

**RING-OPENING OF 4-ISOXAZOLINES: COMPETITIVE FORMATION OF ENAMINO DERIVATIVES AND  $\alpha,\beta$ -ENONES**

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**Abstract** – Ring-opening of 3-substituted 4-isoxazolines, proceeding through the intermediate isoxazolinium salts, follows two competing reaction pathways leading to  $\alpha,\beta$ -enones and enamines respectively. The rearrangement courses can be controlled as a function of substitution pattern and experimental conditions.

Isoxazolines, 1,3-dipolar cycloadducts from nitrones and alkynes,<sup>1</sup> represent a valuable and original source of intramolecular rearrangements which lead to deep and well-defined chemical transformations of the initial cycloadducts.<sup>2-14</sup>

The conversion of the heterocyclic precursor in different functionalities through the opening of the five-membered ring appears to be interesting in organic synthesis; on this basis the chemistry of the isoxazoline nucleus has been the aim of our intense study,<sup>15-19</sup> together with the evaluation of parameters which control and define the regiochemistry of the initial cycloaddition process.<sup>18-20</sup>

The most general feature of 4-isoxazolines is the thermal conversion to 2-acylaziridines, following the 1,4-migration of the nitrogen atom, consequent to the cleavage of N-O bond.<sup>3</sup> The subsequent conversion to intermediate azomethine ylides proceeds probably *via* conrotatory ring-opening; the resulting dipole gives ring closure to oxazolines or undergoes an internal proton shift followed by cyclization to pyrrole nucleus.<sup>21-23</sup> Alternatively, the rearrangement pathway can be oriented towards the formation of substituted indoles.<sup>17</sup>

A number of additional chemical transformations have been shown to involve the C-C and C-H bonds at position

3 of the N-O heterocyclic nucleus. Recently, there have been found rearrangement reactions with the 2,3-migration of several groups,<sup>6,8,19</sup> together with some N-O bond cleavages induced by prototropic processes when a hydrogen atom is present at the position 3 of 4-isoxazoline ring system.<sup>1,13,24</sup>

Quaternization of the nitrogen atom discloses new alternatives for the chemical conversion of the primary cycloadducts.<sup>25</sup> Treatment of 3,3-disubstituted 4-isoxazolines with MeI affords  $\alpha,\beta$ -enones in excellent yields via the intermediate isoxazolinium salts:<sup>26</sup> the novel rearrangement channel is interpretable according to the basic removal of the acid hydrogen atom at N-Me group.

In this context, the presence of an abstractable hydrogen atom at the position 3 of the ring could open a new reaction route; this hypothesis is the object of the present study, which deals with the competitive rearrangement process originated from the treatment of 3-aryl-substituted 4-isoxazolines with MeI.

## RESULTS AND DISCUSSION

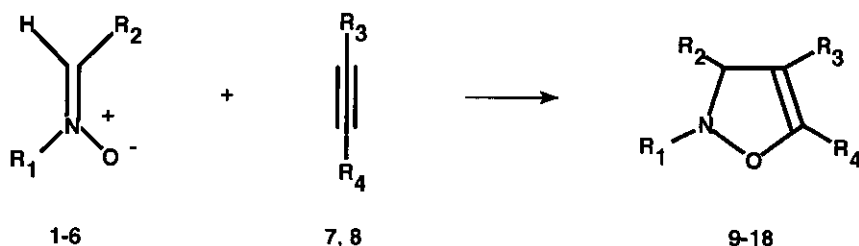
A series of 3-aryl-substituted nitrones was treated with an excess of ethyl propiolate and ethyl phenylpropiolate in anhydrous THF at reflux for 18-24 h. (Scheme 1, Table 1).

The reaction of nitrones (1-6) with ethyl phenylpropiolate gives only the 4-ethoxycarbonyl substituted isoxazolidines (11, 12, 15-18) as stable adducts; with ethyl propiolate, nitrones (1) and (3) give a 3:2 mixture of regioisomeric cycloadducts (isoxazolines 9,10 and 13,14 respectively). The regioselectivity of these reactions is interpretable in terms of the FMO theory: the cycloaddition process is controlled by HOMO dipole stabilizing interaction.

Structural assignments for the obtained isoxazolines are based on their spectroscopic features. In 4-isoxazolines, the 5-proton is well known to resonate as a singlet at lower field than 4-proton, owing to the deshielding effect of the oxygen atom. In fact for compounds (9) and (13) the vinyl proton absorbs in the aromatic region, while for compounds (10) and (14) the resonance appears as a doublet at  $\delta$  5.87 and 5.81 respectively. Mass spectra support the assigned structure: the 4-substituted isoxazolines (9, 13) show the diagnostic fragmentation of  $M^+$  -29 due to the 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  $\text{COCO}_2\text{Et}$  fragment. In the case of derivatives 11,12,15-18, the assignment of regioisomeric structure is straightforward on the basis of the following evidence: 3-H protons resonate as a singlet in the region 4.70-5.10  $\delta$ ; irradiation at the resonance of the  $\text{CO}_2\text{Et}$  group induces positive NOE enhancements (15%) of the 3-H resonances. These results are indicative of the close proximity of 3-H to ethyl group present at the position 4

of the heterocyclic ring.

Scheme 1



1:  $R_1$ =Me;  $R_2$ =Ph.

2:  $R_1$ =Cyclohexyl;  $R_2$ =Ph.

3:  $R_1$ =Me;  $R_2$ =*p*-ClC<sub>6</sub>H<sub>4</sub>.

4:  $R_1$ =Me;  $R_2$ =*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

5:  $R_1$ =Me;  $R_2$ =*p*-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>.

6:  $R_1$ =Me;  $R_2$ =CO<sub>2</sub>Et.

7:  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =H.

8:  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =Ph.

9:  $R_1$ =Me;  $R_2$ =Ph;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =H.

10:  $R_1$ =Me;  $R_2$ =Ph;  $R_3$ =H;  $R_4$ =CO<sub>2</sub>Et.

11:  $R_1$ =Me;  $R_2$ =Ph;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =Ph.

12:  $R_1$ =Cyclohexyl;  $R_2$ =Ph;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =Ph.

13:  $R_1$ =Me;  $R_2$ =*p*-ClC<sub>6</sub>H<sub>4</sub>;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =H.

14:  $R_1$ =Me;  $R_2$ =*p*-ClC<sub>6</sub>H<sub>4</sub>;  $R_3$ =H;  $R_4$ =CO<sub>2</sub>Et.

15:  $R_1$ =Me;  $R_2$ =*p*-ClC<sub>6</sub>H<sub>4</sub>;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =Ph.

16:  $R_1$ =Me;  $R_2$ =*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =Ph.

17:  $R_1$ =Me;  $R_2$ =*p*-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =Ph.

18:  $R_1$ =Me;  $R_2$ =CO<sub>2</sub>Et;  $R_3$ =CO<sub>2</sub>Et;  $R_4$ =Ph.

Table 1. Reaction of nitrones (1-6) with ethyl propiolate (7) and ethyl phenylpropiolate (8).<sup>a</sup>

Nitrone	Alkyne	$\Delta^4$ Isoxazoline	Yield(%) <sup>b</sup>
1	7	9; 10 <sup>c</sup>	68
1	8	11	78
2	8	12	78
3	7	13; 14 <sup>d</sup>	60
3	8	15	90
4	8	16	43
5	8	17	63
6	8	18	65

<sup>a</sup>Reaction at reflux temperature in tetrahydrofuran. <sup>b</sup>Isolated yields by column chromatography on SiO<sub>2</sub>. <sup>c</sup>Regioisomer ratio is 58:42.

<sup>d</sup>Regioisomer ratio is 55:45.

4-Isoxazolines (9-12, 14-17) were reacted with MeI in excess at room temperature, until tlc showed the

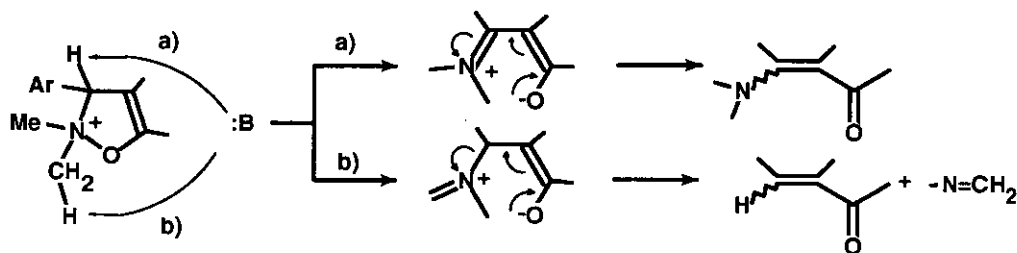


These compounds have been characterized on the basis of spectroscopic data as reported in the Experimental section. In particular, nmr analysis showed that enones (**20**, **22**) have been obtained as a separable mixture of E and Z-isomers in a ratio of 6:1, and enones (**21**, **23-25**) as a separable mixture of Z and E-isomers in a ratio of 6:1, while compound (**19**) is obtained as a nearly equimolar non resolvable mixture of Z and E-isomers.<sup>27</sup>

In analogy with the previously reported behaviour of the 3,3-disubstituted isoxazolines with MeI, the obtained results are amenable to a ring-opening process starting from a not isolated isoxazolinium salt, formed under MeI treatment.<sup>26</sup> With respect to the reaction pathway starting from 3,3-disubstituted isoxazolinium salts and leading to the exclusive formation of  $\alpha,\beta$ -enones, the presence at C-3 of an abstractable benzylic hydrogen atom induces a clear modification in the chemistry of the system.

Accordingly, two competing ring opening pathway are operating: the already suggested basic removal of the hydrogen atom at the N-Me group, which leads to  $\alpha,\beta$ -enones through elimination of the positively charged nitrogen,<sup>28</sup> and the abstraction of the hydrogen atom at C-3 leading exclusively to enamines (Scheme 3).

Scheme 3



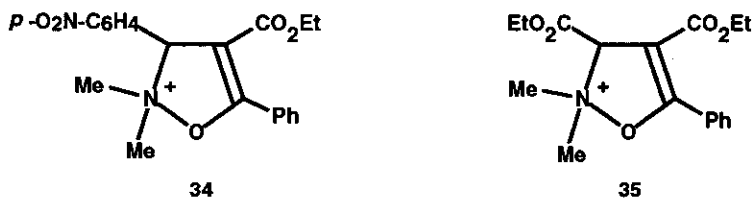
On this basis, structural features of the substrate should affect deeply the competitive reaction pathways; the reaction course leading to enamines should be controlled by the electronic characteristics of substituents on the aromatic ring which determine the acidity of the hydrogen atom at C-3.

Electron withdrawing groups favour the removal of the hydrogen atom at C-3 so improving the reaction channel towards enamines. In fact, we observed, on going from isoxazolines (**9-12**) to isoxazolines (**14-16**), that the preferred reaction course becomes the one leading to enamines whose yields increase with the increasing of the

electron withdrawing features of the substituent in the aromatic ring. Conversely, the presence of an electron donating group, as in isoxazoline (17), depresses the formation of enamines in favour of  $\alpha,\beta$ -enones (Table 2). However, as suggested for 3,3-disubstituted isoxazolines,<sup>26</sup> the formation of  $\alpha,\beta$ -enones in the treatment with MeI could be rationalized also on the basis of the N-O bond cleavage induced by a complex redox reaction with the formation of iodine, experimentally ascertained, from the iodide oxidation, probably by a single-electron transfer mechanism. In fact, a different temperature dependence of the two competing routes a) and b) is shown in Table 2; an increase of the reaction temperature improves as expected,<sup>29</sup> the electron transfer mechanism, and the radical pathway, leading to  $\alpha,\beta$ -enones, becomes clearly the preferred one.

In order to provide additional support to the suggested overall process starting from isoxazoline and proceeding through a not isolated isoxazolinium salt, we have performed the rearrangement process in two steps. Isoxazoline (16) was treated with methyl triflate in anhydrous  $\text{CCl}_4$  at 0 °C for 2 h. The reaction proceeded quite smoothly and gave rise in a quantitative yield to the expected isoxazolinium salt (34), which has been isolated and characterized. Compound (34) was, then, subjected to the ring-opening process by treatment with bases of increasing strength (Table 3).

**Table 3.** Reaction of  $\Delta^4$ -isoxazolinium triflate (34) and (35) with base at room temperature in ethanol.



$\Delta^4$ -isoxazolinium salt	Base	Enone (%) <sup>a</sup>	Enamine (%) <sup>a</sup>	Ratio enone/enamine
34	$\text{CF}_3\text{CO}_2^-$	24 (26)	32 (52)	0.50
34	$\text{MeCO}_2^-$	24 (26)	32 (28)	0.93
34	$\text{EtO}^-$	24 (40)	32 (10)	4.00
34	$\text{I}^-$	24 (40)	32 (40)	1.00
35	$\text{MeCO}_2^-$		36 (95)	
35	$\text{I}^-$	37 (63)	36 (32)	1.97

<sup>a</sup>Isolated yields by column chromatography on  $\text{SiO}_2$ .

The obtained data show that a weak base, as the trifluoroacetate ion, is more selective and leads to the removal of the hydrogen atom at C-3, more acidic than the hydrogen atom at N-Me group; the reaction course is thus driven towards the preferential formation of enamine in a 2:1 ratio with respect to the corresponding  $\alpha,\beta$ -enone.

Accordingly, the strong base ethoxide does not discriminate between two different types of hydrogen atom; as a consequence, the distribution pattern approximates to that expected from a purely statistical basis. The comparison between the data obtained when acetate and iodide ions have been used (a nearly equimolar mixture of enamine and enone in both cases) appear to be a further confirmation of the existence of two competing reaction courses towards the  $\alpha,\beta$ -enones. With  $I^-$ , the electron transfer mechanism is operating, together with the ionic one, and leads to the observed composition of rearrangement products.

Furthermore, isoxazolinium salt (**35**), obtained from isoxazoline (**16**) with the above reported procedure (see experimental), upon treatment with sodium acetate in ethanol at room temperature for 2 h, give enamine (**36**) in 95% yield; the presence of  $\alpha,\beta$ -enone was not detected. This result is in agreement with the enhanced acidity of 3-H, due to the presence of carboxyethyl group, which shifts the competition channels towards path a.

In conclusion, the ring-opening reaction of 3-arylsubstituted 4-isoxazolines, activated by conversion into isoxazolinium salts, follows two competing reaction pathways, leading to  $\alpha,\beta$ -enones and enamines respectively. The rearrangement courses can be controlled as a function of the electron characteristics of the substituent at C-3 and of the experimental conditions used.

## EXPERIMENTAL

Melting points 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 tlc on silica gel GF 254 (Merck) and the spots were detected under uv light (254nm). Flash chromatography was carried out with Kieselgel 60 (Merck).

### Reaction of Nitrones (1-6) with Alkynes (7, 8).

**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 tlc showed the disappearance of the starting nitron. The solvent was removed at room temperature with rotary evaporator and the residue was subjected to flash chromatography on silica gel column with hexane-ether 96:4 as eluent.

**Reaction of N-methyl- $\alpha$ -phenylnitron (1) with ethyl propiolate (7).** Reaction time 21 h. First eluted product was 2-methyl-4-ethoxycarbonyl-3-phenyl-4-isoxazoline (9), 40% yield; pale yellow oil;  $\nu_{\max}$  3050, 2930, 1720, 1620, 1100  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.15 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 2.80 (3H, s, N- $\text{CH}_3$ ), 4.08 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 4.83 (1H, d,  $J=1.8$  Hz, 3-H), 7.21-7.40 (6H, m, aromatic protons and 5-H);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.95, 46.72, 61.51, 75.74, 109.50, 128.7, 128.9, 129.2, 131.3, 145.2, 158.8; ms:  $m/z$  233 ( $\text{M}^+$ ), 204, 160. Anal. Calcd for  $\text{C}_{13}\text{H}_{15}\text{NO}_3$ : C, 66.93; H, 6.43; N, 6.00. Found: C, 66.91; H, 6.39; N, 6.03. Further elution gave 2-methyl-5-ethoxycarbonyl-3-phenyl-4-isoxazoline (10), 28% yield; pale light yellow oil;  $\nu_{\max}$  3080, 2950, 1710, 1630, 1100  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.26 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 2.86 (3H, s, N- $\text{CH}_3$ ), 4.23 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 4.83 (1H, d,  $J=2.9$  Hz, 3-H), 5.87 (1H, d,  $J=2.9$  Hz, 4-H), 7.24 (5H, s, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.95, 46.72, 61.51, 75.74, 109.50, 128.7, 128.9, 129.2, 131.31, 145.20, 158.81; ms:  $m/z$  233 ( $\text{M}^+$ ), 160 (base), 132. Anal. Calcd for  $\text{C}_{13}\text{H}_{15}\text{NO}_3$ : C, 66.93; H, 6.43; N, 6.00. Found: C, 66.91; H, 6.47; N, 6.02.

**Reaction of N-methyl- $\alpha$ -phenylnitron (1) with ethyl phenylpropiolate (8).** Reaction time 20 h. First fractions gave 2-methyl-4-ethoxycarbonyl-3,5-diphenyl-4-isoxazoline (11), 78% yield; light white solid, mp 78-80 °C (from hexane-benzene);  $\nu_{\max}$  3060, 2980, 1685, 1620  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.08 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 3.02 (3H, s, N- $\text{CH}_3$ ), 4.01 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 5.10 (s, 1H, 3-H), 7.20-7.90 (10H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 15.37, 48.42, 61.14, 78.5, 128.8, 129.3, 129.9, 131.23, 132.8, 153.2, 154.3. Anal. Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_3$ : C, 73.76; H, 6.19; N, 4.52. Found: C, 73.81; H, 6.15; N, 4.54.

**Reaction of N-cyclohexyl- $\alpha$ -phenylnitron (2) with ethyl phenylpropiolate (8).** Reaction time 18 h. First fraction gave 2-cyclohexyl-4-ethoxycarbonyl-3,5-diphenyl-4-isoxazoline (12), 73% yield; pale yellow oil;  $\nu_{\max}$  3060, 2980, 1780, 1650 and 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.08 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 1.26-2.24 (10H, m,  $\text{CH}_2$ ), 2.85-3.15 (1H, m, N-CH-), 4.03 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 5.10 (1H, s, 3H), 7.32-7.90 (10H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.86, 24.78, 25.97, 29.11, 29.77, 59.77, 66.33, 71.66, 127.48, 127.79, 128.31, 129.77, 130.88, 142.75, 155, 162.25; ms:  $m/z$  377 ( $\text{M}^+$ ), 105(base), 77. Anal. Calcd for  $\text{C}_{24}\text{H}_{27}\text{NO}_3$ : C, 63.58; H, 7.15; N, 3.71. Found: C, 63.60; H, 7.17; N, 3.69.

**Reaction of N-methyl- $\alpha$ -(4-chlorophenyl)-nitron (3) with ethyl propiolate (7).** Reaction time 24 h. First eluted product was 3-(4'-chlorophenyl)-4-ethoxycarbonyl-2-methyl-4-isoxazoline (13), 33% yield; light yellow oil,  $\nu_{\max}$  3060, 2960, 2920, 1705, 1610, 1100  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.14 (3H, t,  $J=6.8$  Hz,  $\text{CH}_3$ ), 2.88 (3H, s, N- $\text{CH}_3$ ),



4.07 (2H, q, J=6.8 Hz, CH<sub>2</sub>), 4.85 (1H, d, J=1.6 Hz, 3-H), 7.00-7.86 (6H, m, aromatic protons and 5-H); <sup>13</sup>C nmr: δ (CDCl<sub>3</sub>) 13.63, 46.83, 59.47, 76.81, 126.45, 130.25, 134.28, 158.62; ms: m/z 269, 267 (M<sup>+</sup>), 238, 194, 131, 75. Anal. Calcd. for C<sub>13</sub>H<sub>14</sub>NO<sub>3</sub>Cl: C, 58.32; H, 5.23; N, 5.27; Cl, 13.25. Found : C, 58.27; H, 5.19; N, 5.28; Cl, 13.19. Further elution gave 3-(4'-chlorophenyl)-5-ethoxycarbonyl-2-methyl-4-isoxazoline (**14**), 27% yield; pale yellow oil; ν<sub>max</sub> 3100, 2920, 2860, 1700, 1620, 1100 cm<sup>-1</sup>; <sup>1</sup>H nmr: δ (CDCl<sub>3</sub>) 1.27 (3H, t, J=7.1 Hz, CH<sub>3</sub>), 2.87 (3H, s, N-CH<sub>3</sub>), 4.23 (2H, q, J=7.1 Hz, CH<sub>2</sub>), 4.77 (1H, d, J=2.9 Hz, 3-H), 5.81 (1H, d, J=2.9 Hz, 4-H), 7.24 (s, 4H, aromatic protons); <sup>13</sup>C nmr: δ (CDCl<sub>3</sub>) 13.97, 46.77, 61.54, 75.7, 109.51, 128.26, 128.78, 133.84, 138.34, 145.21, 158.84; ms: m/z 269, 267 (M<sup>+</sup>), 194, 168, 166, 159, 151, 131(base), 125, 89. Anal. Calcd for C<sub>13</sub>H<sub>14</sub>NO<sub>3</sub>Cl: C, 58.32; H, 5.23; N, 5.27; Cl, 13.25. Found: C, 58.29; H, 5.27; N, 5.30; Cl, 13.21.

Reaction of N-methyl-α-(4-chlorophenyl)nitron (3) with ethyl phenylpropiolate (8). Reaction time 22 h. First fractions gave 2-methyl-4-ethoxycarbonyl-3-(4'-chlorophenyl)-5-phenyl-4-isoxazoline (**15**), 90% yield; pale yellow solid, mp 156-158 °C (from hexane-benzene); ν<sub>max</sub> 3060, 2980, 2920, 1710, 1640, 1600, 1230, 1060 cm<sup>-1</sup>; <sup>1</sup>H nmr: δ (CDCl<sub>3</sub>) 1.06 (3H, t, J=6.5 Hz, CH<sub>3</sub>), 2.96 (3H, s, N-CH<sub>3</sub>), 4.00 (2H, q, J=6.5 Hz, CH<sub>2</sub>), 5.0 (1H, s, 3-H), 7.18-7.83 (9H, m, aromatic protons); <sup>13</sup>C nmr: δ (CDCl<sub>3</sub>) 15.30, 48.31, 61.12, 78.39, 126.5, 126.7, 129.9, 131.3, 134.9, 135.2, 153.1, 154.2; ms: m/z 343 (M<sup>+</sup>), 298, 270, 238, 232, 165, 105(base), 103, 77. Anal. Calcd for C<sub>19</sub>H<sub>18</sub>NO<sub>3</sub>Cl: C, 69.19; H, 5.46; N, 4.24; Cl, 10.75. Found: C, 69.22; H, 5.43; N, 4.23; Cl, 10.74.

Reaction of N-methyl-α-(4-nitrophenyl)nitron (4) with ethyl phenylpropiolate (8). Reaction time 12 h. First fraction gave 4-ethoxycarbonyl-2-methyl-3-(4'-nitrophenyl)-5-phenyl-4-isoxazoline (**16**), 43% yield; pale yellow solid, mp 114-115 °C (from hexane-benzene); ν<sub>max</sub> 3060, 2985, 1720, 1625, 1510, 1335, 1270, 1090, 740, 690 cm<sup>-1</sup>; <sup>1</sup>H nmr: δ (CDCl<sub>3</sub>) 1.11 (3H, t, J=7.1 Hz, CH<sub>3</sub>), 3.05 (3H, s, N-CH<sub>3</sub>), 4.07 (2H, q, J=7.1 Hz, CH<sub>2</sub>), 5.18 (1H, s, 3-H), 7.40-8.25 (9H, m, aromatic protons); <sup>13</sup>C nmr: δ (CDCl<sub>3</sub>) 13.86, 46.94, 60.19, 75.85, 123.68, 127.85, 128.09, 129.75, 131.37, 148.67, 167.28. Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>: C, 58.94; H, 5.58; N, 8.69. Found: C, 58.92; H, 5.60; N, 8.66.

Reaction of N-methyl-α-(4-methoxyphenyl)nitron (5) with ethyl phenylpropiolate (8). Reaction time 24 h. First fraction gave 4-ethoxycarbonyl-3-(4'-methoxyphenyl)-2-methyl-5-phenyl-4-isoxazoline (**17**), 64% yield; pale yellow solid, mp 105-108 °C (from hexane-benzene); ν<sub>max</sub> 3055, 2980, 2840, 1710, 1625, 1300, 1100, 1035 cm<sup>-1</sup>; <sup>1</sup>H nmr: δ (CDCl<sub>3</sub>) 1.08 (3H, t, J=6.5 Hz, CH<sub>3</sub>), 2.86 (3H, s, N-CH<sub>3</sub>), 3.62 (3H, s, O-CH<sub>3</sub>), 4.02 (2H, q, J=6.5 Hz, CH<sub>2</sub>), 4.85 (1H, s, 3H), 6.78-7.40 (9H, m, aromatic protons); <sup>13</sup>C nmr: δ (CDCl<sub>3</sub>) 13.83, 45.94, 61.35, 75.89, 114.02, 120.4, 125.3, 128.4, 129.3, 137.7, 153.3, 154.1, 158.5; ms: m/z 339 (M<sup>+</sup>), 294, 266, 216, 161, 146, 105(base), 77. Anal. Calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub>: C, 58.93; H, 6.18; N, 4.12. Found: C, 58.96; H, 6.16; N, 4.10.

**Reaction of N-methyl- $\alpha$ -carboxyethylnitrone (6) with ethyl phenylpropiolate (8).** Reaction time 12 h. First fraction gave 2-methyl-3,4-diethoxycarbonyl-5-phenyl-4-isoxazoline (**18**), 65% yield; pale yellow solid, mp 54 °C (from hexane-benzene);  $\nu_{\max}$  2990, 1740, 1665, 1660, 1625, 1085  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.18 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 1.27 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 2.97 (3H, s, N- $\text{CH}_3$ ), 4.14 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 4.23 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 4.69 (1H, s, 3H), 7.35-7.91 (5H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 14.07, 47.93, 60.14, 61.47, 75.53, 98.80, 127.86, 129.65, 131.29, 163.15, 169.79; ms:  $m/z$  305 ( $\text{M}^+$ : 50%), 232, 204, 105, 91, 77. Anal. Calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}_5$ : C, 62.94; H, 6.27; N, 4.59. Found: C, 62.61; H, 6.28; N, 4.54.

#### **Rearrangement reactions of isoxazolines (9-12, 14-18).**

A solution of isoxazoline (1 mmol) in 5ml (80 mmol) of iodomethane was stirred at room temperature at different times, from 2 to 7 days, according to the substituents (see Table 2). After the evaporation of the solvent the residue was subjected to flash chromatography on silica gel column with cyclohexane/ethyl acetate 97:3 as eluent.

**Reaction of isoxazoline (9) with iodomethane.** First fraction gave (Z)-ethyl 2-formyl-3-phenyl-2-propenoate (**19**), 24% yield; yellow oil;  $\nu_{\max}$  3050, 2980, 1680, 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.10 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 4.09 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 6.91-7.89 (6H, m, aromatic protons and 3-H), 9.89 (1H, s, aldehydic proton);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.72, 61.13, 126.74, 127.23, 128.35, 128.54, 128.71, 129.67, 130.01, 133.34, 141.37, 150.13, 165.08, 189.3; ms:  $m/z$  190 ( $\text{M}^+$ ), 159, 158, 130, 103, 77, 51. Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{O}_3$ : C, 70.57; H, 5.92. Found: C, 70.97; H, 5.83. Second fraction gave (E)-ethyl 2-formyl-3-phenyl-2-propenoate (**19**), 20% yield; yellow oil;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.06 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 3.96 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 6.90-7.79 (6H, m, aromatic protons and 3-H), 9.48 (1H, s, aldehydic proton).  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.65, 59.83, 126.69, 127.34, 128.36, 128.59, 128.73, 129.66, 130.08, 1303.31, 141.35, 150.11, 163.25, 187.25; Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{O}_3$ : C, 70.57; H, 5.92. Found: C, 70.95; H, 5.81. Further elution gave ethyl 3-dimethylamino-2-formyl-3-phenyl-2-propenoate (**26**), 42% yield; yellow oil;  $\nu_{\max}$  3055, 2980, 2810, 1685, 1085  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 0.73 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 3.19 (6H, s, N- $\text{CH}_3$ ), 3.72 (2H, q,  $J=7.1$ ,  $\text{CH}_2$ ), 7.04-7.76 (5H, m, aromatic protons), 9.52 (1H, s, aldehydic proton);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.21, 43.88, 59.49, 127.79, 128.24, 129.77, 130.23, 130.54, 136.94, 188.35; ms:  $m/z$  233 ( $\text{M}^+$ ), 218(base), 204, 172, 146, 129, 102, 77. Anal. Calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_3$ : C, 68.00; H, 6.93; N, 5.66. Found: C, 68.34; H, 6.85; N, 5.57.

**Reaction of isoxazoline (10) with iodomethane.** First fraction gave (E)-ethyl 2-oxo-4-phenyl-3-butenoate (**20**), 38% yield; light yellow solid, mp 23-24 °C (from hexane-benzene) (lit.,<sup>28</sup> 22-23 °C);  $\nu_{\max}$  3050, 2980, 1690, 1120  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.08 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 4.12 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 6.78-7.98 (7H, m, aromatic protons and 3,4-H);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 15.07, 59.61, 120.47, 128.15, 128.9, 130.11, 131.47, 133.87, 148.37; ms:

$m/z$  204 ( $M^+$ ), 176, 131(base), 103, 77. Anal. Calcd for  $C_{12}H_{12}O_3$ : C, 70.57; H, 5.92. Found: C, 70.96; H, 5.82. Second fraction gave (Z)-ethyl 2-oxo-4-phenyl-3-butenoate (**20**), 8% yield; yellow oil;  $^1H$  nmr:  $\delta$  ( $CDCl_3$ ) 1.02 (3H, t,  $J=7.0$  Hz,  $CH_3$ ), 4.02 (2H, q,  $J=7.0$  Hz,  $CH_2$ ), 6.71 (1H, d,  $J=12.2$  Hz), 7.35-7.60 (6H, m, aromatic protons and 4-H); ms:  $m/z$  204 ( $M^+$ ), 176, 131(base), 77, 51. Further elution gave ethyl 3-dimethylamino-2-oxo-4-phenyl-3-butenoate (**27**), 50% yield; yellow oil;  $\nu_{max}$  3055, 2980, 1715, 1095  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  ( $CDCl_3$ ) 1.10 (3H, t,  $J=6.9$  Hz,  $CH_3$ ), 2.99 (6H, s, N- $CH_3$ ), 4.15 (2H, q,  $J=6.9$  Hz,  $CH_2$ ), 5.82 (1H, s, vinylic proton), 7.22-7.46 (5H, m, aromatic protons);  $^{13}C$  nmr:  $\delta$  ( $CDCl_3$ ) 13.86, 46.68, 58.97, 117.35, 125.15, 128.32, 129.12, 137.8, 151.21; ms:  $m/z$  247 ( $M^+$ ) 174(base) 103, 77. Anal. Calcd for  $C_{14}H_{17}NO_3$ : C, 68.00; H, 6.93; N, 5.66. Found: C, 68.31; H, 6.89; N, 5.55.

**Reaction of isoxazoline (11) with iodomethane.** First fraction gave (Z)-ethyl 2-benzoyl-3-phenyl-2-propenoate (**21**), 38% yield; pale white solid, mp 95-96 °C (from hexane-benzene);  $\nu_{max}$  3050, 2980, 1720, 1695, 1090  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  ( $CDCl_3$ ) 1.12 (3H, t,  $J=7.1$  Hz,  $CH_3$ ), 4.18 (2H, q,  $J=7.1$  Hz,  $CH_2$ ), 6.89-8.01 (11H, m, aromatic protons, and 3-H);  $^{13}C$  nmr:  $\delta$  ( $CDCl_3$ ) 13.64, 61.08, 126.8, 127.43, 127.66, 128.14, 128.44, 128.71, 129.77, 129.97, 133.49, 142.06, 149.05, 164.55; ms:  $m/z$  280 ( $M^+$ ), 251, 206, 178, 135, 105(base), 77. Anal. Calcd for  $C_{18}H_{16}O_3$ : C, 77.12; H, 5.75. Found: C, 77.18; H, 5.74. Second fraction gave (E)-ethyl 2-benzoyl-3-phenyl-2-propenoate (**21**), 8% yield; pale white solid mp 83-86 °C (from hexane-benzene);  $^1H$  nmr:  $\delta$  ( $CDCl_3$ ) 1.08 (3H, t,  $J=7.0$  Hz,  $CH_3$ ), 4.02 (2H, q,  $J=7.0$  Hz,  $CH_2$ ), 6.83-7.96 (11H, m, aromatic protons and 3-H);  $^{13}C$  nmr:  $\delta$  ( $CDCl_3$ ) 16.62, 61.02, 126.02-129.96, 148.2, 164.5. Anal. Calcd for  $C_{18}H_{16}O_3$ : C, 77.12; H, 5.75. Found: C, 76.78; H, 5.80. Further elution gave ethyl 2-benzoyl-3-dimethylamino-3-phenyl-2-propenoate (**28**), 40% yield; yellow oil;  $\nu_{max}$  3070, 2975, 1720, 1695, 1300  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  ( $CDCl_3$ ) 0.62 (3H, t,  $J=7.1$  Hz,  $CH_3$ ), 7.07-7.78 (10H, m, aromatic protons);  $^{13}C$  nmr:  $\delta$  ( $CDCl_3$ ) 13.22, 43.86, 59.5, 127.79, 128.25, 129.77, 130.24, 130.54; ms:  $m/z$  323 ( $M^+$ ), 306, 276, 250, 200, 172, 129, 105, 77(base). Anal. Calcd for  $C_{20}H_{21}NO_3$ : C, 74.28; H, 6.55; N, 4.33. Found: C, 74.11; H, 6.55; N, 4.40.

**Reaction of isoxazoline (12) with iodomethane.** First fraction gave (Z, 30%) and second fraction gave (E, 5%) of ethyl 2-benzoyl-3-phenyl-2-propenoate (**21**) respectively, see above. Further elution gave ethyl 2-benzoyl-3-(N-cyclohexyl-N-methylamino)-3-phenyl-2-propenoate (**29**), 30% yield; sticky white solid;  $\nu_{max}$  1680, 1625, 1080  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  ( $CDCl_3$ ) 0.62 (3H, t,  $J=7.1$  Hz,  $CH_3$ ), 0.90-2.13 (11H, m, N-cyclohexylic protons), 2.87 (3H, s, N- $CH_3$ ), 3.64 (2H, q,  $J=7.1$  Hz,  $CH_2$ ), 7.28-7.76 (10H, m, aromatic protons);  $^{13}C$  nmr:  $\delta$  ( $CDCl_3$ ) 13.43, 25.21, 25.49, 26.42, 30.96, 37.11, 59.6, 62.68, 125.07, 127.88, 128.29, 129.52, 130.2, 130.6, 137.83, 142.23, 192.16; ms:  $m/z$  391( $M^+$ ), 318, 286, 240, 212, 118, 105, 77. Anal. Calcd for  $C_{25}H_{29}NO_3$ : C, 76.72; H, 7.41; N, 3.58. Found:

C, 76.67; H, 7.39; N, 3.62.

**Reaction of isoxazoline (14) with iodomethane.** First fraction gave (E)-ethyl 4-(4'-chlorophenyl)-2-oxo-3-butenolate (**22**), 34% yield; yellow oil;  $\nu_{\max}$  1690, 1630, 1400, 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.06 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 4.09 (2H, q,  $J=7.1$ ,  $\text{CH}_2$ ), 6.93-8.23 (6H, m, aromatic protons and 3,4-H protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 15.1, 60.3, 125.4, 128.87, 131.45, 131.76, 133.49, 135.57, 140.36; ms:  $m/z$  240 ( $M+2$ ), 238 ( $M^+$ ), 165, 137, 101. Anal. Calcd for  $\text{C}_{12}\text{H}_{11}\text{O}_3\text{Cl}$ : C, 60.39; H, 4.64; Cl, 14.85. Found: C, 59.87; H, 4.68; Cl, 14.92. Second fraction gave (Z)-ethyl 4-(4'-chlorophenyl)-2-oxo-3-butenolate (**22**), 6% yield; light yellow oil;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.12 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 4.30 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 6.91-7.85 (6H, m, aromatic protons and 3,4-H); ms:  $m/z$  240 ( $M+2$ ), 238 ( $M^+$ ), 165, 137, 101, 73. Further elution gave ethyl 4-(4'-chlorophenyl)-4-dimethylamino-2-oxo-3-butenolate (**30**), 52% yield; yellow oil;  $\nu_{\max}$  1690, 1630, 1390, 1090  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.24 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 2.93 (6H, s, N- $\text{CH}_3$ ), 4.08 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 5.79 (1H, s, 3-H), 6.95-7.57 (4H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.74, 40.53, 61.05, 92.5, 128.74, 129.15, 133.92, 134.35, 165.75; ms:  $m/z$  281 ( $M^+$ ), 208, 180, 136. Anal. Calcd for  $\text{C}_{14}\text{H}_{16}\text{NO}_3\text{Cl}$ : C, 59.68; H, 5.72; N, 4.97; Cl, 12.58. Found: C, 59.84; H, 5.69; N, 5.00; Cl, 12.47.

**Reaction of isoxazoline (15) with iodomethane.** First fraction gave (Z)-ethyl 2-benzoyl-3-(4-chlorophenyl)-3-propenoate (**23**), 33% yield; yellow oil;  $\nu_{\max}$  3060, 2990, 2880, 1720, 1230, 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.20 (3H, t,  $J=7.5$  Hz,  $\text{CH}_3$ ), 4.26 (2H, q,  $J=7.5$  Hz,  $\text{CH}_2$ ), 7.09-8.11 (10H, m, aromatic and 3-H protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.59, 61.15, 125.62, 128.15, 128.52, 128.63, 130.9, 131.14, 131.8, 133.63, 135.7, 135.93, 140.46, 142.08, 164.2, 194.68; ms:  $m/z$  316 ( $M+2$ ), 314 ( $M^+$ ), 268, 240, 205, 178, 136, 105(base), 77. Anal. Calcd for  $\text{C}_{18}\text{H}_{15}\text{O}_3\text{Cl}$ : C, 68.48; H, 4.80; Cl, 11.26. Found: C, 68.60; H, 4.86; Cl, 11.22. Second fraction gave (E)-ethyl 2-benzoyl-3-(4'-chlorophenyl)-3-propenoate (**23**), 6% yield; yellow oil;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.18 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 4.24 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 7.20-8.10 (10H, m, aromatic protons and 3-H); ms:  $m/z$  316 ( $M+2$ ), 314 ( $M^+$ ), 268, 240, 206, 205, 178, 165, 141, 110, 105(base), 77. Further elution gave ethyl 2-benzoyl-3-(4'-chlorophenyl)-3-dimethylamino-2-propenoate (**31**), 56% yield; yellow oil;  $\nu_{\max}$  3065, 2985, 2920, 1710, 1635, 1230, 1060  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 0.67 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 3.11 (6H, s, N- $\text{CH}_3$ ), 3.99 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 7.44-8.25 (9H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.61, 48.29, 61.2, 125.34, 128.2, 128.53, 128.59, 130.7, 131.23, 131.79, 134, 135.8, 164.1; ms:  $m/z$  357 ( $M^+$ ), 340, 312, 252, 234, 139, 105(base), 77. Anal. Calcd for  $\text{C}_{20}\text{H}_{20}\text{NO}_3\text{Cl}$ : C, 70.49; H, 5.63; N, 3.91; Cl, 9.90. Found: C, 69.97; H, 5.84; N, 3.88; Cl, 10.02.

**Reaction of isoxazoline (16) with iodomethane.** First fraction gave (Z)-ethyl 2-benzoyl-3-(4'-nitrophenyl)-2-propenoate (**24**), 26% yield; pale white solid, mp 116 °C (from hexane-benzene);  $\nu_{\max}$  3100, 1720, 1660, 1520,

1340, 1240, 1220, 1190, 840, 710, 680  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.14 (3H, t,  $J=7.3$  Hz,  $\text{CH}_3$ ), 4.23 (2H, q,  $J=7.3$  Hz,  $\text{CH}_2$ ), 7.32-8.32 (10H, m, aromatic protons and 3-H proton);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.94, 62.08, 123.91, 129.06, 130.55, 134.42, 135.42, 139.09, 139.42, 140.73, 164.21, 194.41. ms:  $m/z$  325 ( $\text{M}^+$ ), 279, 105(100), 77. Anal. Calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_5$ : C, 66.46; H, 4.65; N, 4.31. Found: C, 66.45; H, 4.59; N, 4.38. Second fraction gave (E)-ethyl 2-benzoyl-3-(4'-nitrophenyl)-2-propenoate (**24**), 5% yield; pale white solid, mp 105-108  $^\circ\text{C}$  (from hexane-benzene);  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.19 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 4.26 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 7.32-8.32 (10H, m, aromatic protons and 3-H proton);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.9, 61.98, 123.83, 128.99, 130.48, 134.47, 135.36, 135.60, 138.00, 139.36, 148.14, 164.14, 194.11. Anal. Calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_5$ : C, 66.46; H, 4.65; N, 4.31. Found: C, 66.46; H, 4.64; N, 4.33. Further elution gave ethyl 2-benzoyl-3-dimethylamino-3-(4'-nitrophenyl)-2-propenoate (**32**), 57% yield; yellow solid, mp 126  $^\circ\text{C}$  (from hexane-benzene);  $\nu_{\text{max}}$  1690, 1630, 1530, 1350, 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 0.56 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 2.86 (6H, s, N- $\text{CH}_3$ ), 3.62 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 7.17-8.27 (9H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.67, 46.3, 59.93, 125.7, 127.1, 128.47, 129.07, 132.9, 133.51, 133.61, 137.68, 150; ms:  $m/z$  368 ( $\text{M}^+$ ), 294, 249, 222, 129, 105(100), 77. Anal. Calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_5$ : C, 65.21; H, 5.47; N, 7.60. Found: C, 65.60; H, 5.45; N, 7.40.

**Reaction of isoxazoline (17) with iodomethane.** First fraction gave (Z)-ethyl 2-benzoyl-3-(4-methoxyphenyl)-2-propenoate (**25**), 39% yield; pale white solid, mp 73-77  $^\circ\text{C}$  (from hexane-benzene);  $\nu_{\text{max}}$  1680, 1625, 1390, 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.35 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 3.73 (3H, s, O- $\text{CH}_3$ ), 4.35 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 6.69-8.11 (10H, m, aromatic protons and 3-H proton);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 14.05, 55.24, 61.26, 114.33, 125.56, 128.83, 129.14, 132.25, 133.76, 136.52, 142.24, 164.07; ms:  $m/z$  310 ( $\text{M}^+$ ), 264, 236, 205, 165, 137, 105, 77. Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{O}_4$ : C, 73.55; H, 5.80. Found: C, 73.57; H, 5.83. Second fraction gave (E)-ethyl 2-benzoyl-3-(4-methoxyphenyl)-2-propenoate (**25**), 6% yield; pale white solid, mp 65-69  $^\circ\text{C}$  (from hexane-benzene);  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.13 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 3.69 (3H, s, O- $\text{CH}_3$ ), 4.19 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 6.65-8.02 (10H, m, aromatic protons and 3-H proton);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.96, 55.09, 59.84, 114.27, 125.48-136.87, 142.05, 163.78. Anal. Calcd for  $\text{C}_{19}\text{H}_{16}\text{O}_4$ : C, 73.55; H, 5.80. Found: C, 73.42; H, 5.86. Further elution gave ethyl 2-benzoyl-3-dimethylamino-3-(4'-methoxyphenyl)-2-propenoate (**33**), 30% yield; sticky yellow solid;  $\nu_{\text{max}}$  1690, 1630, 1380, 1090  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 0.66 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 2.96 (6H, s, N- $\text{CH}_3$ ), 3.68 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 3.79 (3H, s, O- $\text{CH}_3$ ), 6.81-7.68 (9H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.53, 43.98, 55.32, 59.61, 113.92, 127.89, 130.56, 131.74, 161.59; ms:  $m/z$  353 ( $\text{M}^+$ ), 308, 280, 230, 177, 135, 105(100), 77. Anal. Calcd for  $\text{C}_{21}\text{H}_{23}\text{NO}_4$ : C, 71.38; H, 6.51; N, 3.96. Found: C, 71.36; H, 6.48; N, 3.98.

**Reaction of Isoxazolines (16) and (18) with Methyl trifluoromethane-sulphonate.**

**General procedure.** To a stirred solution of isoxazoline (10 mmol) in 10 ml of anhydrous carbon tetrachloride at 0 °C under nitrogen atmosphere was added dropwise methyl trifluoromethanesulfonate (2.132 g, 13 mmol). The mixture was slowly brought to room temperature and was stirred at 25 °C for 2 h. At the end of this time the solvent was removed under reduced pressure and the residue was subsequently washed with anhydrous carbon tetrachloride (2 x 5 ml).

**Reaction of isoxazoline (16) with methyl triflate** gave 2,2-dimethyl-3-(4'-nitrophenyl)-4-etoxy carbonyl-5-phenyl-4-isoxazolinium triflate (**34**), 100% yield; pale yellow solid, mp 89 °C (from carbon tetrachloride);  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.06 (3H, t,  $J=7.1$  Hz,  $\text{CH}_3$ ), 3.42 (3H, s, N- $\text{CH}_3$ ), 4.10 (2H, q,  $J=7.1$  Hz,  $\text{CH}_2$ ), 4.29 (3H, s, N- $\text{CH}_3$ ), 6.59 (1H, s, 3-H), 7.55-8.43 (9H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.59, 51.49, 56.81, 62.21, 83.43, 124.54, 128.93, 130.17, 132.95, 134.06, 136.93, 163.84. Anal. Calcd for  $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_8\text{F}_3\text{S}$ : C, 48.65; H, 4.08; N, 5.40; F, 10.99; S, 6.18. Found: C, 46.34; H, 4.16; N, 5.31; F, 11.15; S, 6.19.

**Reaction of isoxazoline (18) with methyl triflate** gave 2,2-dimethyl-3,4-dioxy carbonyl-5-phenyl-4-isoxazolinium triflate (**35**), 100% yield; sticky light yellow oil;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.24 (3H, t,  $J=7.2$  Hz,  $\text{CH}_3$ ), 1.39 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 3.99 (3H, s, N- $\text{CH}_3$ ), 4.19 (3H, s, N- $\text{CH}_3$ ), 4.23 (2H, q,  $J=7.2$  Hz,  $\text{CH}_2$ ), 4.44 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 5.98 (1H, s, 3-H), 7.48-7.96 (5H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.60, 52.65, 58.03, 61.99, 64.56, 81.38, 101.09, 121.83, 128.53, 129.91, 133.49, 159.54, 162.73. Anal. Calcd for  $\text{C}_{18}\text{H}_{22}\text{NO}_8\text{F}_3\text{S}$ : C, 46.05; H, 4.72; N, 2.98; F, 12.14; S, 6.83. Found: C, 51.46; H, 4.54; N, 2.95; F, 12.16; S, 6.80.

**Reaction of isoxazolinium triflate (35) with lithium iodide** in ethanol at room temperature for 2 h. First fraction gave diethyl benzoylbutendicarboxylate (**37**), 63% yield; yellow oil;  $\nu_{\text{max}}$  2985, 1715, 1675, 1235, 1190, 1025  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 1.05 (3H, t,  $J=7.2$  Hz,  $\text{CH}_3$ ), 1.18 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 4.05 (2H, q,  $J=7.2$  Hz,  $\text{CH}_2$ ), 4.23 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 7.07 (1H, s), 7.32-7.95 (5H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.38, 13.65, 61.45, 62.20, 128.51, 129.32, 130.36, 133.55, 135.53, 144.94, 162.94, 163.52, 192; ms:  $m/z$  276 ( $\text{M}^+$  7.8%), 247, 105, 77. Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{O}_5$ : C, 65.21; H, 5.84. Found: C, 65.16; H, 5.92. Further elution gave diethyl benzoyl-*N,N*-dimethylaminobutendicarboxylate (**36**), 32% yield; yellow oil;  $\nu_{\text{max}}$  2980, 2955, 1735, 1725, 1680, 1620, 1550, 1270, 1205, 1185  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 0.78 (3H, t,  $J=7.2$  Hz,  $\text{CH}_3$ ), 1.33 (3H, t,  $J=7.0$  Hz,  $\text{CH}_3$ ), 2.90 (6H, s, N- $\text{CH}_3$ ), 3.88 (2H, q,  $J=7.2$  Hz,  $\text{CH}_2$ ), 4.35 (2H, q,  $J=7.0$  Hz,  $\text{CH}_2$ ), 7.29-7.81 (5H, m, aromatic protons);  $^{13}\text{C}$  nmr:  $\delta$  ( $\text{CDCl}_3$ ) 13.47, 13.73, 43.46, 60.12, 62.47, 128.05, 128.48, 131.63, 140.11, 158.87, 165.07; ms:  $m/z$  319 ( $\text{M}^+$ ), 276, 247, 173, 105, 91, 77. Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_5$ : C, 63.94; H, 6.63; N, 4.39. Found: C, 64.28; H, 6.55; N, 4.00.

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