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REACTIONS OF A STABLE BENZONITRILE OXIDE WITH AMINOPYRIDINES.

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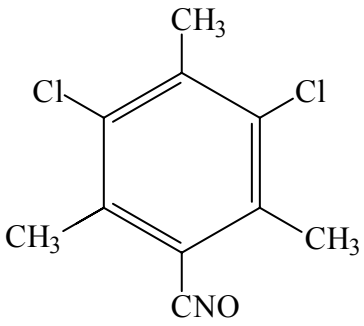
Abstract -Stable aryl nitrile oxide (**1**) and isomeric aminopyridines (**2**) undergo different reactions depending on both the isomer and the conditions. The nitrile oxide gives 1,3-cycloaddition to the 4-aminopyridine (**2c**) in its iminic form if acids are present to promote the formation of imine. In such a case, the stable products 3,5-dichloro-2,4,6-trimethyl-*N*'-(4-pyridinyloxy)benzene carboximidamide (**3***E*) and (**3***Z*) are observed, otherwise, **2c** catalyzes the dimerization, with the loss of an oxygen atom, of **1**, leading to 3,5-bis-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,4-oxadiazole (**4**) as the main product. A similar 1,3-cycloaddition is given by 2-aminopyridine (**2a**): the compounds (5*R* and 5*S*)-(±)-3-(3,5-dichloro-2,4,6-trimethylphenyl)-1-oxa-2,4,6-triazaspiro [4,5]-deca-2,7,9-triene (**6**) and (5*R* and 5*S***)**-(±)-3-(3,5-dichloro-2,4,6-trimethylphenyl)-1-oxa-2,4,6-triazaspiro[4,5]-deca-3,7,9-triene (**7**) have been identified, although subsequent reactions give the stable products (*NZ,N'Z*)-3,5-dichloro-2,4,6-trimethyl-*N*-[2(1*H*)-pyridinylidene]-*N***'**-(2-pyridinyloxy)benzene carboximidamide (**8**) and (*NE,N'Z*)-3,5-dichloro-2,4,6-trimethyl-*N*-[2(1*H*)-pyridinylidene]-*N'*-(2-pyridinyloxy) benzene carboximidamide (**9**); these reactions proceed even in the absence of acids with no dimerization of **1,** but acids (pyridinium chloride) speed them up remarkably. Addition of **1** onto the 3-aminopyridine (**2b**) leads to *N*-hydroxybenzenecarboximidamides (**12**), as well as to small amounts of a benzamide (**13**), and the effect of the pyridinium chloride is negligible.

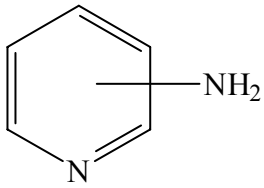
INTRODUCTION

After studying the addition of arylamines to aromatic nitrile oxides,[1] we extended the study to heteroaromatic amines; our interest was also stimulated by the existence, for some of them, of an equilibrium between the aminic and the iminic form. The latter was expected to be particularly prone to the 1,3-cycloaddition by nitrile oxides.

The following reagents were chosen: 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (**1**) and amino-substituted pyridines (**2**):



1



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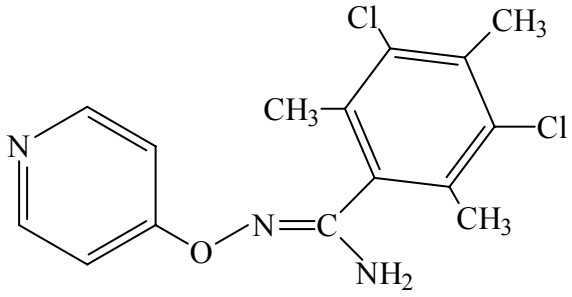
a: (2-NH_2)
b: (3-NH_2)
c: (4-NH_2)

Of the three isomers, **2a** and **2c** have an iminic form and could be thus expected to give similar products, whereas it was anticipated that the reaction would be different for **2b**. From the point of view of acid-base behavior, **2c** differs considerably from the other isomers, the pK_A-values in water being 6.86 for **2a**, 5.98 for **2b**, 9.17 for **2c**.[2] As a result of these differences it was found that not only was the nature of the reaction products characteristic of each isomer, but the product itself sometimes depended on the reaction conditions.
The reaction of the most basic isomer shall be reported first, followed by those of the other isomers.

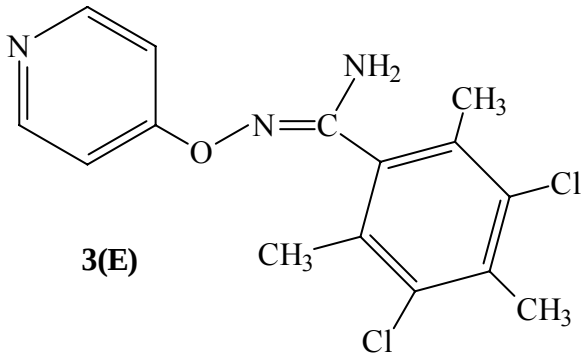
RESULTS AND DISCUSSION

4-Aminopyridine.

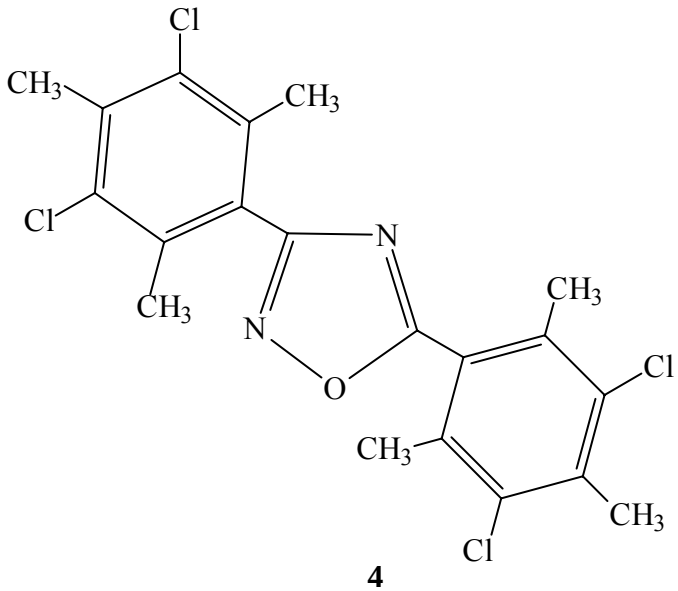
In the presence of acids like pyridinium chloride and AcOH, the reaction **1** + **2c** gives rise to a benzenecarboximidamide (**3**), an adduct, although rearranged, of **1** with **2c**.



3(Z)



3(E)



4

However, in neutral conditions, the reaction did not give such an adduct as the main product, but an already known oxadiazolic derivative (**4**),[3,4] which is substantially a product of the dimerization, with the loss of an oxygen atom, of **1**.

This reaction course was evidenced by HPLC analysis of the products resulting from a series of experiments. Using $CHCl_3$ /DMF mixtures as the solvents, the main identified product was always **4** (Table 1), sometimes in molar fractions exceeding 90% with respect to the sum **3** + **4.** Also produced were oligomers of ArCNO, but they were not separated out by HPLC and this lowered the yield of identified products. The formation of both diphenyloxadiazole and oligomers from benzonitrile oxide in the presence of an amine is well known.[5]

A completely different result was obtained employing TCE/DMF mixtures (from 8 to 16% DMF) as solvents: there were excellent yields of products (**3**) and (**4**), the former prevailing markedly (*ca.* 99%) the latter present only as an impurity (*ca.* 1%).

It was found that due to the basicity of **2c** the solvent 1,1,2,2-tetrachloroethane (TCE) underwent β-elimination, producing enough hydrochloric acid to modify the reaction course: the presence of 1,1,2-trichloroethene was evidenced by GC/MS analysis of solutions of **2c** in TCE/DMF and by ^{13}C-NMR spectra of solutions containing equal amounts of **2c** and TCE in $CDCl_3$/DMSO-d_6.

Some runs were carried out in $CHCl_3$/DMF mixtures, with small additions of TCE. It was found that in the presence of 2-3% of TCE there is still enough acidity to produce **3** almost quantitatively; only when the dose of TCE in the solvent is further reduced to ≤ 1% are both the overall yields of **3** + **4** and the selectivity to **3** progressively diminished, until **4** becomes the main detectable product.

Table 1 - Product distribution for **1** + **2c** in $CHCl_3$/DMF mixtures ($C_1°$= 0.02 mol/L; $C_{2c}°$ = 0.085 mol/L).[a]

DMF in the mixture (% v/v)	T = 35°C Molar fractions		T = 45°C Molar fractions		T = 55°C Molar fractions	
	3	**4**	**3**	**4**	**3**	**4**
8			0.34	0.66	0.17	0.83
16	0.29	0.71	0.20	0.80		
24	0.30	0.70	0.03	0.97	0.07	0.93
40	0.19	0.81	0.06	0.94	0.06	0.94

[a] HPLC of the mixture identified molar fractions of (**3**) and (**4**); also unidentified oligomers of ArCNO were produced, consequently the overall yield of **3** + **4** was around 50%.

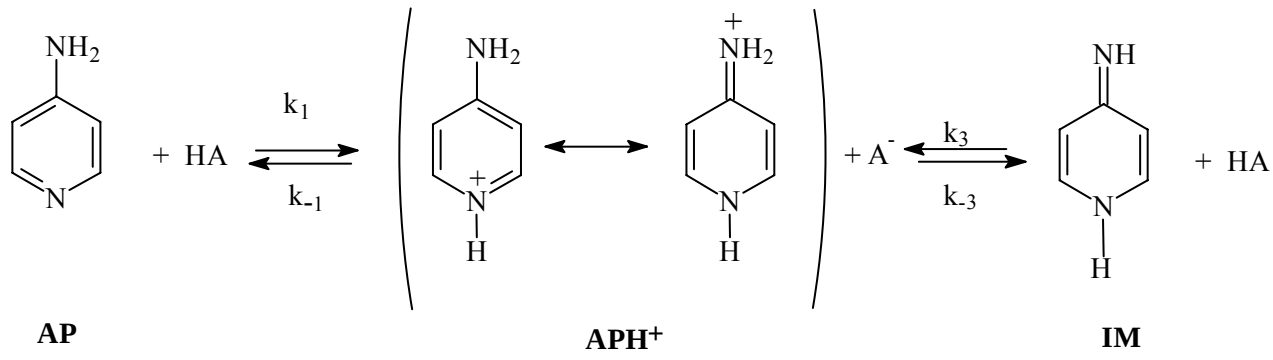
Once it had been established that the presence of an acid is necessary to produce **3** with high selectivity, experiments were carried out in $CHCl_3$ /DMF mixtures, adding aliquots of an acid, such as pyridinium chloride (PyHCl). Runs in the presence of pyridinium chloride at 35°C (Table 2) proved that the effect of pyridinium chloride is related to the concentration level of the amine (**2c**) and the added acid**:** with $C_{2c}°$ approximately constant (0.12 – 0.13 mol/L), increasing $C_{PyHCl}°$ leads to a progressive decrease in the production of **4** and other nitrile oxide derivatives until reaching $C_{PyHCl}°/C_{2c}° \geq 0.3$ when 90% or more of the product is **3**. The two runs carried out at $C_{PyHCl}°/C_{2c}$ = 0.12 show that higher amine concentrations favor product (**3**).

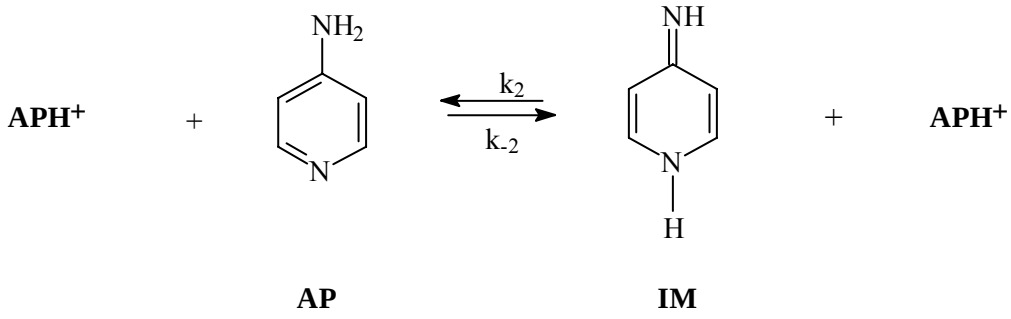
^{1}H-NMR identified the product (**3**) as a mixture of stereoisomers *E* and *Z*, in the ratio 73:27, as shown by the signals assigned to NH_2. The assignment of structure *Z* was based on the higher δ-value for NH_2 [13.04 *vs* 9.05 for stereoisomer *E*], attributed to hydrogen-bonding with the oxygen atom of the O-N=C group. The adduct (**3**) was further characterized by ^{13}C-NMR and MS. In the MS spectrum it can be seen that the molecular ion (*m/z* 323) indicates **1** to **2c** addition, and the fragmentation is consistent with the assigned structure. In fact the most abundant ion at *m/z* 229 (prevalently aryldiazirine ion) corresponds to a loss of $PyO^{\cdot}$, which is consistent with a nucleophilic attack of the oxygen atom of ArCNO at the C=N bond of **2c** in its iminic form. The other fragments, apart from those typical of this aryl group (i.e. loss of a chlorine atom or HCl, loss of methyl group, etc.), are a consequence of the structure of the diazirine ion. The presence of ions at *m/z* 95 and *m/z* 94 ($PyOH^+$ and $[PyO]^{+\cdot}$) support the assignment.

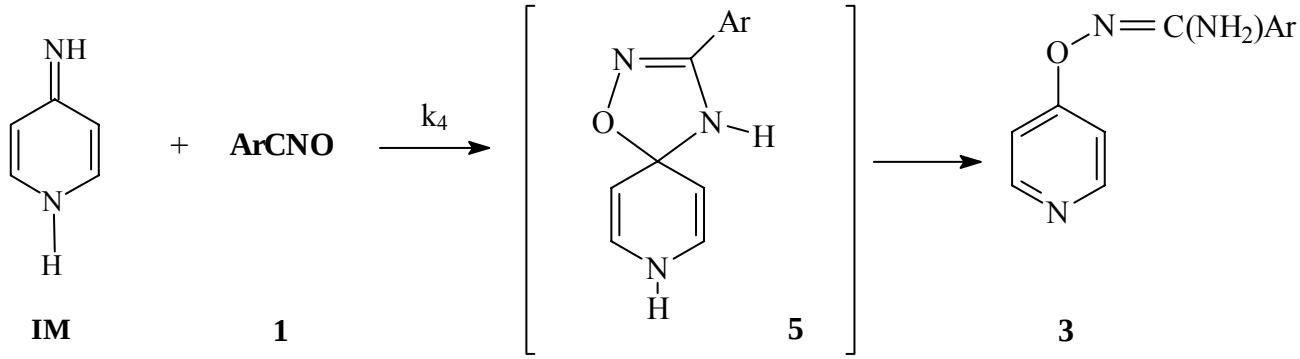
Table 2 - Product distribution for **1** + **2c** in $CHCl_3$/DMF (70:30 v/v) at 35°C, in the presence of pyridinium chloride ($C_1° = 0.02$ mol/L).

$C_{2c}°$ mol/L	$\frac{C_{PyHCl}°}{C_{2c}°}$	Molar fractions **3**	**4**	Overall yield of **3** + **4** %
0.201	0.12	0.82	0.18	79
0.122	0.12	0.64	0.36	66
0.120	0.18	0.80	0.20	75
0.126	0.23	0.88	0.12	96
0.125	0.29	0.90	0.10	98
0.122	0.40	0.96	0.04	100
0.129	0.51	0.98	0.02	101

It was found experimentally that without any acid the reaction giving product (**3**) is far from being the main reaction, but it stops completely if an acid like pyridinium chloride is added in the stoichiometric amount required to protonate the amine.
Thus it can be deduced that the active reagent is an uncommon form of the amine that requires an acid to promote its formation through a protonation step; however the overall process is based on the unprotonated amine, or *free amine;* this means that when the *free amine* disappears, the reaction ceases. It is a reasonable assumption that the active reagent is the *iminic form* (**IM**) of **2c**, which is a dipolarophile able to react with a 1,3-dipolar molecule such as **1**. The formation of the *imine* could occur *via* protonation, according to the mechanism proposed in the Scheme, where HA is the added acid, A^- is its conjugate base, and ArCNO is the nitrile oxide.
Treatment, with reference to IM, can be applied by stationary state approximation, taking into account that (a) the protonated amine APH^+ can be written not only in the most stable form with the charge on the annular nitrogen, but also in the quinoid form with the charge on the aminic nitrogen; (b) the concentration of IM must be very low;[6] (c) when the acid HA is pyridinium chloride or AcOH, the protonation of AP can be considered as shifted to the right (in water: $pK_A = 5.23$ for the pyridine's conjugate acid,[2] 4.75 for AcOH[7]) i.e. provided the amine is in excess, the amount of amine corresponding to the amount of added HA is protonated, the excess remaining in the AP form (neglecting the small amount of IM); (d) as a consequence of point c, C_{HA} is close to zero, and k_3C_{HA} is negligible; (e) since the aminopyridine AP is a stronger base than pyridine (**A^-**), $k_{-2} >> k_{-3}$ and $k_{-3}C_A - < k_{-2}C_{AP}$; (f) the acid-base exchange is faster than the 1,3-cycloaddition, $k_2C_{APH}+ >> k_4 C_{ArCNO}$. Point (c) above is also supported by ^{15}N-NMR experiments in $CDCl_3$/DMSO-d_6 (70:30 v/v) mixtures, carried out with the addition of known quantities of pyridinium chloride.







Scheme

The result of the stationary-state treatment is:

$$C_{IM} \cong \frac{k_{-2}\, C_{APH^+}\, C_{AP}}{k_2 C_{APH^+}} = K_{-2}\, C_{AP}$$

where K_{-2} is the equilibrium constant (= k_{-2}/k_2) for the conversion of AP to IM.
If the cycloaddition is the rate-determining step it follows that:

$$r = k_4 C_{IM} C_{ArCNO} = k_4 \cdot K_{-2} C_{AP} C_{ArCNO}$$

In the case under examination, this corresponds to kinetics of the first order with respect to **1,** and with respect to the *amine in its non-protonated form* (i.e. the *free amine*). When the amount of added acid is less than the amount of *free amine*, it can be shown that the reaction consumes the AP form almost exclusively, the contribution of the APH^+ form being negligible. Thus as a good approximation for a reaction carried out with an ArCNO defect with respect to the amine, it is:

$$C_{AP} \cong C_{AP}^{\circ} - C_{ArCNO}^{\circ} .y$$

where y is the fractional conversion of the nitrile oxide.
The *spiro*-cycloadduct (**5**) in the proposed mechanism (Scheme) could be neither isolated nor identified in solution. However, in the case of the 2-aminopyridine (**2a**) (reported later), the corresponding *spiro*-cycloadduct was detected, and its two tautomeric forms were separated and identified by ^{1}H-NMR and MS spectra, although again it was not possible to isolate them.
Kinetic measurements were carried out on the reaction in $CHCl_3$/DMF (70:30), mainly at 35°C, but also at 45 and 55°C. The reactions were interpreted, according to the proposed mechanism, as first-order in **1** and first-order in the *free amine* AP ($r = k C_{AP} C_{ArCNO}$). Table 3 shows the results. It can be appreciated that when the acid was AcOH the k value obtained was the same as when the acid was pyridinium chloride, the temperature always being 35°C. This result is consistent with the proposed mechanism since k, being equal to $k_4 \cdot K_{-2}$, would be independent of the choice of the acid HA provided the acid is able to shift to the right the first protonation reaction. The dependence of k on temperature gives an apparent activation energy of 35.9 kJ/mol**:** the low value of E_{act} also highlights the complexity of the k coefficient.
When an acid is not present the main product is **4**, and sometimes it is the greatly prevailing one. Therefore it was possible to measure rates that are approximately the dimerization rates of **1**. In these conditions, the reaction kinetics were actually second order in **1**. Table 4 shows the rate coefficients (k_d) from runs in $CHCl_3$/DMF mixtures. These coefficients refer to different temperatures (35, 45 and 55°C), different solvent compositions, and different levels of amine (**2c**). Surprisingly, there is almost no dependence of k_d on temperature, evidence that also k_d is a complex coefficient.

Table 3 - Kinetic runs for **1** + **2c** in $CHCl_3$/ DMF (70:30) in the presence of an acid HA ($C_1° \approx 0.02$ mol/L). The concentration of only the *free amine* is considered kinetically active.

$C_{HA}°$ mol/L	$C_{2c}°$ mol/L	no. of runs	$10^3 k$ L/mol s
		Runs at 35°C, HA = AcOH	
0.038	0.090	3	39.0 ± 2.3
0.071	0.165	3	46.9 ± 2.1
		average value for 6 runs:	43.0 ± 4.7
		Runs at 35°C, HA =Pyridinium Chloride	
0.019	0.058	3	44.5 ± 4.9
0.021	0.111	6	34.2 ± 4.3
0.026	0.085	2	36.7 ± 4.1
0.028	0.085	6	44.3 ± 8.9
0.030	0.090	7	42.6 ± 4.2
0.038	0.086	2	41.0 ± 1.6
0.039	0.111	2	40.3 ± 1.3
0.042	0.096	2	48.2 ± 2.7
		average value for 30 runs:	41.1± 6.5
		Runs at 45°C, HA = Pyridinium Chloride	
0.020	0.058	4	64.6 ± 5.1
0.025	0.086	2	68.2 ± 5.2
0.034	0.097	1	55.7 ± 1.0
0.040	0.083	5	61.8 ±5.9
0.059	0.130	3	71.9 ± 3.4
		average value for 15 runs:	65.0 ± 6.4
		Runs at 55°C, HA = Pyridinium Chloride	
0.025	0.086	1	92.4 ± 7.2
0.034	0.097	2	102.0 ± 6.8
		average value for 3 runs:	98.8 ± 7.4

Activation parameters :
log A (L/mol s) = 4.70± 0.18
E_{act} = 35.9 ± 1.1 kJ / mol

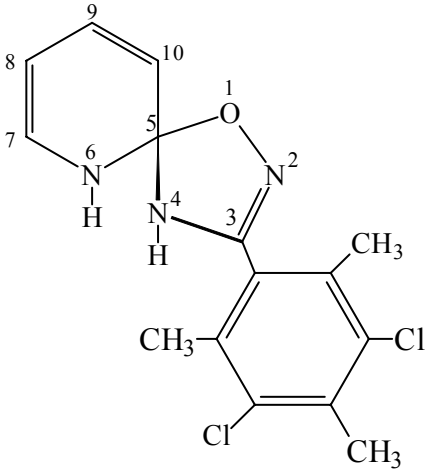
Table 4 - Kinetic runs for the conversion of **1** to oxadiazole (**4**) in the presence of **2c**, in $CHCl_3$/DMF mixtures and at various temperatures ($C_1° \approx 0.02$ mol/L).

DMF in the mixture (% v:v)	T = 35°C no.of runs	T = 35°C $10^3 k_d$ L/mol s	T = 45°C no. of runs	T = 45°C $10^3 k_d$ L/mol s	T = 55°C no. of runs	T = 55°C $10^3 k_d$ L/mol s
		Runs with $C_{2c}° \cong 0.09$ mol/L				
10	1	7.6 ± 0.1	2	10.3 ± 2.5	2	9.7 ± 0.9
15	4	11.2 ± 3.6				
16	2	14.2 ± 3.4	2	15.4 ± 0.1		
24	2	35.9 ± 0.7	3	34.9 ± 2.2	1	35.5 ± 0.1
30	5	54.7 ± 6.1			3	63.4 ± 2.5
40			2	88.3 ± 6.9	3	86.7 ± 3.2
		Runs with $C_{2c}° \cong 0.18$ mol/L				
30	2	126 ± 11	2	122 ± 4	3	117 ± 4
40			5	221 ±17		

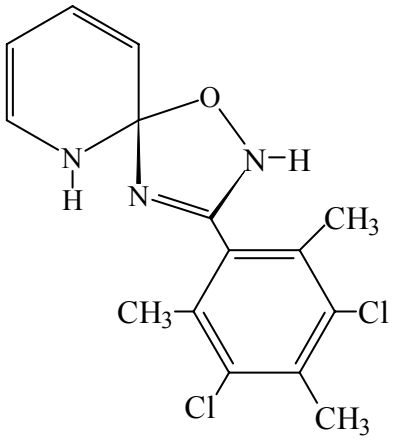
It seems reasonable to assume that ArCNO and **2c** form an unidentified adduct that reacts further with a second molecule of ArCNO to give **4**. The presence of such an intermediate would also explain why the coefficients k_d increase, roughly proportionally, with $C_{2c}°$, indicating that the nucleophile **2c** favors the reaction without being involved stoichiometrically. This is in agreement with the inhibition of this reaction when acids are present in the system. A similar dimerization, that of arylnitrile oxides in ethanol to give diaryldioxadiazines, has been found to be kinetically promoted by nucleophiles such as pyridine and substituted pyridines.[8]

2-Aminopyridine.

Differently from **2c**, the 2-aminopyridine (**2a**), in the absence of acids, reacts with the aryl nitrile oxide (**1**), to give reaction products without dimerization of **1**; in effect 3,5-diaryl-1,2,4-oxadiazole was not found. Therefore, the reaction **1** + **2a** could be studied in both the presence and absence of acids. The latter condition also includes runs in solvent 1,1,2,2-tetrachloroethane (TCE), since **2a** is a base that is not strong enough to promote HCl elimination from TCE (as observed with **2c**). ^{13}C-NMR experiments confirmed the stability of TCE in the presence of **2a**.
In the absence of acids, HPLC analysis for reactions in TCE or $CHCl_3$ mixed with DMF or MeOH, revealed the reaction products to be the compounds (**6**) and (**7**), products resulting from the 1,3-cycloaddition of **1** to **2a** in its iminic form (see Table 5 for a run in TCE/MeOH).

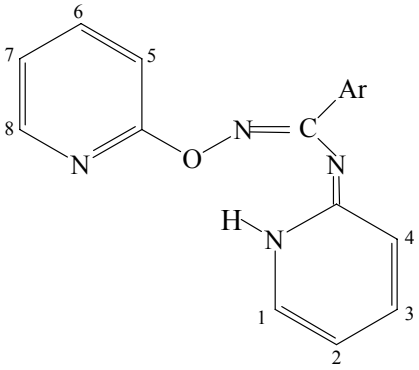


(±) **6**

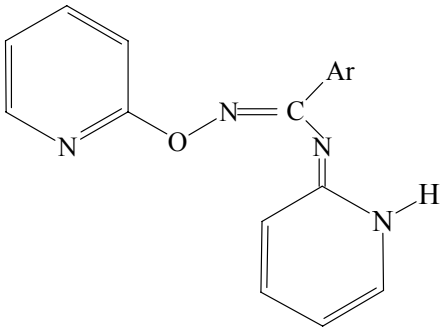


(±) **7**

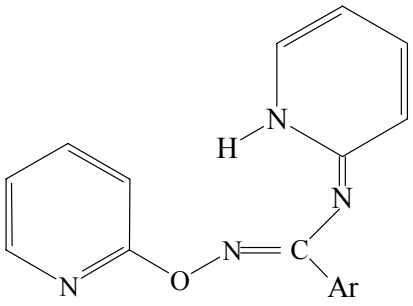
In several different solvent and temperature conditions two *spiro* compounds, tautomers (**6**) and (**7**), were detected. Their isolation by flash-chromatography failed but after separation by HPLC they were identified by the MS and ^{1}H-NMR spectra. Nucleophilic attack of a molecule of **2a** on carbon 3, followed by elimination of NH_3, could lead to several adducts, if both the pyridinic and the aminic nitrogen centers are considered to be nucleophiles. As aminic nitrogen is the stronger nucleophilic site,[9] only adducts (**8-11**) were considered:



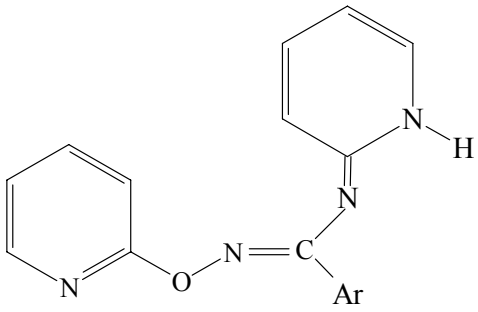
8 *(Z,Z)*



9 *(Z,E)*



10 *(E,Z)*



11 *(E,E)*

Ar = 3,5-Cl_2-2,4,6-Me_3-phenyl

The properties of the two stable products that were isolated are compatible with the structures of benzenecarboximidamides: ^{1}H-NMR spectra present a doublet for NH and a triplet for 1-H, which changes to a doublet by H/D exchange. However, because of the equivalence of the *ortho*-CH_3 signals in the ^{1}H-NMR spectra, it appears that there is free rotation of the Ar groups; in fact molecular modelling and molecular mechanics calculations using the Merck force field implemented in the Spartan simulation package show this to be possible in structures (**8**) and (**9**), but not in **10** and **11**. The assignment of structure *Z,Z* to **8** was based on the higher δ-value for N-H [7.22 *vs* 6.97 for **9**], which can be attributed to hydrogen-bonding with the nitrogen of the O-N=C group.

Table 5 - Product distribution for **1** + **2a** in TCE and in TCE/MeOH (70:30, v/v) at 40°C ($C_1°$ = 0.022 mol/L), resulting from HPLC.

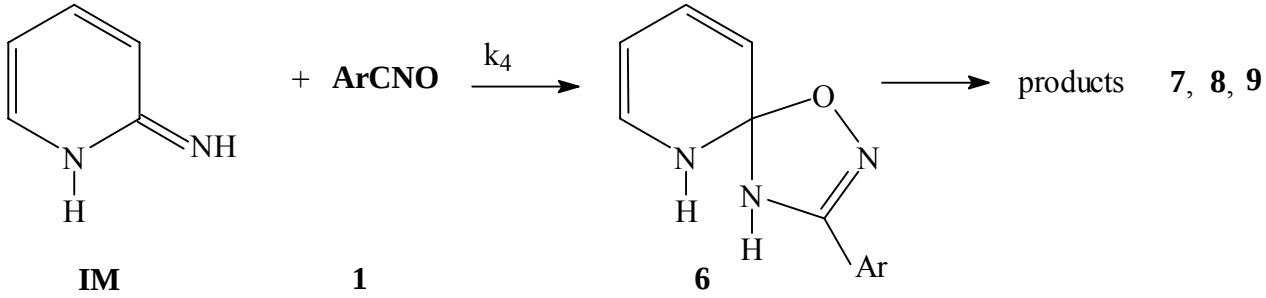
Time (min)	Fractional conversion of ArCNO	Ratios ($Area_{adduct}/Area_{standard}$) for the adducts				
		6	**7**	**8**	**9**	Sum of ratios
		solvent TCE/MeOH; $C_{2a}°$ = 0.087 mol/L				
2	11%	0.19	0	0	0	0.19
5	21%	0.43	0.20	0	0	0.63
8	41%	0.77	0.35	0	0	1.12
12	60%	0.92	0.89	0	0	1.80
15	70%	1.37	1.32	0	0	2.69
25	88%	1.66	1.80	0	0	3.46
150	100%	4.61	8.54	0.14	0	13.29
		Solvent TCE; $C_{2a}°$ = 0.084 mol/L				
20	3%	0.03	0	0.11	0.05	0.19
40	5%	0.15	0	0.23	0.10	0.49
60	8%	0.31	0.06	0.41	0.17	0.95
100	13%	0.54	0.11	0.56	0.18	1.40
140	17%	0.82	0.16	0.73	0.19	1.90
180	21%	0.87	0.18	0.74	0.21	1.99
		Solvent TCE; $C_{2a}°$ = 0.30 mol/L				
10	5%	0.40	0	1.99	0.56	2.95
15	7%	0.48	0	2.04	0.61	3.14
25	11%	0.72	0.17	2.37	1.02	4.28
35	16%	0.98	0	3.15	0.98	5.11
45	20%	1.11	0	3.10	0.99	5.20

In the presence of low concentrations of pyridinium chloride (0.0066 mol/L), HPLC analysis evidenced that, in the initial reaction stage, the products are **6** + **7;** at high conversion also small amounts of **8** and **9** are produced and these derive from the reaction of **6** and **7** with the amine (**2a**), which can be present as unreacted reagent or originated by the partial decomposition of the primary products (**6** + **7**). In the event of decomposition, i.e. when the amine is not in excess, the partial conversion of **6** + **7** into **8** + **9** decreases the total moles of adducts, in fact the "sum of ratios" was found to reach a maximum.
In the presence of pyridinium chloride at higher concentration (Table 6) the product distribution changes because, already in the initial reaction stage, the transformation of **6** + **7** into **8** is favored. When the primary reaction is completed, products (**6**) and (**7**) decrease because of this further reaction.

Table 6 – Product distribution for **1** + **2a** in $CHCl_3$/DMF (70:30 v/v) at 35°C ($C_1°$ = 0.022 mol/L; $C_{2a}°$ = 0.117 mol/L), in the presence of pyridinium chloride (0.041 mol/L), resulting from HPLC.

Time (min)	Fractional conversion of ArCNO	Ratios ($Area_{adduct}/Area_{standard}$) for the adducts				
		6	**7**	**8**	**9**	Sum of ratios
0.67	15%	0.08	0	0.06	0	0.14
1.5	29%	0.31	0.09	0.17	0	0.57
4	59%	0.46	0.36	0.64	0	1.46
10	88%	2.04	1.29	1.42	0	4.75
120	100%	1.20	4.74	2.42	0	8.36
1440	100%	0.42	3.58	2.29	1.87	8.16

The reaction kinetics, first order in both **1** and **2a**, agree with a rate-determining step of 1,3-cycloaddition of the nitrile oxide on the C=N double bond of the iminic form of **2a**. The protonation in the presence of pyridinium chloride is not quantitative, as it is for **2c;** this is supported by the above described ^{15}N-NMR experiments, and by the fact that even when $C_{HA}° > C_{AP,tot}°$ the reaction occurs, whereas for **2c** in the same acid conditions no reaction was observed. By assuming the mechanism that has been suggested to explain the reaction of **2c**, but still not knowing to exactly what extent the initial protonation equilibrium was displaced, we were unable to evaluate the *free amine* concentration $C_{AP}°$ as a function of the total concentration $C_{AP,tot}°$ and of $C_{HA}°$. Thus it was decided to work at low acid concentrations, this rendering C_{APH}^+ negligible and $C_{AP} \cong C_{AP,tot}$ (neglecting the concentration of the iminic form C_{IM}, on the basis of literature data[6]). It should be noted that in the present case the mechanism outlined above ends with the final steps:



IM **1** **6**

where the *spiro*-compound (**6**) and its tautomer (**7**) are relatively stable products, clearly detectable and identified, while the corresponding **5** in the case of **2c** was an unidentified intermediate. However, even **6** and **7** were not isolated products, as they have been converted into **8** and **9**.
Table 7 shows the results obtained in $CHCl_3$/DMF (70:30) at 35°C, in the absence of acids or in the presence of pyridinium chloride ≤ 0.021 mol/L, i.e., $C_{PyHCl}°/C_{AP,tot}° <$ 0.25. The reaction is *ca.* 50-fold faster if pyridinium chloride is present. The same reaction rate was measured using either **2a** in excess with respect to **1** or in an almost stoichiometric ratio of the reactants.

Table 7 - Kinetic runs for **1** + **2a** in $CHCl_3$/DMF (70:30 v/v) at 35°C and in the presence of pyridinium chloride ($C_1° \cong 0.02$ mol/L). The total amine concentration has been used for the calculations.

$C_{PyHCl}°$ mol/L	$C_{\mathbf{2a}}°$ mol/L	no. of runs	10^3k L/mol s
0	0.20-0.32	3	0.25 ± 0.03
0.008	0.07	2	11.0 ± 1.8
0.010	0.07	2	10.9 ± 1.8
0.016	0.07	3	12.9 ± 2.2
0.017	0.07	4	15.0 ± 1.1
0.021	0.12	3	12.6 ± 0.4
Average values for 14 runs: 12.86 ± 2.00			
0.007	0.02	2	13.8 ± 1.0

Table 8 shows the results of several runs carried out in TCE/DMF, without the addition of acids. For the same solvent composition the kinetic parameter increases with increasing T, whilst, at the same temperature (40-41°C), the TCE/DMF mixture containing 30% of DMF appears to be the best compared with the mixtures containing either 10% or 50% of it. In TCE/DMF (70:30 v/v), at 40°C, in the absence of acids, the reaction rate is *ca.* 30-fold higher than in $CHCl_3$/DMF (70:30 v/v) at 35°C (Table 7): the effect is attributable only minimally to temperature, being due, above all, to the difference in solvent.

Table 8 - Kinetic runs for **1** + **2a** in TCE or in TCE/DMF mixtures at various temperatures ($C_1° \cong 0.02$ mol/L; $C_{2a}° \cong 0.12 \div 0.30$ mol/L), in the absence of acid. The total amine concentration has been used for the calculations.

DMF in the mixture(% v/v)	Temperature/°C	no. of runs	10^3k L/mol s
0	40	6	0.27 ± 0.05
	60	5	0.76 ± 0.09
	70	4	0.96 ± 0.04
	80	3	2.24 ± 0.43
10	41	2	1.34 ± 0.40
	60	2	4.21 ± 0.88
	70	2	5.85 ± 0.27
30	40	3	8.45 ± 0.58
	70	3	38.11 ± 4.69
50	41	2	4.40 ± 0.04

On the basis of the product distribution it can be considered that the primary reaction, of which the rate was measured, is the 1,3-cycloaddition of ArCNO to the iminic form **IM** of **2a;** this was obtained, as indicated in the Scheme, by the action of a molecule of *free amine* **AP** on **APH**$^+$, as proposed for **2c**. The cycloaddition is followed by conversion to products (**8**) and (**9**), the amine (**2a**) being available as either an excess reactant or partial decomposition product of the primary cycloadducts. Without any added acid a slow parallel reaction appears to occur: this reaction was probably also present in the case of **2c** but in that case it went unobserved because, without acid addition, ArCNO dimerization occurred.

When the reaction of **1** with **2a** is carried out in pure TCE or $CHCl_3$, the product distribution is quite different**:** adduct **8,** associated with **9**, is often the most abundant product, both in $CHCl_3$ at 35°C and in TCE at 40 and at 70°C.

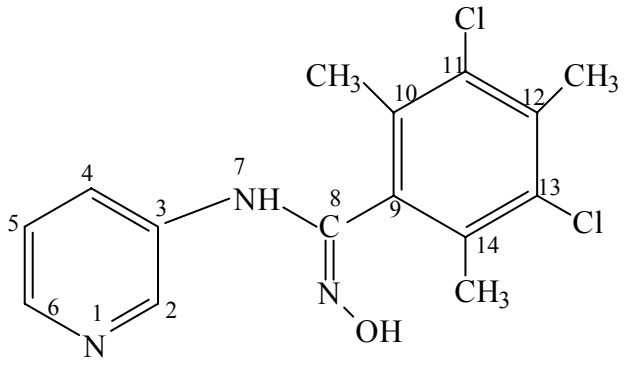
For example, Table 5 shows the results in TCE at 40°C**:** note that the sum of adducts (**8** and **9)** predominates over the sum of adducts (**6** and **7)** when $C_{2a}°$ has the highest value, whereas when its values are lower this preponderance is less evident.

When, at the same temperature, TCE is employed as the solvent the reaction kinetics show a distinctly lower rate than in the TCE/DMF reaction (see Table 8).

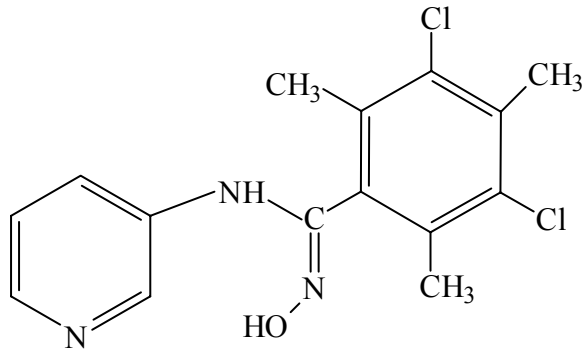
Also in these pure solvents, the proposed reaction mechanism for the mixed solvents is quite possibly valid, but, because of the slowing down of the cycloaddition rate and the increased instability of the adducts **6** + **7**, due to lack of DMF, high molar fractions of **8** + **9** are produced.

3-Aminopyridine.

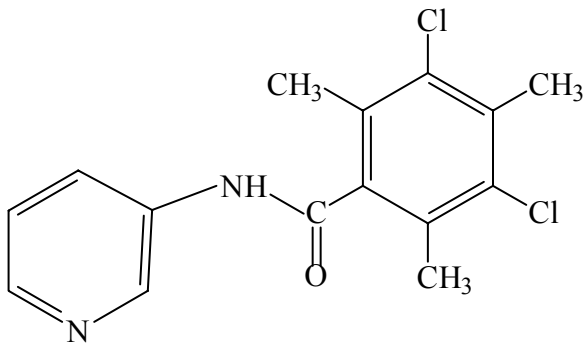
Nitrile oxide (**1**) reacts with **2b** in chlorinated solvents (sometimes mixed with DMF) by open addition, giving rise to product (**12**) in the form of its two stereoisomers *E* and *Z*.
However, small quantities of a benzamide (**13**) were also produced, presumably by a consecutive reaction of **12**.



12E



12 Z



13

The *E*+*Z* mixture (**12**) was characterized by ^{1}H-NMR, ^{13}C-NMR and MS spectra and elemental analysis. The ^{1}H-NMR spectrum in DMSO allowed the *E* and *Z* isomers to be detected separately: the chemical shift for the OH group for *E* is at 9.64, for *Z* at 10.49; furthermore, the δ values for NH are 8.60 and 8.90, respectively. Higher δ values can be justified by hydrogen-bonding with the NH group for the *Z* stereoisomer. Also the *ortho* and *para* CH_3 signals of the two stereoisomers differ. The abundance ratio in all the above cases was *E*:*Z* = 55:45.

Compound (**13**) was isolated and identified by ^{1}H-NMR, IR and MS spectra, as well as by elemental analysis. Following complete reaction at 60°C in different conditions, HPLC revealed the importance of **13** in the overall product mixture. When there was no effect due to the acid the fraction of **13** was lower than 3% (Table 9); larger fractions were found in the presence of added pyridinium chloride and AcOH. For a high Acid/Amine ratio the overall yield was less. The behavior in TCE/DMF (70:30 v/v), not reported, was observed to be similar to that in $CHCl_3$/DMF (Table 9).
The conversion of **12** to **13** by the formal loss of an NH group, despite the use of anhydrous solvents, was no further investigated.

Table 9 - Product distribution for **1** + **2b** in $CHCl_3$/DMF (70:30 v/v) at 60°C ($C_1°$ = 0.02 mol/L; $C_{2b}°$ = 0.24 mol/L).

$C_{Acid}°$ (mol/L)	Molar fractions **12**	**13**	Overall yield %
	Acid: pyridinium chloride		
0	0.975	0.025	98
0.02	0.975	0.025	87
0.04	0.974	0.026	93
0.08	0.965	0.035	88
0.12	0.971	0.029	86
0.16	0.960	0.040	88
0.22	0.950	0.050	66
	Acid: AcOH		
0	0.973	0.027	98
0.07	0.945	0.055	88
0.12	0.950	0.050	83
0.18	0.931	0.069	70
0.26	0.921	0.079	67

The reaction rate was found to be proportional to C_1 and C_{2b}, as for a second-order reaction.
The runs in $CHCl_3$/DMF (70:30 v/v), at 60°C, summarized in Table 10, show very similar kinetic parameters in both the presence and absence of pyridinium chloride.

Table 10. Kinetic runs for **1** + **2b** in $CHCl_3$/DMF (70:30) at 60°C, in the presence of pyridinium chloride ($C_1°$≅ 0.02 mol/L; $C_{2b}°$ ≅ 0.24 mol/L). The total amine concentration has been used for the calculations.

$C_{PyHCl}°$ mol/L	no. of runs	10^3k L/mol s
0	1	0.61 ± 0.00
0.02	2	0.49 ± 0.03
0.04	2	0.53 ± 0.04
0.08	2	0.56 ± 0.16

Table 11 shows the kinetic measurements in TCE/DMF mixtures for the runs with no added acid. An increasing content of the more polar component exerts a very weak solvent effect, at variance with what was observed for the reaction of 2-aminopyridine (**2a**) with the same nitrile oxide. The effect of temperature corresponds to an E_{act} value notably greater than that reported in Table 3.

Table 11 - Kinetic runs for **1** + **2b** in TCE and in TCE/DMF mixtures, at various temperatures ($C_1°$≅ 0.02 mol/L; $C_{2b}°$ = 0.12 ÷ 0.24 mol/L), without acid addition. The total amine concentration has been used for the calculations.

DMF in the mixtures (% v/v)	Temperature/°C	no. of runs	10^3 k L/mol s
0	60	1	0.78 ± 0.00
10	60	2	0.61 ± 0.13
30	60	3	0.69 ± 0.02
	70	2	1.46 ± 0.00
50	40	2	0.27 ± 0.01
	50	1	0.40 ± 0.00
	60	2	1.02 ± 0.09
	70	1	1.61 ± 0.02

Activation parameters (TCE/DMF 50:50):
log A (L/mol s) = 6.85 ± 1.04
E_{act} = 56.8 ± 6.5 kJ/mol

A comparison of the kinetic parameters (k) measured in TCE and TCE/DMF mixtures of different composition (Table 11) with those obtained in $CHCl_3$/DMF (70:30 v/v) (Table 10) confirms the very weak solvent effect: in fact at a temperature of 60°C the k values are very similar.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian VXR-300 spectrometer (300 MHz for ^{1}H and 73 MHz for ^{13}C, Me_4Si as internal standard; $CDCl_3$ or DMSO-d_6 or N,N-DMF-d_7/$CDCl_3$ as the solvents; J values are given in Hz). MS spectra were recorded, at 70 eV, with a HP 5989 A MS spectrometer, using the DIP (direct insertion probe) method. The MS spectra of cycloadducts (**6**) and (**7**) were obtained by LC/MS particle beam interface. IR spectra were recorded and kinetics followed with a Nicolet FT-IR 205 spectrophotometer.

MATERIALS

Reagent grade reagents and solvents were used. Aryl nitrile oxide (**1**) was obtained as previously described.[11] Aminopyridines and pyridinium chloride were purchased from Aldrich Italia.

Procedure for the Reaction of Aryl Nitrile Oxide (**1**) with 4-Aminopyridine (**2c**) with Formation of **3**

A solution of **1** (2.3 g, 0.01 mol) and **2c** (2.6 g, 0.028 mol) in a mixture of 1,1,2,2-tetrachloroethane (TCE)/*N,N*-dimethylformamide (DMF) (70:30, v/v) (50mL) was kept at 50°C for 24 h. The solvent was evaporated under reduced pressure and the residue was fractionated by flash chromatography on a Merck silica gel (230-400 mesh) column of 40 cm length and 2.5 cm internal diameter, eluting initially with a mixture of light petroleum (bp 40-60°C) and ethyl acetate (90:10, v/v) to isolate low amounts (3%) of product (**4**). The separation was then continued by elution with a mixture of light petroleum/ethyl acetate (70:30, v/v) to obtain the adduct (**3**) and the 4-aminopyridine in excess. The yield of adduct (**3**) was of *ca.* 97%. An even better selectivity was obtained at 35°C.
From the reaction of aryl nitrile oxide (**1**) (2.3 g, 0.01 mol) with amine (**2c**) (2.82 g, 0.03 mol), with the addition of pyridinium chloride (2.31 g, 0.02 mol) in a mixture of chloroform/DMF (70:30, v/v) (50 mL), at 35°C for 12 h, fractionated as described above, the same results were obtained. When equal molar amounts of pyridinium chloride and **2c** were added, unreacted aryl nitrile oxide (**1**) was recovered.
The adduct (**3)** was obtained as white crystals and recrystallized from ethanol.

3,5-Dichloro-2,4,6-trimethyl-*N'*-(4-pyridinyloxy)benzenecarboximidamide(**3**). At 202-205°C it was converted into an amorphous solid which melted and charred at 240-250°C. ^{1}H-NMR (DMSO-d_6) δ ppm:13.04 and 9.05 (2H, s, NH_2, *Z* and *E* stereoisomers, in the ratio 27:73, respectively), 8.21 (2H, d, J = 7.5 Hz, H-2 and H-6), 6.91 (2H, d, J= 7.5Hz, H-3 and H-5), 2.53 (3H, s, *para* CH_3), 2.27 (6H, s, *ortho* CH_3); ^{13}C-NMR (DMSO-d_6) 159.6 (C-4), 141.2 (C-2, C-6), 139.9 (C-9), 136.6 (C-13), 135.3 (C-11, C-15), 133.1 (C-12, C-14), 129.8 (C-10), 108.8 (C-3, C-5), 19.0 (*para* CH_3), 18.8 (*ortho* CH_3). MS-EI m/z(rel. intensity): 327 (0.06 %), 325 (0.27), 323 (M^+ for $C_{15}H_{15}N_3OCl_2$, 0.38), 306 (0.9, M^+-NH_3), 231(62,m/z 325-PyO·], 230 (32, m/z 325-PyOH), 229 (100,

$ArCNO^+$ and M^+-$PyO^{\cdot}$), 228 (27, m/z 229- H), 213 (10, $ArCN^*$), 201 (8.1, m/z 229-N_2 and m/z 229-CO), 200 (7.8, m/z 201-H), 178 (18, m/z 213-$Cl^{\cdot}$), 164 (1.5, m/z 200-HCl), 139 (44, m/z 213-C_3H_3Cl), 138 (16, m/z139-H), 128 (37, m/z 164-HCl), 95 (63, Py-OH^+), 94 (78, $PyNH_2^+$), 77 (15, m/z 94-NH_3), 67 (29, m/z 94-HCN).
UV (MeOH): 292 nm (log ε, 4.32).

3,5-Bis-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,4-oxadiazole (4). mp 200°C (lit.,[3,4] mp 200°C).

Procedure for the Reaction of Aryl Nitrile Oxide (**1**) in the Presence of **2c** with Formation of **4**

A solution of **1** (2.3 g, 0.01 mol) and **2c** (2.6 g, 0.028 mol) in 50 mL of a mixture of $CHCl_3$/DMF (70:30, v/v) was kept at 50°C for 48 h. The solvent was evaporated under reduced pressure and the residue fractionated by flash chromatography as described above. Elution with a mixture of light petroleum (bp 40-60°C)/ethyl acetate (90:10, v/v), gave not only amorphous and insoluble material, corresponding to oligomers of arylnitrile oxide, but also the 3,5-diaryl-1,2,4-oxadiazole (**4**) (1.2 g, 54%). Successive elution with a mixture of light petroleum and ethyl acetate (70:30, v/v) led to the isolation of only small amounts of **3**.

Procedure for the Reaction of Aryl Nitrile Oxide (**1**) with 2-Aminopyridine (**2a**) and the Separation of Stable Products (**8**) and (**9**)

A solution of **1** (2.3 g, 0.01 mol) and **2a** (2.6 g, 0.028 mol) in a mixture of $CHCl_3$/*N*,*N*-dimethylformamide (DMF) (70:30, v/v) (50mL) was kept at 40°C for 48 h. The solvent was evaporated under reduced pressure and the residue fractionated by flash chromatography on a Merck silica gel (230-400 mesh) column of 40 cm length and 2.5 cm internal diameter, eluting with a mixture of light petroleum (bp 40-60°C)/ethyl acetate (90:10, v/v) and collecting fractions of 50 mL.
Crystallization from light petroleum/ethyl acetate resulted in the adducts (**8**) and (**9**), which presented the same mass spectrum. The selective irradiation experiments allowed the unequivocal attribution of the protons belonging to the two pyridine rings.
HPLC analysis of the reaction mixtures, particularly in solvents containing DMF, proved that, apart from **8** and **9** there were two other products which, in suitable conditions, converted easily to **8** and **9**.

Procedure for the Identification of *Spiro*-Cycloadducts (**6**) and (**7**) from the Reaction of **1** with **2a**

To separate the two further compounds, the best operating conditions were found to be as follows.
Solutions of **1** (0.02 mol/L) and **2a** (0.12 mol/L), in TCE/DMF (50:50,v/v)(50 mL), were kept at 40°C from 15 to 270 min. The solutions were diluted with methanol and analyzed by HPLC employing a Supelcosil ABZ + Plus reverse phase column of 25 cm length and 3.0 mm internal diameter, methanol/water (86:14) as eluant (1 mL/min). The

UV detector was positioned at 360 nm. Analysis of the reaction mixtures revealed two products presenting retention times at 7.5 and 8.1 min, respectively identified as the cycloadducts (**6**) and (**7**), and small amounts of products (**8**) and (**9**). Area ratios in HPLC showed **6**+**7** to predominate markedly over products (**8**+**9**).
A preparative Supelco ABZ HPLC Column (of 25 cm length and 10 mm internal diameter) was used to separate the mixture of **6** and **7**. The solution was evaporated at 40-50°C under reduced pressure and the residue, extracted with chloroform, was dried on anhydrous sodium sulfate, the chloroform being evaporated as described above and the residue then dissolved in deuterochloroform for storage under refrigeration.
The mixture of adducts (**6**) and (**7**) was analyzed by NMR and MS spectrometry.
In a further experiment, the mixture was separated by HPLC-MS, using the analytical column described above, thus recording the separate MS spectra of the two products. ^{1}H-NMR and MS spectra indicated the presence of the *spiro*-cycloadducts (**6**) and (**7**): area ratios in HPLC were a function of reaction time. On the NMR spectrum of the mixture, chemical shift assignment was done with the help of the simulation program ACD-HNMR.[12]

Distribution of Products (**6-9**)

In order to verify the product distribution of the reaction of **1** with the amine (**2a**), the mixtures were analyzed by HPLC (same analytical conditions as described above) during the following experimental runs: solutions (1ml) of **1** and **2a** in various solvents such as $CHCl_3$/DMF and TCE/MeOH, at various temperatures, but usually at 35°C, in the absence or presence of PyHCl as an acid, were left to react for different reaction times, from low to complete conversion of ArCNO, and then quenched by cooling (-50°C); dilution with methanol gave concentrations suitable for HPLC analysis (*ca* 2.10^{-4} mol /L). The samples were added with known amounts of 4-nitroaniline (as the standard) and analyzed rapidly to avoid decomposition and change due especially to exposure to the light.
Since calibration factors could not be determined for adducts (**6**) and (**7**) because of their instability, factors equal to 1 were assumed for all the adducts and a constant concentration of standard was employed, so that the ratios of areas (the adduct on the standard), listed in Tables 5-6, can be taken as rough indexes of molar content.

(5*R* and 5*S*)-(±)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-1-oxa-2,4,6-triazaspiro[4,5]-deca-2,7,9-triene (6). ^{1}H–NMR(CDCl$_3$), δ ppm 6.80 (1H, m, H-8), 6.74 (1H, t, J = 14.4 Hz, H-9), 5.88 (1 H, d, $J_{7,8}$ = 10.0 Hz, H-7), 5.67 (1H, d, $J_{9,10}$ = 11.2 Hz, H-10), 4.31 (1H, s, 4-NH), 4.27 (1H, s, 6-NH), 2.61 (3H, s, *para* CH_3), 2.24 (6H, s, *ortho* CH_3). MS(EI), m/z (rel. Intensity): 327(0.68%), 325(7.2); 323 (M^+ for $C_{15}H_{15}N_3OCl_2$, 10), 310 (10), 309 (5.7), 308 (25), 307 (7.5), 306 (21, M-NH_3), 293 (5.3), 291 (8.8), 270 (6.3), 231 (5.6), 230 (11), 229 (9.4, $ArCNO^+$, retrocycloaddition (RCA), and M^+-$PyO^{\cdot}$ corresponding to $ArCN_2H_2^+$), 228 (9.2), 227 (4.8), 217 (5.7), 216 (6.4), 215 (29), 214 (15, m/z 229 –Me), 213 (46, $ArCN^+$), 212 (12), 195 (4.7), 193 (13), 180 (30), 179 (13), 178 (91, m/z 213-Cl), 143 (5.6), 142 (13, m/z 178-HCl), 141 (6.1), 140 (10), 128 (5.2), 116 (13), 115 (28, m/z 142-HCN), 114 (6.7), 113 (5.0), 96 (100, M-$ArCN_2$), 95 (18), 94 (37, PyO^+ and $PyNH_2^+$), 89 (7.6).

(5*R* and 5S) - (±) - 3 - (3,5-Dichloro-2,4,6-trimethylphenyl)-1-oxa-2,4,6-triazaspiro-[4,5]-deca-3,7,9-triene (7). ^{1}H–NMR ($CDCl_3$), δ ppm ($CDCl_3$), 7.50 (1H, dd, J = 12 Hz and 12 Hz, H-9), 6.80 (1H, t, J = 8.7 Hz, H-8), 6.12 (1H, d, $J_{7,8}$ = 15.3 Hz, H-7), 5.63 (1H,d, $J_{9,10}$ = 11.3 Hz, H-10), 4.38 (2H, br s, 4-NH, 6-NH), 2.62 (3H, s, *para* CH_3), 2.26 (6H, s, *ortho* CH_3). MS(EI), m/z (rel. Intensity): 327 (0.61%), 325 (7.3); 323 (M^+ for $C_{15}H_{15}N_3OCl_2$, 11), 310 (10), 309 (5.9), 308 (27), 307 (8.3), 306 (23, M-NH_3), 293 (5.4), 291 (9.0), 270 (6.5), 231 (5.7), 230 (10), 229 (10, $ArCNO^+$, RCA, and M-$PyO^·$ corresponding to $ArCN_2H_2^+$), 228 (9.5), 227 (4.9), 217 (4.4), 216 (5.5), 215 (23), 214 (13, m/z 229 –Me), 213 (36, $ArCN^+$), 212 (11), 195 (4.9), 193 (13), 180 (24), 179 (11), 178 (74, m/z 213-Cl), 143 (4.3), 142 (10, m/z 178-HCl), 141 (5.3), 140 (8.9), 128 (5.1), 116 (11), 115 (22, m/z 142-HCN), 114 (5.4), 113 (4.5), 96 (100, M^+-$ArCN_2$), 95 (15), 94 (34, PyO^+ and $PyNH_2^+$), 89 (6.5).

(*NZ,N'Z*)-3,5-Dichloro-2,4,6-trimethyl-*N*-[2(1*H*)-pyridinylidene]-*N'*-(2-pyridinyloxy)-benzenecarboximidamide (**8**). mp 175°C (light petroleum/ethyl acetate). ^{1}H–NMR ($CDCl_3$), δ ppm 8.24 (1H, d, $J_{7,8}$ = 5.1 Hz, H-8), 7.80 (1H, t, J = 12.6 Hz, 1-H), 7.55 (1H, t, J = 7.9 Hz, H-6), 7.22 (1H, d, $J_{NH,1}$ = 12.3, NH), 7.10 (1H, t, J = 12.6 Hz, H-2), 6.84 (2H, m, H-7, H-3), 6.62 (1H,d, $J_{5,6}$ = 8.4 Hz, H-5), 6.03 (1H, d, $J_{3,4}$ = 8.4, H-4), 2.58 (3H, s, *para*-CH_3), 2.22 (6H, s, *ortho*-CH_3). MS-EI the same as for **6**. UV($CHCl_3$): 378 nm (log ε,, 4.66), 254.7 (3.94) and 243. Anal. Calcd for $C_{20}H_{18}N_4OCl_2$: C, 59.86; H, 4.52; N, 13.96. Found: C, 59.64; H, 4.67; N, 13.75.

(*NE,N'Z*)-3,5-Dichloro-2,4,6-trimethyl-*N*-[2(1*H*)-pyridinylidene]-*N'*-(2-pyridinyloxy) benzenecarboximidamide (**9**). mp 187°C (from light petroleum/ethyl acetate). ^{1}H-NMR ($CDCl_3$),, δ ppm 8.24 (1H, d, $J_{7,8}$ = 6.0, H-8), 7.70 (1H, t, J= 12.6 Hz, 1-H), 7.60 (1H, m, H-3), 7.60 (1H, m, H-6), 6.97 (1H, d, $J_{NH,1}$ = 12.3, NH), 6.88 (1H, m, H-7), 6.67 (1H, d, $J_{3,4}$ = 8.1, H-4), 6.27 (1H, d, $J_{5,6}$ = 15.6, H-5), 5.90 (1H, dd, J = 12.6 Hz and 11.4 Hz, H-2), 2.57 (3H, s, *para* CH_3), 2.21 (6H, s, *ortho* CH_3). MS(EI),m/z (rel. Intensity): 400 (M^+, 2.7 %), 357 (0.54), 309 (5.7), 307 (8.7, M-93), 271 (5.6, m/z 307–HCl), 230 (4.6), 229 (3.3, $ArCNO^+$), 228 (5.4), 217 (1.3), 216 (1.6), 215 (4.8), 214 (4.0), 213 (6.3, m/z 307 - $PyO^·$), 212 (3.9), 194 (1.0, m/z 229 – Cl), 193 (1.8), 188 (15), 187 (96, $PyONHPy^+$), 186 (49), 178 (18), 173 (15), 172 (4.2), 171 (18, $PyNHPy^+$), 170 (6.0), 159 (18, m/z 194 - Cl), 158 (4.1), 155 (7.5), 145 (15), 144 (24, m/z 144 – HCN), 143 (11), 133 (4.7), 132 (4.9), 131 (11), 119 (14), 118 (17), 117 (11), 116 (15), 115 (7.5), 114 (1.9), 105 (40), 104 (1.9), 103 (2.0), 94 (7.6), 89 (3.2), 79 (24), 78 (100, pyridinium ion, corresponding to m/z 171 - 1H-diazirine), 67 (8.7), 63 (3.4), 52 (11), 51 (20, m/z 78 – HCN).
UV($CHCl_3$): 378 nm (log ε, 4.60), 243 (4.11) and 240(4.12). Anal. Calcd for $C_{20}H_{18}N_4OCl_2$: C, 59.86; H, 4.52; N, 13.96. Found: C, 59.60; H, 4.61; N, 13.72.

Procedure for the Reaction of Aryl Nitrile Oxide (**1**) with 3-aminopyridine **(2b)**

A solution of **1** (2.3 g, 0.01 mol) and **2b** (2.6 g, 0.028 mol) in a mixture of 1,1,2,2-tetrachloroethane (TCE)/*N,N*-dimethylformamide (DMF) (70:30, v/v) (50 mL) was kept at 60°C for 48 h. The solvent was evaporated under reduced pressure and the residue was fractionated by flash chromatography on a Merck silica gel (230-400 mesh) column 40 cm length and 2.5 cm internal diameter, eluting with a mixture of light petroleum (bp 40-60°C)/ ethyl acetate (90:10, v/v) and by collecting fractions of 50 mL. Products (**12**) and **(13**) were obtained.

The reaction was repeated in $CHCl_3$/DMF (70:30, v/v) solution, in the presence of pyridinium chloride or acetic acid, and the same products were obtained. The best overall yields (>98%) were obtained without any acid addition.

3.5-Dichloro-2,4,6-trimethyl-*N'*–hydroxy–*N*–(3-pyridinyl)benzenecarboximidamide (12). (2.9-3.15 g, 90-95%), mp 181°C (from EtOH/H_2O). ^{1}H–NMR ($CDCl_3$), δ ppm 8.98 (1H, s, OH), 8.24 (1H, d, J = 3.9 Hz, H-2), 8.05 (1H, d, J = 2.7 Hz, H-6), 7.70 (1H, s, NH), 7.07 (1H, dd, J = 4.8 Hz and 4.5 Hz, H-5), 6.80 (1H, d, J = 4.5 Hz, H-4), 2.59 (3H, s, *para* CH_3), 2.34 (6H, s, *ortho* CH_3). The NMR spectrum repeated in DMSO–d_6 evidenced the stereoisomers *Z* and *E*, in particular for isomer *Z* (45%): ^{1}H–NMR (DMSO–d_6), δ ppm 10.49 (1H, s, OH), 8.90 (1H, s, NH), 2.53 (3H, s, *para* CH_3), 2.26 (6H, s, *ortho* CH_3); for isomer *E* (55%):^{1}H–NMR (DMSO–d_6), δ ppm 9.64 (1H, s, OH), 8.60 (1H, s, NH), 2.52 (3H, s, *para* CH_3), 2.22 (6H, s, *ortho* CH_3); ^{13}C-NMR ($CDCl_3$), δ ppm 149.1 (C=NOH), 144.1 (C-6), 141.4 (C-2), 136.4 (C-3), 135.2 (C-12), 134.5 (C-10, C-14), 133.6 (C-9), 129.7 (C-11, C-13), 126.2 (C-4), 123.6 (C-5). MS(EI), m/z (rel. Intensity):327 (3.5%), 326 (4.8), 325(21); 324(10), 323 (M^+,31), 310 (11), 309 (16), 308 (37), 307(34, M-O), 306 (49), 305 (23, M-H_2O), 304 (11), 293 (32, M-NO), 292 (15), 291 (50, M-NHOH), 270 (17), 235 (18), 229 (9, M-$PyNH_2$), 216 (10), 215 (17), 214 (23); 213 (23, $ArCN^+$), 180 (13, $ArCO^+$-Cl), 179 (11, $ArCO^+$ - HCl), 178 (38, $ArCN^+$-Cl), 140 (12), 117 (11), 116 (20); 115 (39), 95 (17), 94 (100, $PyNH_2^+$), 93 (14), 92 (3.4, M^+-H_2O-ArCN), 89 (9.3), 78 (37), 77 (11); 67 (21, $PyNH_2^+$-HCN), 66 (14), 65 (14, m/z 92 – HCN), 62 (12), 52 (11), 51 (44). Anal. Calcd for $C_{15}H_{15}N_3OCl_2$: C, 55.57; H, 4.66; N, 12.96. Found: C, 55.66; H, 4.87; N, 12.88.

3,5-Dichloro-2,4,6-trimethyl-*N*-(3-pyridinyl)benzamide (13). (0.09-0.3g, 3-10%), mp 179°C (from light petroleum/ethyl acetate) (70:30). IR (KBr): 3107 cm^{-1} (NH), 1665 cm^{-1} (C=O).^{1}H–NMR ($CDCl_3$), δ ppm 8.62 (1H, br s, H-2); 8.35 (1H, br s, H-6); 8.33 (1H, d, J= 4.5 Hz, H-4); 8.08 (1H, br s, NH); 7.35 (1H, dd, J = 5.1 Hz and 4.8 Hz, H-5); 2.54 (3H, s, *para* Me); 2.38 (6H, s, *ortho* Me). MS(EI), m/z (rel. Intensity):311 (2.1 %), 310 (9.6), 309 (3.6), 308 (M^+, 4.9), 219 (10), 218 (7.2), 217 (64), 216 (13), 215 (100, $ArCO^+$), 187 (14, $ArCO^+$-CO), 152 (8.8), 151 (10, *m/z* 187 – HCl), 117 (14), 116 (22, *m/z* 151 – Cl), 115 (42, m/z 151–HCl), 93 (9.0), 92 (1.7, M-ArCHO), 91 (5.4), 78 (4.2), 77 (3.8), 75 (5.5), 66 (20), 65 (9.4, M-ArCHO-HCN). Anal. Calcd for $C_{15}H_{14}N_2OCl_2$: C, 58.27; H, 4.83; N, 9.07. Found: C, 58.30; H, 4.56; N, 9.06.

Distribution of Products (**12**) and (**13**)

Besides the excess of 3-aminopyridine, the analysis showed the occurrence of the adducts described above. The adducts were determined in the reaction mixtures, after reaction of the nitrile oxide (0.02 mol/L) with the aminopyridine (**2b**) (0.24 mol/L), at 60°C, for *ca.*10 half-lives, in solvent mixtures containing either 1,1,2,2-tetrachloroethane (TCE) and *N,N*-dimethylformamide (DMF) or chloroform and DMF, in both cases in the ratio 70:30 (v/v). The samples were diluted with methanol and analyzed by reverse phase HPLC analysis. A column ABZ Supelco (length 25 cm, i.d. 4.6 mm) was employed. The eluant (1 mL/min) was a mixture methanol-water (75:25, v/v) and the UV detector was positioned at 243 nm. All determinations were carried out on the basis of calibration plots on the pure compounds. A cycloadduct obtained from 4-methyl-1-ethoxycarbonyl-1,2-diazepine (**3ef**) [13] was used as reference. At least two analyses of each sample were carried out and the results averaged.

Kinetic Measurements

Kinetic runs for all aminopyridines were carried out and interpreted as previously described,[4] using the equation for second-order reactions

$$\ln (C_2/C_1) = (C_2° - C_1°)kt + \text{constant}$$

In the case of amine (**2c**), C_2 was meant as the concentration of *free amine*, taking into account that, according to the proposed mechanism, complete protonation requires $C_2° = (C_2°)_{total} - C_{HA}°$; instead for the amines (**2a**) and (**2b**), C_2 was the total concentration of the amine, and $C_2°$ its initial value, without taking into account the protonated fraction when small amounts of acids had been added. In any case, the C_2 values were obtained as

$$C_2 = C_2° - (C_1° - C_1).$$

The plots of $\ln[C_2/C_1]$ vs time were linear, with correlation coefficients not less than 0.994. Runs were carried out up to at least 76% fractional conversion of ArCNO.
Kinetic runs for the conversion of **1** to **4** were carried out in the absence of acids and interpreted by employing the following equation:

$$1/C_1 = k_d t + \text{constant}$$

with linear plots having correlation coefficients ≥ 0.999. Runs were carried out up to at least 79% fractional conversion of ArCNO.
In the Tables, when the results of two or more runs are averaged, the standard deviation of the mean value is indicated; when only one run is available, the standard deviation was obtained from the linear regression that gave *k*.

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