Reaction of β-Aminocinnamonitrile and its *N*-Mono- and *NN*-Di-substituted Derivatives with Benzonitrile Oxides

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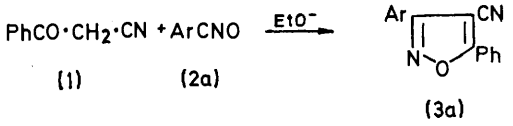
β-Aminocinnamonitrile (4a) reacts with benzonitrile oxides (2) to give, as primary products, the 3-aryl-5-(β-aminostyryl)-1,2,4-oxadiazoles (6) together with lesser amounts of 3-aryl-4-cyano-5-phenylisoxazoles (3). In the case of *p*-nitrobenzonitrile oxide (2c), 3-(*p*-nitrophenyl)-5-phenyl-1,2,4-oxadiazole (7) is also obtained. The *N*-monosubstituted aminocinnamonitriles behave similarly, whereas the *NN*-disubstituted compounds yield only the 3-aryl-4-cyano-5-phenylisoxazoles (3). A mechanism is proposed.

ω-CYANOACETOPHENONE (1) reacts with benzonitrile oxide (2a) in basic medium to give 4-cyano-3,5-diphenyl-



(1) (2a) (3a)

a; Ar = Ph
b; Ar = *p*-ClC$_6$H$_4$
c; Ar = *p*-O$_2$N·C$_6$H$_4$

SCHEME 1

isoxazole (3a) (Scheme 1).[1] No similar reaction is reported for the corresponding imine (4a).

In connection with our interest in the influence of differently substituted amino-groups on the course of organic reactions,[2] we have studied the reactions of compounds (4) and (5) with benzonitrile oxides (2), in order to ascertain whether dipolarophilic sites other than the expected vinyl group (i) take part in the cycloaddition, *i.e.* >C=N–H (or >C=N–R)[3] (ii) or the usually less reactive –C≡N group[4] (iii). In each reaction a 2 : 1

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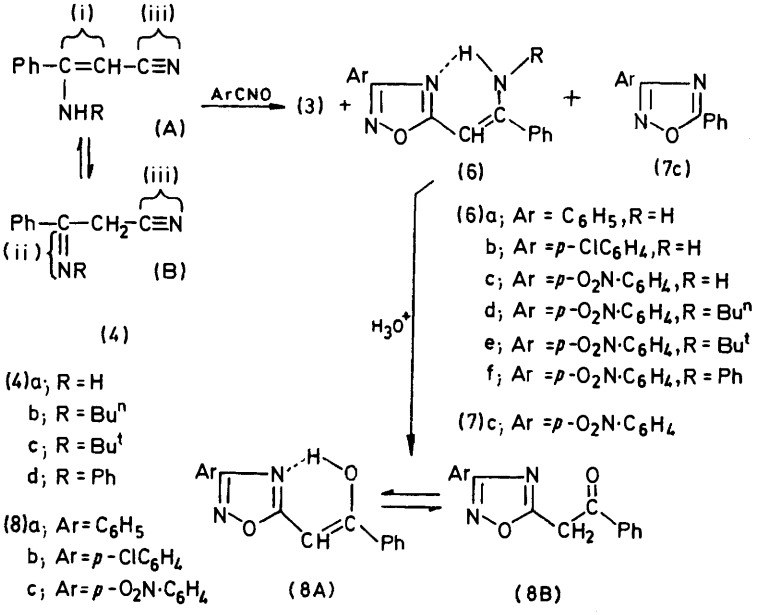
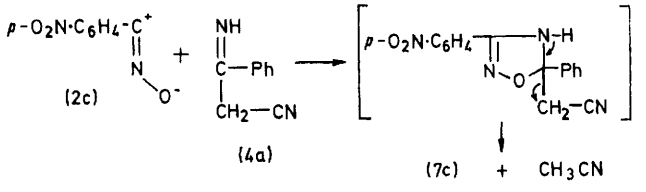
ratio of (2) to (4) or (5) was used in order to facilitate any double attack of (2) on (4) or (5).

From the benzonitrile oxide (2a) or its *p*-chloro- (2b) or *p*-nitro- (2c) derivative with (4a), two compounds



SCHEME 2

were obtained, of which the minor component was the expected 3-aryl-4-cyano-5-phenylisoxazole (3). The



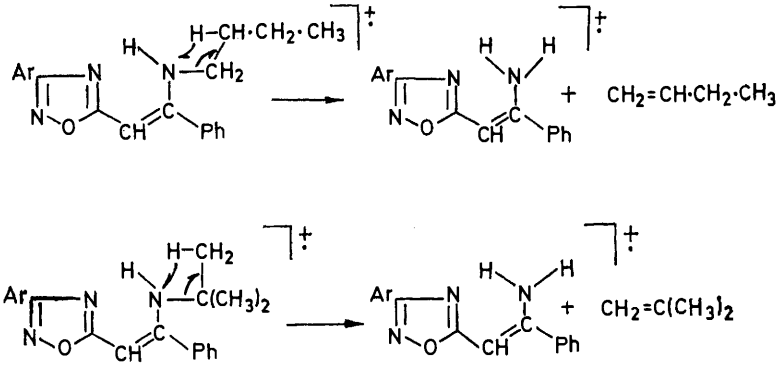
SCHEME 3

main component was the 3-aryl-5-(β-aminostyryl)-1,2,4-oxadiazole (6). Moreover from (4a) and *p*-nitrobenzonitrile oxide (2c) a third compound, 3-(*p*-nitrophenyl)-5-phenyl-1,2,4-oxadiazole (7), was obtained (Scheme 2).

Compound (7) must be derived from attack of (2c) on the >C=N–H group (ii), followed by spontaneous elimination of acetonitrile (Scheme 3).

The identification of compounds (6) follows from spectral and chemical data. The i.r. spectra shows the disappearance of the –C≡N group, and the n.m.r. spectra do not exhibit $-CH_2-$ signals but only those due to =CH– and $-NH_2$, thus indicating the exclusive presence of the enamine form of compounds (6).

The mass spectra show the expected molecular ions and fragmentation pattern. In particular compounds (6d—f) show two strong peaks due to $(M - R)^+$ (at *m/e* 307) and to R^+ [at *m/e* 57 for (6d—e) and at *m/e* 77 for (6f)]. In all cases R^+ provides the base peak. The spectra of (6d and e) display three other peaks at *m/e* 146, 144, and 117, which are also present in those of (6a—c). In the case of (6d and e) they could be generated by incorporation of H˙ in the course of the fragmentation of $(M - R)^+$. In effect their origin can also be traced to the *m/e* 308 fragment ion, which in its turn can originate by rearrangement of the molecular ion (Scheme 4). However the high abundance of R^+ and the low

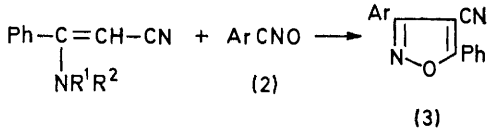


SCHEME 4

abundance of *m/e* 308 do not seem to support this sequence. In the case of (6f) instead of *m/e* 146, 144, and 117, three peaks at *m/e* 222, 220, and 193 are present, due to the corresponding *N*-phenyl-substituted ions.

Hydrolysis of compounds (6) with dilute hydrochloric acid (15%) gave the 3-aryl-5-phenacyl-1,2,4-oxadiazoles (8), as indicated by spectral data and elemental analyses. The i.r. spectra of these compounds in KBr discs do not exhibit the carbonyl band, which appears in the range 1 665—1 695 cm^{-1} in the spectra of solutions in $CHCl_3$; their n.m.r. spectra confirm the existence of a tautomeric equilibrium between (8A) and (8B) which can be followed by n.m.r.

The *N*-monosubstituted compounds (4b—d) react with *p*-nitrobenzonitrile oxide (2c) to give compounds (3c) and (6d—f) in low yields (Table); the product ratios are similar to that obtained in the case of (4a) (Scheme 2). However the *NN*-disubstituted compounds (5a—c) with (2c) give only compounds (3) (Scheme 5).



a; $R^1R^2 = C_4H_8$
b; $R^1R^2 = C_5H_{10}$
c; $R^1R^2 = C_4H_8O$

SCHEME 5

The yield is higher from (5a and b) than from (5c) (Table).

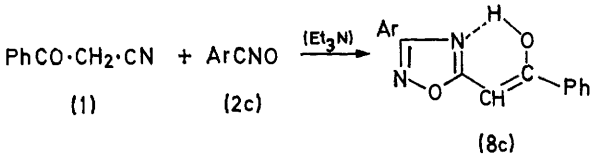
DISCUSSION

The lack of oxadiazoles (6) among the products from (5a—c) indicates that the –C≡N group, contrary to expectation, is not activated by conjugation with the enamine system; thus the reaction involves only the vinyl group and not the whole enaminonitrile system.

Furthermore the fact that the yields from (5a) and (5b) are similar but higher than that from (5c) indicates that, unlike other processes with the same compounds,[2] the electronic effect of the substituted amino-group rather than the steric effect determines the reaction course.

On the other hand the absence of (6) as a product from compounds such as (5a—c), for which only the enamine structure is possible, could indicate that in the case of compounds (4a—d) the imine structure (4B) rather than the enamine structure (4A) is responsible for the production of compounds (6). If so, the more the RN=CAr– group is electron-withdrawing, the more it must activate the –C≡N group; this agrees with our observations.

In the case of the *N*-phenyl derivative (4d) the overall yield is higher than that in the case of the *N*-butyl derivatives (4b and c). This suggests that compound (1) itself could react at the –C≡N rather than at the >C=C< group in neutral or mildly basic medium. In confirmation of this hypothesis, compound (1) with *p*-nitrohydroxamoyl chloride with or without small amounts of



SCHEME 6

triethylamine gave, besides compound (3), the oxadiazole (8c) (Scheme 6).

EXPERIMENTAL

I.r. spectra were determined with a Perkin-Elmer 137 spectrophotometer. U.v. spectra were obtained from a Beckmann DB-GT spectrophotometer (1 cm quartz cells; aqueous 95% ethanol as solvent). N.m.r. spectra were recorded for solutions in $CDCl_3$ with a Varian A-60 spectrometer (tetramethylsilane as internal standard). Mass spectra were measured with an A.E.I. MS-9 spectrometer. T.l.c. were carried out with silica gel F-254 plates [developing solvents light petroleum–benzene (20 : 80) and benzene]. Merck silica gel (0.05—0.2 mm) was used for chromatographic separations. Elemental analytical data for compounds (3), (6), and (8) are available as Supplementary Publication No. SUP 22100 (2 pp.).*

Materials.—The benzonitrile oxides (2a—c) were not isolated but prepared directly in solution ($CHCl_3$) from equivalent amounts of purified triethylamine and the corresponding benzohydroxamoyl chlorides.[5,6] The enamines (4a) and (5a—c) were prepared by reported procedures.[2,7] The enamines (4b—d) were obtained from phenylpropiolonitrile and the corresponding amines in ethanolic solution at reflux temperature. The crude material was recrystallized from light petroleum–benzene (80 : 20).

The enamine (4b) was a dense oil, $\lambda_{max.}$ (EtOH) 282 nm, $\nu_{max.}$ (NaCl) 2 938 (NH), 2 935 (CH), and 2 198 cm^{-1} (CN), δ ($CDCl_3$) 1.2 (7 H, m, C_3H_7), 2.9 (2 H, q, CH_2), 3.9 (1 H, s, CH), 5.1 (1 H, t, NH), and 7.5 (5 H, m, arom.); the enamine (4c) had m.p. 113—115 °C, $\lambda_{max.}$ (EtOH) 278 nm, $\nu_{max.}$ (KBr) 3 300 (NH), 2 960 (CH), and 2 210 cm^{-1} (CN), δ ($CDCl_3$) 1.3 (9 H, s, $3CH_3$), 4.1 (1 H, s, CH), 4.4br (1 H, NH), and 7.5 (5 H, m, arom.); the enamine (4d) [8] consisted of a mixture of two isomers with $\lambda_{max.}$ (EtOH) 238 and 242 nm, $\nu_{max.}$ (KBr) 3 230 (NH) and 2 200 cm^{-1} (CN), δ ($CDCl_3$) 4.3 and 4.7 (1 H, s, CH), 6.1br (2 H, NH), and 7.3 (10 H, m, arom.), and was used as such.

Phenylpropiolonitrile was prepared according to the following procedure (a modified version of the literature procedure [9,10]). Cyanomethyltriphenylphosphonium

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

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chloride (30 g) [from triphenylphosphine (30 g) and chloroacetonitrile (8.5 ml) in dry benzene (200 ml) by heating at 70 °C] was added with stirring to sodium ethoxide (5 g) in ethanol (100 ml) at room temperature. After 1 h cyanomethylenetriphenylphosphorane (15 g), m.p. 180 °C (lit.,[10] 186—187 °C) was filtered off. By dilution with water another 3.2 g of the product were obtained. To a solution of cyanomethylentriphenylphosphorane (18.2 g) in dry benzene (500 ml), benzoyl chloride (9 g) in dry benzene (20 ml) was added with stirring. The mixture was set aside overnight at room temperature. Cyanomethyltriphenylphosphonium chloride was filtered off and the filtrate evaporated. Crystallization of the residue from aqueous ethanol gave α-cyanophenacylidenetriphenylphosphorane (7 g), m.p. 205—206 °C (lit.,[9] 208 °C). On heating α-cyanophenacylidenetriphenylphosphorane at 280 °C and 10 mmHg for 1 h in a Claisen flask immersed in a Woods metal bath, the phenylpropiolonitrile distilled over and was collected in a receiver cooled in liquid nitrogen; m.p 40 °C (lit.,[9] 38—39 °C).

General Procedure for the Reactions of Compounds (2a—c) *with Enamines* (4a—d) *and* (5a—c).—A solution of triethylamine (6 mmol) in chloroform (10 ml) was added dropwise to a mixture of the appropriate benzohydroxamoyl chloride (6 mmol) and enamine (4) or (5) (3 mmol) in chloroform (30 ml) with stirring. The mixture was then kept at room temperature for 48 h. Triethylammonium hydrochloride was filtered off and the filtrate was distilled under reduced pressure. From the residue large amounts of dimers of (2) were eliminated by treatment with cold ethanol, in which they are insoluble. The products were separated by column chromatography. In each instance the order of elution was isoxazole (3), dimers, oxadiazole (6), starting enamine, with the exception of the reaction of (2b), for which the elution order was dimers, isoxazole (3), oxadiazole (6), starting enamine. In the case of the reaction of (4d) with (2c) the eluted first product was the oxadiazole (7c).[11] In the case of (5a—c) besides dimers and the starting enamine the only substance isolated was the isoxazole (3). Where necessary, further purification was achieved by crystallization from ethanol. M.p.s and yields are reported in the Table.

Compounds (3) showed $\lambda_{max.}$ (EtOH) 272—280 nm, $\nu_{max.}$ (KBr) 2 240 cm^{-1} (C≡N), and aromatic proton n.m.r. signals ($CDCl_3$). Compounds (6) showed $\lambda_{max.}$ (EtOH) 320—352 and 243—275 nm; $\nu_{max.}$ (KBr) 3 040—3 430br cm^{-1} (bonded NH), and δ ($CDCl_3$) 5.6 (1 H, s, CH), 6.7br (2 H, NH_2), and 7.3—8.5 (m, arom.) [in the case of (6a—c)], 0.6—1.8 (8 H, m, C_3H_7 and NH), 3.2 (2 H, q, CH_2), 5.2 (1 H, s, CH), and 7.2—8.5 (9 H, m, arom.) [for (6d)], 1.2 (9 H, s, $3CH_3$), 2.2 (1 H, s, NH), 5.2 (1 H, s, CH), and 7.3—8.5 (9 H, m, arom.) [for (6e)], or 5.6 (1 H, s, CH), 6.7—8.5 (14 H, m, arom.), and 10.1br (1 H, NH) [for (6f)]. Compound (7c), m.p. 202 °C (EtOH) (lit.,[11] 198 °C), showed $\lambda_{max.}$ (EtOH) 268 nm and aromatic proton n.m.r. signals ($CDCl_3$); it showed no −C≡N i.r. absorption.

M.p.s (°C) and yields (%) of compounds (3) and (6)

From		M.p.	Yield		M.p.	Yield %
(4a) and (2a)	(3a)	98—99	15	(6a)	119—121	39
(4a) and (2b)	(3b)	130—131	13	(6b)	179	56
(4a) and (2c)	(3c)	202—204	14	(6c)	216—218	54
(4b) and (2c)	(3c)		2	(6d)	165—167	7
(4c) and (2c)	(3c)		Trace *	(6a)	184—186	5
(4d) and (2c)	(3c)		5	(6f)	163—164	19
(5a) and (2a)	(3a)		30			
(5a) and (2b)	(3b)		56			
(5a) and (2c)	(3c)		40			
(5b) and (2a)	(3a)		31			
(5b) and (2b)	(3b)		55			
(5b) and (2c)	(3c)		36			
(5c) and (2a)	(3a)		18			
(5c) and (2b)	(3b)		36			
(5c) and (2c)	(3c)		No reaction			

* Identified only by t.l.c.

Hydrolysis of Compounds (6a—f).—A solution of compound (6) (0.1 mmol) in ethanol (15 ml) containing 15% hydrochloric acid (3 ml) was refluxed for 4 h [hydrolysis of (6c) required 36% HCl and 12 h]. On dilution with water compound (8) was precipitated. It was filtered off and washed repeatedly with water. Crystallization from ethanol gave nearly quantitative yields. M.p.s of (8a), (8b), and (8c) were 95, 123, and 171—173 °C respectively. Compounds (8) showed $\lambda_{max.}$ (EtOH) 278—316 and 248—252 nm, $\lambda_{max.}$ (KBr) in the range 3 300—3 350br cm^{-1} (bonded OH), δ ($CDCl_3$) 4.7 (s, CH_2 of keto form), 6.3 (s, CH of enol form) [ratio (8A) : (8B) 2 : 1], 7.3—8.5 (9 H, m, arom.), and 10.7br (1 H, OH). The OH signal was observed only in the case of (8b); in the other cases the signals were too broad.

Reaction of ω-Cyanoacetophenone (1) *with the Nitrile Oxide* (2c).—Triethylamine (<0.1 mmol) in chloroform (5 ml) was added dropwise to a solution of the ketone (1) (0.1 mmol) and the nitrile oxide (2c) (0.2 mmol) in chloroform (20 ml) and the mixture was set aside at room temperature for 48 h. T.l.c. indicated the presence of the oxadiazole (8c), which was separated by preparative t.l.c. and its identification confirmed by u.v. and i.r. ($CHCl_3$) spectra and by m.p. and mixed m.p. [authentic sample obtained from hydrolysis of (6c)].

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