table 3

Typical UV Absorption Bands of New Cycloadducts **3** in Methanol
(λ max/nm; Molar Absorption in Parenthesis)

	a	c		d		f
r	280	271 sh	278 sh	270 sh	278 sh	282
	(1200)	(390)	(360)	(600)	(560)	(2100)
s	280	268 sh	274 sh	270 sh	278 sh	283
	(1400)	(670)	(710)	(680)	(600)	(1700)
t	280	268	274	270 sh	278 sh	288
	(1300)	(690)	(730)	(690)	(610)	(1800)
u	280	269	274	270 sh	278 sh	283
	(1600)	(650)	(660)	(750)	(650)	(1700)

Table 4

Rate Coefficients (10^5k/s^{-1}) for Reactions of Acetonitrile (**2r**)

Nitrile oxide Temperature (°C)	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
50.0	3.16	—	1.78	2.43	—	1.83
60.0	7.64	—	4.43	6.35	—	4.29
70.0	18.0	14.3	10.80	14.8	16.8	11.33
log A	8.48		9.19	8.88		8.85
ΔE_{act}/kJ mole^{-1}	80.3		86.3	83.4		84.1
$\Delta S^{\ddagger}$/J mole^{-1}K^{-1}	-89.1		-78.4	-84.4		-82.1

Table 5

Rate Coefficients (10^5k/s^{-1}) for Reactions of Propionitrile (**2s**)

Nitrile oxide Temperature (°C)	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
50.0	5.76	—	2.99	4.49	—	4.53
60.0	14.4	—	9.67	13.8	—	10.47
70.0	29.0	23.1	19.9	29.0	31.8	21.6
80.0	61.8	—	43.0	62.5	—	42.7
log A	7.78		8.92	8.97		7.11
ΔE_{act}/kJ mole^{-1}	74.3		82.9	82.1		70.8
$\Delta S^{\ddagger}$/J mole^{-1}K^{-1}	-102.5		-83.5	-82.7		-115.2

absorption at wavelengths between 220 and 260 nm, were characterized by typical weak bands, often shoulders, around 270-280 nm (Table 3). There was practically no interference with the absorption maxima of nitrile oxides **1** that were employed for analytical determinations of kinetic interest, since the latter have ϵ-values of the order of 10^4.

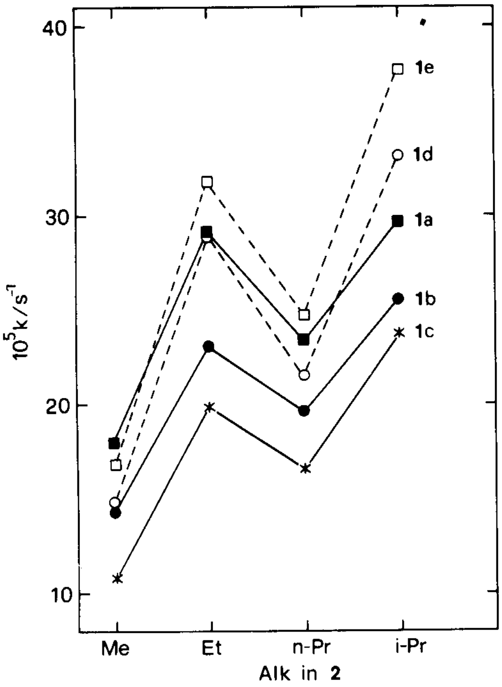


Figure 1. Rate coefficients at 70.0°C for reactions of **1a-e** with different aliphatic nitriles **2**.

Table 6

Rate Coefficients ($10^5k/s^{-1}$) for Reactions of *iso*-Butyronitrile (**2t**)

Nitrile oxide Temperature (°C)	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
50.0	6.57	—	3.92	5.67	—	3.45
60.0	16.2	—	9.75	13.8	—	9.73
70.0	29.6	25.5	23.7	33.1	37.6	20.2
80.0	71.7	—	48.6	64.0	—	40.6
log A	7.74		8.56	8.27		8.06
ΔE_{act}/kJ mole^{-1}	73.7		80.2	77.4		77.3
$\Delta S^{\ddagger}$/J mole^{-1}K^{-1}	-103.2		-90.4	-93.0		-100.0

Table 7

Rate Coefficients ($10^5k/s^{-1}$) for Reactions of Butyronitrile (**2u**)

Nitrile oxide Temperature (°C)	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
50.0	4.42	—	2.80	3.97	—	2.41
60.0	11.08	—	7.22	10.10	—	6.31
70.0	23.4	19.6	16.5	21.5	24.7	14.4
80.0	50.6	—	39.3	57.3	—	29.8
log A	8.03		8.87	9.02		8.25
ΔE_{act}/kJ mole^{-1}	76.6		83.0	83.1		79.5
$\Delta S^{\ddagger}$/J mole^{-1}K^{-1}	-97.7		-84.6	-81.6		-96.3

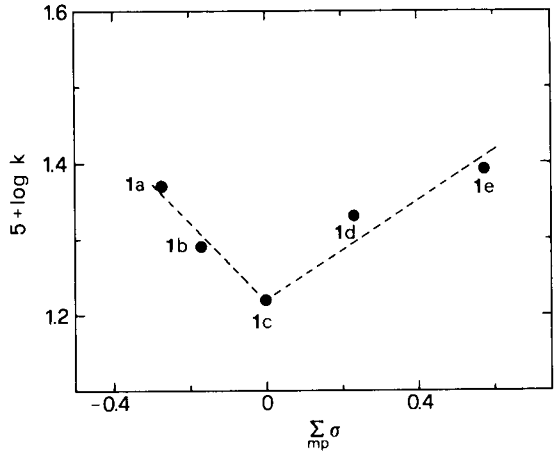


Figure 2. Hammett plot for the reaction of **1a-e** with **2u** at 70.0°C. Sums of σ-values refer to Y and R substituents only.

Kinetic results are presented in Table 4-7 as first-order rate coefficients. Each value is usually the average of two measurements; deviations are of the order of 3-4%. Besides kinetic runs for **1a**, **1c**, **1d**, and **1f** in the range 50-80°, also the reactivities of **1b** and **1e** at 70° were measured, although they had been the object of previous determinations. This procedure was followed in order to be able to evaluate weak kinetic effects from data as nearly homogeneous as possible, not affected by changes in analytical procedures and possibly in solvent purity.

Significant trends can be found by examining in detail the results at a common temperature, here 70.0°. There is a regular dependence of rate on alkyl group: for all nitrile oxides, Et > Me; *i*-Pr > *n*-Pr. When compounds **1a-e**, which have a common structure *o,o'* to the CNO group ($Z = Z' = CH_3$) are considered, rates appear to depend on the alkyl group of **2** according to the same order: Me < *n*-Pr < Et < *i*-Pr (Figure 1). An accelerating effect of the progressive branching of the alkyl group is recognized. However, since aliphatic nitriles are both reactants and solvents of the cycloadditions, the observed effect is a mixed one, including a solvent effect. The importance of the latter is suggested by the fact that the reactivity order is close to that of the dipole moments of the nitriles [3].

The kinetic effect of substituents Y and R at *meta* and *para* sites on the aromatic nitrile oxide can be appreciated by examining Tables 4-7 or Figure 1. Whichever the nitrile interested, rates depend on Y and R substituents in the order **1a** > **1b** > **1c** for electron-donating substituents, and in the order **1e** > **1d** > **1c** when the sum of the σ-values for the *para* and *meta* positions is positive. Rates are at a minimum for **1c** (Y = R = H). For the temperature of 70°, reactivity ratios k(**1e**)/k(**1c**) are all in the range 1.5-1.6, independently of the nitrile. Ratios k(**1a**)/k(**1c**), on the other hand, vary from 1.67 (for acetonitrile), down to 1.25 for *iso*-butyronitrile, *i.e.* decrease with increasing branching of the alkyl group. In other words, if Hammett plots are drawn, using $\sigma_p = -0.268$ for **1a**, $\sigma_p = -0.170$

for **1b**, $\sigma_p = +0.232$ for **1d**, and $\Sigma\sigma = +0.576$ for **1e**, roughly V-shaped plots are obtained (an example is given in Figure 2): while the right-hand branches are quite similar lines, from which a $\varrho \doteq 0.3$ can be derived, the left-hand branches have different slopes, according to the alkyl group on the nitrile: Me, $\varrho = -0.8 \pm 0.1$; Et, $\varrho = -0.6 \pm 0.2$; *n*-Pr, $\varrho = -0.6 \pm 0.1$; *i-p*Pr, $\varrho = -0.3 \pm 0.1$. Thus, increasing branching of the alkyl group on the nitrile attenuates the rate-accelerating effect of methoxy and methyl substituents *para* to CNO. A steric effect of the nitrile as reactant is suspected; however, it is difficult to dissect it from a possible solvent effect.

In any case, the common feature of Hammett plots with a minimum is the central result. Such shallow minima for the unsubstituted reactant have been found in several 1,3-cycloadditions and are indicative of a concerted mechanism [7]. In a kinetic study of the 1,3-cycloaddition of mesitonitrile oxide **1b** to several benzonitriles in carbon tetrachloride [1b], the substituent effect on the nitriles was also anomalous: the Hammett plott was found to present two distinct straight lines, with $\varrho = 1.32$ on the side of the electron-withdrawing groups, and $\varrho = 0.43$ on the side where $\sigma < 0$. Although no change of the sign of ϱ was found in that case, the analogy with the present results is apparent. Both for substituents on the 1,3-dipole and on the dipolarophile, a variation in the charge distribution at the transition state has been thus evidenced for the nitrile oxide-nitrile system.

Runs at different temperatures for reactions of nitrile oxides **1a, 1c, 1d**, and **1f** gave similar activation energies (from 71 to 86 kJ mol^{-1}) and large negative activation entropies (from −115 to −78 J mol^{-1}K^{-1}). Ranges of these activation parameters are similar to those previously found for reactions of **1b** and **1e** [3], and are consistent with the usual concerted mechanism of 1,3-cyacloaddition.

Nitrile oxide **1f** was found to be less reactive than its isomer **1a** by factors in the range 1.3-1.9, according to nitrile and temperature. This explains why in the previous work, where **1f** was an impurity of **1a**, the latter seemed to be less reactive than **1b**, while the reverse order comes out of the present measurements.

EXPERIMENTAL

The ^{1}H-nmr spectra were taken by a Varian FT-80 spectrometer using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. The uv were recorded on a Perkin-Elmer 402 spectrophotometer.

4-Methoxy-2,6-dimethyllbenzaldehyde and 2-Methoxy-4,6-dimethylbenzaldehyde [4].

These compounds were synthesized in the reaction of 3,5-dimethylanisole with *N,N*-dimethylformamide and phosphorus oxychloride [4]. The mixture of benzaldehydes produced in this reaction was separated by chromatography on silica gel, eluting with petroleum ether (bp 40-70°).

2-Methoxy-4,6-dimethylbenzaldoxime.

This oxime was prepared from 2-methoxy-4,6-dimethylbenzaldehyde to give white needles, mp 166-167°; nmr: δ 2.31 (s, *o*-CH$_3$, 3H), 2.42 (s, *p*-CH$_3$, 3H), 3.83 (s, OCH$_3$, 3H), 6.61 (m, ar, 2H), 8.50 (s, CH, 1H), 8.96 (s, OH, 1H).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.9. Found: C, 67.0; H, 7.3; N, 7.9.

2-Methoxy-4,6-dimethylbenzonitrile Oxide (**1f**).

This nitrile oxide was prepared by the method used by Grundmann [8], mp 112°; uv (methanol): λ max 222 (ϵ = 21,900), 260 sh (11,200), 267 (11,500), 305 (4,000); nmr: δ 2.33 (s, *o*-CH$_3$, 3H), 2.37 (s, *p*-CH$_3$, 3H), 3.84 (s, OCH$_3$, 3H), 6.60 (m, ar, 2H).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.3; N, 7.9. Found: C, 67.8; H, 6.3; N, 7.9.

4-Methoxy-2,6-dimethylbenzonitrile Oxide (**1a**) and the Other Nitrile Oxides.

4-Methoxy-2,6-dimethylbenzonitrile oxide was prepared by Grundmann's method [8]. The other nitrile oxides were prepared according to the published procedures [5]. The aliphatic nitriles were commercially available as pure reagents (>99%). However, propionitrile was redistilled before it was used.

General Procedure for the 1,2,4-Oxadiazoles.

The 1,2,4-oxadiazole derivatives were obtained by refluxing a nitrile oxide (2 g) in a nitrile (200 ml). After refluxing the solution, the product was obtained by evaporating the solvent. In some cases, the products were crystalline or could be crystallized from petroleum ether, but more often they were isolated as oils. Refractive indices of the latter are listed in Table 1. Products having unsatisfactory elemental analysis were further purified by column chromatography on silica gel eluting with petroleum ether (bp 40-70°). Distillation of products was avoided, owing to their thermal instability.

Kinetics.

For each reaction, a nitrile oxide **1** was dissolved (*ca.* 10^{-4}mol ℓ^{-1}) in the appropriate nitrile **2** at the reaction temperature. The decrease in absorbance at the λ max of the nitrile oxide (in the range from 264 to 270 nm) was measured, within the thermostated cell, as a function of time. The difference in molar extinction coefficients was, for instance (in solvent acetonitrile): at λ = 267 nm, ϵ = 18800 (**1a**); 1200 (**3ar**); 11500 (**1f**); 1100 (**3fr**); at λ = 264 nm; 11200 (**1c**); 400 (**3cr**); 19400 (**1d**); 600 (**3dr**).

Rate coefficients were obtained by plotting $\ln(A_t - A_\infty)$ *vs.* time and applying linear regression analysis. Reactions were followed for at least two half-lives.

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