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Novel Approach to the Ring-Opening of 4-Isoxazolines: One-Pot Synthesis of α,β-Enones

Ugo Chiacchio,[a] Angelo Liguori,[b] Antonio Rescifina,[a] Giovanni Romeo,[c] Flavia Rossano,[c] Giovanni Sindona[b] and Nicola Uccella[b]

[a]Dipartimento di Scienze Chimiche, Università, 95125 Catania, Italy
[b]Dipartimento di Chimica, Università, 87036 Arcavacata di Rende, Italy
[c]Dipartimento Farmaco-chimico, Università, 98168 Messina, Italy

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Abstract: *Treatment of 4-isoxazoline derivatives with methyl iodide affords α,β-enones in excellent yields. The novel rearrangement pathway, proceeding through an intermediate isoxazolinium salt, is interpretable on the basis of the base removal of the hydrogen atom at N-CH3 group.*

Recently it has been reported that the activation of isoxazolidine nucleus, obtained by quaternization of the nitrogen atom, induces different unimolecular rearrangement pathways leading to new functionalities.[1-9] These reaction routes appear to be controlled by the substitution pattern and by the experimental conditions.[2-5,9-11]

In view of our continuous interest in the investigation of the chemistry of endo- and exocyclic N,O-vinyl functionality as remarkably powerful approach to the formation of carbon-carbon and carbon-oxygen bonds,[12-15] we have applied the similar strategy to the ring-opening process of several 4-isoxazolines easily accessible in good yields from the 1,3-dipolar cycloaddition of nitrones to electron-deficient alkynes.

The reactivity of this ring system is identifiable with the relatively low thermochemical stability of the N-O bond, connected to a π system, which is further weakened with aryl substitution.[12,16] In this way N-aryl- substituted 4-isoxazolines have produced a dazzling array of rearrangement products, giving rise, by thermal treatment, to amines, aziridines, and 1,3-oxazolines according to the substitution patterns.[12,13,17]

On the contrary the examined N-alkyl-substituted derivatives **6-20**, generated from 1,3-dipolar cycloaddition of trisubstituted nitrones **1-5** (Scheme 1) to ethyl propiolate and phenylpropiolate have been proved thermally stable.

Hower, treatment of compounds **6-15**, **17** and **20** with methyl iodide allows the development of a novel and convenient method for the transformation of the five-membered ring of the model

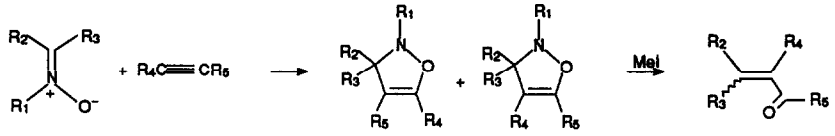
4-isoxazoline compounds into open-chain molecules, through a rearrangement pathway which leads to the one-pot formation of α,β-enones in satisfactory yields.

This paper documents the results of these studies.

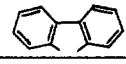
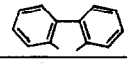
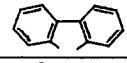
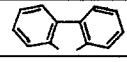
RESULTS AND DISCUSSION

The reaction of nitrones **1-5** with ethyl propiolate and phenylpropiolate was carried out in anhydrous THF at 40° C using a 1:3 relative ratio of dipole-dipolarophile at different times, from 1 to 6 h, according to the substituents. The reaction mixture gave the 4-isoxazolinic adducts **6-20** (Scheme 1).

The relative ratio of regioisomers in the reaction with ethyl propiolate varied with the nature of nitrones; however, the regiochemistry of the cycloaddition processes can be rationalized in terms of a maximum overlap of the nitrone HOMO-dipolarophile LUMO orbitals.[18]



1-5 6-15 16-20 21-31

	R_1	R_2	R_3	R_4	R_5
1, 6, 16, 21, 22	CH_3	CH_3	Ph	H	CO_2Et
7, 23	CH_3	CH_3	Ph	Ph	CO_2Et
2, 8, 17, 24, 30	i-Pr	CH_3	CH_3	H	CO_2Et
9, 25	i-Pr	CH_3	CH_3	Ph	CO_2Et
3, 10, 18, 26	CH_3	$--(CH_2)_5--$		H	CO_2Et
11, 27	CH_3	$--(CH_2)_5--$		Ph	CO_2Et
4, 12, 19, 28	CH_3			H	CO_2Et
13, 29	CH_3			Ph	CO_2Et
5, 14, 20, 28, 31	Ph			H	CO_2Et
15, 29	Ph			Ph	CO_2Et

Scheme 1

The 4-isoxazolinic structures **6-15** were assigned on the basis of analytical and spectroscopic data. Both IR and ^{1}H NMR spectra compare well with the literature data for 4-isoxazolines.[12-14] In particular, for isoxazolines **6, 8, 10, 12, 14**, the regiochemical assignments are based on the chemical shift of the vinyl proton at C-5 in the ^{1}H NMR spectra, which appears as a singlet in the range 6.80-8.03 ppm, because of the deshielding effect of adiacent oxygen atom.[16] In derivatives **17-20**, the vinyl proton at C-4 resonates in the region 5.69 - 6.00 ppm.

Mass spectra support the assigned structures: the 4-substituted regioisomers **6, 8, 10, 12, 14** show the diagnostic fragmentation at M^+ –29 due to loss of CHO radical from the molecular ion, while the 5-ones give rise to an intense peak from the molecular ion by loss of the COCOR fragment.[12] In the case of derivatives **7, 9, 11, 13, 15**, the assignment of regioisomeric structures is unequivocal on the basis of the diagnostic fragmentation from the molecular ion by loss of PhCO radical.[12] These findings are only consistent with the phenyl group located at the position 5 of the heterocyclic ring.

When 4-isoxazolines **6-15, 17** and **20** were heated in anhydrous THF at 40 °C with an excess of methyl iodide, until t.l.c. showed the disappearance of the starting material (1-3 days), the α,β-enones **21-31** were obtained in yields ranging from 75 to 100%, according to the isoxazoline precursor, as shown in Scheme 1.

Structures of the isolated products (see Table) have been assigned on the basis of spectroscopic data, as reported in the experimental section. Moreover, NMR analysis showed that mixtures of *Z* and *E*-isomers were obtained which could be separated in all but one case. NOEDS data allowed to define the exact stereochemistry to the obtained stereoisomers (see experimental).

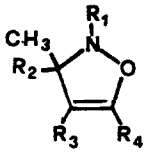
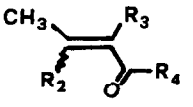
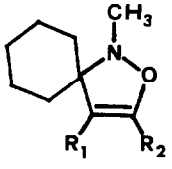
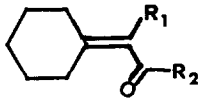
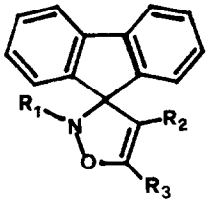
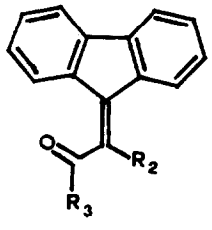
The obtained results are amenable to a ring-opening reaction pathway proceeding from a not isolated isoxazolinium salt formed from 4-isoxazolines under CH_3I treatment. The formation of a positively charged nitrogen atom improves the lability of the N-O bond; then, analogously to isoxazolidinium salts, the process could be rationalized on the basis of a complex redox reaction with the formation of iodine, experimentally ascertained, from the iodide oxidation: the reaction channel probably proceeds through a single electron-transfer mechanism.[5,19]

Alternatively, the isoxazolinium intermediate can collapse to α,β-enone by base removal of the hydrogen atom at N-CH_3 group; subsequently the imminium derivative evolves to the final product by elimination of the nitrogen moiety.[10]

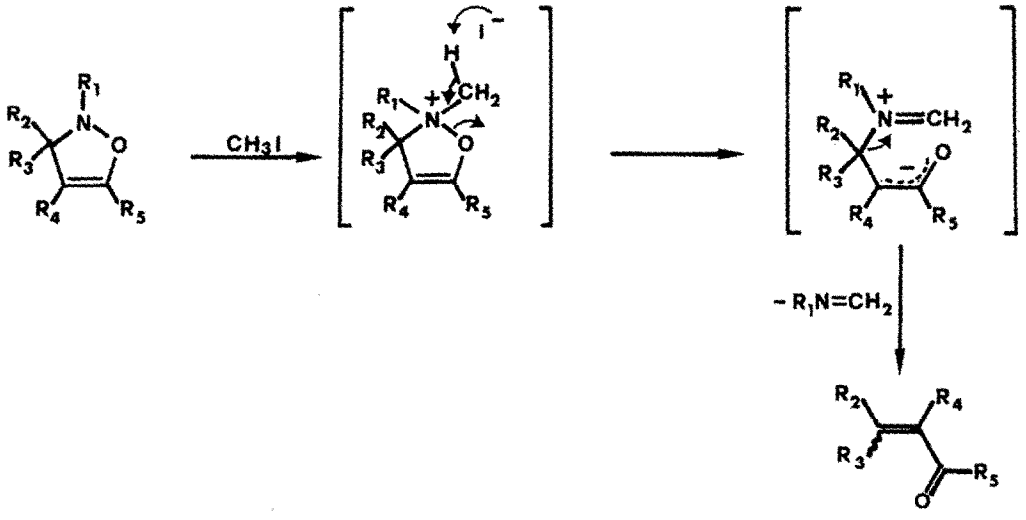
In order to provide additional support to the suggested mechanisms, we have performed the rearrangement process in two steps. In a typical experiment, isoxazoline **11** was treated with methyl triflate in anhydrous CCl_4 at 0 °C for 2 hours. The reaction proceeded quite smoothly and gave rise

in a quantitative yield to 2,2-dimethyl-3-spirocyclohexyl-4-ethoxycarbonyl-5-phenyl-4-isoxazolinium triflate **32**; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.14 (t, 3H, CH_3, J=7.1 Hz), 1.76 (m, 6H, CH_3), 2.33 (m, 4H, CH_2), 3.81 (s, 3H, N-Me), 4.16 (q, 2H, CH_2, J=7.1 Hz), 4.23 (s, 3H, N-Me), 7.34-7.99 (m, 5H, aromatic protons).

Table. Isolated yields of Δ^4-isoxazoline obtained from reaction of nitrones and alkynes, and isolated yields of α,β-enones obtained from isoxazolines and CH_3I.

Δ^4-ISOXAZOLINE(%)					ENONE(%)
					
6 (88%)	R_1=CH_3;	R_2=Ph;	R_3=COOEt;	R_4=H	**21**(10%) (*Z*); 22 (82%) (*E*)
7 (80%)	R_1=CH_3;	R_2=Ph;	R_3=COOEt;	R_4=Ph	**23** (78%) *E/Z* mixture
8 (74%)	R_1=*i*-Pr;	R_2=CH_3;	R_3=COOEt;	R_4=H	**24** (75%)
9 (80%)	R_1=*i*-Pr;	R_2=CH_3;	R_3=COOEt;	R_4=Ph	**25** (100%)
17 (17%)	R_1=*i*-Pr;	R_2=CH_3;	R_3=H;	R_4=COOEt	**30** (91%)
16 (5%)	R_1=CH_3;	R_2=Ph;	R_3=H	R_4=COOEt	
					
10 (82%)	R_1=COOEt;	R_2=H			**26** (75%)
11 (80%)	R_1=COOEt;	R_2=Ph			**27** (80%)
18 (11%)	R_1=H;	R_2=COOEt			
					
12 (70%)	R_1=CH_3;	R_2=COOEt;	R_3=H		**28** (90%)
13 (100%)	R_1=CH_3;	R_2=COOEt;	R_3=Ph		**29** (98%)
14 (70%)	R_1=Ph;	R_2=COOEt;	R_3=H		**28** (85%)
15 (72%)	R_1=Ph;	R_2=COOEt;	R_3=Ph		**29** (95%)
20 (20%)	R_1=Ph;	R_2=H;	R_3=COOEt		**31** (90%)
19 (20%)	R_1=CH_3;	R_2=H;	R_3=COOEt		

This material was readily converted to the expected α,β-enone **27** as exclusive product upon treatment with triethylamine in THF at room temperature for 2 hours. Altough the electron-transfer mechanism cannot be excluded, this result indicates that conversion to α,β–enone proceeds through an ionic pathway promoted by the iodide ion (Scheme 2).



Scheme 2

Furthermore, the 5-substituted 4-isoxazoline **17** has been made to react with methyl iodide in CD_3OD as a solvent. Incorporation of deuterium at the α-position in the obtained α,β-enone confirms that the rearrangement process, starting from the isoxazolinium salt, occurs in two steps and involves the formation of an enolate ion as good leaving group.

In conclusion, in the continuing search of simple and different procedures for functional group transformation of isoxazolines to the open-ring products, the quaternary ammonium cations of isoxazolinium structure have showed new alternatives for the chemical conversion of the primary cycloadducts. The results summarized in the Table show that the two-step sequence outlined in Scheme 1 is an excellent alternative to aldolic condensation or other similar methods for the preparation of α,β-enones.

The novel ring-opening of isoxazoline system can be performed in one step on 1,3-dipolar cycloaddition adducts between nitrones and alkynes, following the chemical activation of the five-membered heterocyclic nucleus by methiodide formation.

EXPERIMENTAL

M.p.s. 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 spectra on Bruker WP 200 SY instrument; chemical shifts are reported in ppm from internal Me_3Si and refer to $CDCl_3$ solutions. NOE measurements were performed by the FT difference method on carefully degassed $CDCl_3$ solutions: the data were obtained by the PAPS sequence. Mass spectra were determined on a Varian Mat CH-5 DF and GC-MS HP 5890 A instruments. Reaction mixtures were analyzed by t.l.c. 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).

Reaction of Nitrones 1-5 with Alkynes.

General procedure. A solution of nitrone (10 mmol) and alkyne (30 mmol) in anhydrous THF (50 ml) was heated at 40 °C, under stirring, until t.l.c. showed the disappearance of the starting nitrone. The solvent was removed at room temperature with rotary evaporator and the residue subjected to flash-chromatography on silica gel column with hexane-ether 60:40 as eluent.

Reaction of α,*N-dimethyl-a-phenylnitrone* **1** *with ethyl propiolate.* Reaction time 1.5 h. First eluted product was *2,3-dimethyl-3-phenyl-4-ethoxycarbonyl-4-isoxazoline* **6**, 88% yield; light yellow oil; ν_{max} 1700, 1630 cm^{-1} ; ^1H NMR: δ ($CDCl_3$) 1.14 (t, 3H, CH_3, J=7.09 Hz), 1.80 (s, 3H, 3-CH_3), 2.57 (s, 3H, N-CH_3), 4.07 (q, 2H, CH_2, J=7.09 Hz), 7.22-7.56 (m, 5H, aromatic protons), 7.43 (s, 1H, 5-H); ^{13}C NMR: δ ($CDCl_3$) 6.96, 25.24, 45.48, 74.60, 108.90, 112.86, 113.29-113.89, 126.65, 152.00, 164.10; MS: *m/z* 247 (M^+, 10%), 232 (100), 218 (35), 204 (31), 184 (10), 174 (11), 142 (36), 129 (17), 118 (51), 115 (35), 91 (16), 77 (44). (Found: C, 68.05; H, 6.97; N, 5.62%. Calc. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66%). Further elution gave *2,3-dimethyl-3-phenyl-5-ethoxycarbonyl-4-isoxazoline* **16**, 5% yield; light yellow oil; ^1H NMR: δ ($CDCl_3$) 1.10 (t, 3H, CH_3, J=7.10 Hz), 1.82 (s, 3H, 3-CH_3), 2.56 (s, 3H, N-CH_3), 4.05 (q, 2H, CH_2, J=7.1 Hz), 5.68 (s, 1H, 4-H), 7.22-7.60 (m, 5H, aromatic protons); MS: *m/z* 247 (M^+, 18%), 232 (22), 218 (13), 172 (50), 145 (38), 144 (100), 117 (20), 114 (57), 105 (15), 102 (10), 91 (31), 77 (13). (Found: C, 68.02; H, 6.98; N, 5.63%. Calc. for $C_{14}H_{17}NO_3$: C, 67.9; H, 6.93; N, 5.66%).

Reaction of α,*N-dimethyl-α-phenylnitrone* **1** *with ethyl phenylpropiolate.* Reaction time 2.5 h. Cromatographic purification gave *2,3-dimethyl-3,5-diphenyl-4-ethoxy carbonyl-4-isoxazoline* **7**, 80% yield; light yellow solid, m.p. 90 °C; ν_{max} 1705, 1630 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.94 (t, 3H, CH_3, J=7.18 Hz), 1.88 (s, 3H, 3-CH_3), 2.64 (s, 3H, N-CH_3), 3.99 (q, 2H, CH_2, J=7.18 Hz), 7.23-7.77 (m, 10H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 13.63, 20.68, 38.47, 59.47, 84.69, 108.99, 127.10, 127.29, 127.71, 127.92, 129.35, 130.60, 142.29, 162.90, 164.07; MS: *m/z* 323 (M^+, 8%), 308 (35), 305 (35), 280 (15), 250 (31), 246 (21), 233 (40), 218 (25), 191 (16), 144 (16), 118 (32), 104 (100), 89 (20), 77 (63). (Found: C, 74.4; H, 6.5; N, 4.2%. Calc. for $C_{20}H_{21}NO_3$: C, 74.32; H, 6.55; N, 4.33%).

Reaction of α,α*-dimethyl-N-isopropylnitrone* **2** *with ethyl propiolate.* Reaction time 1.5 h. First eluted product was *2-isopropyl-3,3-dimethyl-4-ethoxycarbonyl-4-isoxazoline* **8**, 74% yield; light yellow oil; ν_{max} 1670, 1615 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.18 (d, 6H, CH_2, J=6.1 Hz), 1.26 (t, 3H, CH_3, J=6.9 Hz), 1.48 (s, 6H, 3-CH_3), 3.33 (m, 1H, N-CH), 4.16 (q, 2H, CH_2, J=6.9 Hz), 7.24 (s, 1H, 5-H); ^{13}C NMR: δ ($CDCl_3$) 14.15, 21.01, 23.95, 59.26, 67.06, 115.16, 152.55, 168.14; MS: *m/z* 213 (M^+, 2%), 198 (33), 184 (13), 156 (100), 128 (34), 110 (7), 82 (5), 67 (6), 56 (9). (Found: C, 62.00; H, 8.96; N, 6.59%. Calc. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57%). Further elution gave

2-isopropyl-3,3-dimethyl-5-ethoxycarbonyl-4-isoxazoline **17**, 17% yield; light yellow oil; ν_{max} 1680,1620 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.19 (d, 6H, CH_3, J=6.07 Hz), 1.20 (t, 3H, CH_3, J=6.9 Hz), 1.36 (s, 6H, 3-CH_3), 3.35 (m, 1H, N-CH), 4.23 (q, 2H, CH_2, J=6.9 Hz), 5.69 (s, 1H, 4-H); ^{13}C NMR: δ ($CDCl_3$) 13.94, 21.01, 24.74, 52.48, 60.94, 67.23, 119.0, 146.20, 164.22; MS: *m/z* 213 (M^+, 30%), 198 (33), 156 (100), 140 (31), 112 (11), 108 (31), 70 (34), 59 (15). (Found: C, 61.97; H, 8.92; N, 6.61%. Calc. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57%).

Reaction of α,α*-dimethyl-N-isopropylnitrone* **2** *with ethyl phenylpropiolate.* Reaction time 3 h. Chromatographic separation gave *2-isopropyl-3,3-dimethyl-4-ethoxycarbonyl-5-phenyl-4-isoxazoline* **9**, 80% yield; pale yellow solid m.p. 51-2 °C; ν_{max} 1675, 1620 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.11 (t, 3H, CH_3, J=6.85 Hz), 1.25 (d, 6H, CH_3, J=6.72 Hz), 1.57 (s, 6H, 3-CH_3), 3.41 (m, 1H, N-CH), 4.10 (q, 2H, CH_2, J=6.85 Hz), 7.27-7.66 (m, 5H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 13.85, 20.98, 24.05, 29.61, 52.69, 59.40, 69.69, 109.77, 127.62, 129.23, 130.20, 141.20, 162.50, 166.20; MS: *m/z* 289 (M^+, 3%), 274 (54), 232 (100), 204 (27), 186 (23), 184 (17), 105 (65), 77 (45). (Found: C, 70.6; H, 8.06; N, 5.0%. Calc. for $C_{17}H_{23}NO_3$: C, 70.55; H; 8.00; N, 4.84%).

Reaction of N-methyl-cyclohexylidenimine-N-oxide **3** *with ethyl propiolate.* Reaction time 1.5 h. First eluted fractions gave *cyclohexanespiro-3'-(2'-methyl-4'-ethoxycarbonyl-4'-isoxazoline)* **10**, 82% yield; light yellow solid, m.p. 45° C; ν_{max} 1705, 1610 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.27 (t, 3H, CH_3, J=7.06 Hz), 1.60-2.09 (m, 10H, CH_2), 2.70 (s, 3H, N-CH_3), 4.15 (q, 2H, CH_2, J=7.06 Hz), 7.33 (s, 1H, 5-H); ^{13}C NMR: δ ($CDCl_3$) 13.54, 22.00, 24.56, 38.89, 58.71, 68.77, 112.15, 153.19, 162.99; MS: *m/z* 225 (M^+, 23%), 196 (23), 182 (43), 179 (100). (Found: C, 63.6; H, 8.6; N, 6.1%. Calc. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22%). Further elution gave *cyclohexanespiro-3'-(2'-methyl-5'-ethoxycarbonyl-4'-isoxazoline)* **18**, 11% yield; yellow oil; ν_{max} 1710, 1625 cm^{-1} ;^1H NMR: δ ($CDCl_3$) 1.41 (t, 3H, CH_3, J=7.8 Hz), 1.62-2.01 (m, 10H, CH_2), 2.69 (s, 3H, N-CH_3), 4.25 (q, 2H, CH_2, J=7.8 Hz), 6.00 (s, 1H, 4-H); ^{13}C NMR: δ ($CDCl_3$) 13.79, 23.08, 25.21, 38.24, 60.90, 71.61, 114.35, 144.74, 170.61; MS: *m/z* 225 (M^+, 11%), 182 (100), 169 (11), 154 (20), 124 (7), 97 (13), 82 (12), 68 (20). (Found: C, 63.36; H, 8.58; N, 6.28%. Calc. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22%).

Reaction of N-methyl-cyclohexylidenimine-N-oxide **3** *with ethyl phenylpropiolate.* Reaction time 1 h. First fractions gave *cyclohexanespiro-3'-(2'-methyl-4'-ethoxycarbonyl-5'-phenyl-4'-isoxazoline)* **11**, 80% yield; light yellow solid, m.p. 50 °C; ν_{max} 1710, 1615 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.09 (t, 3H, CH_3, J=7.1 Hz), 1.26-2.18 (m, 10H, CH_2), 2.77 (s, 3H, N-CH_3), 4.08 (q, 2H, CH_2, J=7.1 Hz), 7.24-7.62 (m, 5H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 13.60, 22.45, 25.17, 38.79, 59.38, 72.32, 107.35, 127.43, 128.74, 129.01, 130.04, 162.14, 164.43; MS: *m/z* 301 (M^+, 20%), 283 (100), 258 (83), 254 (26), 238 (15), 230 (21), 211 (94), 210 (73), 196 (32), 183 (48), 182 (35), 167 (21), 166 (18), 139 (22), 128 (16), 115 (37), 105 (64), 76 (54). (Found: C, 71.4; H, 7.6; N, 4.8%. Calc. for C_{18} $H_{23}NO_3$: C, 71.74; H, 7.69; N, 4.65%).

Reaction of N-methyl-fluorenonimine-N-oxide **4** *with ethyl propiolate.* Reaction time 6 h. First eluted product was *spiro[fluorene-9,3'-(2'-methyl-4'-ethoxycarbonyl-4'-isoxazoline)]* **12**, 70% yield; light yellow solid, m.p. 129-33 °C; ν_{max} 1710, 1665 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.85 (t, 3H, CH_3, J=7.0 Hz), 2.60 (s, 3H, N-CH_3), 3.90 (q, 2H, CH_2, J=7.0 Hz), 7.35-7.95 (m, 8H, aromatic protons), 7.55 (s, 1H, 5-H); MS: *m/z* 307 (M^+, 20%), 278 (20), 249 (44), 205 (28), 204 (49), 181 (33), 177 (49), 176 (100). (Found: C, 74.4; H, 5.7; N, 4.6%. Calc. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56%). Further eluted fractions gave *spiro[fluorene-9,3'-(2'-methyl-5'-ethoxycarbonyl-4'-isoxazoline)]* **19**, 20% yield; yellow oil; ν_{max} 1700, 1625 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.36 (t, 3H, CH_3, J=7.8 Hz), 2.36 (s, 3H, N-CH_3), 4.28 (q, 2H, CH_2, J=7.8 Hz), 5.81 (s, 1H, 4-H), 7.3-7.83 (m, 8H, aromatic protons); MS: *m/z* 307 (M^+, 30%), 206 (30), 177 (100), 181 (22), 135 (26). (Found: C, 74.31; H, 5.61; N, 4.51%. Calc. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56%).

Reaction of N-methyl-fluorenonimine-N-oxide **4** *with ethyl phenylpropiolate.* Reaction time 6 h. First eluted product was *spiro[fluorene-9,3'-(2'-methyl-4'-ethoxycarbonyl-5'-phenyl-4'-isoxazoline)]* **13**, 100% yield, light yellow oil; ν_{max} 1700, 1625 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.60 (t, 3H, CH_3, J=7.0 Hz), 2.50 (s, 3H, N-CH_3), 3.65 (q, 2H, CH_2, J=7.0 Hz), 7.15-8.10 (m, 13H, aromatic protons); MS: *m/z* 383 (M^+, 34%), 310 (17), 306 (12), 278 (35), 154 (15), 105 (100), 77 (45). (Found: C, 78.29; H, 5.48; N, 3.60%. Calc. for $C_{25}H_{21}NO_3$: C, 78.27; H, 5.52; N, 3.65%).

Reaction of N-phenyl-fluorenonimine-N-oxide **5** *with ethyl propiolate.* Reaction time 3 h. First elution gave *spiro[fluorene-9,3'-(2'-phenyl-4'-ethoxycarbonyl-4'-isoxazoline)]* **14**, 70% yield; light yellow solid, m.p. 93-4 °C; ν_{max} 1715, 1630 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.85 (t, 3H, CH_3, J=7.1 Hz), 3.90 (q, 2H, CH_2, J=7.1 Hz), 6.48-7.93 (m, 13H, aromatic protons), 8.03 (s, 1H, 5-H); MS: *m/z* 369 (M^+, 21%), 340 (12), 296 (18), 292 (32), 260 (17), 181 (100). (Found: C, 78.0; H, 5.2; N, 3.6%. Calc. for $C_{24}H_{19}NO_3$: C, 78.04; H, 5.18; N, 3.79%). Further fractions gave *spiro[fluorene-9,3'-(2-phenyl-5'-ethoxy carbonyl-4'-isoxazoline)]* **20**, 20% yield; yellow solid, m.p. 83-4 °C; ν_{max} 1730, 1640 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.33 (s, 3H, CH_3, J=7.0 Hz), 4.33 (q, 2H, CH_2, J=7.0 Hz), 5.73 (s, 1H, 4-H), 6.5-7.6 (m, 13H, aromatic protons); MS: *m/z* 396 (M^+, 26%), 296 (30), 268 (74), 192 (17), 180 (13), 165 (100), 104 (92), 77 (31). (Found: C, 78.0; H, 5.2; N, 3.6%. Calc. for $C_{24}H_{19}NO_3$: C, 78.02; H, 5.20; N, 3.70%).

Reaction of N-phenyl-fluorenonimine-N-oxide **5** *with ethyl phenylpropiolate.* Reaction time 3 h. First fractions gave *spiro[fluorene-9,3'-(2',5'-diphenyl-3-spiro-(9-fluorenyl)-4'-ethoxycarbonyl-4'-isoxazoline)]* **15**, 72% yield; pale yellow oil; ν_{max} 1700, 1660 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.53 (t, 3H, CH_3, J=7.1 Hz), 3.61 (q, 2H, CH_2, J=7.1 Hz), 6.51-8.02 (m, 18H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 12.94, 59.19, 83.68, 106.82, 116.48, 119.51, 123.12, 125.28, 127.10, 127.56, 127.91, 128.86, 129.45, 131.00, 140.51, 145.51, 146.13, 162.30, 163.12; MS: *m/z* 445 (M^+, 20%), 340 (23), 241 (27), 190 (11), 181 (32), 165 (11), 164 (20), 105 (100), 77 (42). (Found: C, 80.81; H, 5.22; N, 3.07%. Calc. for $C_{30}H_{23}NO_3$: C, 80.87; H, 5.20; N, 3.14%).

Rearrangement of Isoxazolines.

General procedure. A solution of isoxazoline (1 mmol) and iodomethane (3 ml) in anhydrous THF (20 ml) was heated at 40 °C under stirring for a period of 1-3 days. The solvent was removed at reduced pressure and the residue was subjected to flash-chromatography on silica gel column with cyclohexane-ethyl acetate 97:3 as eluent.

Reaction of isoxazoline **6** *with iodomethane.* Reaction time 1 day. First fractions gave (Z) *ethyl 2-formyl-3-methyl-cinnamate* **21**, 10% yield; light yellow oil; ν_{max} 1670, 1615 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.39 (t, 3H, CH_3, J=7.2 Hz), 2.55 (s, 3H, CH_3), 4.39 (q, 2H, CH_2, J=7.2 Hz), 6.92-7.62 (m, 5H, aromatic protons), 10.07 (s, 1H, CHO); ^{13}C NMR: δ ($CDCl_3$) 13.22, 19.94, 60.66, 126.10, 128.05, 129.27, 131.60, 133.70, 165.12, 187.05; MS: *m/z* 218 (M^+, 25%), 189 (6), 172 (33), 145 (15), 144 (100), 117 (18), 116 (42), 115 (77), 105 (16), 77 (18). (Found: C, 71.32; H, 6.52%. Calc. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46%). Further elution gave (E) *ethyl 2-formyl-3-methyl-cinnamate* **22**, 82% yield; light yellow oil; ν_{max} 1670, 1615 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.36 (t, 3H, CH_3, J=7.25 Hz), 2.34 (s, 3H, CH_3), 4.36 (q, 2H, CH_2, J=7.25 Hz), 6.9-7.58 (m, 5H, aromatic protons), 9.35 (s, 1H, CHO); ^{13}C NMR: δ ($CDCl_3$) 13.82, 23.61, 61.12, 126.67, 128.25, 128.81, 129.27, 138.2, 160.01, 188.75; MS: *m/z* 218 (M^+, 7%), 216 (21), 173 (30), 172 (72), 145 (28), 144 (100), 117 (18), 116 (45), 115 (96), 103 (15), 91 (16), 77 (12). (Found: C, 71.35; H, 6.51%. Calc. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46%).

Reaction of isoxazoline **7** *with iodomethane.* Reaction time 1 day. (E) + (Z) *ethyl 2-benzoyl-3-methyl-cinnamate* **23** have been obtained as not separable mixture, 78% yield; light yellow solid; ν_{max} 1710, 1695 cm^{-1}; ^1H NMR: δ ($CDCl_3$) (Z: Minor Isomer) 0.85 (t, 3H, CH_3, J=7.10 Hz), 2.07 (s, 3H, CH_3), 3.90 (q, 2H, CH_2, J=7.10 Hz), 7.11-7.80 (m, 10H,

aromatic protons); (*E*: Major Isomer) 1.09 (t, 3H, CH_3, J=7.19 Hz), 2.59 (s, 3H, CH_3), 4.16 (q, 2H, CH_2, J=7.19 Hz), 7.11-7.80 (m, 10H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 12.13, 20.91, 59.11, 125.65, 126.48, 127.23, 131.07, 154.11, 164.40, 192.01; MS: *m/z* 294 (M^+, 22%), 186 (16), 158 (43), 115 (9), 105 (100), 77 (60).

Reaction of isoxazoline **8** *with iodomethane.* Reaction time 2 days. *Ethyl 2-formyl-3-methyl-crotonate* **24**; 75% yield; light yellow oil; ν_{max} 1675, 1615 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.32 (t, 3H, CH_3, J=7.1 Hz), 2.08 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.29 (q, 2H, CH_2, J=7.1 Hz), 9.95 (s, 1H, CHO); ^{13}C NMR: δ ($CDCl_3$) 13.63, 20.21, 24.14, 60.51, 133.00, 160.29, 168.20, 187.45; MS: *m/z* 156 (M^+, 3%), 128 (34), 113 (25), 111 (69), 100 (42), 85 (47), 83 (76), 82 (100), 67 (62), 55 (52). (Found: C, 61.59; H, 7.77%. Calc. for $C_8H_{12}O_3$: C, 61.52; H, 7.74%).

Reaction of isoxazoline **9** *with iodomethane.* Reaction time 2 days. *Ethyl 2-benzoyl-3-methyl-crotonate* **25**; 100% yield; light yellow oil; ν_{max} 1705, 1690 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.00 (t, 3H, CH_3, J=7.2 Hz), 1.80 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.06 (q, 2H, CH_2, J=7.2 Hz), 7.41-7.93 (m, 5H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 13.57, 21.91, 23.75, 60.06, 128.40, 128.64, 129.20, 133.02, 137.07, 154.11, 164.40, 192.00; MS: *m/z* 232 (M^+, 12%), 186 (16), 158 (43), 115 (9), 105 (100), 77 (60), 67 (22). (Found: C, 72.36, H, 6.97%: Calc. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94%).

Reaction of isoxazoline **10** *with iodomethane.* Reaction time 2 days. *Ethyl 2-formyl-cyclohexylidenacetate* **26**, 75% yield; light yellow oil; ν_{max} 1710, 1695 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.31 (t, 3H, CH_3, J=7.0 Hz), 1.43-2.96 (m, 10H, CH_2), 4.30 (q, 2H, CH_2, J=7.0 Hz), 9.92 (s, 1H, CHO); MS: *m/z* 196 (M^+, 20%), 167 (23), 150 (62), 122 (100), 107 (24), 105 (7), 94 (51), 80 (30), 77 (29), 67 (25), 53 (20). (Found: C, 67.52; H, 8.26%: Calc. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%).

Reaction of isoxazoline **11** *with iodomethane.* Reaction time 3 days. *Ethyl 2-benzoyl-cyclohexylidenacetate* **27**, 80% yield; light yellow oil; ν_{max} 1740, 1715 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.02 (t, 3H, CH_3, J=7.23 Hz), 1.43-2.96 (m, 10H, CH_2), 4.09 (q, 2H, CH_2, J=7.23 Hz), 7.41-7.99 (m, 5H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 13.74, 26.00, 28.14, 31.20, 33.84, 128.53-129.96, 133.17, 137.49, 160.71, 164.80; MS: *m/z* 272 (M^+, 8%), 226 (18), 198 (77), 170 (14), 142 (9), 105 (100), 77 (54). (Found: C, 74.92; H, 7.37%. Calc. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%).

Reaction of isoxazoline **12** *with iodomethane.* Reaction time 3 days. *Ethyl 2-formyl(9-fluorenyliden)acetate* **28**, 90% yield; light yellow oil; ν_{max} 1730, 1690 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 0.95 (t, 3H, CH_3, J=7.0 Hz), 4.10 (q, 2H, CH_2, J=7.0 Hz), 6.70-7.50 (m, 8H, aromatic protons), 10.20 (s, 1H, CHO); ^{13}C NMR: δ ($CDCl_3$) 13.47, 59.13, 126.17-127.98, 161.57, 164.23, 187.24; MS: *m/z* 278 (M^+, 23%), 249 (40), 233 (16), 176 (100), 165 (30), 151 (27), 150 (27), 88 (26). (Found: C, 76.60; H, 5.12%. Calc. for $C_{18}H_{14}O_3$: C, 76.68; H, 5.07%).

Reaction of isoxazoline **13** *with iodomethane.* Reaction time 3 days. *Ethyl 2-benzoyl-(9-fluorenyliden)acetate* **29**, 98% yield; light yellow oil; ν_{max} 1705, 1665 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.21 (t, 3H, CH_3, J=7.0 Hz), 4.33 (q, 2H, CH_2, J=7.0 Hz), 6.93-8.20 (m, 13H, aromatic protons); ^{13}C NMR: δ ($CDCl_3$) 13.83, 59.27, 125.73-128.27, 161.34, 163.58; MS: *m/z* 354 (M^+, 24%), 325 (23), 253 (14), 252 (13), 176 (17), 105 (100), 77 (45). (Found: C, 81.29; H, 5.22%. Calc. for $C_{24}H_{18}O_3$: C, 81.34, H, 5.2%).

Reaction of isoxazoline **14** *with iodomethane.* Reaction time 2 days. *Ethyl 2-formyl-(9-fluorenyliden)acetate* **28**, 85% yield.

Reaction of isoxazoline **15** *with iodomethane.* Reaction time 2 days. *Ethyl 2-benzoyl-(9-fluorenyliden)acetate* **29**, 95% yield.

Reaction of isoxazoline **17** *with iodomethane.* Reaction time 2 days. *Ethyl 2-oxo-4-methyl-3-pentenoate* **30**, 91% yield; light yellow oil; ν_{max} 1705, 1695, 1685 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.37 (t, 3H, CH_3, J=7.3 Hz), 2.02 (d, 3H, CH_3, J=1.4 Hz), 2.25 (d, 3H, CH_3, J=0.68 Hz), 4.31 (q, 2H, CH_2, J=7.3 Hz), 6.76 (m, 1H); ^{13}C NMR: δ ($CDCl_3$)

13.99, 21.73, 28.38, 62.11, 119.18, 164.37, 173.15, 197,20; MS: *m/z* 156 (M^+, 3%), 83 (100), 55 (49). (Found: C, 61.50; H, 8.26%. Calc. for $C_8H_{11}O_3$: C, 61.52; H, 8.30%).

Reaction of isoxazoline **20** *with iodomethane.* Reaction time 2 days. *Ethyl 2-oxo-3-(9-fluorenyliden)-propenoate* **31**, 90% yield; light yellow oil, ν_{max} 1700, 1692, 1685 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 1.21 (t, 3H, CH_3, J=7.1 Hz), 4.16 (q, 2H, CH_2, J=7.1 Hz), 6.95-8.12 (m, 9H, aromatic protons and 3-H); MS: *m/z* 278 (M^+, 13%), 167 (44), 150 (14), 149 (100), 113 (18), 85 (10), 71 (21), 57 (32). (Found: C, 77.59; H, 5.10%. Calc. for $C_{18}H_{14}O_3$: C, 76.68; H, 5.07%).

Preparation and reaction of 2,2-dimethyl-3-spirocyclohexyl-4-ethoxycarbonyl-5-phenyl-4-isoxazolinium triflate **32** *with triethylamine.* To a stirred solution containing 602 mg of *cyclohexanespiro-3'-(2'-methyl-4'-ethoxycarbonyl-4'-isoxazoline)* **11** in 10 ml of anhydrous carbon tetrachloride at 0 °C under nitrogen was added dropwise 350 mg of methyl trifluoromethanesulfonate. The mixture was slowly brought to room temperature and was stirred at 25 °C for 2h. At end of this time the solvent was removed under reduced pressure and the residue, a white sticky oil, was identified as *2,2-dimethyl-3-spirocyclohexyl-4-ethoxycarbonyl-5-phenyl-4-isoxazolinium triflate* **32**; ^{1}NMR: δ ($CDCl_3$) 1.14 (t, 3H, CH_3 J=7.1 Hz), 1.76 (m, 6H, CH_3), 2.33 (m, 4H, CH_2), 3.81 (s, 3H, N-CH_3), 4.16 (q, 2H, CH_2, J=7.1 Hz), 4.23 (s, 3H, N-CH_3), 7.34-7.99 (m, 5H, aromatic protons). A solution containing 400 mg of **32** in 20 ml of dry tetrahydrofuran was treated with 120 mg of triethylamine under nitrogen atmosphere. After stirring for 2 h, the solvent was removed under reduced pressure and the residue was subjected to flash-chromatography on a silica gel column with cyclohexane-ethyl acetate 97:3 as eluent. The major fraction contained 250 mg (92%) of light yiellow oil which was identified as ethyl 2-benzoyl-cyclohexylidenacetate **27**.

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