FUNCTIONALIZED γ-LACTONES *VIA* INTRAMOLECULAR NITRILE *OXIDE CYCLOADDITION.*♥,[1]

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Abstract — The intramolecular nitrile oxide cycloaddition of a series of unsaturated hydroxyimino esters has been investigated. The reaction has been found to be stereospecific, with the configuration of the reacting double bond maintained in the final product. Lack of intramolecular pathway has been observed when R, R_1 or R_2 are hydrogen atoms. AM1 calculation help rationalizes the observed reactions .

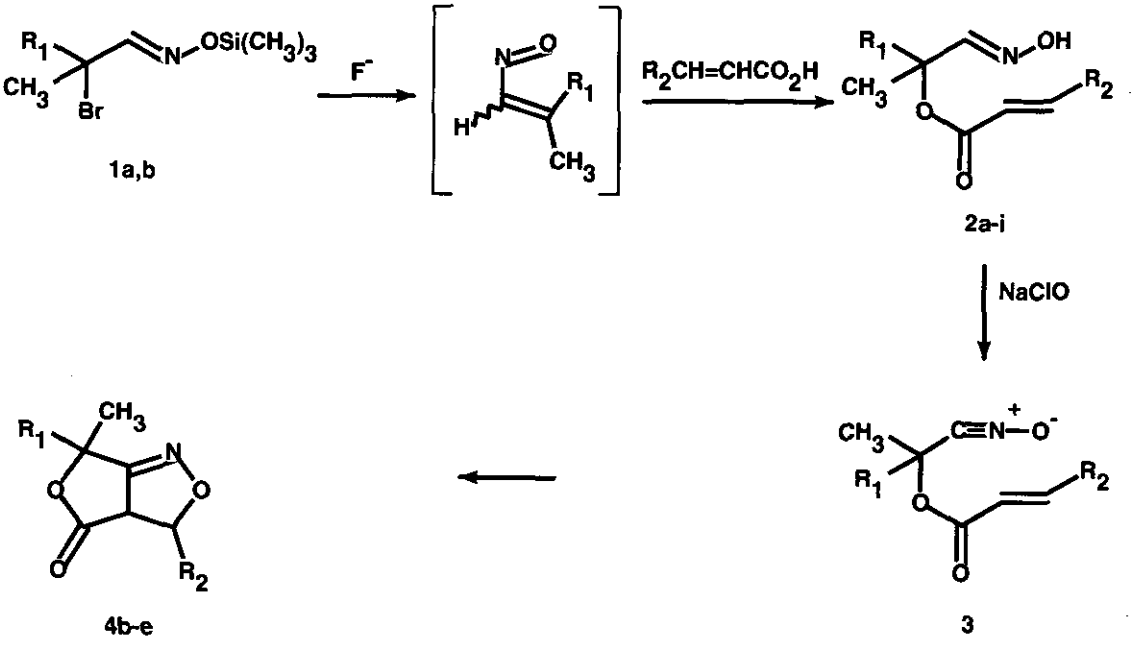
Intramolecular 1,3-dipolar cycloadditions have been successfully exploited.[2-4] These cycloadditions open a large possibilities for the construction of fused heterocycles.[5] A number of dipoles which undergo this reaction have been summarized and the general outlines and potential analogies for these reactions noted.[6] Recently one of us reported that reaction of *O*-trimethylsilyloximes (1) with alcohols affords α-oximino ethers, from which functionalized tetrahydrofurans and tetrahydropyrans, have been obtained *via* intramolecular nitrile oxide cycloaddition (INOC).[7,8]

On the basis of these results we envisioned a new general approach to functionalized γ- and δ-lactones. In particular, substituted γ- and δ-lactones are potentially of interest in medicinal chemistry;[9,10] this is particularly true if these compounds can be prepared in a stereoselective manner.

♥Dedicated to Prof. Giovanni Purrello on the occasion of his 70th birthday.

The overall synthetic approach is based on hydroxyimino esters (**2**), which have been prepared by reaction of a α-brominated *O*-trimethylsilyloximes (**1**) with unsaturated carboxylic acids in the presence of tetrabutylammonium fluoride (TBAF) (Scheme 1).

Scheme 1



As suggested,[8] the conversion occurs *via* nucleophilic addition of the carboxy function to the nitrosoalkene formed by action of fluoride ions on the silyl oximes (**1a,b**) (Scheme 1, Table 1). In fact , in the absence of TBAF , the reaction does not proceed towards compound (**2**), but only decomposition products were obtained .

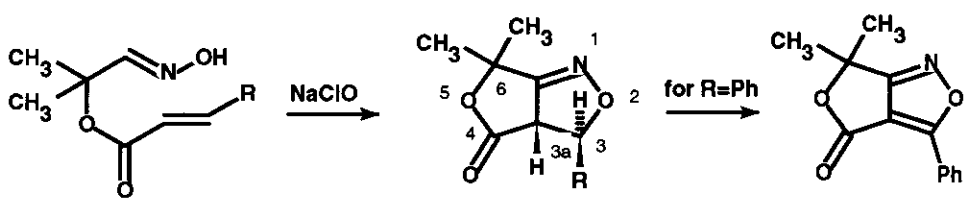
Treatment of derivatives (**2b-e**) with sodium hypochlorite in dichloromethane solution at 0 °C or with *N*-chloro-*N*-sodio-4-methylbenzenesulfonamide (CAT)[5d] in refluxing ethanol gave the bicyclic compounds (**4b-e**) in moderate to good yield (Table 2).

The obtained derivatives have been characterized on the basis of analytical and spectrometric data. FAB spectra show the correct molecular ions. The ir absorption of the carbonyl group is at 1770-1780 cm^{-1} in accord with γ-lactones. The ^1H nmr spectra show the H-3 protons as doublets in the range 4.66-5.70 ppm , while H-3a protons resonate at 3.78-4.55 ppm . Moreover, the methyl groups in the lactone ring (at C-6) show different chemical shifts, while their resonances are coincident in the hydroxyimino ester precursors (**2b-e**).

Table 1. Isolated yields of hydroxyimino esters (**2a-i**) obtained from reaction of *O*-trimethylsilyl-2-bromo oximes **1a,b** with α,β-unsaturated carboxylic acids.

Bromo oxime	R_1	R_2	Hydroxyimino ester	Yield %
1a	Me	H	**2a**	62
1a	Me	Me	**2b**	65
1a	Me	Et	**2c**	60
1a	Me	Pr	**2d**	60
1a	Me	Ph	**2e**	70
1b	H	H	**2f**	50
1b	H	Me	**2g**	50
1b	H	Et	**2h**	55
1b	H	Ph	**2i**	60

Table 2. Isolated yields of lactones (**4b-e**) obtained from reaction of hydroxyimino esters (**2b-e**) with NaClO.



2b-e **4b-e** **15**

Hydroxyimino ester	R	Lactone	Yield %
2b	Me	**4b**	35
2c	Et	**4c**	38
2d	Pr	**4d**	35
2e	Ph	**4e**	68[a]

[a]As sum of the yield of (**4e**) and its aromatic analog (**15**) in the ratio 1:1.

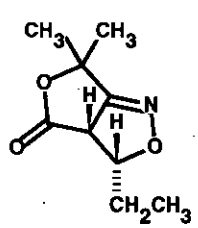
The stereochemical course of these intramolecular ring closures is a point of interest in stereoselective synthesis and has been also investigated. We have found that formation of substituted γ-lactones proceeded with complete

retention of configuration of the reacting double bond.

In particular, reaction of *trans* and *cis* isomers of the hydroxyimino ester (**2c**), gave rise to exclusive cycloadducts (**4c**), and (**5**) respectively, as detected by the ^1H nmr spectra of the crude reaction mixture. Retention of stereochemistry is a common feature of the 1,3-dipolar cycloadditions.

During attempts to establish the scope and limitations of the investigated reaction, we have examined also the structurally related substrates (**2f-i**) which contain different substituents at C-3 and C-7. However, treatment of hydroxyimino esters (**2a**, **2f-i**) in which either R_1 or R_2 or both are H, under the same experimental conditions resulted in tarry mixtures, from which no lactone could be isolated.

We have also tested the possibility of forming stereoselectively a six-membered cyclic lactone by this INOC approach. Unfortunately, reaction of 1-hydroxyimino-2-methylprop-2-yl but-3-enoate (**6**) and 1-hydroxyimino-prop-2-yl but-3-enoate (**7**) did not lead to the expected cycloadducts (δ-lactones). Similar reluctance towards ring closure to δ-lactones had been also shown[11] in intramolecular cycloaddition of glyoxalate ester derivatives of type (**8**) and alkenyl-2-chloro-2(4-chlorophenylhydrazono)acetates (**9**).



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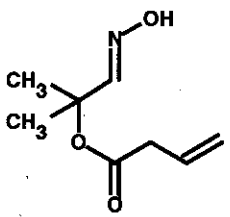

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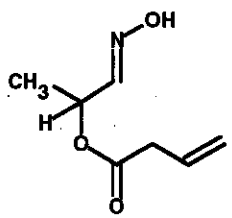

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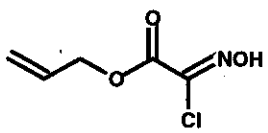

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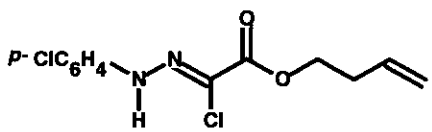

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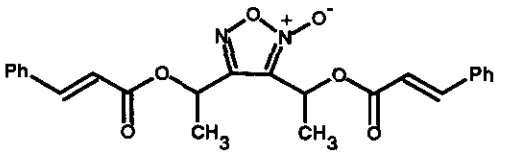
That the lack of intramolecular cycloaddition to form functionalized lactones, in the case of derivatives (**2a**, **2f-i**, **6**, **7**), was not due to the absence of nitrile oxide formation was established by analysis of the reaction mixture.

In a typical experiment, treatment of (**2i**) (R_1= H, R_2= Ph) with NaClO led to a mixture of nitrile oxide oligomers. Chromatographic separation by gel permeation gave the corresponding trimer, tetramer, and pentamer which were

characterized by FAB spectrometry. Conversely, CAT treatment of the above compound led primarily to furoxan (**10**) (nitrile oxide dimer).



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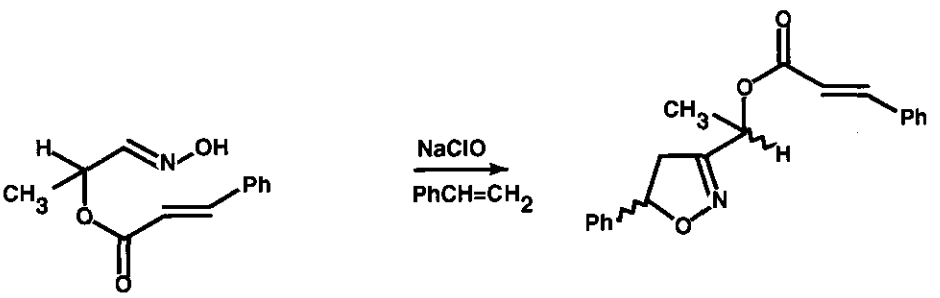
Moreover, the intermediate 1,3-dipole was trapped by cycloaddition reaction with styrene to give isoxazoline (**11**), which has been characterized on the basis of spectrometric data.



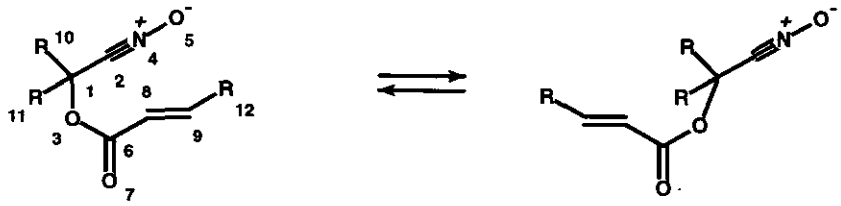
2i 11

The differences in behaviour within the series of the investigated nitrile oxide merits some comments. Altough it is reasonable to think that the propensity to the intramolecular cycloaddition might decrease when increasing the distance between the reacting groups as in the case of hydroxyimino esters (**6**) and (**7**), the failure towards the intramolecular reaction pathway in the case of **2a**, **2f-2i** is somewhat surprising if compared with the formation of **4b-e** from **2b-e**.

Rationalization of these apparently divergent data has been obtained on the following grounds. The most favorable molecular geometry for INOC requires that the C-N-O and alkene moieties lie in two parallel planes on the same side with respect to the R_{3-6} bond (*s-cis*-conformation, Figure 1), and that the dipolar reacting centres are at a favorable distance.

This means that *s-cis*-conformation of (**12**) must be more stable than the *s-trans* one or at least the energy difference between *cis* and *trans* conformers should be sufficiently small to allow a reasonably rapid *cis-trans* equilibrium.

Figure 1



12 ***s-cis*** **12** ***s-trans***

For this aim, among the numerous rotamers deriving from the high molecular flexibility, we selected - with the help of Dreiding models - the conformations more favorable for cycloaddition and optimized their geometries (as well as the geometries of the corresponding *trans* structures) by means of the semiempirical AM1 method.[12] The molecular geometries and the related energies of *s-cis* and *s-trans* conformations, reported in Tables 3 and 4, are in good agreement with the obtained results. Tables 3 and 4 show also the same calculations performed on the nitrile oxides (**13**) and (**14**) derived from α-allyloxypropanal oxime[7] and α-allyloxy-2-methylpropanal oxime[7]respectively. The numbering system adopted in the present study is shown in Figure 1.

13 **14**

Although other stable conformers are possible, we assume that the relative energy difference of the lowest energy conformations of **12** will parallel the energy difference in the transition states leading to the corresponding cycloadducts. For nitrile oxides (**13**) and (**14**), which give rise to bicyclo adducts in very good yields,[7] the *s-cis* stereochemistry shows a torsional angle ($\omega_{6\text{-}3\text{-}1\text{-}2}$) ranging from 63° to 79° and the *s-trans* conformation does not reveal any stable energy minimum.

Nitrile oxide (**3e**) which gave rise to cycloadduct (**4e**) in high yield, showed the *s-cis* form to be more stable by 1.59 Kcal than *s-trans* with a torsional angle ($\omega_{6\text{-}3\text{-}1\text{-}2}$) of 59.1° and with a distance $r_{2\text{-}8}$ and $r_{5\text{-}9}$ of 3.013 and 3.672 Å respectively. These values are more suitable for the cyclization if compared to those of nitrile oxides (**13**) and (**14**) (e.g. **14**: R_{10}= R_{11}= Me; $r_{2\text{-}8}$=2.996 Å; $r_{5\text{-}9}$= 4.367 Å). In the case of nitrile oxide (**3c**), the lower yield of cycloadduct can be explained by the greater stability of the *s-trans* form with respect to the *s-cis* one, though the

distance between interacting centre and the torsional angle ($\omega_{6\text{-}3\text{-}1\text{-}2}$) are comparable to the nitrile oxides (**13**) and (**14**). On the other hand, the lack of cyclization in nitrile oxides (**3a**, **3b-i**) can be justified by the very high stability of the *s-trans* form with respect to the *s-cis* one.

In conclusion, the results reported herein constitute a new facile approach to fused isoxazoline-lactones, altough the reaction appears to suffer from severe limitations linked to the substitution pattern.

Table 3. Optimized geometries of the *s-cis* and *s-trans* conformations of nitrile oxides (**3a**, **3f**, **13**, and **14**) (bond length in Å, angles in degrees, energies in Kcal mol^{-1}).

	3f		**3a**		**13**[a]	**14**[a]
	cis	*trans*	*cis*	*trans*	*cis*	*cis*
$r_{1\text{-}2}$	1.452	1.450	1.456	1.458	1.454	1.459
$r_{1\text{-}3}$	1.430	1.447	1.432	1.453	1.424	1.429
$r_{2\text{-}4}$	1.170	1.169	1.170	1.169	1.169	1.169
$r_{4\text{-}5}$	1.177	1.178	1.178	1.179	1.180	1.180
$r_{3\text{-}6}$	1.380	1.371	1.377	1.368	1.425	1.432
$r_{6\text{-}7}$	1.233	1.233	1.235	1.233	—	—
$r_{6\text{-}8}$	1.466	1.468	1.466	1.471	1.488	1.495
$r_{8\text{-}9}$	1.335	1.334	1.336	1.333	1.330	1.330
$r_{2\text{-}8}$	3.184	—	2.934	—	3.069	2.996
$r_{5\text{-}9}$	5.377	—	4.779	—	4.787	4.367
$r_{1\text{-}10}$	1.524	1.521	1.527	1.525	1.524	1.532
$r_{1\text{-}11}$	1.129	1.128	1.535	1.525	1.131	1.529
$\delta_{2\text{-}1\text{-}3}$	111.0	105.0	112.0	103.5	111.5	111.3
$\delta_{1\text{-}3\text{-}6}$	119.8	118.0	123.5	120.3	115.1	116.8
$\delta_{3\text{-}6\text{-}7}$	110.9	118.6	110.2	119.8	—	—
$\delta_{3\text{-}6\text{-}8}$	121.9	112.6	123.7	111.6	112.5	111.0
$\delta_{6\text{-}8\text{-}9}$	121.3	121.4	121.0	121.4	123.2	123.1
$\omega_{6\text{-}3\text{-}1\text{-}2}$	- 79.1	180.0[b]	-65.1	180.0[b]	-79.9	-63.4
$\omega_{7\text{-}6\text{-}3\text{-}1}$	-173.1	8.2	-168.5	0.2	—	—
$\omega_{8\text{-}6\text{-}3\text{-}1}$	7.3	-173.4	13.4	-179.8	79.2	85.1
$\omega_{9\text{-}8\text{-}6\text{-}3}$	-165.6	180.0[b]	180.0[b]	180.0[b]	-157.0	-161.1
H_f	-22.57	-26.01	-22.73	-27.42	6.70	11.98
$E_{t\text{-}c}$	-3.44		-4.69			

[a]No minimum was obtained for the *trans* conformation. [b]Assumed value.

Table 4. Optimized geometries of the *s-cis* and *s-trans* conformations of nitrile oxides (**3c**, **3e**, **3h**, and **3i**) (bond length in Å, angles in degrees, energies in Kcal mol^{-1}).

	3h		**3c**		**3i**[a]		**3e**[a]	
	cis	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
r_{1-2}	1.451	1.451	1.458	1.459	1.453	1.451	1.456	1.460
r_{1-3}	1.421	1.438	1.431	1.452	1.429	1.438	1.434	1.444
r_{2-4}	1.170	1.169	1.170	1.169	1.170	1.169	1.169	1.169
r_{4-5}	1.178	1.179	1.178	1.179	1.178	1.179	1.179	1.178
r_{3-6}	1.381	1.377	1.379	1.370	1.381	1.376	1.378	1.381
r_{6-7}	1.235	1.233	1.235	1.234	1.233	1.233	1.231	1.233
r_{6-8}	1.462	1.464	1.462	1.468	1.463	1.464	1.468	1.464
r_{8-9}	1.342	1.340	1.342	1.339	1.344	1.343	1.338	1.343
r_{2-8}	3.096	—	3.097	—	3.201	—	3.013	—
r_{5-9}	5.416	—	5.406	—	5.869	—	3.672	—
r_{1-10}	1.518	1.520	1.535	1.524	1.524	1.522	1.534	1.529
r_{1-11}	1.139	1.131	1.525	1.524	1.129	1.131	1.527	1.525
r_{9-12}	1.481	1.480	1.481	1.480	1.456	1.455	1.458	1.456
δ_{2-1-3}	112.8	109.5	111.5	103.5	110.9	109.5	111.2	103.7
δ_{1-3-6}	123.2	118.1	123.4	120.2	119.6	118.1	122.8	121.3
δ_{3-6-7}	110.2	118.3	110.1	119.7	111.0	118.3	110.6	111.3
δ_{3-6-8}	123.1	112.2	123.5	111.6	121.6	112.2	122.7	121.6
δ_{6-8-9}	120.9	120.9	120.8	120.9	120.7	120.7	123.2	121.0
δ_{12-9-8}	122.8	125.2	122.9	125.3	124.7	119.7	123.7	119.7
$\omega_{6-3-1-2}$	68.2	- 91.1	- 69.3	180.0	-81.6	-91.4	-59.1	-155.7
$\omega_{7-6-3-1}$	168.1	-2.3	-164.9	0.	-170.9	-2.1	179.9	146.9
$\omega_{8-6-3-1}$	- 13.6	177.7	17.4	180.0	9.1	177.8	-1.6	-38.4
$\omega_{9-8-6-3}$	176.3	-179.8	-175.1	179.9	-161.6	-179.5	98.1	166.3
$\omega_{12-9-8-6}$	180.0[b]	180.0[b]	180.0[b]	180.0[b]	180.0[b]	180.0[b]	180.0[b]	180.0[b]
H_f	-38.56	-44.64	-39.73	-43.81	-0.10	-5.56	1.70	3.29
E_{t-c}	-6.08		-4.08					

[a]For the phenyl group the standard benzene geometry was assumed (r_{cc} = 1.397 Å; δ_{CCC} = 120°). [b]Assumed value.

EXPERIMENTAL

Mp were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 225 spectrophotometer and ^1H and ^{13}C nmr on Bruker WP 200 SY instrument; chemical shifts are reported in ppm from internal Me_4Si and refer to $CDCl_3$ solutions. Mass spectra were obtained with a double focusing Kratos MS 50S equipped with the standard FAB source and a DS 55 data system. Samples were mixed with glycerol. Reaction mixtures were analyzed by tlc on silica gel GF 254 (Merck) and the spots were detected under uv light (254 nm). Flash chromatography was carried out with Kieselgel 60 (Merck). Gpc analyses were performed on a Waters 6000A apparatus equipped with four ULTRASTYRAGEL columns (in the order 103-, 500-, 500-, and 100-Å pore size). A model R 401 differential refractometer from waters was used as the detector. The analyses were performed at 25 °C in THF.

Preparation of Hydroxyimino Esters (2a-i and 6, 7).

General procedure. To a stirred solution containing 6.8 mmol of α-bromosilyloximes (**1a,b**) and 27.5 mmol of corresponding α,β-unsaturated acid in 30 ml of anhydrous tetrahydrofuran was added, under nitrogen, 6 ml of a 1.0 M of tetrabutylammonium fluoride solution. The solution was stirred at 25 °C for 90 min. At the end of this time the solvent was removed under reduced pressure, and the mixture was taken up in 50 ml of methylene chloride and extracted with water. The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulphate and concentrated under reduced pressure to give a residue which was subjected to silica gel chromatography using a ethyl acetate/hexane 20:80 mixture as eluent.

Reaction of O-trimethylsilyl-2-bromo-2-methylpropanal oxime (**1a**) with 2-propenoic acid. First fractions gave 658 mg of 1-hydroxyimino-2-methylprop-2-yl prop-2-enoate (**2a**), 62% yield ; light yellow oil; ν_{max} 3410, 3090, 2980, 2920, 1715, 1630, 1615, 1400, 1300, 1200, 1120, 1040, 860, 800 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.61 (6H, s), 5.71-6.49 (3H, m), 7.71 (1H, s, C<u>H</u>=N), 9.0 (1H, s, N-O<u>H</u>). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.66; H, 6.97; N, 8.61.

Reaction of O-trimethylsilyl-2-bromo-2-methylpropanal oxime (**1a**) with trans-2-butenoic acid. The major product isolated was *trans* 1-hydroxyimino-2-methylprop-2-yl but-2-enoate (**2b**), 65% yield (755 mg); light yellow oil; ν_{max} 3330,3000, 2960, 1605, 1560, 1495, 1390, 1180, 1140, 980, 945, 755, 690, 600 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.61 (6H,s, CH_3), 1.84 (3H, d, J=7.1 Hz, CH_3), 5.81 (1H, d, J=15.6 Hz, OCOC<u>H</u>), 6.96 (1H, dq, J= 15.6 and 7.1 Hz, C=C<u>H</u>), 7.69 (1H, s,C<u>H</u>=N), 9.1 (1H, s, N-O<u>H</u>). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.30; H, 7.59; N, 8.25.

Reaction of O-trimethylsilyl-2-bromo-2-methylpropanal oxime (**1a**) with trans-2-pentenoic acid. First eluted product was *trans*-1-hydroxyimino-2-methylprop-2-yl pent-2-enoate (**2c**), 60% yield (755 mg); light yellow oil; ν_{max} 3360, 2960, 2920, 2870, 1715, 1600, 1460, 1380, 1340, 1180,1140, 1120, 960, 750 cm^{-1}.^{1}H Nmr: δ ($CDCl_3$) 1.06 (3H, s, J= 7.3 Hz, CH_3), 1.60 (6H, s, CH_3,), 2.31 (2H, m, CH_2), 5.76 (1H, dt, J= 15.7 and 1.5 Hz, OCOCH), 7.07 (1H, dt, J= 15.7 and 7.3 Hz, C=CH), 7.45 (1H, s, CH=N), 8.18 (1H, s, C=NOH); Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.55; H, 8.13; N, 7.25.

Reaction of O-trimethylsilyl-2-bromo-2-methylpropanal oxime (**1a**) with cis-2-pentenoic acid. First fractions gave 730 mg of *cis*-1-hydroxymino-2-methylprop-2-yl pent-2-enoate (**2c**), 58% yield; light yellow oil; ν_{max} 3340, 2940, 2920, 2860, 1710, 1630, 1400, 1380, 1360, 1180, 1120, 950, 810 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.04 (3H, t, J= 7.3 Hz, CH_3), 1.59 (6H, s, CH_3,), 2.43 (2H, m, CH_2), 5.76 (1H, dt, J= 11.7 and 1.5 Hz,OCOCH), 6.37 (1H, dt, J= 11.7 and 7.3 Hz, C=CH), 7.11 (1H, s, CH=N), 7.56 (1H, s, C=NOH); Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.41; H, 8.17; N, 7.48.

Reaction of O-trimethylsilyl-2-bromo-2-methylpropanal oxime (**1a**) with trans-2-hexenoic acid. The major product isolated was *trans*-1-hydroxyimino-2-methylprop-2-yl hex-2-enoate (**2d**), 60% yield (811 mg); light yellow oil; ν_{max} 3340, 2965, 2920, 2860, 1715, 1640, 1400, 1375, 1360, 1130, 1115, 975, 950 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$), 0.93 (3H, t, J= 7.1 Hz, CH_3),1.41 (2H, m, CH_2), 1.59 (6H, s, CH_3), 2.17 (2H, m, CH_2), 5.76 (1H, dt, J= 15.4 and 1.5 Hz, OCOCH),6.94 (1H, dt, J= 15.4 and 7.1 Hz, C=CH), 7.70 (1H, s, CH=N), 7.65 (s, C=NOH); Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.12; H, 8.61; N, 7.32.

Reaction of O-trimethylsilyl-2-bromo-2-methylpropanal oxime (**1a**) with trans-cinnamic acid. First eluted product was *trans*-1-hydroxyimino-2-methylprop-2-yl cinnamoate (**2e**), 70% yield (1.11g); white solid, mp 131-132 °C (from hexane-benzene); ν_{max} 3420, 3060, 2980, 2920, 1718, 1640, 1380, 1360, 1320, 1180, 1130, 950 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.65 (6H, s), 6.38 (1H, d, J=15.8 Hz, OCOCH), 6.73 (1H, s, N-OH), 7.37-7.55 (6H, m, aromatic and olefinic protons), 7.76 (1H, s, CH=N). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.93; H, 6.52; N, 6.32.

Reaction of O-trimethylsilyl-2-bromo-2-methylpropanal oxime (**1a**) with 3-butenoic acid. The major product isolated was 1-hydroxyimino-2-methylprop-2-yl but-3-enoate (**6**), 65% yield (756 mg); light yellow oil; ν_{max} 3420, 3080, 2980, 2920, 1740, 1640, 1260, 1130, 920, 860, 795 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.57 (6H, s),3.07 (2H, dt, J=6.0 and 1.8 Hz, $OCOCH_2$), 5.02-5.31 (2H, m, CH_2), 5.62-6.06 (1H, m), 7.50 (1H, s, CH=N), 8.02 (1H, s, N-OH). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.33; H, 7.52; N, 8.27.

Reaction of O-trimethylsilyl-2-bromopropanal oxime (**1b**) with 2-propenoic acid. The major product isolated was 1-hydroxyiminoprop-2-yl prop-2-enoate (**2f**), 50% yield (486 mg); light yellow oil; ν_{max} 3400, 3080, 2980, 2920, 1718, 1640, 1620, 1400, 1180, 1050, 960, 800 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.45 (3H, d, J= 6.2 Hz), 5.55 (1H, m), 5.89-6.75 (3H, m), 7.47 (1H, d, J= 5.4 Hz, C<u>H</u>=N), 8.30 (1H, s, N-O<u>H</u>). Anal. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.00; H, 6.34; N, 9.76.

Reaction of O-trimethylsilyl-2-bromopropanal oxime (**1b**) with trans-2-butenoic acid . First fractions gave 581 mg of *trans*-1-hydroxyiminoprop-2-yl but-2-enoate (**2g**), yield 50%; light yellow oil; ν_{max} 3420, 3080, 2980, 2920, 1740, 1640, 1260, 1130, 920, 860, 795 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.57 (6H, s),3.07 (2H, dt, J=6.0 and 1.6 Hz, OCOC<u>H</u>$_2$), 5.02-5.31 (2H,m, C<u>H</u>$_2$), 5.62-6.06 (1H, m), 7.50 (1H, s, C<u>H</u>=N), 8.02 (1H, s, N-O<u>H</u>). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18%. Found: C, 56.28; H, 7.49; N, 8.21.

Reaction of O-trimethylsilyl-2-bromopropanal oxime (**1b**) with trans-2-pentenoic acid. The major product isolated was *trans*-1-hydroxyiminoprop-2-yl pent-2-enoate (**2h**), 55% yield (640 mg); light yellow oil; ν_{max} 3320, 2960, 2920, 2870, 1720, 1650, 1460, 1340, 1180, 1120, 1050, 965, 950, 850 cm^{-1}.^1H Nmr: δ ($CDCl_3$) 1.07 (3H, t, J= 7.3 Hz, CH_3), 1.42 (3H, d, J=6.3 Hz, CH_3), 2.20 (2H, m, CH_2), 5.37 (1H, m), 5.70 (1H, dt, J= 15.7 and 1.5 Hz, OCOC<u>H</u>), 7.06 (1H, dt, J= 15.7 and 7.3 Hz, C=C<u>H</u>), 7.45 (1H, d, J=5.5 Hz, C<u>H</u>=N), 8.21 (1H,s, C=NO<u>H</u>). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.31; H, 7.58; N, 8.24.

Reaction of O-trimethylsilyl-2-bromopropanal oxime (**1b**) with trans-cinnamic acid. First fractions gave 893 mg of *trans*-1-hydroxyiminoprop-2-yl cinnamoate (**2i**), 60% yield; light yellow oil; ν_{max} 3480, 3070, 3030, 2920, 1730, 1440, 1450, 1200, 1170, 1050, 920, 770, 720 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.47 (3H, d, J=7.0 Hz, CH_3,), 5.36 (1H, m), 6.42 (1H, d , J=15.7 Hz, OCOC<u>H</u>,), 7.12-7.90 (7H, m, aromatic protons, C<u>H</u> =, and C<u>H</u>=N), 9.17 (s, 1H, N-O<u>H</u>). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.95; H, 5.90; N, 6.10.

Reaction of O-trimethylsilyl-2-bromopropanal oxime (**1b**) with 3-butenoic acid. The major product isolated was 1-hydroxyiminoprop-2-yl but-3-enoate (**7**), 68% yield (726 mg); light yellow oil; ν_{max} 3350, 3080, 2960, 1740, 1660, 1400, 1250, 1160, 1050, 950, 920 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.41 (3H, d, J=7.1 Hz, CH_3), 3.19 (2H, dt, J=6.0 and 1.6 Hz, OCOC<u>H</u>$_2$), 5.08-5.25 (2H, m, C<u>H</u>$_2$), 5.42-6.18 (1H, m), 7.43 (1H, d, J= 5.4 Hz, C<u>H</u>=N), 8.15 (1H, s, N-O<u>H</u>). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.64; H, 7.08; N, 8.65.

Lactonization of Hydroxyimino Esters (2b-e).

General procedure. To a solution of hydroxyimino esters (**2b-e**) (1 mmol) in 30 ml of methylene chloride was added 5 ml of a 4.9% sodium hypochlorite solution at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred vigorously for 1.5 h. At the end of this time the organic layer was washed with water, dried over sodium

sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel plate using a 5% ethyl acetate-cyclohexane mixture as eluent.

Reaction of hydroxyimino ester (**2b**) with NaClO.

The first fractions contained 76 mg of *trans*-3-methyl-6,6-dimethyl-3a-hydro-3*H*,4*H*-furo[3,4-*c*]isoxazol-4-one (**4b**), 35% yield; white solid, mp 140-143°C (from hexane-benzene); ν_{max} 2940, 2930, 1780, 1640, 1450, 1230, 1070, 870 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.68 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.76 (3H, d, J=6.9 Hz, CH_3), 4.18 (1H,d, J=9.7 Hz, H3a), 4.69 (1H, dq, J=9.7 and 6.9 Hz, H3); ^{13}C nmr: δ ($CDCl_3$) 23.84, 24.28, 24.73, 55.87, 79.99, 87.45, 158,20, 166.7. FAB (+) ms: m/z 170 (MH^+). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.67; H, 6.63; N, 8.15.

Reaction of trans hydroxyimino ester (**2c**) with NaClO.

The first fractions contained 70 mg of *trans*-3-ethyl-6,6-dimethyl-3a-hydro-3*H*,4*H*-furo[3,4-*c*]isoxazol-4-one (**4c**), 38% yield; white solid, mp 155-157 °C (from hexane-benzene); ν_{max} 2980, 2930, 1770, 1620, 1460, 1330, 1280, 1140, 910, 840 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 0.99 (3H, t, J=6.7 Hz, CH_3), 1.62 (3H, s, CH_3), 1.70, (2H, m, CH_2), 1.89 (3H, s, CH_3), 3.83 (1H, d, J=9.0 Hz, H3a), 4.98 (1H, dt, J=9.0 and 6.7 Hz, H3); ^{13}C nmr: δ ($CDCl_3$) 9.72, 24.32, 24.79, 26.20, 56.30,80.4, 87.50, 166,18, 167.73. FAB (+) ms: m/z 184 (MH^+). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.75; H, 7.21; N, 7.93.

Reaction of cis hydroxyimino ester (**2c**) with NaClO.

The major fraction was *cis*-3-ethyl-6,6-dimethyl-3a-hydro-3*H*,4*H*-furo[3,4-*c*]isoxazol-4-one (**5**), 38% yield (70 mg); white solid, mp 82-85 °C (from hexane-benzene); ν_{max} 2960, 2920, 1780, 1645, 1500, 1380, 1360, 1240, 1170, 970, 920, 860 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.09 (3H, t, J=7.5 Hz, CH_3), 1.69 (3H, s, CH_3), 1.73, (3H, s, CH_3), 1.95 (2H, m, CH_2), 4.18 (1H, d, J=11.5 Hz, H3a), 4.66 (1H, dt, J=11.5 and 6.7 Hz, H3); ^{13}C nmr: δ ($CDCl_3$) 9.67, 24.33, 24.82, 26.30, 56.38, 80.20, 87.47, 166,20, 167.81. FAB (+) ms: m/z 184 (MH^+). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.02; H, 7.13; N, 7.87.

Reaction of hydroxyimino ester (**2d**) with NaClO.

The major fraction was *trans*-3-propyl-6,6-dimethyl-3a-hydro-3*H*,4*H*-furo[3,4-*c*]isoxazol-4-one (**4d**), 35% yield (69 mg); white solid, mp 105-110 °C (from hexane-benzene); ν_{max} 2960, 2940, 1770, 1660, 1580, 1460, 1380, 1360, 1290, 1130, 920 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 0.94 (3H, t, J=7.1 Hz, CH_3), 1.61 (3H, s, CH_3), 1.87, (3H, s, CH_3), 1.72 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 3.78 (1H, d, J=10.4 Hz, H3a), 4.97 (1H, dt, J=10.4 and 6.1 Hz, H3); ^{13}C nmr: δ ($CDCl_3$) 13.81, 18.23, 24.62, 26.96, 57.00, 80.02, 85.20, 155,00, 166.87. FAB (+) ms: m/z 198 (MH^+). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.03; H, 7.66; N, 6.72.

Reaction of hydroxyimino ester (**2e**) with NaClO.

The first eluted product was 3-phenyl-6,6-dimethylfuro[3,4-*c*]isoxazol-4-one (**15**), 38% yield (87 mg); white solid, mp 180-183 °C (from hexane-benzene); ν_{max} 3040, 2990, 2940, 1795, 1635, 1460, 1390, 1380, 1260, 1230, 1070, 1020, 870, 750 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.66 (3H, s, CH_3), 1.89, (s, 3H, CH_3), 7.36 (s, 5H, aromatic protons). FAB (+) ms: m/z 230 (MH^+). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.83; H, 4.89; N, 6.43. Further eluted product was *trans*-3-phenyl-6,6-dimethyl-3a-hydro-3*H*,4*H*-furo[3,4-*c*]isoxazol-4-one (**4e**), 30% yield (69 mg); white solid, mp 205-208 °C (from hexane-benzene); ν_{max} 3020, 2990, 2940, 1775, 1635, 1460, 1370, 1350, 1250, 1140, 1050, 970, 870 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.71 (3H, s, CH_3), 1.78, (3H, s, CH_3), 4.55 (1H, d, J=11.7 Hz, H3a), 5.70 (1H, d, J=11.7, H3), 7.35 (5H, m, aromatic protons); ^{13}C nmr: δ ($CDCl_3$) 13.81, 18.23, 24.62, 26.96, 57.00, 80.02, 85.20, 155.00, 166.87. FAB (+) ms: m/z 232 (MH^+). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.52; H, 5.71; N, 6.11.

Reaction of hydroxyimino ester (**2i**) with NaClO. First fraction gave a mixture of trimer, tetramer and pentamer of the intermediate nitriloxide that was separated by gel permeation chromatography: FAB (M^-) ms: trimer m/z 652 (M^-); tetramer m/z 867 (M^-); pentamer m/z 1084 (M^-).

Reaction of hydroxyimino ester (**2i**) with styrene and NaClO. First fraction gave an inseparable mixture, 60:40 ratio, of epimeric *trans*-3-(1-cinnamoyloxyethyl)-5-phenylisoxazoline (**11**), 58% yield (186 mg); light yellow oil; ν_{max} 3100-2980, 1720, 1620, 1459, 1200, 1160, 920, 770 cm-1. ^1H Nmr: δ ($CDCl_3$) 1.59 (3H, d, J= 6.6 Hz, CH_3), 1.61 (3H, d, J= 6.6 Hz, CH_3), 3.09-3.37 (4H, m, $4H_4$), 5.57 (2H, dd, J= 8.2 and 11.8 Hz, $2H_5$),5.83 (2H,m, $2CH_3CH$), 6.43 (2H, d, J= 15.7 Hz, OCOCH), 7.34-7.82 (22H, m, aromatic and 2C=CH protons). FAB (+) ms: m/z 322 (MH^+). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.77; H, 5.90; N, 4.38.

Reaction of hydroxyimino esters (2b-e) with *N*-chloro-*N*-sodio-4-methylbenzenesulfonamide.

General procedure.[5d] A solution of hydroxyimino esters (**2b-e**) (1 mmol) was heated in ethanolic solution (30 ml) with chloramine T (1 mmol) for 3 h. The organic solution was filtered. The solvent was removed under reduced pressure to gave an oil which was subjected to silica gel chromatography.

Reaction of hydroxyimino ester (**2b**) with chloramine T. First eluted fraction gave lactone (**4b**), 35% yield.

Reaction of trans hydroxyimino ester (**2c**) with chloramine T. First eluted fraction gave lactone (**4c**), 40% yield.

Reaction of hydroxyimino ester (**2d**) with chloramine T. First eluted fraction gave lactone (**4d**), 38% yield.

Reaction of hydroxyimino ester (**2e**) with chloramine T. First eluted fraction gave lactone (**15**), 40% yield. Further elution gave lactone (**4e**), 30% yield.

Reaction of hydroxyimino ester (**2i**) with chloroamine T. First eluted product was nitriloxide dimer (**10**), 95% yield

(207 mg); light yellow oil; vmax 3050, 3000, 2980, 1760, 1640, 1475, 1355, 1250, 1170, 1050, 920, 770, 720; ^{1}H nmr: δ ($CDCl_3$) 1.71 (3H, d, J=6.6 Hz, CH_3), 5.99 (1H, q, J= 6.6 Hz,CH_3-CH), 6.47 (1H,d, J= 15.7 Hz, OCOCH), 7.26-7.97 (m, 6H, aromatic and =CH protons).

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