4,5-Dihydroisoxazole and 4,5-Dihydro-1,2,4-oxadiazole Derivatives from Cycloaddition Reactions of Nitrile Oxides to Alkyl *N*-(Diphenylmethylene)-α,β-dehydroamino Acids

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Received March 24, 1992

The alkyl *N*-(diphenylmethylene)-α,β-dehydroamino acids **1** have been submitted to 1,3-dipolar cycloadditions with nitrile oxides. The reactivity of these compounds depends on the type and on the stereochemistry of the β-substituents. With the unsubstituted terms **1a,b** the reaction occurs on the C,C double bond, providing a good method for the synthesis of the 4,5-dihydroisoxazole derivatives **3a,b,c** and for the gem-functionalized 4,5-dihydroisoxazoles amino carboxylic ester **5**. The β-substituted compounds **1c,d,e**, inert to 1,1-dimethylethylnitrile oxide, undergo the reaction to the N,C double bond, thus giving with **2a,b** the 4,5-dihydro-1,2,4-oxadiazole derivatives **4**. All the reactions occur with high site- and regioselectivity.

J. Heterocyclic Chem., **29**, 1593 (1992).

Several examples of addition reactions to the double bond of α,β-dehydroamino acids have found application in synthesis. Most of the literature on this subject deals with additions of hydrogen, nucleophiles and electrophiles giving α- and β-substituted amino acids [1].

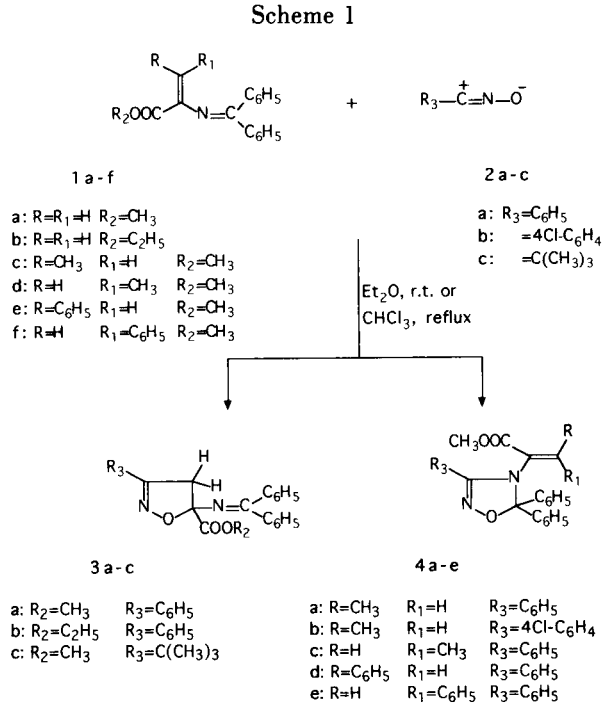
Much less work has dealt with the cycloaddition reactions of α,β-dehydroamino acids; nevertheless, the Diels-Alder reactions, where these compounds react as dienophiles [2-4] or as dienes [5], have been investigated, and 1,3-dipolar cycloadditions of diazoalkanes are used in the synthesis of cyclopropane derivatives *via* pyrazolines [6].

To our knowledge, different 1,3-dipolar cycloadditions have been reported only in connection with ethyl *N*-acetyl-α,β-dehydroalaninate [7]. This compound reacts with benzonitrile oxide, *C,N*-diphenylnitrone and diazomethane, likewise a normal acrylate system, giving heterocyclic α-acetamido carboxylic acid esters, regiospecifically and in high yields. In principle, these reactions are suitable for the preparation of amino acids, however some problems may arise in the hydrolysis of acetamido group, for example, because of its nucleofugicity in acidic media [7].

We have described recently the chemistry of new α,β-dehydroamino acid derivatives **1** containing the new protection *N*-(diphenylmethylene) (*N*-DPM) [8-11], and it seemed to us of interest to submit these compounds to 1,3-dipolar cycloadditions with nitrile oxides in order to obtain cycloadducts where the amino group should by effectively deblocked in mild, acidic conditions [12].

The dehydroamino acid derivatives **1** have the structural skeleton of 2-azadienes. The contemporary presence of the C,C and N,C double bonds gives rise to a problem of site-selectivity that joins that of regioselectivity one could

Scheme 1



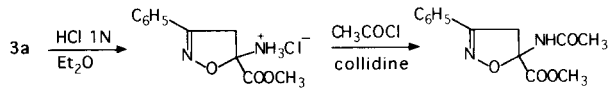
meet in 1,3-dipolar cycloadditions [13]. Site-selectivity has already been observed for a small number of substituted 1-aza and 2-aza conjugated polienes, where the addition to N,C double bond was the preferred reaction [14-20]. In the absence of a systematic treatment of this subject, we were prompted to study the reactions of these potential 1,3-dipolarophiles with nitrile oxides.

As outlined in the Scheme 1, both benzonitrile and 1,1-dimethylethylnitrile oxides **2a** and **2c** react with the dehydroalanine derivatives **1a,b** to give the substituted 4,5-dihydroisoxazole **3a,b,c** in satisfactory yields.

The cycloadditions have been performed following conventional methods using hydroxymic acid chlorides as precursors of nitrile oxides. No traces of different site- and regioisomers have been detected in the reaction mixtures.

The highest yield (90%) has been observed in the reaction of 1,1-dimethylethylnitrile oxide, and this could be ascribed either to the high half-life time of this reagent or to favourable kinetic factors. The ms and ^1H nmr spectra of compounds **3a,b,c** are compatible with the given structures, which have been furtherly confirmed as follows. The DPM protection of **3a** was selectively deblocked by a two-phases hydrolysis (hydrochloric acid 1*N*/diethyl ether, rt) to the 3-phenyl-5-amino-5-carbomethoxy-4,5-dihydroisoxazole **5**, which was then treated with acetylchloride, thus obtaining the known 5-acetamido derivative **6** [7].

Scheme 2



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The success in the deprotection of amino group points out one of the convenient uses of *N*-(DPM)-dehydroamino acids in synthesis.

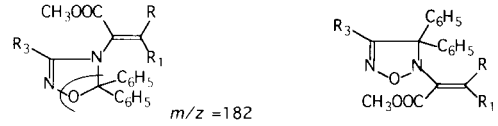
Working the β-substituents as an internal chemical switch, the cycloadditions of benzonitrile oxide to the β-substituted substrates **1c,d,e** occurred exclusively to the N,C double bond. Besides the customary quantities of diphenylfuroxane, only the 4-substituted-5,5-diphenyl-4,5-dihydro-1,2,4-oxadiazoles adducts **4a,c,d** have been isolated. In fact, the (*E*)-β-methyl **1c** and the (*E*)-β-phenyl **1e** react at rt in diethyl ether much faster than the corresponding (*Z*)-isomers **1d,f**; the (*Z*)-β-phenyl **1f** is completely unreactive. Site- and regiospecificities were also observed in the case of the less reactive (*Z*)-**1d**, that gave the corresponding cycloadduct **4c** in only 31% yield after a 100 hours heating in refluxing chloroform. Probably in consequence of adverse steric interactions, none of the compounds **1c-f** gave the cycloaddition with 1,1-dimethylethylnitrile oxide.

TABLE 1

Comp.	Equiv. of R_3-CNO	Temp./Solv.	Reaction Time (h)	Yield(%) [a]
3a	2.0	r.t./Et_2O	20	62
3b	2.0	r.t./Et_2O	20	68
3c	2.0	r.t./$CHCl_3$	48	90
4a	3.0 [b]	r.t./Et_2O	72	84
4b	2.0	r.t./Et_2O	20	83
4c	3.0 [b]	r.t./Et_2O	72	0
	3.0 [b]	reflux/$CHCl_3$	100	31
4d	2.0	r.t./Et_2O	48	43
	3.0 [b]	reflux/$CHCl_3$	72	38
4e	2.0	r.t./Et_2O	48	0
	6.0 [c]	reflux/$CHCl_3$	100	0

[a] Yield of crystallized products. [b] One of them added after 48 hours. [c] Three of them added after 48 hours.

The structures of the compounds **4** were established by submitting **4b**, the product of the cycloaddition of 4-chlorobenzonitrile oxide with **1c**, to X-ray crystallographic analysis. This was necessary in order to exclude unambiguously the alternative, even less probable, regioisomer **7** with the 1,2,5-oxadiazole ring structure. In fact, the structures **4** or **7** could hardly be distinguished by nmr, whereas mass spectroscopy offers some clarification. In a similar case [14], for the identification of an *N*-substituted 3,5-diphenyl-4,5-dihydro-1,2,4-oxadiazole derivative, the presence of the benzoyl cation in the mass spectrum has been assumed as diagnostic since a similar fragment can not derive from the alternative 1,2,5-oxadiazole isomer. The EI-ms spectra of compounds **4a-d** show peaks m/z = 182, which most are probably associated with the benzophenone cation, and the peak of greatest abundance, m/z = 105, which is also probably due to the benzoyl cation. Both are indicative of structure **4**. Conclusive proof could have been found by ms-ms experiments on the peak 182, nevertheless we preferred to submit **4b** to X-ray crystal analysis. The reason for this choice lies in the need to assign definitively the geometries of the C,C double bond of compounds **1c-f**, previously indicated by NOE experiments [9]. The results of the X-ray crystallography of **4b** confirmed the 1,2,4-oxadiazole ring structure as well as the double bond stereochemistry of **4a-c**, and consequently the stereochemistry of their precursors **1c-d**.



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X-ray Structure of **4b**.

The molecular structure of **4b** is shown in Figure 1 together with the atom-numbering scheme. The most important bond distances and angles are given in Table 2.

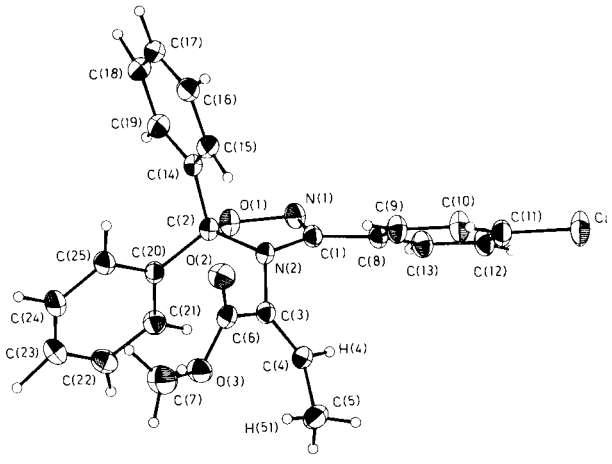

Figure 1. Ortep view of the molecular structure of 4b. The thermal ellipsoids are drawn at the 30% probability level.

In the 4,5-dihydro-1,2,4-oxadiazole ring the bond distances and angles are normal and fall in the range minimum-maximum values found in other 4,5-dihydro-1,2,4-oxadiazole derivatives retrivied from the Cambridge Structural Database (CSD) [21]. The heterocyclic ring adopts a conformation which is intermediate between the "twist" and the "envelope" with the asymmetry parameters $\Delta C_2(C(1)) = 0.0174(9)$ and $\Delta C_S(C(2)) = 0.0366(12)$ [22]. The O(1) and C(2) atoms are 0.117(2) and -0.274(2) Å out of the N(1)C(1)N(2) plane. The four O(1)N(1)C(1)N(2) atoms are coplanar to within 0.026(2) Å and C(2) is 0.373(2) Å out of this plane. The *p*-chlorophenyl ring is tilted with respect to the O(1)N(1)C(1)N(2) moiety by 29.1(1)° nevertheless the C(1)-C(8) and C(1)-N(1) bond distances (1.477(3) and 1.279(3) Å respectively) correspond to the unweighted sample means (1.476(14) and 1.279(8) Å) for a C_{ar}-C=N- conjugated system. The N(2) exocyclic

Table 2

Selected Bond Distances (Å) and Angles (deg) with Estimated Standard Deviations in Parentheses for 4b

O(1)-N(1)	1.429(3)	C(3)-C(6)	1.500(3)
N(1)-C(1)	1.279(3)	C(6)-O(2)	1.199(3)
C(1)-N(2)	1.402(3)	C(6)-O(3)	1.328(3)
N(2)-C(2)	1.492(3)	O(3)-C(7)	1.448(4)
C(2)-O(1)	1.449(2)	C(1)-C(8)	1.477(3)
N(2)-C(3)	1.431(3)	C(2)-C(14)	1.531(3)
C(3)-C(4)	1.327(3)	C(2)-C(20)	1.518(3)
C(4)-C(5)	1.495(4)		
N(1)-O(1)-C(2)	107.0(2)	C(3)-C(6)-O(2)	123.8(2)
O(1)-N(1)-C(1)	106.6(2)	C(3)-C(6)-O(3)	112.0(2)
N(1)-C(1)-N(2)	115.1(2)	O(2)-C(6)-O(3)	124.2(2)
C(1)-N(2)-C(2)	103.1(2)	C(6)-O(3)-C(7)	116.3(3)
O(1)-C(2)-N(2)	102.0(2)	N(1)-C(1)-C(8)	121.1(2)
C(1)-N(2)-C(3)	119.8(2)	N(2)-C(1)-C(8)	123.6(2)
C(2)-N(2)-C(3)	121.6(2)	O(1)-C(2)-C(14)	108.4(2)
N(2)-C(3)-C(4)	122.8(2)	O(1)-C(2)-C(20)	107.8(2)
N(2)-C(3)-C(6)	113.3(2)	N(2)-C(2)-C(14)	110.6(2)
C(4)-C(3)-C(6)	123.6(2)	N(2)-C(2)-C(20)	114.5(2)
C(3)-C(4)-C(5)	128.1(2)	C(14)-C(2)-C(20)	112.9(2)

Table 3

Selected Torsion Angles (deg) with Estimated Standard Deviations in Parentheses for 4b

C(2)-O(1)-N(1)-C(1)	19.3(2)	C(3)-C(4)-C(5)-H(53)	125(4)
O(1)-N(1)-C(1)-N(2)	-4.9(3)	H(4)-C(4)-C(5)-H(51)	175(3)
N(1)-C(1)-N(2)-C(2)	-10.9(3)	H(4)-C(4)-C(5)-H(52)	54(4)
C(1)-N(2)-C(2)-O(1)	21.1(2)	H(4)-C(4)-C(5)-H(53)	-65(4)
N(2)-C(2)-O(1)-N(1)	-24.8(2)	N(2)-C(3)-C(6)-O(2)	-37.1(3)
O(1)-N(1)-C(1)-C(8)	179.1(2)	N(2)-C(3)-C(6)-O(3)	143.8(2)
N(1)-C(1)-N(2)-C(3)	128.1(2)	C(4)-C(3)-C(6)-O(2)	136.5(3)
C(8)-C(1)-N(2)-C(2)	165.0(2)	C(4)-C(3)-C(6)-O(3)	-42.7(3)
C(8)-C(1)-N(2)-C(3)	-56.0(3)	C(3)-C(6)-O(3)-C(7)	177.9(3)
C(1)-N(2)-C(2)-C(14)	-93.9(2)	O(2)-C(6)-O(3)-C(7)	-1.3(4)
C(1)-N(2)-C(2)-C(20)	137.2(2)	C(6)-O(3)-C(7)-H(71)	-45(3)
C(3)-N(2)-C(2)-C(14)	128.1(2)	C(6)-O(3)-C(7)-H(72)	65(3)
C(3)-N(2)-C(2)-C(20)	-0.8(3)	C(6)-O(3)-C(7)-H(73)	-168(3)
C(3)-N(2)-C(2)-O(1)	-116.8(2)	N(1)-C(1)-C(8)-C(9)	147.7(3)
N(1)-O(1)-C(2)-C(14)	91.9(2)	N(1)-C(1)-C(8)-C(13)	-31.0(4)
N(1)-O(1)-C(2)-C(20)	-145.7(2)	N(2)-C(1)-C(8)-C(9)	-27.9(4)
C(2)-N(2)-C(3)-C(4)	117.3(3)	N(2)-C(1)-C(8)-C(13)	153.4(2)
C(2)-N(2)-C(3)-C(6)	-69.1(3)	O(1)-C(2)-C(14)-C(15)	-139.6(2)
C(1)-N(2)-C(3)-C(4)	-14.0(3)	O(1)-C(2)-C(14)-C(19)	44.7(3)
C(1)-N(2)-C(3)-C(6)	159.6(2)	N(2)-C(2)-C(14)-C(15)	-28.6(3)
N(2)-C(3)-C(4)-H(4)	0(1)	N(2)-C(2)-C(14)-C(19)	155.7(2)
N(2)-C(3)-C(4)-C(5)	168.8(3)	O(1)-C(2)-C(20)-C(21)	38.3(3)
C(6)-C(3)-C(4)-H(4)	-173(1)	O(1)-C(2)-C(20)-C(25)	-142.2(2)
C(6)-C(3)-C(4)-C(5)	-4.1(4)	N(2)-C(2)-C(20)-C(21)	-74.4(3)
C(3)-C(4)-C(5)-H(51)	5(3)	N(2)-C(2)-C(20)-C(25)	105.1(3)
C(3)-C(4)-C(5)-H(52)	-115(3)		

substituent occupies the equatorial position and the N(2) atom is out of 0.329(2) Å from the C(1)C(2)C(3) plane. The bond angles involving N(2) show that the nitrogen atom hybridization is intermediate between sp^2 and sp^3. The bulky isocrotonic derivative radical interacts strongly with the equatorial phenyl ring being the C(3) atom eclipsed with respect to the C(20) atom (Table 3).

The dihedral angle between the C(3)C(6)O(2)O(3)C(7) and N(2)C(3)C(6)C(4)H(4)C(5) moieties is 41.2(1)°. The most significant interactions concerning this group are exchanged with the phenyl and *p*-chlorophenyl groups: C(3)...C(20) = 2.878(3), C(6)...C(20) = 3.117(3), C(3)...C(8) = 3.153(3), C(4)...C(8) = 3.183(3) Å. Two relatively strong intramolecular hydrogen bonds (C(5)...O(3) = 2.932(4), H(51)...O(3) = 2.22(5), C(15)...O(2), 3.199(4), H(15)...O(2) = 2.37(3) Å) counterbalance these repulsive interactions. The packing is determined by van der Waals interactions and a very weak hydrogen bond (C(7)...O(2^i) = 3.452(5), H(72)...O(2^i) = 2.51(5) Å, i = 1-x, -y, 1-z) determines dimers.

Summing up, it has been shown that the reactivity of the dehydroamino acids derivatives **1** with nitrile oxides changes as a function of the structures of both reagents, and in every case a high site- and regiochemical control has been observed. Furthermore, the first example of site-selectivity of 1,3-dipolar cycloadditions on the C,C double bond of a conjugate azadiene system has been described. A better understanding of this trend needs a suitable FMO approach, and the work is already in progress. Their specificity and yield values, placed in the normal range of the 1,3-dipolar cycloadditions, make these reactions useful and promising in the synthesis of heterocyclic compounds.

EXPERIMENTAL

All the solvents and reagents were the highest grade commercially available and were used without additional purification. Evaporations *in vacuo* were conducted on a Büchi rotavapor at water aspirator pressures. Column chromatography purifications were performed under "flash" conditions [23] using Merck 230-400 mesh silica gel. Melting points (mp) were taken on a Büchi

Table 4

Fractional Atomic Coordinates (x10^4) and Isotropic Thermal Parameters (Å^2 x 10^4) with Estimated Standard Derivations in Parentheses for the Atoms of 4b

Atom	x/a	y/b	z/c	*U*	Atom	x/a	y/b	z/c	*U*
Cl	5724(1)	1743(1)	-312(1)	1061(4) [a]	C(22)	363(4)	-2289(2)	3555(2)	804(11) [a]
O(1)	-636(2)	-165(1)	2160(1)	627(6) [a]	C(23)	554(5)	-2137(2)	4286(2)	874(12) [a]
O(2)	4785(3)	352(1)	3794(1)	770(7) [a]	C(24)	821(5)	-1284(2)	4552(2)	885(13) [a]
O(3)	5097(3)	-1124(1)	3816(1)	759(6) [a]	C(25)	844(4)	-577(2)	4082(1)	704(10) [a]
N(1)	4(3)	180(1)	1554(1)	620(7) [a]	H(4)	3599(23)	-1008(12)	1754(11)	514(43)
N(2)	2241(2)	113(1)	2510(1)	499(5) [a]	H(51)	6329(56)	-1470(29)	2887(26)	1251(142)
C(1)	1624(3)	285(1)	1769(1)	526(7) [a]	H(52)	6673(64)	-1406(32)	2086(28)	1582(172)
C(2)	635(3)	35(2)	2808(1)	534(7) [a]	H(53)	5578(69)	-2166(35)	2283(29)	1821(181)
C(3)	3656(3)	-482(1)	2725(1)	505(7) [a]	H(71)	6840(56)	-623(30)	4601(23)	1122(151)
C(4)	4209(3)	-1024(2)	2262(1)	570(8) [a]	H(72)	5354(57)	-848(30)	4938(26)	1416(152)
C(5)	5826(4)	-1561(2)	2382(2)	802(11) [a]	H(73)	6583(68)	-1611(35)	4715(27)	1454(162)
C(6)	4560(3)	-358(2)	3500(1)	565(7) [a]	H(9)	4495(33)	1280(17)	2031(15)	720(68)
C(7)	6042(7)	-1073(4)	4560(2)	1019(16) [a]	H(10)	6115(54)	1861(25)	1244(21)	1029(117)
C(8)	2709(3)	623(1)	1272(1)	551(7) [a]	H(12)	2815(37)	585(18)	-479(16)	780(77)
C(9)	4138(4)	1135(2)	1518(1)	692(9) [a]	H(13)	1285(45)	54(22)	349(18)	820(93)
C(10)	5090(4)	1482(2)	1034(2)	803(10) [a]	H(15)	2616(42)	1420(20)	3367(15)	818(84)
C(11)	4574(4)	1294(2)	303(1)	712(10) [a]	H(16)	1831(42)	2759(21)	3869(17)	778(89)
C(12)	3190(4)	771(2)	47(1)	728(9) [a]	H(17)	-968(48)	3077(24)	4004(19)	1058(103)
C(13)	2252(4)	432(2)	531(1)	669(8) [a]	H(18)	-3226(65)	1953(31)	3512(23)	1356(143)
C(14)	176(3)	930(2)	3109(1)	570(7) [a]	H(19)	-2411(46)	646(22)	2945(19)	905(104)
C(15)	1408(4)	1555(2)	3384(1)	648(8) [a]	H(21)	255(31)	-1655(16)	2584(14)	635(63)
C(16)	930(5)	2331(2)	3702(2)	746(11) [a]	H(22)	184(45)	-2823(24)	3332(18)	907(102)
C(17)	-748(5)	2480(2)	3743(2)	820(11) [a]	H(23)	653(50)	-2678(26)	4636(20)	1234(127)
C(18)	-1993(5)	1863(2)	3469(2)	855(12) [a]	H(24)	962(46)	-1161(22)	5081(20)	913(98)
C(19)	-1544(4)	1083(2)	3148(2)	735(10) [a]	H(25)	1036(31)	61(16)	4263(13)	609(60)
C(20)	635(3)	-725(1)	3340(1)	532(7) [a]					
C(21)	435(4)	-1588(2)	3079(2)	659(9) [a]					

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized Uij tensor.

SMP-510 capillary apparatus, and are uncorrected. Infrared spectra (ir) were obtained on a Perkin-Elmer 257 spectrometer and elemental analyses for C, H and N on a Perkin-Elmer CHN analyser 240 C. Mass spectra (EI, 70 eV) were taken on a gc-ms HP 5995 instrument. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded in deuteriochloroform (unless otherwise reported) on a Varian EM 360L spectrometer using TMS as internal standard.

X-ray Data Collection, Structure Determination and Refinement of **4b**.

Compound **4b** ($C_{25}H_{21}ClN_2O_3$) crystallizes in the monoclinic $P2_1/c$ space group with a = 7.931(3), b = 15.044(9), c = 18.740(8) Å, β = 101.29(2)°, V = 2193(2) Å^3, M = 432.906, Z = 4, D_{calcd} = 1.311 g cm^{-3}, F(000) = 904, Ni-filtered Cu-Kα (λ = 1.541838 Å), μ = 17.80 cm^{-1}. Unit cell parameters were determined from the θ values of 30 carefully centered reflections, having 20 < θ < 40°. The intensity data were collected on a Siemens AED diffractometer at 295 K, using the $\theta/2\theta$ scan technique, with a variable scan speed in the range 3-12° min^{-1} and a scan width of (1.20 + 0.142 tan θ)°. The individual profiles were analyzed by the method of Lehmann and Larsen [24]. Intensities were corrected for Lorentz and polarization effects. 4177 unique reflections were measured with θ in the range 3-70° and 3116 having $I \geq 2\sigma(I)$ were used in the refinement. The structure was solved by means of direct and Fourier methods [25] and refined by full-matrix least-squares procedures with anisotropic thermal parameters in the last cycles of the refinement for all the non-hydrogen atoms. The hydrogen atoms were clearly located in a difference map and refined isotropically. After the final cycles, no parameter shifted by more than 0.88 e.s.d. and the biggest remaining peak in the final difference map was equivalent to about 0.24 e Å^{-3} (close to the Cl atom). In the final cycles of refinement a weighting scheme, $w = K[\sigma^2(Fo) + gFo^2]^{-1}$ was used, at convergence the K and g values were 1.0000 and 0.0072 respectively and the goodness of fit 0.8519 (No of refined parameters: 364). The R and R_w values were 0.0538 and 0.0800 respectively. The analytical scattering factors, corrected for the real and imaginary parts of the anomalous dispersion were taken from International Tables for X-ray Crystallography [26]. All calculations were carried out on the GOULD POWERNODE 6040 of the "Centro di Studio per la Strutturistica Diffrattometrica del C.N.R., Parma." The final fractional atomic coordinates and isotropic thermal parameters are given in Table 4.

Reactions of *N*-(Diphenylmethylene)dehydroamino Acid Derivatives **1a-f** with Benzonitrile Oxides **2a,b**. General Procedure for **3a,b** and **4a-d**.

The nitrile oxides were prepared according to a literature method [27]. The solution of the suitable hydroximic acid chloride (20 mmoles) in 40 ml of water was treated under stirring at 0° with sodium hydroxide 14% (60 mmoles). After ten minutes, the nitrile oxide was extracted with diethyl ether or chloroform (2 x 50 ml). The solution of nitrile oxides **2a,b**, containing approximately 20 mmoles in 100 ml, was added with stirring at 0° to the substrate **1a-f** [9] (10 mmoles) dissolved in 30 ml of diethyl ether or chloroform, then the stirring was continued at rt or at reflux for 20-100 hours. In some instances, further quantities of nitrile oxide, obtained as described above, were added. The reaction mixture was then washed with water (2 x 50 ml), dried over sodium sulphate, and evaporated; the residue was fractionated by column flash-chromatography (cyclohexane-ethyl acetate 85:15). The solid compounds were purified further by crystallization. Details on reaction conditions and yields are reported in Table 1.

3-Phenyl-5-carbomethoxy-5-(diphenylmethyleneamino)-4,5-dihydroisoxazole (**3a**).

This compound was obtained as white crystals (ether-petroleum ether), mp 86°; ir (nujol): ν 1735 (C=O), 1615 (N=C) cm^{-1}; ^{1}H nmr: δ 3.53, 4.15 (2d, 2H, CH_2), 3.57 (s, 3H, OCH_3), 7.20-7.67 (m, 15H arom); ms: (m/z) 384 (M$^+$), 325, 204, 180, 77, 103, 208 (100).

Anal. Calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.91; H, 5.29; N, 7.18.

3-Phenyl-5-carbethoxy-5-(diphenylmethyleneamino)-4,5-dihydroisoxazole (**3b**).

This compound was obtained as an oil; ir (chloroform): ν 1725 (C=O), 1620 (N=C) cm^{-1}; ^{1}H nmr: δ 1.10 (t, 3H, CH$_2$-CH_3), 3.50, 4.13 (2d, 2H, CH_2), 4.07 (q, 2H, CH_2-CH$_3$), 7.06-8.15 (m, 15H arom); ms: (m/z) 398 (M$^+$), 325, 218, 208 (100), 180, 77, 103.

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 74.98; H, 5.35; N, 7.20.

(*E*)-Methyl 3-(3-Phenyl-4,5-dihydro-1,2,4-oxadiazol-4-yl)-2-butenoate (**4a**).

This compound was obtained as white crystals (ether-petroleum ether), mp 137°; ir (nujol): ν 1715 (C=O), 1630 (N=C) cm^{-1}; ^{1}H nmr: δ 1.67 (d, 3H, CH_3), 3.40 (s, 3H, OCH_3), 5.95 (q, 1H, =CH-CH$_3$), 7.15-7.95 (m, 15H arom); ms: (m/z) 398 (M$^+$), 216, 182, 321, 77, 157, 105 (100).

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.31; H, 5.52; N, 7.13.

(*E*)-Methyl 3-[3-(4-Chlorophenyl)-4,5-dihydro-1,2,4-oxadiazol-4-yl]-2-butenoate (**4b**).

This compound was obtained as white crystals (ether-petroleum ether), mp 152°; ir (nujol): ν 1715 (C=O), 1635 (N=C) cm^{-1}; ^{1}H nmr: δ 1.66 (d, 3H, CH_3), 3.40 (s, 3H, OCH_3), 5.93 (q, 1H, =CH-CH$_3$), 7.15-7.85 (m, 14H arom); ms: (m/z) 432 (M$^+$), 355, 250, 191, 182, 105 (100), 77.

Anal. Calcd. for $C_{25}H_{21}ClN_2O_3$: C, 69.36; H, 4.89; N, 6.47. Found: C, 69.40; H, 5.57; N, 7.05.

(*Z*)-Methyl 3-(3-Phenyl-4,5-dihydro-1,2,4-oxadiazol-4-yl)-2-butenoate (**4c**).

This compound was obtained as white crystals (ether-petroleum ether), mp 142°; ir (nujol): ν 1715 (C=O), 1630 (N=C) cm^{-1}; ^{1}H nmr: δ 1.63 (d, 3H, CH_3), 3.60 (s, 3H, OCH_3), 6.55 (q, 1H, =CH-CH$_3$), 7.13-8.00 (m, 15H arom); ms: (m/z) 398 (M$^+$), 321, 216, 182, 157, 105 (100), 77.

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.26; H, 5.63; N, 6.92.

(*E*)-Methyl 1-Phenyl-2-(3,5,5-triphenyl-4,5-dihydro-1,2,4-oxadiazol-4-yl)acrylate (**4d**).

This compound was obtained as an oil, ir (chloroform): ν 1715 (C=O), 1605 (N=C) cm^{-1}; ^{1}H nmr: δ 3.13 (s, 3H, OCH_3), 6.45 (s, 1H, =CH-C$_6$H$_5$), 6.63-8.05 (m, 20H arom); ms: (m/z) 460 (M$^+$), 401, 383, 278 (100), 219, 182, 105, 77.

Anal. Calcd. for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08. Found: C, 78.49; H, 5.55; N, 5.90.

3-(1,1-Dimethylethyl)-5-carbomethoxy-5-(diphenylmethyleneamino)-4,5-dihydroisoxazole (**3c**).

The 1,1-dimethylethylnitrile oxide **2c** was prepared *in situ* according to a literature method [28]. To a stirred, ice-cooled solution of 1,1-dimethylethyl-hydroximic acid chloride (2.85 g, 20 mmoles) and **1a** (2.65 g, 10 mmoles) in chloroform (50 ml), 3 ml (20 mmoles) of triethylamine were added. The reaction solution was stirred at rt for 48 hours, then was washed twice with water, dried over sodium sulphate, and evaporated. The residue was fractionated by column flash-chromatography (cyclohexane-ethyl acetate 85:15), obtaining 3.30 g (90%) of **3c** as oil; ir (neat): ν 1735 (C=O), 1625 (N=C) cm^{-1}; ^1H nmr: δ 1.20 (s, 9H, $C(CH_3)_3$), 3.07, 3.70 (2d, 2H, CH_2), 7.03-7.83 (m, 10H arom); ms: (m/z) 364 (M^+), 305, 208, 184 (100), 180, 103, 77.

Anal. Calcd. for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.88; H, 6.76; N, 7.49.

Deprotection of **3a** to 3-Phenyl-5-carbomethoxy-5-amino-4,5-dihydroisoxazole Hydrochloride (**5**).

A solution of **3a** (0.384 g, 1 mmole) in 5 ml of diethyl ether was vigorously stirred at 0° for 2 hours, then at rt for complexive 15 hours with 1.5 ml of 1*N* hydrochloric acid. A time-course tlc analysis (silica gel, cyclohexane-ethyl acetate 8:2) showed the progressive disapparence of **3a** and the contemporary formation of benzophenone. The white solid formed was filtered, washed on the filter with a little of diethyl ether, and crystallized from methanol-diethyl ether, obtaining 0.240 g (94%) of **5**, white crystals, mp 174-175°; ir (nujol): ν 1745 (C=O) cm^{-1}; ^1H nmr (deuteriomethanol): δ 3.90, 4.40 (2d, 2H, CH_2), 4.00 (s, 3H, CH_3), 7.35-8.00 (m, 5H arom).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.01; N, 10.91. Found: C, 51.30; H, 5.42; N, 11.12.

3-Phenyl-5-carbomethoxy-5-acetamido-4,5-dihydroisoxazole (**6**).

To an ice-bath cooled, stirred suspension of **5** (0.128 g, 0.5 mmole) in 2.5 ml of diethyl ether, 0.10 ml (0.75 mmole) of collidine and 0.044 ml (0.75 mmole) of acetyl chloride was added. The reaction mixture was stirred at the ice-bath temperature for 2 hours and at rt until the disapparence of **5** in the tlc monitoring (silica gel, ethyl acetate). The mixture was then washed with 0.5*N* hydrochloric acid (2 ml x 2) and water (2 ml x 2). The etheral solution was dried over sodium sulphate and evaporated, the residue was crystallized from ethyl acetate-diethyl ether to give 0.079 g (70%) of **6**, mp 159°, lit [7] 159°.

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