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Reactions of Hydroxylamines with Ethyl Cyanoformate. Preparation of Aminonitrones and their Synthetic Applications.

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Key Words: Ethyl cyanoformate; Hydroxylamine; α-Aminonitrone; Nitrogen heterocycles

Abstract: *The reaction of hydroxylamines with ethyl cyanoformate* **1** *leads to the formation of carbethoxyamino nitrones* **2**. *UV spectroscopy provided information that suggested the nitrone structure for these compounds in solution. X-ray analysis of* **2a** *confirmed that it exists entirely in the nitrone form in the solid state. These nitrones are shown to be excellent starting materials for a variety of nitrogen containg compounds, namely, imidazoles, benzimidazoles, benzimidazolones, oxadiazolones, N-arylamidines and quinoxalone.*

The chemistry of ethyl cyanoformate **1**[1], despite its ready availability, has not been widely studied. The acid catalysed reaction of **1** with aromatic amines to yield N-substituted amidino formic esters and its limitations have been reported[2]. Scattered reports of the use of the reagent as a dienophile[3] and as a partner[4,5] in 1,3-dipolar cycloaddition reactions to generate specific heterocyclic compounds are occasionally encountered in the literature. Recently the reagent has been employed to effect smooth dehydration of aldoximes to the corresponding nitriles[6]. Since the classical Pinner's method of obtaining the imidoylchloride from the nitrile was found not to be preparatively useful, indirect means involving the use of diethyloxalimidate[7] (ethyl carbethoxyformidates) and thiohydroxamic acids[8] have been devised to prepare amidines and various nitrogen heterocycles[9]. Chemically the ester **1** is potentially capable of reacting with nucleophiles either at the *sp* hybridised C atom (addition pathway **A**) or at sp^2 carbon providing derivatives of formic esters (substitution pathway **B**) (Scheme 1). In the latter instance **1** acts as an acyl transfer reagent and in fact, the methyl ester has been shown to be an excellent C-carbomethoxylating agent for carbanions derived from ketone enolates[10].

Our interest in exploring the chemistry of **1**, especially with respect to its reaction with ambident nucleophiles such as hydroxylamines, stemmed largely from the earlier observation that structurally similar aroyl and acyl cyanides afforded products of O-acylation[11] (pathway **B**).

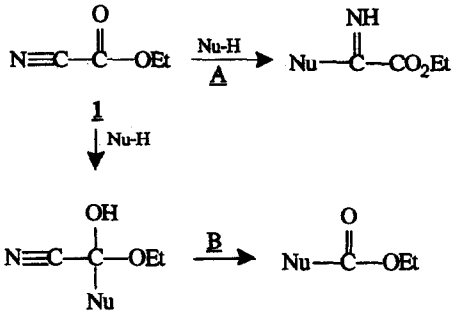
Herein we disclose that:

i) the ester **1** reacts with a variety of hydroxylamines in the absence of any acid catalysis by addition pathway **A** to provide a new, direct and preparatively useful route to α-amino-α-ethoxycarbonylnitrones **2**;

ii) discuss briefly possible structures for these adducts;

and

iii)describe reactions of these substances that lead to, *inter alia*, useful nitrogen containing heterocycles.



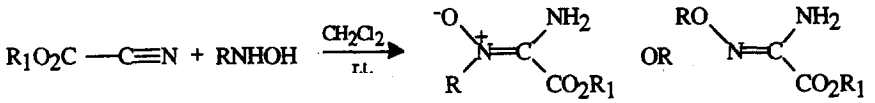
Scheme 1

RESULTS AND DISCUSSION

When N-phenylhydroxylamines (1 eq.) was treated with ethyl cyanoformate (1.2 eq.) in benzene at room temperature it afforded a white crystalline solid in 68% yield. Its elemental analysis, spectral characteristics (IR and ^{1}H NMR), non-identity with ethyl N-phenyl-N-hydroxycarbamate (**5** R_1=Ph, R_2=OH) and chemical reactions (*vide infra*) showed that it was the α-aminonitrone **2d**.

The same reaction proceeded with equal facility but with improved yield (79%) when performed in dry dichloromethane as the solvent (cf. Table 1). Whereas N-(4-methylphenyl)-hydroxylamine reacted smoothly and rapidly to give **2e**, the 4-bromo analogue **2g** required longer time (36h) for its formation, possibly reflecting the reduced nucleophilicity of the nitrogen atom of the latter hydroxylamine.

Hydroxylamine and its N-methyl and N-isopropyl derivatives all reacted under conditions specified above to afford the corresponding addition products **3a**, **2a**, **2b** in 76 , 65 and 73% yields respectively. **3a** is a known compound and had been previously obtained in 58% yield by condensation of ethyl chloro--oximinoacetate and ammonia[12]. From the mother liquors of **3a** a crystalline by-product **3b**, m.p. 130-132°C (lit.[13] 131-131.5°C) was isolated by preparative TLC in 14.5% yield. Its ^{1}H NMR and mass spectra (vide experimental) were consistent with the structure **3b**. The results are summarised (Table 1).



2 **3**

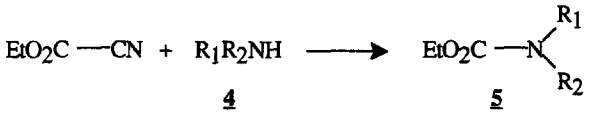
3a: R=H
3b: R=CO_2Et

The almost exclusive formation of the addition compounds in neutral medium prompted us to examine the importance of the free hydroxyl group in the nucleophiles in governing the product formation. Hydroxylamines, their O-methyl ethers and hydrazines are classified as "α-effect nucleophiles" their enhanced reactivity often being ascribed to the lone pair interaction on the vicinal heteroatoms[14]. Accordingly, when NH_2OMe **4a** and MeNHOMe **4b** were allowed to react with **1**, none of the products arising from addition to

the cyanide group could be isolated. Instead, products **5a** and **5b** were obtained in 46 and 36% yields respectively (Scheme 2 - Table 2).

Table 1 - Synthesis of Aminonitrones **2** and Amino-oximes **3**.

Product	R	R_1	Reaction Conditions	Yield (%)
2a	Me	Et	r.t. 2h	65
2b	^iPr	Et	r.t. 24h	73
2c	Me	Me	r.t. 2h	68
2d	Ph	Et	r.t. 6h	79
2e	4-MeC_6H_4	Et	r.t. 2h	72
2f	3-MeC_6H_4	Et	r.t. 3h	62
2g	4-BrC_6H_4	Et	r.t. 36h	67
3a	H	Et	r.t. 20h	76
3b	CO_2Et	Et	r.t. 20h	15



4a - R_1=H:R_2=OMe
4b - R_1=Me:R_2=OMe
4c - R_1=Ph:R_2=OMe
4d - R_1=Ph:R_2=NH_2
4e - R_1=Ph:R_2=H

5a - R_1=H:R_2=OMe
5b - R_1=Me:R_2=OMe
5d - R_1=NHPh:R_2=H
5e - R_1=Ph:R_2=H

Scheme 2

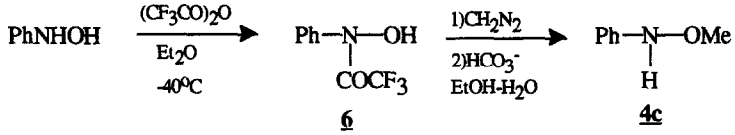
The structures were unequivocally confirmed by comparison with authentic specimens,[15,16] prepared from ethyl chloroformate and the respective hydroxylamine.

Table 2 - Reaction of others nucleophiles with ethyl cyanoformate.

Product	R_1	R_2	Yield (%)
5a	H	OMe	46
5b	Me	OMe	36
5c	Ph	OMe	a)
5d	H	NHPh	50
5e	Ph	H	55

a) Predominantly azobenzene; other products formed were found to have R_f identical with those resulting from decomposition of **4c** when kept in solution for the same length of time.

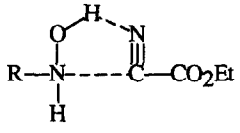
O-Methyl-N-phenylhydroxylamine **4c** required for study had been obtained previously[17] through a three step sequence involving specific O-methylation of N-phenyl-N'-hydroxy-N'-phenylurea and cleavage of the resulting product with diethylamine to liberate the O-methyl derivative. Because of low overall yield (16%) an alternative and a simpler method was developed. It involved the methylation with diazomethane of N--hydroxy-trifluoroacetanilide **6**[18] followed by mild base hydrolysis (aqueous ethanolic sodium bicarbonate). The methyl ether was isolated nearly quantitatively, simply by diluting the mixture with water and extracting with n-hexane (Scheme 3).



6 **4c**

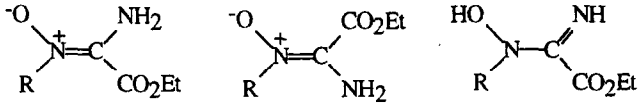
Scheme 3

4c failed again to react with the ester **1** to give the addition product. Azobenzene was the principal product formed slowly over the period of time. Phenylhydrazine **4d** and aniline **4e** gave ethyl N-anilino carbamate[19] **5d** and ethyl N-phenyl carbamate[19] **5e** respectively, identical with authentic samples. These results strongly suggest the involvement of an ordered transition state originating from significant hydrogen bonding provided by the weakly acidic hydrogen of the hydroxylamine which activates the cyanide group for the observed regiospecific nitrogen attack, as depicted below.



Structure:

All compounds represented by the structure **2** are potentially capabable of manifesting geometrical isomerism (**2A** and **2B**), the situation further beset by the possible existence of the tautomer **2C**.



2A **2B** **2C**

In the case of **3a** convincing spectroscopic evidence[20] (^{1}H NMR and IR) in favour of the oxime structure has been presented. However, very little is known about constitution and geometry of the compounds of the type **2**.

Mass spectroscopy[21] had been used to distinguish between α-aminoaryl-N-arylnitrones **7** and their N-

hydroxy tautomers **8**.

7 **8**

Arguments were advanced that a loss of 16 mass units in the mass spectrum was characteristic of the nitrone structure while that of 17 originated from species containing the N-OH group. The fact that the mass spectra of **2b** and **2d** contained fragments resulting from the loss of M-16 and M-17 in equal proportions did not permit any definite conclusion to be drawn as to their structures, except that, at the temperature employed, both forms are present.

A comparative study of the ultraviolet spectra of the compounds **2a**, **2b**, **2d**, **2e**, **2f**, **2g** and **3a** allowed certain tentative structural conclusions to be drawn. While the parent compound **3a** absorbed at 256nm (ε_{max} $5.3x10^3$), all the other N-substituted substances possessed longer wavelength maxima at *ca* 305nm (ε_{max} $7\sim9x10^3$) (Table 3) indicating that the latter have electronically more easily excited funcional group. It is known[22] that whereas alkylation of an oxime on the oxygen leaves its absorption maximum unaltered, that on the nitrogen, with concomitant nitrone formation, is attended by a strong bathochromic shift ($\Delta\lambda\sim50$nm). The compounds (**2a**-**2f**), which can be considered to be formally derived from **3a** by N-alkylation, showed similar large differences ($\Delta\lambda\sim50$ nm).

The nitrone structure also explains best the observed constancy of the absorption maxima for all compounds, be they N-alkyl or N-aryl substituted. It stems from the fact that the N-aryl group is being forced to deviate from coplanarity by the adjacent (cis) substituent, making extended conjugation with the ring not possible. Such a phenomenon[23] is frequently encountered in highly substituted C,N-diarylnitrones.

Table 3 - Absorption maximum in UV.

Compound	λ_{max} (nm)	ε_{max} (EtOH)
3a	256	$5.3x10^3$
2a	305	$9x10^3$
2b	305	$7x10^3$
2d	305	$7x10^3$
2e	305	$8.2x10^3$
2f	307	$7.8x10^3$
2g	310	$8.2x10^3$

The nitrone structure was unambigously shown to be correct by X-ray analysis of **2a**. The two crystallographically independent molecules (A and B on Fig.1) present in the crystal cell possess the nitrone structure. It was the unambiguous location of all the nitrogen atoms in each molecule that was the major determining factor in this conclusion. The degree of bond ordering in the N(2)-C(3), N(2')-C(3') and C(3)-N(3),

C(3')-N(3') bonds is not pronounced though the former are slightly shorter, [1.311(3) and 1.312(4) compared with 1.341(5) and 1.331(4)Å respectively]. Thus, in both molecules there is an appreciable delocalisation with the C(3)-N(3) bond displaying partial double-bond character. In one molecule there are significant departures from coplanarity of the four substituents on the N(2)-C(3) bond. This is due to a slight pyramidalisation at N(2) and associated O(1)-N(2)-C(3)-N(3) and C(2)-N(2)-C(3)-C(4) torsion angles of 2.2(5) and 10.4(5)° respectively. The geometry about N(2')-C(3') however is essentially planar. The most significant difference between the two molecules is in the orientation of the terminal methyl group with respect to the molecular backbone; the geometry about O(5)-C(6) in B is anti, that about O(5')-C(6') in A is gauche.

The packing of the molecules in the crystal (Fig.2) is dominated by intermolecular N-H----O hydrogen bonds. Each independent molecule is hydrogen bonded to its centrosymmetrically related neighbour *via* two equivalent N-H---O bonds, (N---O 2.93 and 2.91, H---O 2.08 and 2.02Å, N-H---O angle 143° and 145° for molecules 1 and 2 respectively). Each H-bonded dimer pair is in turn linked by two non-equivalent N-H---O hydrogen bonds thus forming an infinite hydrogen-bonded chain of molecules [N(3)---O(1') 2.87, H---O(1') 1.94Å, N-H---O angle 158°; N(3')---O(1) 2.86 H---O(1) 1.88Å, N-H---O angle 174° ; (Fig.2)]. The coplanarity in both molecules of the O(1)-N(2), N(2)-C(3), C(3)-N(3) bonds and the amino group results in H---O(1) and H'---O(1') distances of 2.07 and 2.26Å respectively and the possibility of additional intramolecular hydrogen bonds. The H---O(5) and H'---O(5') distances are 2.40 and 2.38Å respectively.

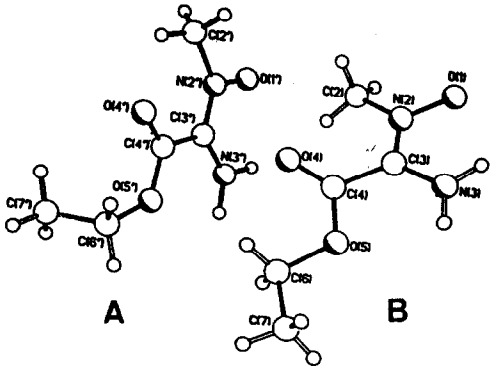


Figure 1 - X-Ray structure for compound **2a**.

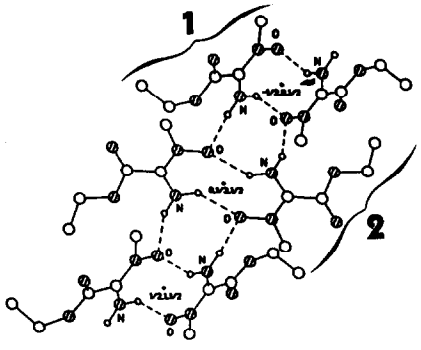
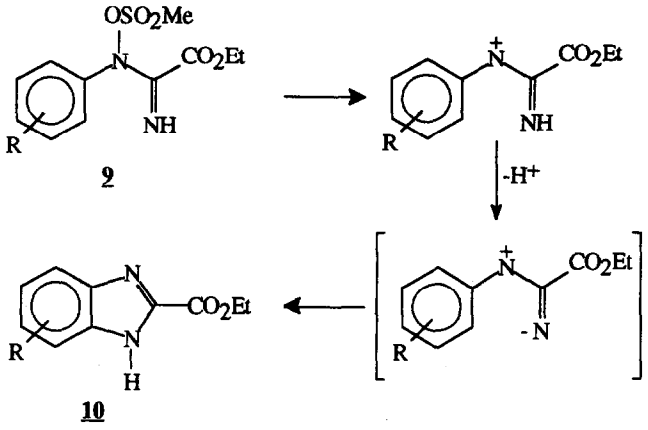


Figure 2 - Packing of the molecules in the crystal.

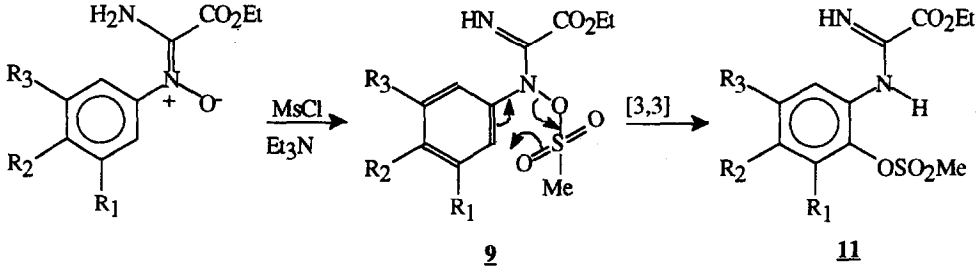
Reactions:

The ready availability of the aminonitrones prompted us to study their reactions with electrophiles with the view to obtain heterocyclic compounds. It was thought that the mesylate **9** would suffer a facile heterolysis of the N-O bond and the resulting nitrenium ion or nitrene[24] would cyclise to the benzimidazole **10** (Scheme 4).



Scheme 4

However **2d** in dichloromethane on mesylation ($MeSO_2Cl/Et_3N$) yielded a white crystalline compound (60%) as the major product. Preparative thin-layer chromatography of the residue from the mother liquor led to the isolation of, albeit in only 7% yield, the known benzimidazole carboxylic ester **10** (R=H)[25]. The molecular weight of the major product (M^+ 286) and its ^1H NMR spectrum which contained a 3H singlet at δ 3.24 and 4 aromatic protons suggested that it was the amidine **11a** formed formally by a 3,3 sigmatropic rearrangement of the intermediate **9**[26] (Scheme 5).



Scheme 5

Compounds (**2e**-**2g**) behaved likewise affording the corresponding mesyloxy amidines (**11b**-**11e**) as principal products. The results are collected in Table 4.

Chemical proof of the ortho disubstitution was provided by base hydrolysis.

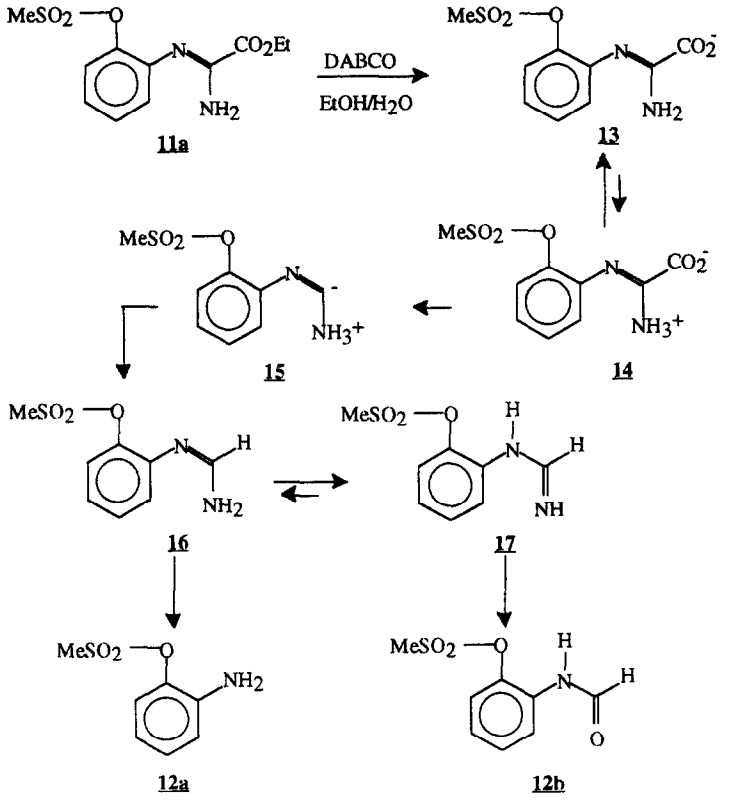
Extended heating of **11a** in aqueous ethanol in the presence of DABCO yielded a mixture of products from which two crystalline compounds (**12a** - 60%) and (**12b** - 20%) were isolated. The former was identified as o-mesyloxyaniline by comparison with an authentic specimen[27] (m.p.; mixed m.p.; IR; ^1H NMR).

Table 4 - Synthesis of N-arylamidines.

Starting Material	Product	R_1	R_2	R_3	Yield (%)
2d	11a	H	H	H	60
2e	11b	H	Me	H	56
2f	11c	H	H	Me	50
	11d	Me	H	H	15
2g	11e	H	Br	H	40

The latter, (M^+ 215) tentatively assigned the formanilide structure **12b** on the basis of its ^1H NMR spectrum [(δ 3.27 3H singlet OSO_2CH_3; 8.15, 8.45 1H NH-CHO, cis and trans, exchangeable in D_2O; 8.37, 8.58 1H, NH-CHO, cis and trans and absence of signals due to CO_2Et group)] was found to be identical with an authentic specimen of o-mesyloxyformanilide obtained from o-mesyloxyaniline and ethylformate.

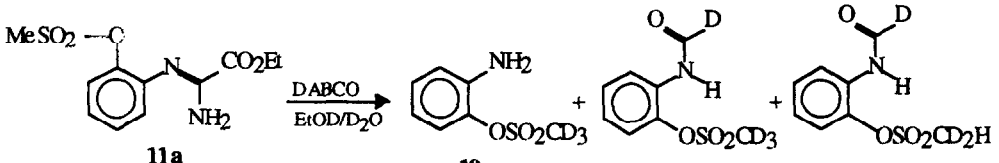
A possible mechanism for the formation os **12a** and **12b** is shown below (Scheme 6).



Scheme 6

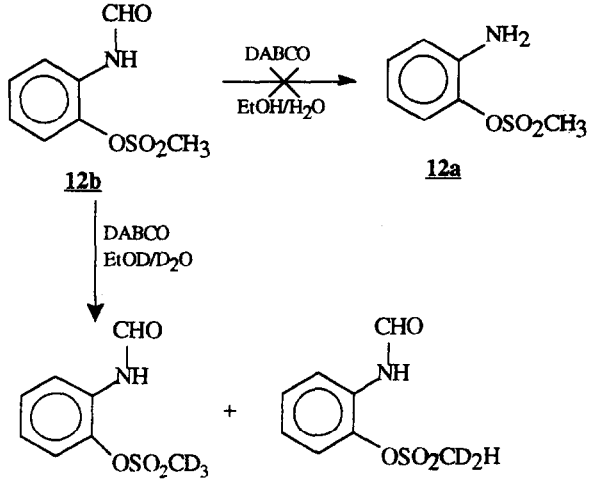
It is assumed that the hydrolysis of the ester **11a** produces the amidine carboxylate ion **13**. The amidinium ion **14** present in small concentration, on decarboxylation yields the ylide **15**. Protonation would, then generate the amidine **16** in equilibrium with its tautomer **17**. The former, on base hydrolysis[28] generates the aniline **12a** and the latter, the formanilide **12b**.

In conformity with this mechanism is the observation that the hydrolysis when carried out in a mixture of EtOD and D_2O yielded after p.t.l.c. the tetradeutero compound **18**. The incorporation of deuterium in the formyl group indicates that a carbanion α to the nitrogen had indeed been formed.



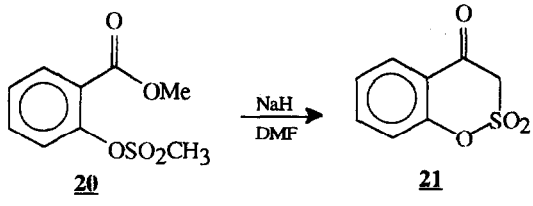
11a **19** **18**

The fact that compound **12b** underwent deuterium exchange solely with hydrogens of the methyl group of the sulphonate showed that it was not the precursor of either **18** or **19**.



12b **12a**

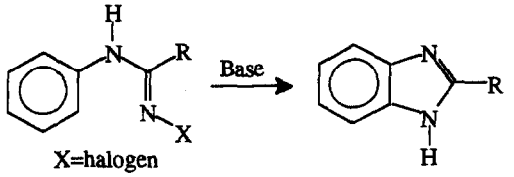
The acidic nature of methyl group of the mesylate is exemplified in the reported base promoted cyclisation of methyl-2-mesyloxybenzoate[29] **20** to the 1,2-benzo-oxathiin-5,5-dioxide **21**.



20 **21**

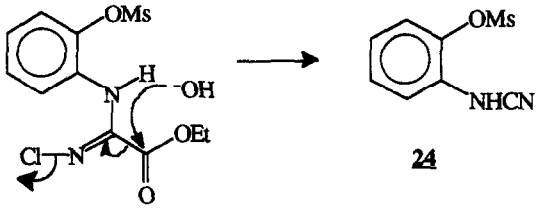
Heterocycles:

One of the useful methods for the preparation of 2-alkyl or 2-aryl benzimidazoles[30] **23** is the cyclisation, induced by base, of the N-halo-N'-arylamidines **22**.



22 **23**

In our hands the method, under a variety of conditions failed to provide the benzimidazole **10** ; instead the cyanamide **24** was the principal product formed.



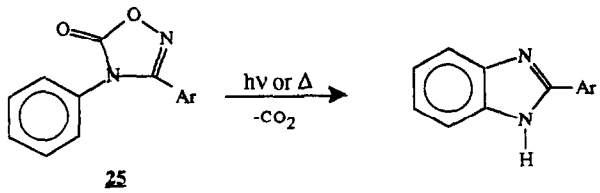
24

To obviate the undesired attack at the carbonyl group by external nucleophile, viz, the hydroxide ion, the DABCO-NBS complex[31] (shown to possess an usually long N-Br bond) was experimented both as the source of positive halogen and as a base. The amidine **11a**, afforded in a slow reaction, the bromo amidine **11e**.

11a **11e**

Thus the DABCO-NBS complex acted in this instance as a nuclear brominating agent. It is possible that the reagent finds a similar use in the bromination of other electron-rich and acid sensitive compounds.

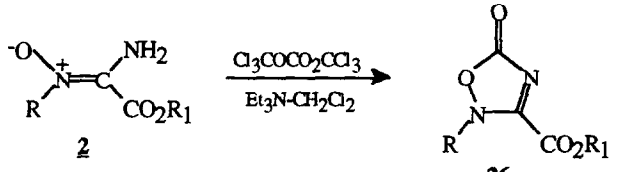
It is known that 3,4-diaryl-Δ^2-1,2,4-oxadiazolin-5-ones **25** on thermolysis[32] or photolysis[32], lead to 2-substituted benzimidazoles, through the intermediacy of the nitrene, in good yield (Scheme 7).



25

Scheme 7

Accordingly, the aminonitrones (**2d**-**2g**) were converted smoothly, by treatment with triphosgene [bis(trichloromethyl)carbonate][33] in the presence of Et_3N to a series of the requisite 2,3-disubstituted oxadiazolinones **26**. All these compounds possessed the characteristic IR absorption at 1790 cm^{-1}. Trace amounts of a minor product (R_f=0) formed in the reaction was very difficult to remove and the crude product necessitated repeated crystallisation before being obtained in a state of purity. In a similar fashion the aliphatic nitrones **2a**, **2b** and **2c** gave the corresponding oxadiazolinones **26a**, **26b** and **26c** in excellent yield (Scheme 8 - Table 5).



2 **26**

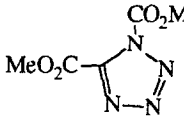
Scheme 8

Table 5 - Synthesis of Δ^3-1,2,4-Oxadiazolin-5-ones

Starting material	R	R_1	Product	Yield (%)
2a	Me	Et	**26a**	89
2b	^iPr	Et	**26b**	78
2c	Me	Me	**26c**	84
2d	Ph	Et	**26d**	72(41)[a]
2e	4-MeC_6H_4	Et	**26e**	65(30)[a]
2f	3-MeC_6H_4	Et	**26f**	70(31)[a]
2g	4-BrC_6H_4	Et	**26g**	54

a) values in parenthesis refer to yields of analytically pure products

A compound purportedly possessing the structure **26c** with δ 5.70(s,CH_3) and 5.97(s,CH_3), was isolated by Moriarty[34] *et al* from the thermolysis of the tetrazole **27**. The chemical shifts observed for our compound **26c** (δ 4.06 and 4.04) obtained in a more straight forward manner are vastly different. Unless the values had been erroneously reported other isomeric structures for Moriarty's compound should be considered.



27

R-NH-CO-NH-CO_2Et

28a: R=Ph
28b: R=4-Me-C_6H_4
28c: R=3-Me-C_6H_4

R—N=C=N—CO_2Et

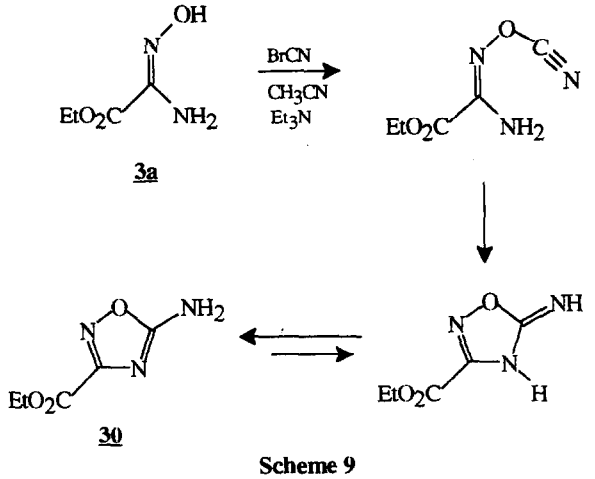
29

Thermolysis of compounds (**26d**-**26g**) in diphenylether under reflux, or photolysis (**26d**-**26g**) in dioxane using a low pressure Hg lamp at room temperature gave the corresponding 2-carbethoxy--benzimidazoles in modest to good yields. The oxadiazolone (**26f**) yield a mixture of two isomers (44%), the major product (28%) arising from ring closure para to the methyl group and for which the indicated structure could be assigned unambigously on the basis of its ^{1}H NMR spectrum (δ 7.44, 1H, aromatic singlet). Also formed consistently as by products (4-10%) were the N,N'-disubstituted ureas **28** arising from the hydration, during the work-up, of the carbodiimides **29** formed on photolysis.

Table 6 - Synthesis of 2-Carbethoxy-benzimidazoles

Starting material	Reaction conditions	Product	R	Yield (%)
26d	hν	**10a**	H	79
26e	hν	**10b**	5-Me	52
26f	hν	**10b**	5-Me	28
		10c	4-Me	16
26g	Δ	**10d**	5-Br	43

The presence of two proximate nucleophilic centres in the aminonitrones **2** and **3a** led us to study their reaction with the powerful bis-electrophile, cyanogen bromide. The oxime **3a** on treatment with cyanogen bromide in the presence of Et_3N at -40ºC rapidly yielded the 1,2,4-oxadiazole derivative[35] **30** in 45% yield (Scheme 9).



3a **30**

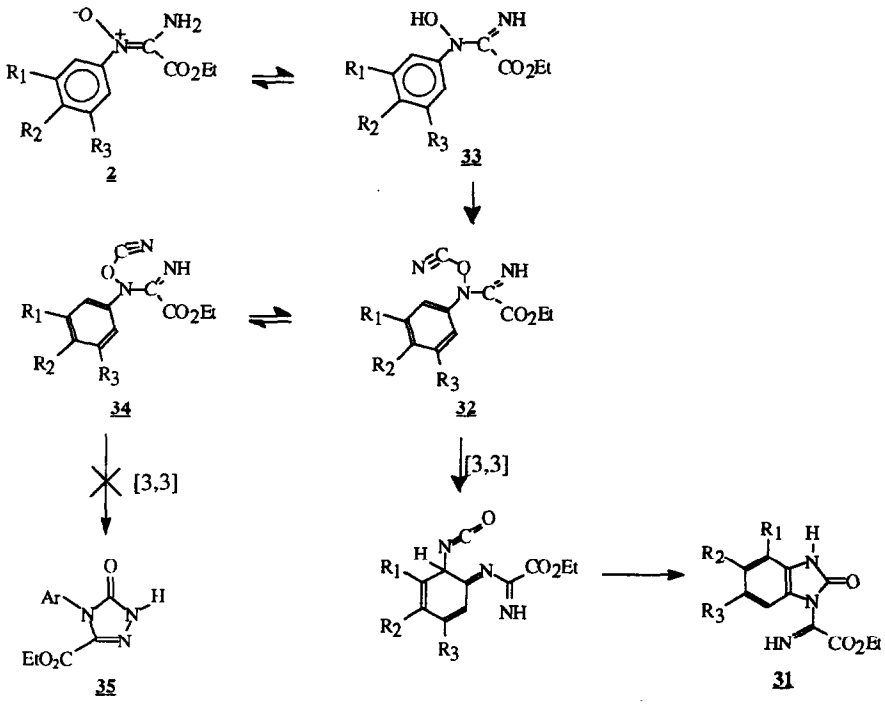
Scheme 9

Whereas the aminonitrone (**2a** and **2b**) with BrCN led to a multitude of products and no characterisable compounds could be isolated, the N-arylamino nitrones (**2d**-**2g**) yielded the corresponding benzimidazolones **31** (Table 7) under exceptionally mild conditions.

Table 7 - Synthesis of 2-Benzimidazolones

Product	R_1	R_2	R_3	Yield (%)
31a	H	H	H	66
31b	H	Me	H	82
31c	Me	H	H	87
31d	H	Br	H	75

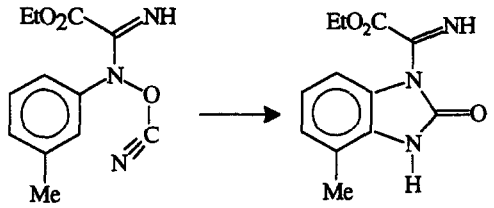
A possible mechanism is outlined below (Scheme 10).



Scheme 10

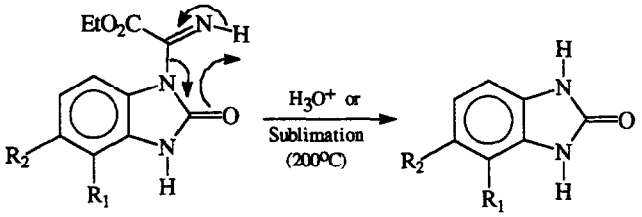
The intermediate **32**, formed either directly from the N-hydroxyamidine **33** or the nitrone, followed by prototropic shift, undergoes a rapid 3,3 sigmatropic rearrangement. Rearomatisation results in the formation of the N-substituted benzimidazolones **31**. It is interesting to note that in none of the compounds studied the alternative 3,3-hetero-oxy Cope rearragement involving the conformer **34** leading to the triazolone **35** was observed. A possible reason, other than conformational in origin, could be due to considerable weakening of the N-O bond with significant positive charge already developed in the aromatic ring in the intermediate **32**.

Also intriguing is the exclusive formation of the benzimidazolone **31c** resulting from attack ortho to methyl group. Obviously the conformation **32c** depicted below is preferred, the reason for such preference however, remains obscure.



32c **31c**

The N-imidoylbenzimidazolones **31** were all sensitive to acid and to heat, the action of both of them leading to the formation of the benzimidazolones. In fact sublimation of these compounds was found to be the method of choice for the generation of benzimidazolones **36** (Scheme 11 - Table 8).



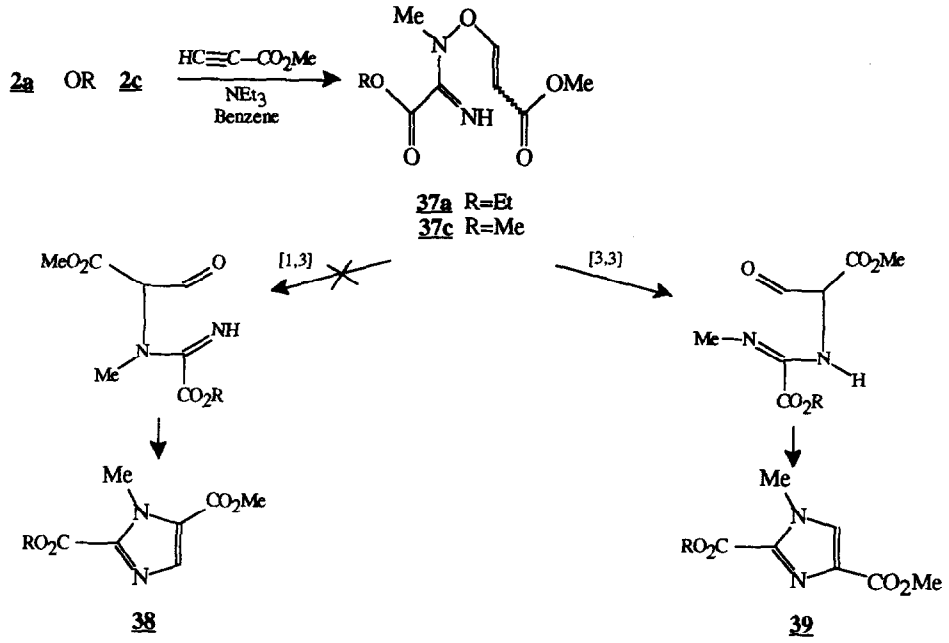
31 **36**

Scheme 11

Table 8 - 2-Benzimidazolones **36** obtained by sublimation of N-imidoylbenzimidazolones **31**.

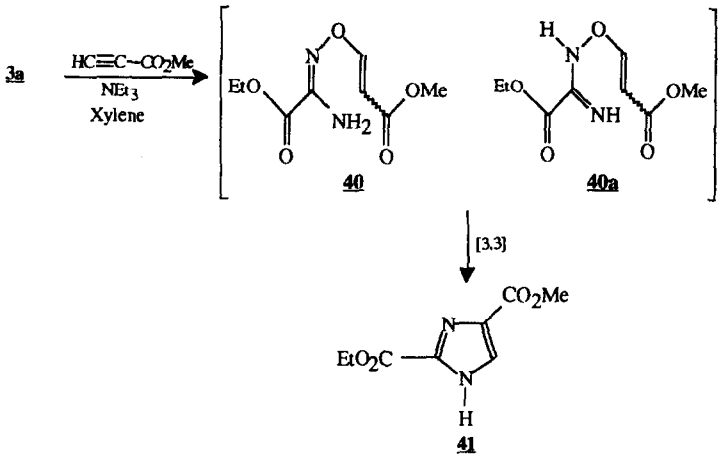
Product	R_1	R_2	Yield (%)
36a[36]	H	H	95
36b[37]	H	Me	93
36c[38]	Me	H	95
36d[38]	H	Br	92

The failure of the aminonitrone (**2a** and **2b**) to give any useful products with cyanogen bromine, led us to employ the less powerful electrophile, the propiolate esters. Indeed, when **2a** in benzene was treated with methyl propiolate in the presence of Et_3N and the mixture, after being kept an hour at room temperature, boiled (15min) it gave an excellent yield of the imidazole dicarboxylic ester. *A priori*, the product formed could be either 2,4-disubstituted or its regioisomer 2,5 depending on the nature of the rearrangement, namely 3,3 or 1,3 suffered by the intermediate **37** . Since the spectral characteristics (^{13}C and ^1H NMR) and the m.p. of the known 2,5-dimethyl ester[39] **38** were significantly different from those found for our product it follows that the latter is to be represented by the structure **39b** (Scheme 12)



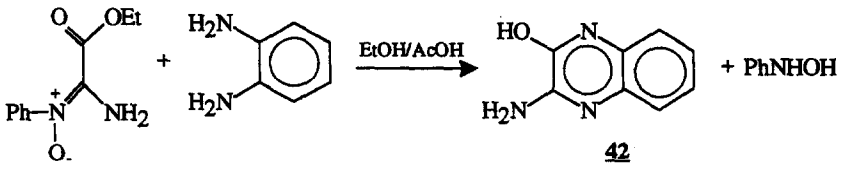
Scheme 12

In the case of the oxime **3a** it was possible to isolate the initial Michael adduct **40** or **40a** (m.p. 50-60°C) consisting of the trans isomer (80%) and the cis isomer (20%). On thermolysis, in boiling xylene, the mixture was cleanly converted into the imidazole derivate **41** in a sequence of reactions involving a 3,3- sigmatropic rearrangement, 1,3- protrotopic shift and dehydration (Scheme 13).



Scheme 13

Finally, the potential of the nitrones to act also as a bis-electrophile is illustrated in the reaction of **2d** with o-phenylenediamine. The physical and spectroscopic properties of the quinoxaline derivative **42** formed in 45% yield, were found to be identical with those reported in the literature [40].



42

CONCLUSIONS

In summary, the products obtained from ethyl cyanoformate with hydroxylamines are shown to possess interesting chemistry that can be, by appropriate choice of reagents, exploited in the synthesis of a variety of useful nitrogen containing compounds.

ACKNOWLEDGEMENT

We are pleased to acknowledge partial financial support from Junta Nacional de Investigação Científica e Tecnológica, Instituto Nacional de Investigação Científica, Calouste Gulbenkian Foundation, NATO, Centro de Química Fina e Biotecnologia da Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa.

EXPERIMENTAL

General Methods. Melting points were either determined with a microscopic hot-stage (Reichert Thermovar) or Buchi 530 for sealed capillaries and are uncorrected. Chromatography was preformed using E. Merck silica gel 60 (70-230 mesh). Preparative thin-layer chromatography (PTLC) was preformed on plates precoated with silica gel GF_{254} (0.5mm).Infrared spectra (IR) were recorded with a Perkin-Elmer 157G and 683 grating infrared spectrophotometer and the frequencies reported in cm^{-1}. Ultraviolet spectra (UV) were recorded with a Shimadzu (UV-240) apparatus and λ expressed in nm. Proton nuclear magnetic resonance spectra (^1H NMR) were obtained at 300 MHz with a Brüker CXP300 or General Electric GE-NMR. Chemical shifts are reported in ppm downfield from tetramethylsilane. High and low resolution spectra (HREIMS and EIMS respectively) were measured in a Kratos MS-25 RF instrument using electron inpact at 70 eV. All solvents were purified by standard methods. Elemental analyses were carried out at the Microanalytical divison of LNETI, Queluz, Portugal.

X-Ray structure determination for compound 2a:

Crystal data: $C_5H_{10}N_2O_3$, M=146.1, triclinic, a=7.556(3), b=9.201(3), c=11.505(3)Å, α=96.63(3), β=103.34(3), γ=103.85(3)°; V=743Å^3, space group $\overline{P1}$, Z=4 (2 crystallographically independent molecules), D_c=1.31 gcm^{-3}, Cu radiation, λ=1.54178Å, μ(Cu-K_α)=9 cm^{-1}, F(000)=312. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. A crystal of dimensions

0.03x0.33x0.83 mm was used. 2002 independent reflections ($2\theta \leq 116^o$) were measured, of wich 1580, had $|Fo|>3\sigma(|Fo|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were located from a ΔF map. Those on N(3) and N(3') were refined isotropically subject to an N-H distance constraint. The positions of the remaining hydrogen atoms were idealised, C-H=0.96Å, assigned isotropic thermal parameters, $U(H)=1.2U_{eq}$ (C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares to R=0.059, $R_w=0.064$ [$w^{-1}=\sigma^2(F)+0.00093F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.33 and -0.22eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.021 and 0.102 respectively. Computations were carried out on a Eclipse S140 computer using the SHELXTL program system.

General Procedure for the Reaction of N-Aryl, N-Alkyl, N-Aryl-O-methyl, N-Alkyl-O-methyl Hydroxylamines with Ethyl cyanoformate.

The appropiate hydroxylamine (0.15-0.2M) in dry CH_2Cl_2 was treated with ethyl cyanoformate (1.2-1.5 eq.) at room temperature. After completion of the reaction (monitored by t.l.c.), the solvent was evaporated under reduced pressure, the residue washed repeatedly with petroleum ether and the solid crystallised.

α-Amino-α-carbethoxy-N-methylnitrone 2a obtained in 65% yield; white crystals; m.p. 93-95°C (from CH_2Cl_2/petroleum ether); IR(KBr): 3300 (N-H), 3200-2900 (N-H), 1740,1735 (C=O), 1620 (C=N); UV λ_{max} (EtOH): 305 (ε 9000); ^{1}H NMR ($CDCl_3$) δ: 1.40 (t,3H,J 7.2Hz,$CH_2\underline{CH_3}$), 4.36 (q,2H,J 7.2Hz,$\underline{CH_2}CH_3$), 4.37 (s,3H,N-$\underline{CH_3}$), 5.79 (bs,2H,$N\underline{H_2}$ exchangeable in D_2O); EIMS m/z(%): 146 (M^+,20), 57 (100); HREIMS Calcd. for $C_5H_{10}N_2O_3$: 146.0691. Found: 146.0698.

α-Amino-α-carbethoxy-N-isopropylnitrone 2b obtained in 73% yield; white crystals; m.p. 83-84°C (from benzene/petroleum ether); IR(KBr): 3180 (N-H), 1725 (C=O), 1630 (C=N); UV λ_{max} (EtOH): 256 (ε 7000); ^{1}H NMR ($CDCl_3$) δ: 1.44-1.37 (m, 9H, $CH_2\underline{CH_3}$, $(\underline{CH_3})_2CH$), 4.40 (q,2H,J 7.3Hz,$\underline{CH_2}CH_3$), 5.47 (m, 1H, J 6.1Hz, $(\underline{CH_3})_2\underline{CH}$), 5.73 (bs,2H,$N\underline{H_2}$ exchangeable in D_2O); EIMS m/z(%): 174 (M^+,22), 55 (100). Anal. Calcd. for $C_7H_{14}N_2O_3$: C 48.28, H 8.05, N 16.09%. Found: C 48.19, H 8.19, N 15.79%.

α-Amino-α-carbomethoxy-N-methylnitrone 2c obtained in 68% yield; white crystals; m.p. 94-96°C (from ethyl acetate/n-hexane, benzene) ; IR(KBr): 3430 e 3260 (N-H), 1735 ,1720 (C=O), 1610(C=N); UV λ_{max} (EtOH) 306 (ε 8150); ^{1}H NMR ($CDCl_3$) δ: 3.92 (s,3H,OCH_3), 4.02 (s,3H,NCH_3), 5.74 (bs,2H,NH_2, exchangeable in D_2O); EIMS m/z(%): 132 (M+,7.1), 57 (100) ; Anal. Calcd. for $C_4H_8N_2O_3$: C 36.36, H 6.10, N 21.20%. Found: C 36.44, H 6.14, N 21.26%.

α-Amino-α-carbethoxy-N-phenylnitrone 2d, obtained in 79% yield; white crystals; m.p. 108-110°C (from CH_2Cl_2/petroleum ether); IR(KBr): 3400 (N-H), 1740 (C=O), 1650 (C=N); UV λ_{max}(EtOH) 305 (ε 7000); ^{1}H NMR (CD_3CN) δ: 1.03 (t,3H,J 7.3Hz,$CH_2\underline{CH_3}$), 4.07 (q,2H,J 7.3Hz, $\underline{CH_2}CH_3$), 6.39 (bs,2H,$N\underline{H_2}$, exchangeable in D_2O), 7.27-7.4 (m,5H,Ar$\underline{H}$); EIMS m/z(%): 208 (M^+, 16.8), 119 (100). Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C 57.69, H 5.77, N 13.46%. Found: C 57.48, H 5.77, N 13.39%.

α-Amino-α-carbethoxy-N-(4-methylphenyl)-nitrone 2e, obtained in 72% yield; white crystals; m.p. 101-103°C (from benzene/petroleum ether); IR(KBr): 3380 (N-H), 3200 (N-H), 1735 (C=O), 1640 (C=N); UV λ_{max} (EtOH) 305 (ε 8200); ^{1}H NMR (CD_3CN) δ: 1.38(t,3H, J 7.3Hz, $CH_2\underline{CH_3}$), 2.36 (s,3H,Ar$\underline{Me}$), 4.07 (q,2H,J 7.3Hz,$\underline{CH_2}CH_3$,), 6.36 (bs,2H,$N\underline{H_2}$, exchangeable in D_2O), 7.14 (d,2H,J 8Hz,Ar$\underline{H}$), 7.2 (d, 2H,J

8Hz,ArH); EIMS m/z(%): 222 (M^+,2.7), 133 (100). HREIMS Calcd. for $C_{11}H_{14}N_2O_3$: 222.1004. Found: 222.0998.

α-Amino-α-carbethoxy-N-(3-methylphenyl)-nitrone 2f, obtained in 62% yield; white crystals; m.p. 105°C (from CH_2Cl_2/petroleum ether); IR(KBr): 3380 (N-H), 3220 (N-H), 1730 (C=O), 1640 (C=N); UV λ_{max} (EtOH) 307 (ε 7800); ^1H NMR (CD_3CN) δ: 1.05 (t, 3H, J 7Hz, CH_2CH_3), 2.38 (s,3H,ArMe), 4.13 (q,2H,J 7Hz,CH_2CH_3), 6.1 (bs,2H,NH_2, exchangeable in D_2O), 7.11 (d,1H,J 7.5Hz,ArH), 7.162 (s,1H,ArH), 7.22 (d,1H,J 7.5Hz,ArH); EIMS m/z(%): 222 (M^+,7), 206 (100). HREIMS Calcd. for $C_{11}H_{14}N_2O_3$: 222.1004. Found: 222.1013.

α-Amino-α-carbethoxy-N-(4-bromophenyl)-nitrone 2g, obtained in 67% yield; white crystals; m.p. 103-105°C (from benzene/petroleum ether); IR(KBr): 3380 (N-H), 1745 (C=O), 1640 (C=N); UV λ_{max} (EtOH) 222 (ε 10025), 305 (ε 8200); ^1H NMR (CD_3CN) δ: 1.07 (t,3H,J 7.2Hz, CH_2CH_3), 4.1 (q,2H,J 7.2Hz,CH_2CH_3), 6.8-6.4 (bs,2H,NH_2, exchangeable in D_2O), 7.21 (d,2H,J 8.7Hz,ArH), 7.56 (d, 2H,J 8.7Hz,ArH); EIMS m/z(%): 270 (M^+-16,1.9), 272 (M^+-16,1.1). Anal. Calcd. for $C_{10}H_{11}BrN_2O_3$: C 41.66, H 3.82, N 9.72%. Found: C 41.40, H 3.75, N 9.68%.

Ethyl α-amino-oximinoacetate 3a, obtained in 76% yield; white crystals; m.p. 97-99°C (from CH_2Cl_2/petroleum ether) (lit[12] 97-98°C); IR(KBr): 3500 (N-H), 3400 (N-H), 3180 (O-H), 1725 (C=O), 1670 (C=N); UV λ_{max} (EtOH): 256 (ε 5300); ^1H NMR ($CDCl_3$) δ: 1.36 (t,3H,J 7.3Hz,CH_2CH_3), 4.33 (q,2H,J 7.3Hz,CH_2CH_3), 5.13 (bs, 2H, NH_2 exchangeable in D_2O), 9.0 (bs, 1H, OH,exchangeable in D_2O); EIMS m/z(%): 132 (M^+,60), 59 (100).

Ethyl α-amino-O-ethoxycarbonyloximinoacetate 3b. The mother liquor from the above reaction was evaporated and the residue chromatographed on silica gel. Elution with CH_2Cl_2/EtOH (9.5/0.5) afforded the oxime ester in 15% yield; m.p. 130-132°C (from CH_2Cl_2/petroleum ether) (lit[13] 131-131.5°C).

Ethyl N-methoxy carbamate 5a: Ethyl cyanoformate and O-methylhydroxylamine gave a product (46%) identified as ethyl N-methoxy carbamate by comparison (t.l.c., IR, NMR) with an authentic material obtained from O-methylhydroxylamine and ethyl chloroformate.

Ethyl N-methoxy-N-methyl carbamate 5b: Ethyl cyanoformate and N-methyl-O-methylhydroxylamine gave a product (36%) identified as ethyl N-methoxy-N-methyl carbamate by comparison (t.l.c., IR, NMR) with an authentic material obtained from N-methyl-O-methylhydroxylamine and ethyl chloroformate.

Reaction between ethyl cyanoformate and O-methyl-N-phenylhydroxylamine: Ethyl cyanoformate (0.07ml) and O-methyl-N-phenylhydroxylamine (0.09g) in benzene (5ml) were kept at r.t. and the reaction monitored (t.l.c.). No products, other than the decomposition of the hydroxylamine derivative, verified by conducting a blank reaction, were formed during 1 month.

Ethyl N-anilino carbamate 5d: A solution of ethyl cyanoformate (0.05ml; 0.51mmol) and phenylhydrazine (0.05ml; 0.51mmol) in benzene (3.5ml) was kept at r.t. (36h). The solvent was evaporated and the residue crystallised to give colourless crystals; m.p. 81-84°C (50% yield) identified as ethyl N-anilino carbamate (lit[19] m.p. 82- 83°C).

Ethyl N-phenyl carbamate 5e: A mixture of aniline (0.28ml; 3mmol) and ethyl cyanoformate (0.3ml) in benzene (5ml) was allowed to stand at r.t. and the progress of the reaction monitored by t.l.c.. After 30 days the solvent was evaporated and the residue purified by preparative t.l.c. (silica; CH_2Cl_2-EtOH 9:1 v/v) to afford as

the major product ethyl N-phenyl carbamate, m.p. 46.5-48°C (lit[19] 53°C) (55% yield) identical in all respects (IR, NMR, t.l.c. and mixed m.p.) with an authentic material obtained from aniline and ethyl chloroformate.

N-Methoxyaniline 4c:

N-Phenylhydroxylamine (0.15g) in ether (15ml) was treated dropwise at -40°C with an ethereal solution of trifluoroacetic anhydride (0.2 ml) and the mixture kept at the same temperature for an additional 40 min. It was then washed with aqueous sodium bicarbonate solution (0,5N) dried (Na_2SO_4) and evaporated to give the crude product which was purified by crystallisation from n-hexane. The hydroxamic acid **6** (70-80% yield) had m.p. 79-80°C; IR(KBr): 3220 (OH), 1650 (C=O); ^{1}H NMR ($CDCl_3$) δ: 7.5 (m, ArH).

The above acid (0.1g) in methanol (10ml) was methylated with an excess of diazomethane. Evaporation of the solvent yielded a residue which was purified by column chromatography on silica gel with CH_2Cl_2. The methyl ether was obtained in 71% yield. IR(film): 1710 (C=O); ^{1}H NMR ($CDCl_3$) δ: 3.76 (s,3H,OMe), 7.44 (m,5H,ArH).

The methyl ether (0.5g) in ethanol (50ml) was hydrolysed with an aqueous solution of sodium bicarbonate (1%) at r.t. until all the starting material had been consumed. Extraction of the mixture, after dilution with water, with n-hexane afforded the N-methoxyaniline **4c** contaminated with traces of azobenzene; ^{1}HNMR ($CDCl_3$) δ: 3.77 (s,3H,OMe), 6.94 (m,3H,ArH), 7.04 (bs,1H,NH exchangeable in D_2O), 7.27 (m,2H,ArH). This compound was used as such for the reaction with ethyl cyanoformate.

General method for the preparation of o-mesyloxy-N-arylamidines

N-Aryl aminonitrone (0.3-0.35mmol) in CH_2Cl_2 was mixed with Et_3N (1.1eq). To the mixture cooled to 0°C, was added mesylchloride in dry CH_2Cl_2. After the completion of the reaction (monitored by t.l.c., usually ca 30 min) H_2O was added and extracted with CH_2Cl_2. The combined extracts were washed with H_2O, dried (Na_2SO_4) and the solvent evaporated. The residue was crystallised from EtOAc/n-hexane.

N-(2-Mesyloxyphenyl)-α-carbethoxyamidine 11a; m.p. 93-94.5°C (60% yield); IR (KBr): 3430, 3310,3190 (N-H), 1750 (C=O), 1680 and 1660 (C=N), 1370 and 1160 (S=O); UV λ_{max} (EtOH): 250 (ε 7040); ^{1}H NMR (CD_3CN) δ: 1.33 (t,3H,J 7.2Hz,CH_2CH_3), 3.24 (s,3H,SO_2CH_3), 4.32 (q,2H,J 7.2Hz,CH_2CH_3), 5.90 (bs,2H,NH,C=NH exchangeable in D_2O), 7.05-7.32 (m,4H,ArH); EIMS m/z(%): 286 (M^+,17), 135 (100). Anal.Calcd. for $C_{11}H_{14}N_2O_5S$: C 46.15, H 4.93, N 9.78, S 11.20%. Found: C 45.98, H 4.90, N 9.75, S 10.76%. Preparative thin-layer chromatography of the residue from the mother liquor led to the isolation of benzimidazole carboxylic ester **10a** in 7% yield; m.p. 222-223°C (mixed m.p. 221-223°C); IR, NMR identical with the compound obtained from photolysis of **26d**.

N-(2-Mesyloxy-4-methylphenyl)-α-carbethoxyamidine 11b; m.p. 99-100°C (57% yield); IR (KBr): 3470, 3360 (N-H), 1730 (C=O), 1640 (C=N), 1380 and 1170 (S=O); UV λ_{max} (EtOH): 280 (ε 3750); ^{1}H NMR (CD_3CN) δ: 1.31 (t,3H,J 6.9Hz,CH_2CH_3), 2.32 (s,3H,CH_3-Ar), 3.24 (s,3H,SO_2CH_3), 4.32 (q,2H,J 6.9Hz,CH_2CH_3), 6.0 (bs,2H,NH,C=NH exchangeable in D_2O), 6.94-7.14 (m,3H,ArH); EIMS m/z(%): 300 (M^+,20), 149 (100). Anal.Calcd. for $C_{12}H_{16}N_2O_5S$: C 47.99, H 5.37, N 9.33, S 10.67%. Found: C 47.92, H 5.40, N 8.98, S 10.92%.

N-(2-Mesyloxy-5-methylphenyl)-α-carbethoxyamidine 11c; m.p. 99-101°C (50% yield); IR (KBr): 3460, 3340 (N-H), 1730 (C=O), 1635 (C=N), 1355 and 1170 (S=O); UV λ_{max} (EtOH): 214 (ε 11800), 278 (ε 3700); ^{1}H NMR (CD_3CN) δ: 1.33 (t,3H,J 7Hz,CH_2CH_3), 2.34 (s, 3H, CH_3Ar), 3.21 (s,3H,SO_2CH_3), 4.32 (q,2H,J

7Hz,C$\underline{H}_2$CH$_3$), 5.8 (bs,2H,N$\underline{H}$,C=N$\underline{H}$ exchangeable in D_2O), 6.8-7.17 (m,3H,Ar$\underline{H}$); EIMS m/z(%): 300 (M^+,17), 149 (100). HREIMS Calcd. for $C_{12}H_{16}N_2O_5S$: 300.0779. Found 300.0782.

N-(4-Bromo-2-mesyloxy-phenyl)-α-carbethoxyamidine 11d; m.p. 119-120°C (40% yield); IR (KBr): 3440, 3325 (N-H), 1730 (C=O), 1640 (C=N), 1370 and 1160 (S=O); UV λ_{max} (EtOH): 235 (ε 7400), 280 (ε 4100); ^{1}H NMR (CD_3CN) δ: 1.32 (t,3H,J 7Hz,CH$_2$C$\underline{H}_3$), 3.26 (s,3H,SO$_2$C$\underline{H}_3$), 4.31 (q,2H,J 7Hz,C$\underline{H}_2$CH$_3$), 5.94 (bs,2H,N$\underline{H}$,C=N$\underline{H}$ exchangeable in D_2O), 6.94-7.57 (m,3H,Ar$\underline{H}$). Anal.Calcd. for $C_{11}H_{13}BrN_2O_5S$: C 36.18, H 3.58, N 7.67, S 8.78%. Found: C 36.00, H 3.54, N 7.56, S 8.67%.

By bromination of 11a: NBS (0.062g; 0.35mmol) in dry THF (4ml) was mixed with DABCO (0.039g;0.35mmol). The amidine (0.1g;0.35mmol) was then added and the reaction allowed to proceed at room temperature (24h). Water was added and the mixture extracted twice with ether. The combined ether extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue (preparative t.l.c., silica, EtOAc/petroleum ether 4/6) yielded the title compound; m.p. 118-119°C (34% yield) identical with **11d** (mixed m.p. 119.5-122°C).

o-Mesyloxy formanilide 12b: o-Mesyloxyaniline (100mg) in ethyl formate (3.5ml) was heated to reflux (5h). The mixture was diluted with ether and the solution washed with aqueous HCl (1%) and water. The etheral extract was dried (Na_2SO_4) and evaporated to afford an oil which crystallised from CH_2Cl_2/petroleum ether; m.p. 94-96°C (79% yield); IR (KBr): 3260 (N-H), 1690 and 1665 (CONH), 1365 and 1165 (S=O); UV λ_{max} (EtOH) 241 (ε 5900); ^{1}H NMR (CD_3CN) δ:3.27 (s,3H,CH_3SO_2), 7.17 (t,1H,J 7.8Hz,ArH), 7.33 (t,1H,J 7.8Hz,ArH), 7.40(d,1H,J 8.4Hz, ArH), 8.15 (bs,1H,NH), 8.30 (d,1H,J 8.4,ArH), 8.37 (s,1H,H-C=O cis), 8.45 (bs,NH cis) 8.58 (d,1H,J 11.1HzH-C=O trans); EIMS m/z(%): 215 (M^+,28), 80 (100). Anal.Calcd.for $C_8H_9NO_4S$: C 44.64, H 4.21, N 6.50, S 14.89%. Found C 44.65, H 4.20, N 6.40, S 14.89%. The ratio of cis and trans isomers (80:20) was calculated from the integration heights measured for the formyl proton.

Reaction between N-(2-mesyloxyphenyl)-α-carbethoxyamidine and DABCO

A solution of amidine **11a** (0.1g) and DABCO (39mg) in 95% ethanol (4ml) was heated under reflux (40h). The solvent, on evaporation gave a mixture which was purified by preparative t.l.c. (silica, EtOAc/petroleum ether 6/4). The formanilide obtained in 20% yield was identical with an authentic sample (IR,NMR,m.p. and mixed m.p.). The other product formed in 62% was shown to be o-mesyloxyaniline **12a** by comparison with an authentic sample.

N-(2-Mesyloxyphenyl)-α-Carbethoxyamidine (87mg) **11a** and DABCO (34mg) in a mixture of EtOD (4ml) and D_2O (25 µl) were heated under reflux (180h). Evaporation of the solvent and purification of the residue by preparative t.l.c. yielded besides the recovered starting material (30mg), o-mesyloxy-d_3-aniline **19** (10.8%) and the deuterated formanilide derivative **18** (6.4%).

N-(2-Mesyloxyphenyl)-cyanamide 24: To a solution of the amidine **11a** (0.2g;0.7mmol) in MeOH (1.4ml) was added aqueous HCl (1N, 0.7ml). After stirring the mixture (5min), aqueous solution of NaOCl (0.25ml; 3M) was added followed by saturated aqueous solution of Na_2CO_3 (0.1g). When the reaction was complete (monitored by t.l.c.), the mixture was acidified and the product extracted with ether. Evaporation of the solvent afforded the cyanamide (45%) as an oil; IR (CH_2Cl_2), 3360 (N-H), 2220 (CN), 1375 and 1160 (S=O); EIMS m/z(%): 212 (M^+, 22), 133 (100); ^{1}H NMR ($CDCl_3$) δ: 3.28 (s,3H,OSO$_2$C$\underline{H}_3$), 7.35 (m,6H,Ar$\underline{H}$, N$\underline{H}$).

General Procedure for the Preparation of Δ^3-1,2,4- Oxadiazolin-5-ones

N-Alkyl or N-aryl-α-amino-α-carbethoxynitrone (0.18-0.22M) in dry CH_2Cl_2 was cooled to -25°C and treated with Et_3N (2 eq.). Triphosgene [bis(trichloromethyl)carbonate][33] (0.33eq) was then added portionwise. After the reaction was complete (monitored by t.l.c.), the mixture was washed with cold aqueous HCl (1N), then with H_2O and dried (Na_2SO_4). Evaporation of the solvent yielded the oxadiazolin-5- ones.

3-Carbethoxy-2-methyl-Δ^3-1,2,4-oxadiazolin-5-one 26a: colourless oil (89.3% yield); IR(CH_2Cl_2): 1790 (C=O), 1745 (C=O); UV λ_{max} (EtOH) 274 (ε 3870); ^{1}H NMR ($CDCl_3$) δ: 1.45 (t,3H,J 7.2Hz, $CH_2C\underline{H}_3$), 4,06 (s,3H,$C\underline{H}_3$), 4.50 (q,2H,J 7.2Hz, $C\underline{H}_2CH_3$); EIMS m/z(%): 172 (M^+, 13.4). HREIMS Calcd. for $C_6H_8N_2O_4$: 172.0484. Found 172.0480.

3-Carbethoxy-2-isopropyl-Δ^3-1,2,4-oxadiazolin-5-one 26b: colourless oil (78% yield); IR(CH_2Cl_2): 1790, 1745 (C=O); UV λ_{max} (EtOH) 274 (ε 3170); ^{1}H NMR ($CDCl_3$) δ: 1.51 (m, 9H, $CH_2C\underline{H}_3$, $(C\underline{H}_3)_2CH$), 4.50 (q,2H,J 7.3Hz, $C\underline{H}_2CH_3$), 5.30 (m,1H,$(CH_3)_2C\underline{H}$); EIMS m/z(%): 200 (M^+, 8.4). HREIMS Calcd. for $C_8H_{12}N_2O_4$: 200.0797. Found 200.0809.

3-Carbomethoxy-2-methyl-Δ^3-1,2,4-oxadiazolin-5-one 26c: colourless oil (84.2% yield); IR(CH_2Cl_2): 1790 (C=O), 1750 (C=O); UV λ_{max} (EtOH) 272 (ε 3890); ^{1}H NMR ($CDCl_3$) δ: 4,06 (s,3H,N-$C\underline{H}_3$), 4.05 (s,3H,$CO_2C\underline{H}_3$); EIMS m/z (%): 158 (M^+,57), 86 (100). HREIMS Calcd. for $C_5H_6N_2O_4$: 158.0327. Found 158.0320.

3-Carbethoxy-2-phenyl-Δ^3-1,2,4-oxadiazolin-5-one 26d: (72% yield); m.p. 108-110°C (from EtOH); IR(KBr) 1780 (C=O), 1750 (C=O); UV λ_{max}(EtOH) 275 (ε 5600); ^{1}H NMR ($CDCl_3$) δ: 1.32 (t,3H,J 7.2Hz,$CH_2C\underline{H}_3$), 4,40 (q, 2H,J 7.2Hz, $C\underline{H}_2CH_3$), 7.57 (m, 5H, Ar$\underline{H}$); EIMS m/z (%): 234 (M^+,4), 91 (100). Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C 56.41, H 4.30, N 11.96%. Found: C 56.04, H 4.22, N 11.86%.

3-Carbethoxy-2-(4-methylphenyl)-Δ^3-1,2,4-oxadiazolin-5-one 26e: (65% yield); m.p. 75-76°C (from EtOH); IR(KBr) 1780 (C=O), 1750 (C=O); UV λ_{max} (EtOH) 280 (ε 5330); ^{1}H NMR ($CDCl_3$) δ: 1.32 (t,3H,J 7.2Hz,$CH_2C\underline{H}_3$), 2.45 (s,3H,Ar-$\underline{Me}$), 4.39 (q,2H,J 7.2Hz, $C\underline{H}_2CH_3$), 7.33 (s,4H,Ar$\underline{H}$); EIMS m/z(%) 248 (M^+, 4.4), 105 (100). Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C 58,06, H 4.87, N 11.28%. Found: C 58.18, H 4.85, N 11.27%.

3-Carbethoxy-2-(3-methylphenyl)-Δ^3-1,2,4-oxadiazolin-5-one 26f: (70% yield); m.p. 59-60°C (from EtOH); IR(KBr) 1790 (C=O), 1755 (C=O); UV λ_{max} (EtOH) 278 (ε 5000); ^{1}H NMR (CD_3CN) δ: 1.20 (t,3H,J 7.2Hz,$CH_2C\underline{H}_3$), 2.4 (s,3H,Ar-$\underline{Me}$), 4.30 (q,2H,J 7.2Hz,$C\underline{H}_2CH_3$), 7.42 (s,4H,Ar$\underline{H}$); EIMS m/z(%) 248 (M^+, 13), 105 (100). Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C 58,06, H 4.87, N 11.28%. Found: C 58.16, H 4.89, N 11.17%.

2-(4-Bromophenyl)-3-carbethoxy-Δ^3-1,2,4-oxadiazolin-5-one 26g: (54% yield); m.p. 113-114°C (from EtOH); IR(KBr) 1790 (C=O), 1750 (C=O); UV λ_{max} (EtOH) 236.5 (ε 9700); ^{1}H NMR ($CDCl_3$) δ: 1.36 (t,3H,J 7.2Hz,$CH_2C\underline{H}_3$), 4.42 (q,2H,J 7.2Hz,$C\underline{H}_2CH_3$), 7.35 (d,2H,J 8.7Hz,Ar$\underline{H}$), 7.67 (d,2H,J 8.7Hz,Ar$\underline{H}$); EIMS m/z(%) 312 (M^+, 1.3), 314 (M^+, 1.3). Anal. Calcd. for $C_{10}H_9BrN_2O_4$: C 42.20, H 2.90, N 8.95%. Found C 42.14, H 2.8, N 8.90%.

General Method for the Preparation of Benzimidazoles by Photolysis of Δ^3-1,2,4-Oxadiazolin-5-ones.

The 2-aryl-oxadiazolin-5-one (0.01M) in dioxane was irradiated with a low pressure mercury lamp (TUV 6W) at 254nm. After the reaction was complete (monitored by t.l.c.), the solvent was evaporated and the products were isolated by preparative t.l.c. and purified by crystallisation.

Products obtained on photolysis of 26d:

Ethyl benzimidazole-2-carboxylate 10a; obtained in 79% yield; m.p. 221-223°C (from EtOAc/n-hexane) (lit[25] 221-222°C); IR(KBr): 2900-2500 (N-H), 1720 (C=O); UV λ_{max}(EtOH): 228 (ε 11600), 289 (ε 13700); ^{1}H NMR ($CDCl_3$) δ: 1.48 (t,3H,J 7.2Hz,CH_2CH_3), 4.54 (q,2H,J 7.2Hz,CH_2CH_3), 7.39-7.92 (m,4H,ArH), 10.36 (bs,1H,NH, exchangeable in D_2O); EIMS m/z(%): 190 (M^+,24.7), 118 (100).

N-Carbethoxy-N'-phenyl urea 28a; obtained in 4.8%; m.p. 100-103°C (from EtOAc/n-hexane); IR($CHCl_3$): 3440, 3320 (N-H), 1730 (C=O); UV λ_{max}(EtOH) 249 (ε 13500); ^{1}H NMR (CD_3CN) δ: 1.29 (t,3H,J 7.1Hz,CH_2CH_3), 4.22 (q,2H,J 7.1Hz,CH_2CH_3), 7.08-7.5 (m,5H,ArH), 8.09 (bs,1H,NH exchangeable in D_2O), 9.86 (bs,1H,NH exchangeable in D_2O); EIMS m/z(%) 208 (M^+,51), 93 (100); HREIMS Calcd. for $C_{10}H_{12}N_2O_3$: 208.0848. Found 208.0843.

Products obtained on photolysis of 26e:

Ethyl 5-methyl benzimidazole-2-carboxylate 10b; m.p. 136-138°C [from EtOAC/n-hexane (sealed capillary)] (52.4% yield); IR(KBr): 2900-2500 (N-H), 1720 (C=O); UV λ_{max} (EtOH) 233 (ε 8400), 298 (ε 11000); ^{1}H NMR ($CDCl_3$) δ: 1.37 (t,3H,J 7.2Hz, CH_2CH_3), 2.47 (s,3H,CH_3Ar), 4.46 (q,2H,J 7.2Hz,CH_2CH_3), 7.16-7.61 (m,3H,ArH), 9-11 (bs,1H,NH exchangeable in D_2O); EIMS m/z(%): 204 (M^+, 61.7), 132 (100). HREIMS Calcd. for $C_{11}H_{12}N_2O_2$: 204.0899. Found 204.0909.

N-Carbethoxy-N'-(4-methylphenyl)urea 28b; m.p. 146-148°C (from EtOAC/n-hexane) (10.5%); IR(KBr): 3220, 3120 (N-H), 1725 (C=O), 1700 (CONH); UV λ_{max} (EtOH): 244 (ε 16500); ^{1}H NMR ($CDCl_3$) δ: 1.34 (t,3H,J 7.2Hz,CH_2CH_3), 2.31 (s,3H,CH_3-Ar), 4.27 (q,2H,J 7.2Hz,CH_2CH_3), 7.13 (d,2H,J 8.4,ArH), 7.23 (bs,1H,NH exchangeable in D_2O), 7.38 (d,2H,J 8.4Hz,ArH), 9.76 (bs,1H,NH exchangeable in D_2O); EIMS m/z(%): 222 (M^+, 46), 133 (100). HREIMS Calcd. for $C_{11}H_{14}N_2O_3$: 222.1004. Found 222,1003.

Products obtained on photolysis of 26f:

3-Carbethoxy-2-(3-methylphenyl)-Δ^3-1,2,4-oxadiazolin-5-one on photolysis afforded a mixture of two isomeric benzimidazoles separated by preparative t.l.c. The 5-methyl benzimidazole-2-carboxylate **10b** obtained in 28% yield was identical with the compound obtained by photolysis of the compound **26e**. 4-Methyl benzimidazole-2-carboxylate **10c** was obtained in 16% yield; IR(CH_2Cl_2): 3420 (N-H), 1720 (C=O); UV λ_{max} (EtOH): 290 (ε 11100), 230 (ε 10600); ^{1}H NMR (CD_3CN) δ: 1.38 (t, 3H, J 7.2Hz, CH_2CH_3), 2.60 (s,3H,CH_3--Ar), 4.43 (q,2H,J 7.2Hz, CH_2CH_3), 7.12 (d,1H,J 7.2Hz,ArH), 7.39 (dd.1H,J 7.2Hz,ArH), 7.58 (sl,1H,ArH), 11.38 (sl,1H,NH, exchangeable in D_2O); EIMS m/z(%): 204 (M^+,0.2). HREIMS Calcd. for $C_{11}H_{12}N_2O_2$: 204.0899. Found 204.0897.

N-carbethoxyN'-(3-methylphenyl) urea 28c; obtained in 45% yield; IR(CH_2Cl_2): 3430 (N-H), 3300 (N-H), 1730 (C=O); UV λ_{max} (EtOH): 251 (ε 11840); ^{1}H NMR (CD_3CN) δ: 1.28 (t,3H,J 7.3Hz,CH_2CH_3), 2.32 (s,3H,CH_3-Ar), 4.22 (q,2H,J 7.3Hz,CH_2CH_3), 6.90 (d, 1H,J 7.3Hz, ArH), 7.17 (t,1H,J 7.3,ArH), 7.28 (m,2H,ArH), 8.05 (sl,1H,NH, exchangeable in D_2O), 9.82 (sl,1H,NH, exchangeable in D_2O); EIMS m/z (%): 222 (M^+,8), 133 (100); HREIMS Calcd. for $C_{11}H_{14}N_2O_3$: 222.1004. Found 222.1018.

2-Carbethoxybenzimidazoles by thermolysis 10a

3-Carbethoxy-2-phenyl-Δ^3-1,2,4-oxadiazolin-5-ones **26d** (155mg; 0.66mmol) in diphenylether (15ml) was heated under reflux (3h). The solvent was then evaporated under reduce pressure and the resulting dark oil on trituration with n-hexane solidified. The material was purified by preparative t.l.c. (silica; EtOAc/n-hexane 6:4) and crystallised to afford the title compound in 42 mg (35% yield) identical with that obtained by photolysis.

Ethyl-5-bromobenzimidazole-2-carboxylate 10d

The bromo compound **26g** (150mg; 0.48mmol) was thermolysed and the product isolated as above; m.p. 70-72°C (from CH_2Cl_2/petroleum ether) (43% yield); IR(KBr) 2900-2600 (N-H), 1720 (C=O); UV λ_{max} (EtOH): 310 (ε 13800); ^{1}H NMR ($CDCl_3$) δ: 1.40 (t,3H,J 7.2Hz,CH_2CH_3), 4.45 (q,2H,J 7.2Hz,CH_2CH_3), 7.50 (d,1H,J 8.7Hz,ArH), 7.63(d, 1H,J 8.7Hz,ArH), 7.92 (s,1H,ArH), 11.45 (bs,1H,NH exchangeable in D_2O); EIMS m/z (%): 270 (M^+,33.4), 268 (M^+,33.6), 196 (100); HREIMS Calcd. for $C_{10}H_9N_2O_2Br$: 267.9848. Found:267.9857.

5-Amino-3-carbethoxy-1,2,4-oxadiazole 30: The amino-oxime **3a** (80mg) in dry CH_2Cl_2 (1.5ml) was mixed with Et_3N (0.084ml) followed by dropwise addition of BrCN (0.064g) in CH_2Cl_2 at -40°C, -50°C. After being kept at this temperature for an addition 15 min. the mixture was allowed to attain room temperature, then washed with water and dried (Na_2SO_4). The solvent was evaporated and the resulting solid crystallised from CH_2Cl_2/n-hexane. The oxadiazole **30** was obtained in 45% yield; m.p. 177-178°C; IR(KBr):3390, 3240, 3180 (N-H), 1725 (C=O), 1660 (C=N); UV λ_{max} (EtOH) 245 (ε 2490); ^{1}H NMR (CD_3CN) δ: 1.34 (t,3H,J 7Hz,CH_2CH_3), 4.34 (q,2H,J 7Hz,CH_2CH_3), 6.45 (bs,2H,NH_2 exchangeable in D_2O); EIMS m/z(%): 157 (M^+,35), 112 (100). Anal Calcd. for $C_5H_7N_3O_3$: C 38.20, H 4.49, N 26.75%. Found: C 38.28, H 4.41, N 26.46%.

General Procedure for the Preparation of N-Carbethoxyimidoyl-2- benzimidazolone

To a solution of α-amino-α-carbethoxy-N-arylnitrone (0.2-0.24M) in acetonitrile was added Et_3N (1.2eq) followed by dropwise addition of a solution (0.5M) of BrCN in THF at -35°C. After the immediate reaction that ensued was complete, water was added and the mixture extracted twice with ether. The combined extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent and crystallisation of the residue provided the benzimidazolone.

1-(N-Carbethoxyimidoyl)-2-benzimidazolone 31a; colourless crystals, m.p. 127-132°C (subl.) (from EtOAc/n-hexane), (66% yield); IR(KBr): 3300 (N-H), 3180-2900 (N-H), 1750 (C=O), 1725 (C=O); UV λ_{max} (EtOH): 222 (ε 12400), 276 (ε 4750); ^{1}H NMR ($CDCl_3$) δ: 1.39 (t,3H,J 7.2Hz,CH_2CH_3), 4.42 (q,2H,J 7.2Hz,CH_2CH_3), 7.07-7.15 (m,3H,ArH), 7.95 (d,1H,J 8.7Hz,ArH), 9.52 (bs,1H,NH exchangeable in D_2O), 9.60 (bs,1H,NH exchangeable in D_2O); EIMS m/z(%): 233 (M^+,9), 134 (100). HREIMS Calcd. for $C_{11}H_{11}N_3O_3$: 233.0800. Found 233.0811.

1-(N-Carbethoxyimidoyl)-5-methyl-2-benzimidazolone 31b; m.p. 123-130°C (subl.) (from ethyl ether/petroleum ether), (82% yield); IR(KBr): 3300 (N-H), 3280 (N-H), 1740 (C=O), 1720 (C=O); UV λ_{max} (EtOH): 224 (ε 13000), 282 (ε 5200); ^{1}H NMR ($CDCl_3$) δ: 1.38 (t,3H,J 7.2Hz,CH_2CH_3), 2.38 (s,3H,CH_3-Ar), 4.42 (q,2H,J 7.2Hz, CH_2CH_3), 6.90 (s,1H,ArH), 6.94 (d,1H,J 8Hz,ArH), 7.81 (d,1H,J 8Hz,ArH), 9.472 (bs,1H,NH exchangeable in D_2O), 9.52 (bs,1H,NH exchangeable in D_2O); EIMS m/z(%): 247 (M^+,0.5), 148 (100). HREIMS Calcd. for $C_{12}H_{13}N_3O_3$: 247.0956. Found 247.0953.

1-(N-Carbethoxyimidoyl)-4-methyl-2-benzimidazolone 31c; (87% yield); IR(KBr): 3280 (N-H), 3240-2800 (N-H), 1740 (C=O), 1725 (C=O), 1640 (C=N); UV λ_{max} (EtOH): 225 (ε 11000), 272 (ε 3570); ^{1}H NMR ($CDCl_3$) δ: 1.38 (t,3H,J 7.2Hz,CH_2CH_3), 2.37 (s,3H,CH_3ArH), 4.04 (q,2H,J 7.2Hz,CH_2CH_3), 7 01 (t,1H,J 7.8Hz,ArH), 7.08 (d,1H,J 7.8Hz,ArH), 7.79 (d,1H,J 7.8Hz,ArH), 9.55 (bs,1H,NH exchangeable in D_2O), 10.10 (bs,1H,NH exchangeable in D_2O); EIMS m/z(%): 247 (M^+,0.5), 134 (100). HREIMS Calcd. for $C_{12}H_{13}N_3O_3$: 247.0957. Found 247.0967.

5-Bromo-1-(N-carbethoxyimidoyl)-2-benzimidazolone 31d; m.p. 150-155°C (subl) (75% yield); IR(KBr): 3300 (N-H), 3240-2900 (N-H), 1755 (C=O), 1735 (C=O); UV λ_{max} (EtOH): 226 (ε 18000), 286 (ε 6300); ^{1}H NMR ($CDCl_3$) δ: 1.39 (t,3H,J 7.2Hz,$CH_2\underline{CH_3}$), 4.43 (q,2H,J 7.2Hz,$\underline{CH_2}CH_3$), 7.23 (m,1H,Ar<u>H</u>), 7.30 (s,1H,Ar<u>H</u>), 7.83 (d,1H,J 8.4Hz,Ar<u>H</u>), 9.16 (bs,1H,N<u>H</u> exchangeable in D_2O), 9.62 (bs,1H,N<u>H</u> exchangeable in D_2O); EIMS m/z(%): 311 (M^+,1.5), 313 (M^+,0.6), 212 (100). HREIMS Calcd. for $C_{11}H_{10}BrN_3O_3$: 310.9906 and 312.9886. Found 310.9892 and 312.9695.

2-Benzimidazolone 36a: The imidoyl compound **31a** (0.02g) in EtOH (0.1 ml) was mixed with dilute HCl (3N). After 10 min., the solvent was removed and the residue crystallised from water. 2-Benzimidazolone obtained as needles (92% yield), m.p. 303-305°C (lit[36] m.p. 308-310°C); IR(KBr): 3300-3260 (N-H), 1740 (C=O); ^{1}H NMR (DMSO-d_6) δ: 6.92 (s,4H,Ar<u>H</u>), 10.58 (bs,2H,N<u>H</u> exchangeable in D_2O).

5-Methyl-2-benzimidazolone 36b: High-vacuum sublimation of the imidoyl compound **31b** gave 5-methyl-2-benzimidazolone (93% yield); m.p. 265-275°C (lit[37] m.p. 293-295°C); IR(KBr): 3300-2700 (N-H), 1740 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.27 (s,3H,$\underline{CH_3}$-Ar), 6.75 (m,3H,Ar<u>H</u>), 10.40 (bs,1H,N<u>H</u> exchangeable in D_2O), 10.42 (bs,1H,N<u>H</u> exchangeable in D_2O).

4-Methyl-2-benzimidazolone 36c: prepared as above had m.p. 273- 280°C (lit.[38] m.p. 297-300°C) (95% yield); IR(KBr): 3300-2700 (N-H), 1740 (C=O).

5-Bromo-2-benzimidazolone 36d: prepared as above had m.p. 328- 330°C (lit.[38] m.p. 336°C) (92% yield); IR(KBr): 3300-2700 (N-H), 1750 (C=O); ^{1}H NMR (DMSO-d_6) δ: 6.85 (d,1H,J 8.4Hz,Ar<u>H</u>), 7.05 (dd,1H,J 8.4Hz,Ar<u>H</u>), 7.10 (s,1H,Ar<u>H</u>), 10.45 (bs,1H,N<u>H</u> exchangeable in D_2O), 10.48 (bs,1H,N<u>H</u> exchangeable in D_2O)

Synthesis of imidazoles

2-Carbethoxy-4-carbomethoxy-1-methylimidazole 39a: The aminonitrone **2a** (0.06g) in benzene (4ml) was mixed with Et_3N (1.2eq) and then treated with methyl propiolate (0.04ml;0.49mmol). When the reaction was complete (1h) the mixture was treated under reflux (15min), the solvent evaporated and the residue crystallised from EtOAc/n-hexane. The imidazole dicarboxylic ester (0.075g) had m.p. 155-156°C. IR(KBr): 1725 (C=O); UV λ_{max} (EtOH) 255 (ε 13800); ^{1}H NMR ($CDCl_3$) δ: 1.43 (t, 3H, J 7.3Hz, $CH_2\underline{CH_3}$), 3.91 (s,3H,N-$\underline{CH_3}$), 4.06 (s,3H,O$\underline{CH_3}$),4.43 (q,2H, J 7.3Hz,$\underline{CH_2}CH_3$), 7.70 (s,1H,=C-<u>H</u>); EIMS m/z(%): 212 (M^+,4.3), 140 (100); Anal. Calcd. for $C_9H_{12}N_2O_4$: C 50.94, H 5.70, N 13.20%. Found: C 50.91, H 5.72, N 13.09%.

2,4-Dicarbomethoxy-1-methylimidazole 39b: The aminonitrone **2c** (0.1g;0.75mmol) and methyl propiolate yield similarly, the dimethylester in 68% yield; m.p. 180-181°C (from EtOAc/n-hexane); IR(KBr): 1720 and 1705 (C=O); UV λ_{max} (EtOH): 255 (ε 12800); ^{1}H NMR ($CDCl_3$) δ: 3.90(s,3H,O$\underline{CH_3}$), 3.95(s,3H,O$\underline{CH_3}$), 4.06 (s,3H,N-$\underline{CH_3}$), 7.70 (s,1H,=C-<u>H</u>); ^{13}CNMR ($CDCl_3$) δ: 36.28 (q,N-Me), 51.68 (q,OMe), 52.28 (q,OMe), 130.79 (d, C-5), 132.83 (s,C-4), 136.89 (s,C-2), 159.12 (s,CO), 162.31 (s,CO); Anal. Calcd. for $C_8H_{10}N_2O_4$: C 48.48, H 5.08, N 14.14%. Found: C 48.63, H 5.07, N 14.36%.

2-Carbethoxy-4-carbomethoxyimidazole 41: The ethyl amino-oximinoacetate **3a** (0.08g;0.6mmol) in xylene (6ml) was mixed with Et_3N (1.2eq) and then treated with methylpropiolate (0.06ml;0.72mmol). When the reaction was complete (1h) water was added to the reaction mixture, the organic phase separated and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded the crude product (**40** or **40a**); m.p. 50-60°C; IR(KBr): 3450, 3310 and 3280 (N-H), 1725 and 1720 (C=O), 1660 and 1635 (C=N); ^{1}H NMR ($CDCl_3$) δ: 1.39 (t,3H,J 7.2Hz,$CH_2\underline{CH_3}$), 3.72 and 3.704 (s,3H,O$\underline{CH_3}$), 4.40 (q,2H,J 7.2Hz,$\underline{CH_2}CH_3$), 4.98 (d, 1H,J

7.2Hz,C=CH cis), 5.36 (bs, 2H, NH,C=NH exchangeable in D_2O), 5.67 (d,1H,J 12.3Hz,C=CH trans), 7.35 (d, 1H, J 7.2Hz, C=CH cis), 7.95 (d,1H,J 12.3Hz,C=CH trans). The ratio of cis and trans isomers (16:84 respectively) was calculated from the integration heights measured for the olefinic protons. The mixture in xylene (6ml) was heated under reflux (14h). Evaporation of the solvent yielded a solid which on purification by preparative thin-layer chromatography (EtOAc/n-hexane 6:4) followed by crystallisation (EtOAc/n-hexane) afforded the diester **41** in 70% yield; m.p. 188-191°C; IR (KBr): 3110 (N-H), 1720 and 1715 (C=O); UV λ_{max} (EtOH): 255 (ε 14000); ^1H NMR ($CDCl_3$) δ: 1.36 (t,3H,J 7.2Hz, CH_2CH_3), 3.91 (s,3H,OCH_3), 4.42 (q,2H,J 7.2Hz, CH_2CH_3), 7.83 (s, 0.3H,C=CH), 7.94 (s,0.7H,C=CH), 11,10 (bs,0.3H,NH exchangeable in D_2O), 11.85 (bs,0.7H,NH exchangeable in D_2O); Analc. Calcd. for $C_8H_{10}N_2O_4$: C 48.48, H 5.08, N 14.13. Found: C 48.86, H 5.02, N 14.07.

Synthesis of 3-amino-2-hydroxy-quinoxaline 42: A solution of phenylenediamine (0.04g;0.37mmol) and **2d** (0.08g;0.038mmol) in ethanol (5ml) was treated with a drop of glacial acetic acid. After the reaction was complete (monitored by t.l.c.), the precipated solid was collected by filtration. Crystallisation from water yielded the quinoxaline derivative **42** in 45%; m.p. 329-331°C (lit[40] 360°C); IR(KBr): 3390 (N-H), 3280 (O-H), 1655 (C=O), 1615 (C=N); 1H NMR(DMSO-d_6) δ: 6.83 (bs,2H,NH exchangeable in D_2O), 7.08 (m,3H,ArH), 7.26 (m,1H,ArH), 12.06 (bs,1H.OH exchangeable in D_2O); EIMS m/z(%): 161 (M+,100).

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