Behaviour of Nitrile Oxides towards Nucleophiles. Part II.[1] Substituent Effect on the Rate of Dimerisation of Aromatic Nitrile Oxides to 3,6-Diaryl-1,4,2,5-dioxadiazines

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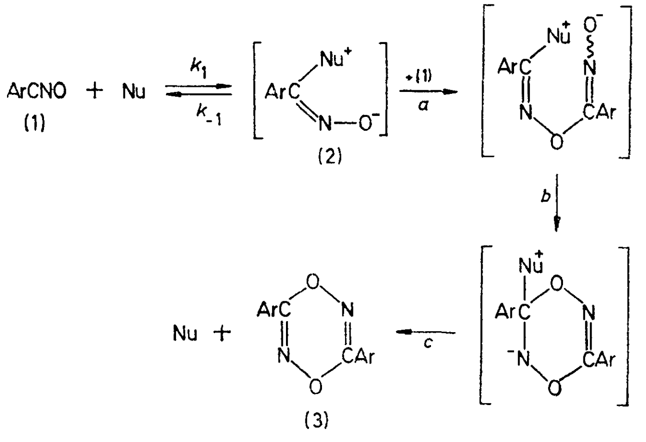
The dimerisation of aromatic nitrile oxides to 3,6-diaryl-1,4,2,5-dioxadiazines catalysed by suitable nucleophiles is shown to follow either second- or third-order kinetics, according to the substituents. An increase in the base strength of the nucleophile causes a change in reaction order from three to two and an increase in rate constant, while an increase in electron-withdrawing power of the nitrile oxide ring shows only this second effect. These results agree with a reaction scheme in which an intermediate adduct between nitrile oxide and nucleophile reacts with more nitrile oxide to give the dimer.

3,6-DIARYL-1,4,2,5-DIOXADIAZINES (3) are produced from aromatic nitrile oxides (1) by dimerisation catalysed by pyridine[1] and similar nucleophiles, such as substituted pyridines or 1-methylimidazole. On the basis of the kinetics of the reaction between 2,4-dichlorobenzonitrile oxide and pyridine,† the reaction scheme (i) was proposed, with pyridine as a nucleophile (Nu). This leads to the rate equation (ii), which can be simplified in the form (iii), if $k_{-1} \gg k_2[(1)]$, or in the form (iv), if $k_{-1} \ll k_2[(1)]$.



$$(1) + \mathrm{Nu} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (2) \xrightarrow[k_2]{+(1)} (3) + \mathrm{Nu} \qquad \text{(i)}$$

$$-\mathrm{d}[(1)]/\mathrm{d}t = 2k_1k_2[(1)]^2[\mathrm{Nu}]/\{k_{-1} + k_2[(1)]\} \qquad \text{(ii)}$$

$$-\mathrm{d}[(1)]/\mathrm{d}t = 2k_1k_2[(1)]^2[\mathrm{Nu}]/k_{-1} \qquad \text{(iii)}$$

$$-\mathrm{d}[(1)]/\mathrm{d}t = 2k_1[(1)][\mathrm{Nu}] \qquad \text{(iv)}$$

In support of this mechanism, we present further kinetic data on the dimerisation of benzonitrile oxide and of 4-substituted benzonitrile oxides with the nucleophiles mentioned above.

These reactions, in ethanol, are almost quantitative if they are fast enough (half life <1 500 s); otherwise several by-products cause a decrease in the yield of (3). Factors increasing the reaction speed, and therefore the yield of dimers (3) are: nucleophile strength,‡ nucleophile concentration, and electron-withdrawing power of the nitrile oxide ring (see Table). The last factor is evidenced also by the yields obtained with such a weak nucleophile as ethyl isonicotinate (pK_a 3.45): an increase of the dimerisation yield is observed from a negligible value for benzonitrile oxide up to 88% for 4-nitrobenzonitrile oxide.

Some of the by-products, identified by t.l.c. comparison with authentic samples, are substituted furoxans, 1,2,4-oxadiazole 4-oxides,[2] and 1,2,4-oxadiazoles.

Since the experimental method requires half-lives to reach at least 800 s, nucleophile concentrations have been selected, as reported in the Table, in order to keep the yields above 85%.

Neither u.v. analysis, as previously pointed out,[1] nor volumetric analysis,[3] because of the basicity of the catalyst, are suitable to follow the reaction kinetics. Therefore, nitrile oxide concentrations were found by measuring by the i.r. absorption near 2 300 cm^{-1}. A thermostatted reaction vessel was connected by silicone tubing to the i.r. cell and with a peristaltic pump. A porous glass sinter within the reaction vessel by the side of the i.r. cell prevented precipitates from going into the

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† Values of k reported in Table 1 of ref. 1 are expressed in l^2 mol^{-2} s^{-1}.

‡ Hereinafter we shall refer to the basic strength, failing a nucleophilicity scale for the compounds considered.

[1] Part I, F. De Sarlo, *J.C.S. Perkin I*, 1974, 1951.

[2] F. De Sarlo and A. Guarna, presented at the Vth International Congress of Heterocyclic Chemistry, Ljubljana, 1975.

[3] G. Barbaro, A. Battaglia, and A. Dondoni, *J. Chem. Soc.* (*B*), 1970, 588.

cell during circulation of the solution. A sample of nitrile oxide was weighed in a standard flask and dissolved in ethanol at 25°: after 5—10 min in the thermostat, the reaction was started by addition of the appropriate amount of nucleophile and the solution poured in the reaction vessel. The method was tested on the 2,4-dichlorobenzonitrile oxide, which gave reaction rates in excellent agreement with those obtained by u.v. analysis.[1]

RESULTS

Kinetics were either first- or second-order in nitrile oxide and always first-order in nucleophile, as clearly indicated by linear plots of $t_{1/2}$[Nu] *versus* $1/a$ ($t_{1/2}$ = half life, a = initial nitrile oxide concentration): slopes (s) from these graphs are given in the Table. From each run, average pseudo-first- or pseudo-second-order rate constants were evaluated: second- (k^{II}) and third-order (k^{III}) rate constants were obtained by dividing by [Nu]. For each reaction, average k^{II} or k^{III} values are reported in the Table.

Kinetics of dimerisation of aromatic nitrile oxides (1) to 3,6-diaryl-1,4,2,5-dioxadiazines (3), at 25° ± 0.3

Reaction	Ar	Nucleophile	pK_a	Concentration range (M) Nitrile oxide	Concentration range (M) Nucleophile	Rate constants *	s †
A	Ph	Pyridine	5.20	0.030—0.061	0.24—0.48	k^{III} = 0.094 ± 0.002	15.5
B	Ph	4-Phenylpyridine	5.55	0.024—0.066	0.053—0.13	k^{III} = 0.38 ± 0.01	2.0
C	Ph	4-Methylpyridine	6.00	0.051—0.10	0.05—0.10	k^{III} = 0.71 ± 0.02	0.78
D	Ph	1-Methylimidazole	7.00	0.023—0.047	0.01—0.019	k^{II} = 0.048 5 ± 0.000 7	0.011
E	Ph	4-Dimethylamino-pyridine	9.70	0.027—0.047	0.0036—0.004	k^{II} = 2.73 ± 0.11	0.011
F	4-$CH_3OC_6H_4$	Pyridine	5.20	0.030—0.048	0.48—0.92	k^{III} = 0.026 0 ± 0.000 7	35.0
G	4-$CH_3OC_6H_4$	1-Methylimidazole	7.00	0.017—0.030	0.015—0.03	k^{II} = 0.037 ± 0.000 5	−0.006
H	4-ClC_6H_4	Pyridine	5.20	0.023—0.045	0.037—0.074	k^{III} = 0.648 ± 0.015	1.07

* k^{II} in l mol^{-1} s^{-1}; k^{III} in l^2 mol^{-2} s^{-1}. † Slope of the plot $t_{1/2}$[Nu] *versus* $1/a$.

Kinetic results can be summarised as follows: all rate constants are increased by electron-withdrawing groups in benzonitrile oxide, as well as by the basic strength of the nucleophile. Further increase in the last factor changes the kinetics from third- to second-order, first-order in each reagent.

The influence of substituents in the benzonitrile oxide ring on reaction orders cannot be established from these results. On the other hand, kinetic measurements carried out by the reported procedure on 4-nitrobenzonitrile oxide were not reliable owing to its poor solubility. Moreover, the reaction of 4-chlorobenzonitrile oxide with γ-picoline gave an irregular plot, thus indicating that no integral reaction order can be obtained in this case; presumably, it falls between two and three [see equation (ii)].

DISCUSSION

The ratio $k_1 : k_{-1}$ is expected to increase with both the nucleophile strength and the electron-withdrawing character of the benzonitrile oxide ring. The effect on k_2 depends on which step is rate-limiting for the third-order process: this can be *a* attack by the adduct (2) on more nitrile oxide, *b* ring closure, or *c* loss of the nucleophile. Steps *b* and *c* may be inverted. It seems reasonable to suppose that step *a* is the slowest of the three: in any case, no substantial increase of k_2 can be caused by an increase in the strength of the nucleophile.

The observed rate enhancement as the nucleophile strengthens (*cf.* reactions A—E, Table) can be ascribed to the increase of k_1, and therefore is consistent with equations (iii) and (iv); the change from third- to second-order (*cf.* reactions D, E, and G) means that k_{-1} decreases with the nucleophile strength, which is equivalent to saying that the first transition state is stabilised to a lesser extent than the intermediate adduct (2).

The effect of substituents in the benzonitrile oxide ring is a rise of both k^{II} and k^{III}, as the electron-withdrawing power increases (*cf.* reactions F, A, and H; D and G). Removal of a *p*-methoxy-group causes a 260% increase of k^{III}, whereas the same change has a lower effect on k^{II} (30% increase) partly because only k_1 is significant [equation (iv)], partly due to the lower selectivity of the stronger nucleophile.

The third-order dimerisation rate constant of 2,4-dichlorobenzonitrile oxide with pyridine (k^{III} = 0.025 ± 0.001), interpolated from the reported data,[1] is very close to the value found for 4-methoxybenzonitrile oxide, steric hindrance compensating for the electronic effect.

EXPERIMENTAL

For i.r. measurements, a Perkin-Elmer model 421 spectrophotometer equipped with CaF_2 cells and 0.1 mm cell path was used.

Materials.—Rectified spirit was used as solvent. Pyridine and its liquid derivatives were distilled before use, and employed either pure or as standard ethanolic solutions; solid derivatives were recrystallised and dissolved in ethanol. *N*-Methylimidazole was prepared by methylating commercial imidazole, as described,[4] b.p. 111° at 57 Torr.

Substituted benzonitrile oxides. Compounds 4-XC_6H_4-CNO (1) were prepared in ether as reported,[1] but were recovered by cooling the ethereal solution in a dry-ice bath or mixing it with an equal amount of light petroleum. They were filtered in a dry-box and recrystallised from methanol at −60°.

Benzonitrile oxide * was crystallised from light petroleum between 0 and −60 °C, then filtered in a dry-box cooled below −5 °C, and stored under dry-ice, m.p. 18—19°. For kinetic experiments, it was weighed in a cool dry-box and dissolved in ethanol at *ca.* 25 °C. Absorption coefficients (molar) for $\nu_{C\equiv N}$ *ca.* 2 300 cm^{-1} refer to ethanolic solutions

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* Dimerisation to furoxan in CCl_4 at 40° was of the second order, with k = (2.9 ± 0.1) × 10^{-3} l mol^{-1} s^{-1}, slightly different from the reported [3] value of 4.15 × 10^{-3}.

[4] M. Höring, *Helv. Chim. Acta*, 1959, **42**, 1845.

and to 0.1 mm cell path: $X = H$, 5.2; $X = OCH_3$, 4.8; $X = Cl$, 6.2; $X = NO_2$, 7.3.

T.l.c. Analysis.—Merck F_{254} silica gel plates, 0.25 mm layer thickness, were used. Reaction products (dioxadiazine, 1,2,4-oxadiazole, 1,2,5-oxadiazole oxide, 1,2,4-oxadiazole oxide) were distinguished using benzene–n-hexane (1 : 1) as eluant; front ratios decreased in the order given.

Dimerisation Yields.—Nitrile oxides (*ca.* 0.04M in EtOH) were allowed to react with nucleophiles at various concentrations. The dimer (3; Ar = 4-ClC_6H_4) from 4-chlorobenzonitrile oxide, sparingly soluble in EtOH, was collected at room temperature in the yields of 90% (0.038M-pyridine) and 95.5% (0.24M-pyridine). The solution of 4-methoxybenzonitrile oxide and pyridine (0.48M) was partially concentrated, then cooled at −50° to give dimer (3; Ar = 4-MeOC_6H_4) (87%). This procedure when applied to benzonitrile oxide gave only 70—80% yield of the dimer (3; Ar = Ph), fairly soluble in EtOH. More precipitate was recovered from the mother liquor by concentrating and drying *in vacuo* over H_2SO_4. Even allowing for the impurities revealed by t.l.c., the lower limit of the yield is 85%.

Reactions of Nitrile Oxides with Ethyl Isonicotinate.—Only traces of 3,6-diphenyl-1,4,2,5-dioxadiazine were identified by t.l.c. when a solution of benzonitrile oxide (100 mg) in ethanol (10 ml) was added with the nucleophile (1 ml). 2,4-Dichloro- and 4-chloro-benzonitrile oxide, under the same conditions, afforded 19 and 54%, respectively, of precipitated dimer. 4-Nitrobenzonitrile oxide (2 mg ml^{-1}) gave 88% yield of dimer, though with lower nitrile oxide concentration.

Kinetics.—I.r. absorptions were measured at the $\nu_{C\equiv N}$ maximum under nitrogen. Usually 10—15 readings were made per run, up to 60—80% completion; $t_{1/2}$ was obtained graphically, from a plot of $(a - x)$ *versus* time. At least 8 runs were made for each reaction.

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