Activation of Nitriles by Hydrogen Bonding in Cycloadditions with Nitrile Oxides

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The dipolarophilic activity of aromatic nitriles in cycloaddition with benzonitrile oxides is remarkably enhanced by *ortho*-acylamino substituents. The activation depends upon the solvent and can be ascribed to a hydrogen bond which assists cycloaddition.

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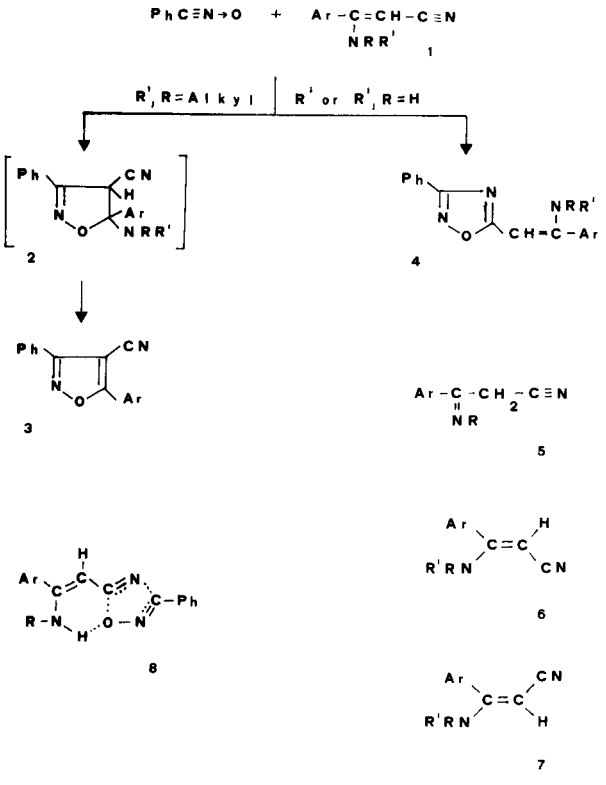
In previous papers we have dealt with the cycloaddition of nitrile oxides to β-aminocinnamonitriles **1** [1,2]. The β,β-dialkylamino derivatives behaved rather regularly and exclusive cycloaddition to the highly activated enaminic C=C double bond was observed. The intermediate cycloadducts **2** split off the amine and fair yields of isoxazoles **3** were obtained (Scheme 1).

Scheme 1



Surprisingly the unsubstituted β-aminocinnamonitrile and its *N*-alkyl or phenyl monosubstituted derivatives underwent mainly cycloadditions on the C≡N bond to yield oxadiazoles **4** along with only minor amounts of isoxazoles **3**.

This unexpected change of site-selectivity could be due to the tautomerism of the unsubstituted and *N*-mono-substituted cinnamonitriles. These dipolarophiles have a free NH bond and could adopt the tautomeric structure **5** which can be viewed as an acetonitrile carrying a β-electronwithdrawing substituent. Acetonitrile is a rather unreactive dipolarophile [3] and can be used even as a solvent for nitrile oxide cycloadditions. β-Electronwithdrawing substituents cause however an enhancement of the dipolarophilic activity of the cyano moiety [4]. On this basis the formation of oxadiazoles **4** in cycloadditions to unsubstituted and *N*-monosubstituted cinnamonitriles was tentatively attributed to the presence of the imine tautomers **5** and to their activating β-benzoylimino substituents [1,2]. Spectroscopic evidence, however, does not support this rationalization. β-Aminocinnamonitriles exist mainly in the fully conjugated (*Z*) structure **6** along with minor amounts of the (*E*) stereoisomer **7**, and no evidence for the presence of significant amounts of the imine tautomer **5** was found [5]. Explanations of the site-selectivity based on very small amounts of the imine tautomers **5** would then require an unprecedented and indeed anomalously high reactivity of their C≡N bond. An alternative explanation, which still involves the NH bonds of the unsubstituted and *N*-monosubstituted β-aminocinnamonitriles, could be considered. These NH bonds are good hydrogen bond donors and could interact with the nitrile oxide oxygen, assisting cycloaddition as shown in **8**. Evidence on the role of hydrogen bonding in nitrile oxide cycloadditions has been recently gained from cycloaddition stereoselectivities of cyclic dipolarophiles. Cyclic allyl alcohol [6,7] and isoxazolines carrying a 5-carbamate moiety

9a-e

	R	R'
a	$COCH_3$	H
b	COC_6H_5	H
c	$SO_2C_6H_4CH_3$	H
d	$COCH_3$	CH_3
e	H	H

[8] undergo preferential syn additions, which maximize hydrogen bonding effects.

To test the hydrogen bonding hypothesis we have studied the cycloadditions of benzonitrile oxide to the *ortho*-aminobenzonitriles **9a-e**. These dipolarophiles seemed very convenient models to us. They retain the same geometrical features of the prevailing (*Z*) stereo isomer **6** of β-aminocinnamonitriles, *i.e.* the *cis* relationship of the amino and cyano groups. Moreover no complicating enamine-imine tautomerism is expected to take place here, because of the presence of the aromatic ring.

Aromatic nitriles are only slightly reactive with nitrile oxides and afford 1,2,4-oxadiazoles **10** [4,9-12]. Fair yields of cycloadducts can be achieved with benzonitriles carrying electron-attracting substituents at the *para*-position in keeping with the HOMO (dipole)-LUMO (dipolarophile) character of these cycloadditions [3,13].

Results.

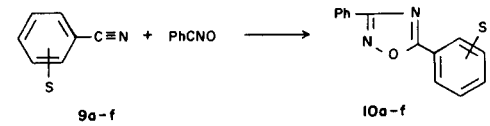
1,2,4-Oxadiazole Formation.

Despite the anticipated low reactivity of *o*-acetylaminobenzonitrile (**9a**) because of the donating character of the *ortho*-sustituent, cycloaddition of an excess of benzonitrile oxide (2 equivalents) to **9a** in tetrahydrofuran afforded a 32% yield of 1,2,4-oxadiazole **10a** which could be easily isolated by column chromatography. Similar yields were obtained with the benzoylamino and tosylamino derivatives **9b** and **9c** (Table 1).

The propensity to cycloadditions is almost entirely lost upon substitution of the proton at nitrogen, or in the *para*-analogue. Thus, under similar conditions only a 2.6% yield of adduct **10d** was obtained in cycloaddition to the *N*-methyl-*o*-acetylaminobenzonitrile (**9d**), while the *p*-acetylamino derivative **9f** afforded oxadiazole **10f** in a 6% yield.

Table 1

Yields of Oxadiazoles **10a-f** Obtained in Cycloadditions of Benzonitrile Oxide (2 equivalents) to Substituted Aminobenzonitriles **9a-f** in Tetrahydrofuran



9a-f **10a-f**

Dipolarophiles S		Yields (%)
9a	*o*-$NHCOCH_3$	32
9b	*o*-$NHCOC_6H_5$	41
9c	*o*-NHTs	41
9d	*o*-$N(CH_3)COCH_3$	2.6
9e	*o*-NH_2	10
9f	*p*-$NHCOCH_3$	6

Cycloaddition to the unsubstituted *o*-aminobenzonitrile (**9e**) also afforded a reasonable yield (10%) of oxadiazole **10e**. No evidence for the formation of products arising by attack of benzonitrile oxide to the amino group of **9e** was found, thus showing that the dipolarophilic activity of C≡N is greater than the 1,3-addition propensity of the amino group of **9e**. Aniline adds to nitrile oxides, indeed, sluggishly, affording amidoximes [14]. The structures of the new 1,2,4-oxadiazoles **10a-f** rely upon chemical and spectroscopic evidence. Alkaline hydrolysis of the *o*-acetylaminooxadiazole **10a** afforded *o*-aminooxadiazole **10e**. The latter gave acetylamino, benzoylamino and tosylamino-1,2,4-oxadiazoles **10a-c** upon treatment with the appropriate chlorides. The ir and pmr spectra (Table 2) are fully consistent with the assigned structures. All cycloadducts exhibit molecular ions (base peaks) which decompose by relatively few and expected paths [15]. Thus in acylamino and benzoylamino derivatives the most intense

Table 2

Physical and Spectral Data of Oxadiazoles **10a-f**

Compound No.	MP (°C)	Crystallization Solvent	IR (cm^{-1}) (Potassium Bromide)	PMR (δ) (Deuteriochloroform)
10a	173-174	Benzene-Light Petroleum	3275 (NH), 1695 (CO)	2.30 (s, $COCH_3$, 3H), 7.05-8.02 (m, aromatic), 7.95 (broad s, NH, 1H)
10b	118-120	Benzene-Light Petroleum	3295 (NH), 1682 (CO)	7.20-8.40 (m, aromatic, 13H), 8.85 (broad s, NH, 1H)
10c	143-145	Ethanol	3150 (NH), 1326 and 1142 (SO_2)	2.4 (s, CH_3, 3H), 7.10-7.95 (m, NH and aromatic, 14H)
10d	94-95	Benzene-Light Petroleum	1674 (CO)	2.00 (s, $COCH_3$, 3H), 3.35 (s, NCH_3, 3H), 7.20-8.00 (m, aromatic, 4H)
10e	128-129	Benzene-Light Petroleum	3415 and 3312 (NH_2)	5.90 (broad s, NH_2, 2H), 6.60-8.40 (m, aromatic, 9H)
10f	195-196	Ethanol	3300 (NH), 1670 (CO)	2.15 (s, $COCH_3$3H), 6.70-7.43 (m, aromatic, 9H), 10.25 (broad s, NH, 1H) [a]

[a] Recorded in deuteriochloroform-dimethyl-d_6 sulfoxide.

fragment ions derive by a α-cleavage with respect to the carbonyl group and N-O bond cleavage of oxadiazole ring. The most characteristic feature of tosylamino derivative is the occurence of ions corresponding to the loss of SO_2 from molecular and *o*-tosylaminobenzoyl ions.

Solvent Effects.

The sharp decrease in reactivity of *N*-methyl-*o*-acetylamino **9d** and *p*-acetyl **9f** derivatives supports the view that a hydrogen bonding between the reactants is assisting the cycloaddition. Such an intermolecular hydrogen bonding should be sensitive to solvent change. Table 3 displays the changes of the yields of cycloaddition to *o*- and *p*-acetylaminobenzonitrile and *p*-tolylnitrile.

Table 3

Solvent Dependence of Oxadiazole Formation in Cycloadditions Between Equimolecular Amounts of Benzonitrile Oxide and *o*-Acetylamino, *p*-Acetylamino and *p*-Methylbenzonitriles.

Solvent	Yields (%) of adducts		
	o-NHCOCH$_3$	*p*-NHCOCH$_3$	*p*-CH$_3$
Benzene	36.2	- [a]	7.8
Chloroform	34.4	2.1	6.7
Tetrahydrofuran	25.1	3.5	8.0
Diethyl ether	21.8	- [a]	6.6
Ethyl acetate	11.4	3.7	6.8
Ethanol	6.2	3.3	6.7
Dimethylformamide	3.2	2.2	5.3
Dimethyl sulfoxide	3.0	2.4	5.2

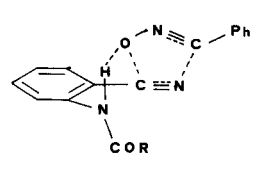
[a] Insoluble.

As shown in Table 3, solvents affect only slightly the cycloadditions to *p*-acetylaminobenzonitrile and *p*-tolylnitrile. As usual in cycloaddition reactions, the dipolarophilic activity are only slightly affected upon changing the solvent [16]. Interestingly, the *p*-acetylaminobenzonitrile is less reactive than *p*-tolylnitrile in all solvents examined. This agrees with the expectations based on the positive *rho* determined in cycloadditions of mesitonitrile oxide to *para*-substituted benzonitriles [12]. The behaviour of the *o*-acetylamino derivative is indeed quite different. Its reactivity is enhanced and shows a remarkable dependence upon the solvent. Only in strongly hydrogen bonding acceptor solvents [17] its reactivity can be depressed to values similar to those shown by the corresponding *para*-derivative.

Discussion.

o-Acylaminobenzonitriles display a somewhat enhanced reactivity towards benzonitrile oxide, relative to the *para*-derivatives. The activation is, however, lost in hydrogen bonding acceptor solvents and in the *N*-methyl derivative as well. This clearly indicates that an intermolecular hydrogen bonding between benzonitrile oxide and the *ortho*-dipolarophile is reasonable for the enhanced reactivity.

Although the chemical consequences are by no means negligeable, the size of the effect is not large. From the data of Table 3, which shows a change of a factor 10, it can be estimated around 1.3 Kcal/mole, a value which is lower relative to the accepted strength of hydrogen bonds (3-5 Kcal/mole) [18]. This can be attributed to the reduced basicity of the nitrile oxide oxygen [19]. Moreover some of the hydrogen bonding stabilization is lost during the delivery of nitrile oxide to the C≡N bond. The rigid backbone of the dipolarophile restricts the flexibility of the hydrogen bonded complex and unfavourable conformations are required to maintain assistance, as shown in **11**. An in plane delivery to C≡N is also conceivable, as shown in **12**. In this transition structure, hydrogen bonding effects are stronger. Charge transfer is however less, since interactions involve the nonconjugated site of the C≡N bond [13].



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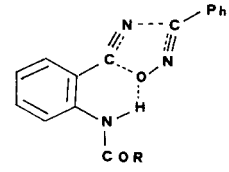

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Aside from the problem of the geometry of the transtion structure, the results discussed above provide evidence that hydrogen bonding is effective in enhancing the reactivity of the slightly reactive C≡N bond of benzonitriles and support the view that the site-selectivity observed with β-aminocinnamonitriles could be due to hydrogen bonding effects.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. The ir spectra were taken on a Perkin-Elmer 281 spectrophotometer. Pmr spectra were taken on a Varian A 60 spectrometer using tetramethylsilane as an internal standard. Mass specra were obtained with a LKB 9000 S instrument. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Column chromatography and tlc were performed with silica gel H and GF_{254} (Merk) respectively. Benzene was used as eluant. Quantitative analyses were carried out by gc on a Varian 2700 chromagraph equipped with a flame-ionization detector and a glass column (4 mm i.d. × 1.8 m) packed with 1.5% OV-17 on Chromosorb G-HP (80-100 mesh). The identification of samples from different experiments was secured by mixed mps and superimposable ir spectra.

Starting Materials.

o-Aminobenzonitrile (**9e**), *p*-aminobenzonitrile and *p*-tolylnitrile are commercially available (Aldrich). *o*-Acetylaminobenzonitrile (**9a**) [20], *o*-benzoylaminobenzonitrile (**9b**) [21] and *p*-acetylaminobenzonitrile (**9f**) [22] were prepared by treatment of the corresponding aminobenzonitriles with the appropriate acyl chloride according to known literature methods. *N*-Methyl-*o*-acetylaminobenzonitrile (**9d**) [23] was prepared by

Table 4

Analytical Data for Oxadiazoles **10a-f**

Compound No.	Molecular Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
10a	$C_{16}H_{13}N_3O_2$	68.81	4.69	15.05	68.50	4.83	15.13
10b	$C_{21}H_{15}N_3O_2$	73.89	4.43	12.31	73.61	4.25	12.26
10c	$C_{21}H_{17}N_3O_3S$	64.43	4.38	10.74	64.18	4.45	10.60
10d	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33	69.46	5.20	14.61
10e	$C_{14}H_{11}N_3O$	70.87	4.67	17.71	70.61	4.71	17.90
10f	$C_{16}H_{13}N_3O_2$	68.81	4.61	15.05	68.73	4.73	14.90

methylation of **9a** with sodium hydride/methyl iodide according to the Fone's procedure [24].

o-Tosylaminobenzonitrile (**9c**).

A solution of 1.2 g (10 mmoles) of **9e** and 2.0 g (10.5 mmoles) of *p*-toluenesulfonyl chloride in 10 ml of pyridine was kept one day at room temperature. Addition of water precipitated 2.5 g (90%) of **9c**, colourless crystals, mp 127-128° (from ethanol); ir (potassium bromide): 3150 cm^{-1} (NH), 1326 and 1142 cm^{-1} (SO_2); pmr (deuteriochloroform): 2.4 (s, CH_3, 3H), 6.5 (broad s, NH, exchangeable with deuterium oxide, 1H); ms: 272 (M), 208 (M-SO_2).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.64; H, 4.35; N, 10.15.

Benzhydroximic acid chloride [26] was obtained by chlorination of the corresponding oxime according to literature procedure. 3-Phenyl-5-(*p*-tolyl)-1,2,4-oxadiazole was prepared according to the literature [9].

General Procedure for the Cycloaddition Reactions.

To stirred ice-cooled solution of 1.55 g (10 mmoles) of benzhydroximic acid chloride and 20 mmoles of the substituted benzonitriles **9a-f** in 50 ml of anhydrous tetrahydrofuran a stoichiometric amount (10 mmoles) of triethylamine in the same solvent (10 ml) was added over one hour period. After keeping two days at room temperature the triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure leaving a residue. Column chromatography of the residue afforded 3,4-diphenylfuroxane and unreacted starting nitrile. Further elution gave **10a-f** in the yields given in Table 1. Mps, crystallization solvents, ir and pmr data of oxadiazoles **10a-f** are gathered in Table 2 and the analytical data in Table 4.

General Procedure for Solvent Effect Determination.

To a stirred solution of 155 mg (1 mmole) of benzhydroximic acid chloride and 1 mmole of the substistuted benzonitrile at 25° in 5 ml of solvent a stoichiometric amount (1 mmole) of triethylamine in the same solvent was added. The mixtures were kept two days at 25° and then diluted to a volume of 25 ml with chloroform, which dissolved any precipitate. A weighted amount of suitable compound was added as an internal standard. The yields of oxadiazoles were determined by gc and are given in Table 3. In two series of experiments, yields were reproducible within ±1% of the given values.

Alkaline Hydrolysis of Oxadiazole **10a**.

A solution of 0.7 g (3 mmoles) of **10a**, 10 ml of ethanol and 5 ml of diluted potassium hydroxide was refluxed for 4 hours. After dilution with water and extraction with chloroform, the extracts were dried over sodium sulfate and evaporated to give 0.5 g (85%) of oxadiazole **10e**, colourless crystals, mp 127-128°, identical with the sample obtained from the cycloaddition of **9e**.

Acylation of Oxadiazole **10e**.

Stoichiometric amounts (2 mmoles) of **10e** and acetic anhydride in pyridine (5 ml) were left one day at room temperature under stirring. Addition of water precipitated 0.5 g (87%) of **10a**, which were filtered off, colourless crystals, mp 173-174°, identical with sample obtained from the cycloaddition of **9a**. Similarly, treatment of **10e** with benzoyl chloride or

Methylation of Oxadiazole **10a**.

To a stirred solution of 0.7 g (3 mmoles) of **10a** in 20 ml of anhydrous benzene 0.15 g (3.75 mmoles) of a 60% dispersion of sodium hydride in mineral oil was added. The mixture was refluxed with stirring for ten hours, under atmosphere of nitrogen, during which time the white sodium salt of **10a** precipitated. After cooling, a slight excess of methyl iodide was added and the reaction mixture was refluxed eight hours more. The hot mixture was filtered off and the filtrate evaporated under reduced pressure. Crystallization from light petroleum of the residue afforded 0.55 g (78%) of oxadiazole **10d**, colourless crystals, mp 93-94°, identical with the sample obtained from the cycloaddition of **9d**.

Acknowledgements.

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