The Site-selectivity of Cycloadditions of Nitrile Oxides to β-Aminocinnamonitriles. A Remarkable Solvent Dependence

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Cycloadditions of nitrile oxides to *N*-mono and unsubstituted β-aminocinnamonitriles are remarkably affected by the hydrogen acceptor ability of the solvent. Addition to C≡N bond predominates in non and weak hydrogen bond acceptor solvents because of the assistance of favourable hydrogen bonding effects. In strong hydrogen bond acceptor solvents the assistance is fully relieved and the regular addition to C=C bond becomes prevalent.

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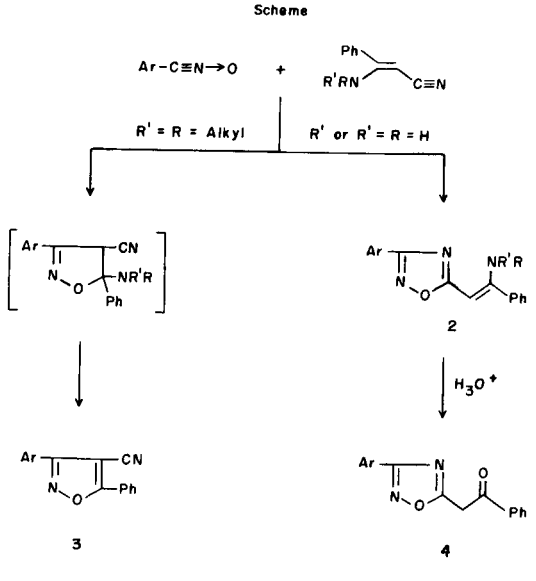
The cycloadditions of nitrile oxides to β-aminocinnamonitrile (**1a**) and its *N*-monosubstituted derivatives is the only reported method for the synthesis of 3-aryl-5-(β-aminostyryl)-1,2,4-oxadiazoles **2**. *N,N*-Disubstituted derivatives cannot be prepared by this method because *N,N*-disubstituted β-aminocinnamonitriles afford exclusively 3,5-diaryl-4-cyano-1,2-oxazoles **3** (Scheme). The latter were also observed in the synthesis of **2** as by-products [1].

Scheme



In an investigation aimed at optimizing the yields of oxadiazoles **2** which appear to be of pharmacological interest [2-4], we found that the yields and the site-selectivity of the cycloadditions of nitrile oxides to β-aminocinnamonitrile (**1a**) and its *N*-monosubstituted derivatives are remarkably affected by the hydrogen acceptor ability of the solvent. We report here a study of the influence of solvents on the site-selectivity of the cycloadditions of 4-chlorobenzonitrile oxide with **1a** and its *N*-cyclohexyl derivative **1b**. The cycloadditions to β-pyrrolidinocinnamonitrile (**1c**), which yields exclusively isoxazole **3**, have been also investigated for reference purposes. 4-Chlorobenzonitrile oxide was chosen since its cycloaddition reaction to **1a** is highly site-selective [1] and its dimerization reaction is slightly affected upon changing the solvent [5].

Results and Discussion.

The reactions were performed by generating the 4-chlorobenzonitrile oxide *"in situ"* in the presence of an equimolar amount of the aminocinnamonitriles **1a-c**. Under these conditions the resulting product composition of the reaction mixtures was more readily and rapidly determined. A 3:1 ratio of dipolarophile to 1,3-dipole remains, however, more suitable for preparative purposes, because of the moderate dipolarophilic activity of β-aminocinnamonitriles, and affords high and easily isolable yields of oxadiazoles **2**. The yields of cycloaddition products have been determined by gc and are listed in the table. For the reactions of **1a,b** the oxadiazole/isoxazole ratios are also given.

The cycloaddition to β-pyrrolidinocinnamonitrile (**1c**) afforded exclusively the isoxazole **3**. Attempts to detect the presence of β-pyrrolidinostyryloxadiazole have been made by subjecting samples of reaction mixtures of **1c** to acid hydrolysis. While oxadiazoles **2** afford quantitatively 3-phenyl-5-phenacyl-1,2,4-oxadiazole (**4**) upon hydrolysis, no traces of **4** could be detected in the hydrolyzed mixtures of **1c**.

As shown in the Table the oxadiazole/isoxazole ratios are high for reactions of **1a,b** performed in non hydrogen bond acceptor (HBA) solvents (solvents 1-5). The ratios decrease slightly in weak HBA solvents (solvents 6-8), but oxadiazoles remain the predominant products. On the other hand in strong HBA solvents (dimethylformamide and dimethylsulfoxide) isoxazole predominates and in amphiprotic solvents (ethanol and methanol) the ratios are close to 1 and nearly equivalent amounts of oxadiazole and isoxazole are formed. More insight can be gained by considering the absolute yields of the products. The Table

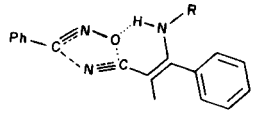
Table

Yields (%) [a] and Ratios of Oxadiazoles **2a,b** and Isoxazole **3** for the Cycloadditions of 4-Chlorobenzonitrile Oxide to Enaminonitriles **1a-c**

		2a	3	2a/3	2b	3	2b/3	3
1	Benzene	39.93	4.39	9.30	15.37	1.53	10.05	38.41
2	Carbon Tetrachloride	32.98	3.69	9.24	13.41	1.40	9.58	36.92
3	Dichloroethane	26.51	2.72	9.40	8.89	1.00	8.89	34.35
4	Dichloromethane	28.19	2.89	9.60	9.70	1.08	8.98	32.55
5	Chloroform	30.10	3.15	9.70	9.70	1.06	9.15	33.64
6	Diethyl Ether	32.61	4.45	7.40	13.80	1.89	7.30	38.62
7	Ethyl Acetate	24.70	3.85	6.50	7.90	1.34	5.90	32.28
8	Tetrahydrofuran	21.70	5.81	3.76	6.79	1.59	4.27	29.60
9	Dimethylformamide	1.90	10.03	0.19	0.23	6.43	0.04	14.32
10	Dimethylsulfoxide	0.45	6.70	0.06	-[b]	5.19	0.00	10.81
11	Ethanol	16.00	7.53	2.10	6.34	3.98	1.59	29.92
12	Methanol	5.00	4.45	1.10	5.95	5.56	1.07	22.50

[a] Yields are based on nitrile oxide. The values are the average of at least six determinations. The maximum variation was ±3%. [b] Trace amounts.

clearly shows that the yields of isoxazole in the different experiments are only slightly affected in line with the slight influence of solvents on 1,3-dipolar cycloadditions [6]. The solvents affect instead remarkably the yields of oxadiazoles **2** and the change of the ratios oxadiazole/isoxazole mainly reflects the change of the yields of oxadiazoles. This remarkable dependence of the dipolarophilic activity of the C≡N bond on the solvent, parallels the unusual behaviour recently observed in cycloadditions to *ortho*-aminobenzonitriles [7]. In the latter reactions the enhanced reactivity of the cyano moiety in apolar solvents was ascribed to an intermolecular hydrogen bond assisting cycloadditions. Thus the similar behaviour points out that the cycloadditions to the C≡N bond of **1a** and **1b** which exist predominantly in the *Z* configuration [8], are also assisted by an intermolecular hydrogen bond between the reactants, as shown in **5**. This assistance is clearly dependent on solvent basicity. It is the greatest in non HBA solvents. while it is relieved in strong HBA solvents which



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compete with nitrile oxide as acceptor of hydrogen bonding. In strong HBA solvents like dimethylformamide and dimethylsulfoxide the fall of the cyano moiety reactivity behind that of the ethylenic bond is in keeping with the regular order of dipolarophilic activity of the C=C and C≡N bonds [9].

The overall results show that the formation of oxadiazoles **2** in the cycloadditions to β-aminocinnamonitriles **1a,b** is due to an enhanced reactivity of the C≡N group because of the hydrogen bonding assistance shown in **5**. The effect of the intermolecular hydrogen bond can be tuned with suitable HBA solvents, thus allowing for a control of the site-selectivity of the cycloadditions. In strong HBA solvents the assistance is fully relieved and the site-selectivity of the cycloadditions are reversed.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. The ir spectra were taken on a Perkin-Elmer 281 spectrophotometer. The pmr spectra were taken on a Bruker WP 80 FT spectrometer operating at 80 MHz and using tetramethylsilane as an internal standard. Mass spectra were obtained with a LKB 9000 S instrument. Elemental analyses were performed on a Carlo Erba 1106 instrument. Column chromatography was performed with silica gel using a mixture of cyclohexane-ethyl acetate (9:1) as eluant. Gc analyses were carried out on a Carlo Erba Fractovap 2350 gas-chromatograph equipped with a hydrogen flame ionization detector and a glass column (2 mm i.d. × 3 m) packed with 3.8% UCW-98 on Supelcoport (80-100 mesh). The identification of samples from different experiments was secured by mixed melting points and superimposable ir spectra.

Materials.

Solvents were purified and dried according to the literature methods [10]. 4-Chlorobenzhydroximic acid chloride [11], β-pyrrolidinocinnamonitrile (**1c**) [12], 3-(4-chlorophenyl)-4-cyano-5-phenyl-1,2-oxazole (**3**) [1], and 3-(4-chlorophenyl)-5-(β-aminostyryl)-1,2,4-oxadiazole (**2a**) [1] were prepared according to reported procedures. β-Aminocinnamonitrile (**1a**) was commercially available (Aldrich).

β-(*N*-Cyclohexylamino)cinnamonitrile (**1b**).

Freshly distilled cyclohexylamine (10 mmoles) was added to a solution of phenylpropiolonitrile [1] (10 mmoles) in ethanol (20 ml). The mixture was refluxed one hour and then evaporated under vacuum. The residue afforded colourless crystals (97%), mp 106-107° (from cyclohexane); ir (potassium bromide): 3342 (NH), 2218 (C≡N), 1628 cm^{-1} (C=C); pmr (deuterium chloroform): δ 1.22-2.15 (m, 10 H, cyclohexyl H), 3.15 (broad, 1 H, cyclohexyl H), 3.92 (s, 1 H, olefinic H), 4.27 (broad, 1 H, NH), 7.42 (m, 5H, phenyl H); ms: 226 (M).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.01; N, 12.38. Found: C, 79.45; H, 8.05; N, 12.41.

3-(4-Chlorophenyl)-5-[β-(*N*-cyclohexylamino)styryl]-1,2,4-oxadiazole (**2b**).

A solution of triethylamine (10 mmoles) in benzene (10 ml) was added dropwise to a stirred mixture of 4-chlorobenzhydroximic acid chloride (10 mmoles) and enaminonitrile **1b** (30 mmoles) in the same solvent (50 ml) at room temperature. After keeping two days at room temperature the triethylamine hydrochloride was filtered off and the filtrate was distilled under reduced pressure. Column chromatography of the residue gave, besides nitrile oxide dimers and starting enaminonitrile, 0.2 g (8%) of isoxazole **3**, mp 130° (Lit [1], mp 130-131°) and 1.4 g (30%) of oxadiazole **2b**, mp 136° (from cyclohexane); ir (potassium bromide): 3420 (NH), 1626 cm^{-1} (C=C); pmr (deuteriochloroform): δ 1.20-1.72 (m, 10 H, cyclohexyl H), 3.25 (broad, 1 H, cyclohexyl H), 4.27 (broad, 1 H, NH), 5.08 (s, 1 H, olefinic H), 7.30 (m, 5 H, unsubstituted phenyl H), 7.32 (d, 2 H, 4-chlorophenyl H), 7.87 (d, 2 H, 4-chlorophenyl H); ms: 379 (M).

Anal. Calcd. for $C_{22}H_{22}ClN_3O$: C, 69.56; H, 5.84; N, 11.06. Found: C, 69.42; H, 5.92; N, 11.20.

General Procedure for the Quantitative Determinations.

A solution of triethylamine (1 mmole) in the appropriate solvent (1 ml) was added dropwise to a mixture of 4-chlorobenzhydroximic acid chloride (1 mmole) and enaminonitrile (1 mmole) in the same solvent (4 ml) at room temperature with stirring. The mixtures were kept two days at room temperature and then diluted to a volume of 10 ml with chloroform which dissolved any precipitate. After addition of a weighted amount of a suitable 4-substituted benzophenone as an internal standard, the mixtures were directly analyzed by gc. In two series of experiments yields were reproducible within ±2% of the given values (Table). Samples of the evaporated cycloaddition mixtures of **1c** were refluxed with ethanol containing 15% hydrochloric acid (3 ml) for 4 hours. A tlc and gc comparison did not show any formation of 3-(4-chlorophenyl)-5-phenacyl-1,2,4-oxadiazole (**4**) [1]. Under similar conditions oxadiazoles **2** were quantitatively converted in **4** [1].

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