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REARRANGEMENTS OF REGIOISOMERIC 4-ISOXAZOLINES: THE NOVEL FORMATION OF ENAMINODERIVATIVES

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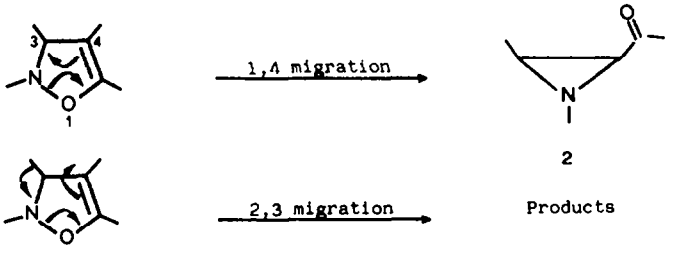
Summary: Regioisomeric 4-isoxazolines are formed by 1,3-dipolar cycloaddition of C-benzoyl-N-phenylnitrone to electron-deficient alkynes. The 4- and 5-substituted cycloadducts react in different modes under the same conditions yielding enaminoderivatives, via a novel rearrangement process, and amines, aziridines and 1,3-oxazolines according to the substitution pattern.

1,3-Dipolar cycloaddition of nitrones[1] to triple bonds, activated by electron-withdrawing groups, yields N,O-heterocyclic systems with the endo-N,O-vinyl moiety which produces a variety of intramolecular rearrangements[2-8]. Similarly, the exocyclic[9-11] and the acyclic[12] N,O-vinyl functional groups give rise to easily accessible molecules via deepseated chemical conversions.

The most general feature of the 4-isoxazolines (1), obtained from nitrones and alkynes reported in Scheme 1, is the thermal isomerization to 2-acylaziridines (2)[2-13], following the migration of the nitrogen atom from position 1 to 4. However, a number of additional chemical transformations have shown to involve the C-C and the C-H bonds at position 3 of N,O-heterocyclic nucleus. Recently, there have been found rearrangement reactions with the 2,3-migration of several groups[5,14,15], together with some N-O bond cleavages induced by prototropic processes when an hydrogen atom is present at the position 3 of the 4-isoxazoline ring system[2,6,16] (Scheme 1).

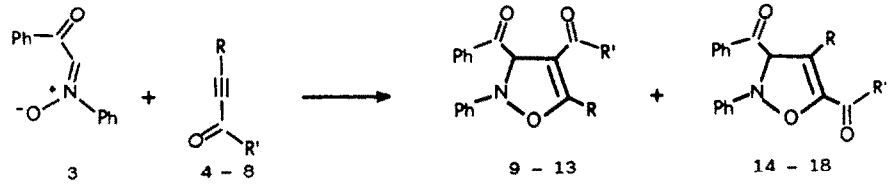


1 2

SCHEME 1

The N,O-heterocyclic regioisomeric derivatives (9-13), generated from the 1,3-dipolar cycloaddition of C-benzoyl-N-phenylnitrone (3) to substituted

alkynes (4-8), in competition with the formation of adducts (14-18) (Scheme 2).

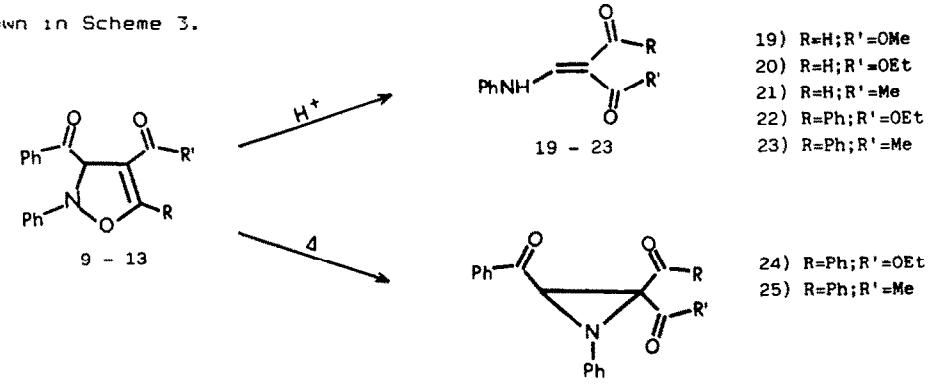


3 4 - 8 9 - 13 14 - 18

4,9,14 : R=H;R'=OMe
5,10,15: R=H;R'=OEt
6,11,16: R=H;R'=Me
7,12,17: R=Ph;R'=OEt
8,13,18: R=Ph;R'=Me

SCHEME 2

reveal a novel reaction process which leads to the formation of enaminoaldehydes and ketones (19-23), according to the substituent groups at C-5, as shown in Scheme 3.



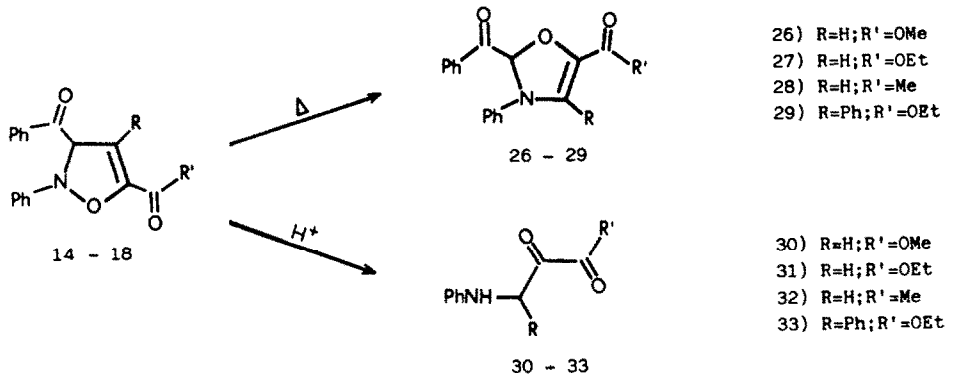
9 - 13 19 - 23 24 - 25

19) R=H;R'=OMe
20) R=H;R'=OEt
21) R=H;R'=Me
22) R=Ph;R'=OEt
23) R=Ph;R'=Me

24) R=Ph;R'=OEt
25) R=Ph;R'=Me

SCHEME 3

On the other hand, the 4-isoxazolines (14-17) undergo intramolecular rearrangements to 4-oxazolines (26-29) and to amines (30-33), reported in Scheme 4, according to the reaction conditions.



14 - 18 26 - 29 30 - 33

26) R=H;R'=OMe
27) R=H;R'=OEt
28) R=H;R'=Me
29) R=Ph;R'=OEt

30) R=H;R'=OMe
31) R=H;R'=OEt
32) R=H;R'=Me
33) R=Ph;R'=OEt

SCHEME 4

Results and Discussion

The reaction of C-benzoyl-N-phenylnitrone with alkynes (4-6) was carried out in anhydrous THF at room temperature, using a 1:3 relative ratio of

dipole-dipolarophile at different times, from 5 to 24 h, according to the substituents. The reaction mixture gave the 4-isoxazolinic adducts (9-11) and (14-16) in very good yields with a relative ratio 40/60. When R was the phenyl group, derivatives (22-25) were isolated as stable products, together with (17) and (18), since the regioisomeric 4-isoxazoline precursors (12) and (13), altough present in the crude reaction mixture, underwent further transformation during the reaction time and the usual work-up, being obtained in poor yields. In fact, the cycloadducts (12) and (13) were found to react at room temperature (e.g. 10 h in THF) to afford the aziridine derivatives (24) and (25). Accordingly compounds (24) and (25) were shown to be absent at an early stage of the cycloaddition reaction.

The loss of regioselection in this 1,3-dipolar cycloaddition process requires a careful FMO treatment, because the large amounts of 4-substituted regioisomers (9-13)[17-20], experimented in the reaction studied can be controlled by HOMO dipole stabilizing interactions[21].

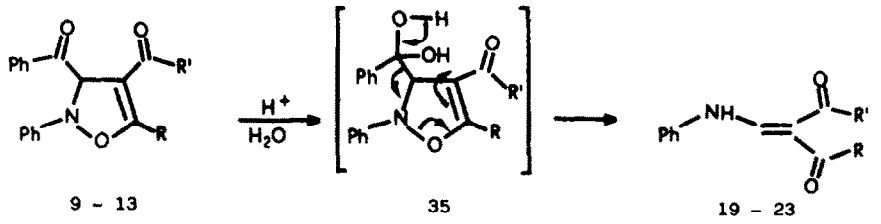
The 4-isoxazoline structures (9-13) and (14-18) were assigned on the basis of analytical and spectral data. Both IR and ^{1}H NMR spectra compare well with the literature data for 4-isoxazolines[2]. In particular, the regiochemical assignments are based on the chemical shift of the vinyl proton in the ^{1}H NMR spectra: for compounds (14-16) the 3-H and 4-H resonances appear as doublets (J=2.45-2.65 Hz) in the range 4.50-4.30 ppm, while in derivatives (9-11) both protons are strongly deshielded and resonate in the region 7.10-8.10 ppm. The downfield shift of the vinyl hydrogen at C-5, linked to the deshielding effect of the adjacent oxygen, agrees with the reported data[2], while the analogous shift of 3-H arises as a consequence of its involvement in a keto-enol equilibrium stabilized by the COR' group at position 4 of the heterocyclic ring. Mass spectra support the assigned structures: the 4-substituted regioisomers (9-11) show the diagnostic fragmentation at M$^+$-29 due to the loss of CHO radical from the molecular ion, while the 5-ones give rise to an intense peak at m/z 222, from the molecular ion by loss of the COCOR' fragment. In the case of derivatives (12-13) and (17-18), the assignment of regioisomeric structures is unequivocal on the basis of the following evidences.Resonances of 3-H appear at 7.38 and 7.35ppm in (12-13) respectively and are shifted at 4.86 and 5.00 ppm in (17-18). Irradiation to the resonances of the COR'groups induces positive NOE enhancements (15%) of the 3-H resonance only in compounds (12-13): these results are indicative of the close proximity of 3-H to ethyl and acetyl groups present at the position 4 of the hetero-

cyclic ring. NOE difference spectroscopy[22] allows also the assignment of 3-H chemical shift, hidden by the aromatic resonances. Moreover, the mass spectra of derivatives (17-18) show peaks at m/z 298 due to the loss of COCOR' fragments from the molecular ions; this finding is only consistent with the ethoxycarbonyl or acetyl groups located at the position 5 of the heterocyclic ring.

When regioisomeric 4-isoxazolines (9-13) were refluxed in THF under acid catalysis for 2-4 h, the enamino-derivatives (19-23) were obtained almost quantitatively, while (22)and(23) were also directly formed during the work-up of the crude cycloaddition mixture together with the aziridine derivatives (24) and (25). The structure of the isolated enamines has been assigned on the basis of spectroscopic data, as reported in the experimental section; both ^{1}H and ^{13}C NMR spectra are available for compounds (19-21). In particular, derivatives (19-23) in $CDCl_3$ solution exist in the chelated structure (34) as indicated by the splitting of the vinylic proton into a doublet (J=12.8-13.6 Hz) as a consequence of its coupling with the NH. Moreover, ^{1}H NMR spectra of enamines (19-21) show further splitting of the olefinic proton (J=3.50-3.80 Hz) for the coupling with the aldehydic proton at 9.95-9.98 ppm. IR and Ms measurements, as well as analytical data for derivatives (19-21), are consistent with the assigned structures. Compounds (19-21) show Z-configuration, as demonstrated by NMR analysis, while (22) and (23) are nearly equimolar mixtures of Z- and E-isomers. Configurational assignments rely upon NOE experiments: by irradiation of the vinylic proton, the positive enhancements (20%) occurring in the aldehydic proton resonance are fully consistent with the proposed stereochemistry.

The isolated aziridines (24) and (25), obtained from 4-isoxazolines (12) and (13) respectively, have their structure assigned according to the ^{1}H NMR spectra, where H-2 resonates at 8.63 and 8.02 ppm respectively, and to the mass spectra, where M -1 peaks are diagnostic for the aziridine mojety.

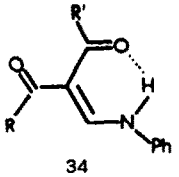
The novel reaction process of the 4-isoxazolines (9-13), under acidic media, can evolve through a sequence of steps where the addition of water to the carbonyl group at position 3 of the N,O-heterocyclic nucleus provides the benzoic acid as good leaving group via a 1,7 proton shift in the intermediate (35), as shown in Scheme 5. That the benzoic acid is a by-product of the reaction process studied has been confirmed by its identification from the reaction mixture. Furthermore, the relevant function of the carbonyl group at position 3 of the five-membered N,O-heterocycles examined is also demon-



9 - 13 35 19 - 23

SCHEME 5

strated by the different reaction channel which is populated when a phenyl ring is at the same position of the nucleus. In this case, amines (36) are formed after benzaldehyde elimination[3,8].



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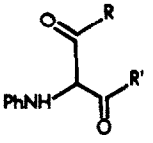


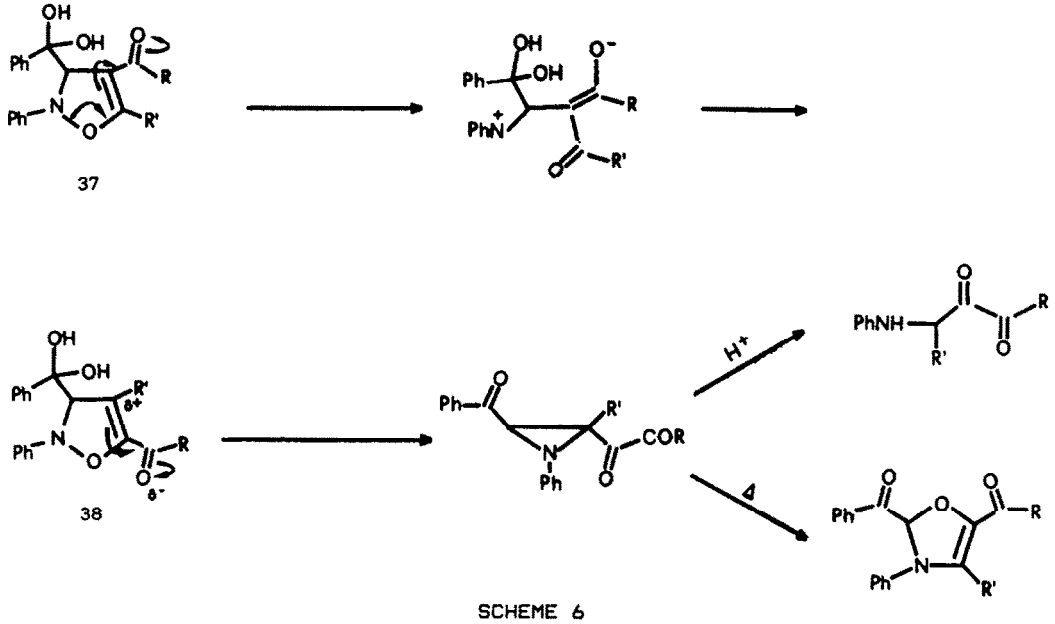
36

When regioisomers (14-17) were reacted in similar conditions as described above, they gave rise to amine products (30-33) quantitatively, even if the 5-substituted regioisomers are reported to be unreactive[23]. The thermal treatment of the same 4-isoxazolines generated also the aziridine-oxazoline rearrangement[13], yielding the corresponding 4-oxazolines (26-29) (Scheme 4). Structures were assigned to these products on the basis of analytical and spectroscopic data. In particular, the location in (26-29) of the methine proton signal at magnetic fields as high as 6.48-6.72 ppm is indicative for the presence of the proton between nitrogen and oxygen atoms[24] and confirms the 4-oxazoline structure[3]. The resonance of the vinylic proton in (26-28) appears in the range of 7 ppm.

In the case of amines (30-33), IR spectra revealed absorption maxima for amino and carbonyl groups at 3450 and 1650-1710 cm^{-1} respectively. MS spectra evidently confirmed the structures. Besides the molecular ion, the interested fragmentation was observed from the molecular ion by loss of the radical COCOR' ; moreover the presence of fragments at m/z 104 and 92, for the $Ph\text{-}\overset{+}{N}\equiv CH$ and $Ph\overset{+}{N}H$ ions, further supports the structure.

The marked difference in the chemistry of 4- and 5-regioisomeric 4-isoxazolines can be explained by the extended conjugation which is experienced in the case of substitution at position 4: this stabilizes the heterolytic bond ruptures with 1,7 H-migration, as reported in Scheme 6 for (37). The cross conjugation in the N,O-vinyl system of (38) causes a lower electron density

on C-4 of the 5-substituted regioisomers than in the 4-substituted ones; this suppresses the reaction channel to the enamines found through the intermediate (35). Similar effect can be invoked to operate for 4-isoxazolines (12) and (13), where a phenyl group is also at position 5 of the N,O-heterocyclic ring. The well known rearrangement to aziridine-oxazoline with different reaction mechanisms [25,26], therefore, becomes competing with the enamine route in the case of 5-substituted 4-isoxazolines.



SCHEME 6

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_4Si 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 intruments. 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 H (Merck).

Reaction of nitrone (3) with alkynes (4-8). - General procedure.
A solution of nitrone (10 mmol) and alkyne (30 mmol) in anhydrous THF (50 ml) was maintained, under stirring, at room temperature 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-cromatography on silica gel column with hexane/ether 60:40 as eluent.

Reaction of nitrone with methyl propiolate (4). Reaction time 5 h. First fractions gave 2-phenyl-3-benzoyl-4-methoxycarbonyl-4-isoxazoline (9) (39 % yield); yellow oil; ν max 3350, 1735, 1650, 1610, 1585, 1500, 1470, 1445, 1420, 1385, 1310, 1280, 1200 cm^{-1}; ^1H NMR δ ($CDCl_3$) 3.78 (s, 3H, CH_3), 7.56 (s, 1H, 5-H), 7.18-8.20 (m, 11H, aromatic protons and 3-H); m/z 309 (M^+ ,5), 281 (10),280 (23), 279 (15), 249 (9), 248 (6), 247 (25), 222 (5), 221 (10), 220 (15), 219 (30), 205 (15), 204 (100), 193 (4), 189 89), 188 (50), 171 (6), 167 (4), 149 (10), 146 (7), 145 (6), 144 (8), 143 (5), 130 (8), 128 (18), 124 (13), 119 (3), 118 (8), 117 (13), 116 (9), 105 (10), 104 (20), 103 (3), 102

(3), 93 (8), 91 (6), 90 (8), 89 (8), 78 (6), 77 (65).
Further elution gave 2-phenyl-3-benzoyl-5-methoxycarbonyl-4-isoxazoline (14); (59 % yield); light yellow oil; ν max 1760, 1670, 1600, 1580, 1500, 1460, 1385, 1260, 1220 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 3.75 (s, 3H, CH_3), 4.43 (d, 1H, 3-H or 4-H, J=2.65 Hz), 4.47 (d, 1H, 3-H or 4-H, J=2.65 Hz), 6.8-8.2 (m, 10H, aromatic protons); m/z 309 (M^+,15), 278 (3), 250 (15), 223 (4), 222 (25), 207 (5), 206 (3), 205 (10), 204 (100), 194 (5), 193 (5), 167 (7), 165 (9), 152 (6), 151 (4), 146 (7), 145 (20), 144 (50), 133 (3), 131 (3), 121 (20), 119 (15), 118 (25),117 (46), 116 (14), 106 (13), 105 (50), 104 (15), 103 (11), 102 (9), 101 (9), 96 (7), 93 (8), 91 (28), 90 (25), 89 (20),78 (30), 77 (70).

Reaction of nitrone with ethyl propiolate (5). Reaction time 5 h. First eluted product was 2-phenyl-3-benzoyl-4-ethoxycarbonyl-4-isoxazoline (10), (38.5% yield); light yellow solid, m.p. 66-8° C (from ether); ν max 3360, 1740, 1655, 1625, 1600, 1580, 1500, 1465, 1450, 1415, 1380, 1320, 1275, 1200 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.30 (t, 3H, CH_3, J=7.20 Hz), 4.18 (q, 2H, CH_2, J=7.20 Hz), 7.44 (s, 1H, 5-H), 7.03-8.20 (m, 11H, aromatic protons and 3-H); m/z 323 (M^+,14), 294 (20), 278 (4), 250 (8), 233 (3), 225 (5), 222 (10), 220 (13), 219 (40), 218 (100), 209 (3), 205 (7), 202 (5), 199 (5), 198 (12), 197 (10), 193 (5), 190 (10), 174 (13), 173 (7), 172 (20), 169 (3), 162 (6), 149 (6), 147 (6), 146 (18), 145 (19), 144 (28), 122 (10), 121 (13), 120 (8), 119 (6), 118 (15), 117 (28), 106 (20), 105 (80), 104 (22), 93 (25), 92 (5), 91 (10), 90 (10), 88 (8), 86 (50), 84 (70), 77 (90). (Found: C, 70.3; H, 5.5; N, 4.3 % . $C_{19}H_{17}NO_4$ requires C, 70.57; H, 5.30; N, 4.33 %).
Further elution gave 2-phenyl-3-benzoyl-5-ethoxycarbonyl-4-isoxazoline (15) (60 % yield); white solid, m.p. 98-9° (from ether); ν max 1758, 1675, 1600, 1580, 1500, 1450, 1375, 1265, 1230 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.40 (t, 3H, CH_3, J=7.10 Hz), 4.38 (q, 2H, CH_2, J=7.10 Hz), 4.40 (d, 1H, 3-H or 4-H, J=2.45 Hz), 4.54 (d, 1H, 3-H or 4-H, J=2.45 Hz), 6.60-8.20 (m, 10H, aromatic protons); m/z 332 (M^+,60), 278 (7), 250 (13), 223 (28), 222 (93), 219 (41), 218 (100), 194 (8), 193 (6), 192 (5), 191 (27), 190 (85), 167 (7), 165 (5), 146 (9), 145 (9), 144 (13), 118 (12), 117 (46), 116 (23), 106 (12), 105 (70), 104 (25), 102 (6), 92 (4), 91 (45), 90 (15), 89 (14), 78 (20), 77 (90). (Found: C, 70.6; H, 5.4; N, 4.4 %).

Reaction of nitrone (3) with 3-butyn-2-one (6). Reaction time 8 h. First eluted product was 2-phenyl-3-benzoyl-4-acetyl-4-isoxazoline (11) (37% yield); pale yellow oil; ν max 3340, 1730, 1660, 1605, 1580, 1520, 1490, 1460, 1430, 1380 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 2.30 (s, 3H, CH_3), 7.38 (s, 1H, 5-H), 7.15-8.10 (m, 11H, aromatic protons and 3-H); m/z 293 (M^+,22), 265 (18), 264 (23), 251 (10), 250 (28), 216 (3), 209 (4), 206 (12), 205 (8), 204 (10), 203 (10), 194 (19), 189 (12), 188 (75), 180 (8), 175 (5), 172 (12), 165 (10), 149 (3), 146 (9), 144 (9), 130 (3), 129 (10), 121 (3), 118 (12), 117 (8), 116 (11), 115 (7), 106 (14), 105 (100), 104 (12), 95 (4), 94 (5), 93 (12), 91 (24), 90 (8), 89 (9), 83 (4), 78 (5), 77 (64).
Subsequent fractions contained 2-phenyl-3-benzoyl-5-acetyl-4-isoxazoline (16), (60 % yield), light yellow oil; ν max 1760, 1675, 1605, 1575, 1510, 1460, 1380 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 2.40 (s,3H,CH_3), 4.38 (d,1H, 3-H or 4-H, J=2.5 Hz), 4.44 (d, 1H, 3-H or 4-H, J=2.5 Hz), 6.70-8.10 (m, 10H, aromatic protons); m/z 293 (M^+,7), 250 (34), 222 (22), 221 (3), 193 (4), 189 (16), 188 (100), 180 (10), 167 (4), 165 (6), 152 (3), 149 (3), 147 (4), 146 (22), 144 (3),130 (3), 122 (3), 118 (10), 117 (9), 116 (3), 115 (3), 106 (5), 105 (35), 104 (18), 103 (4), 102 (5), 94 (9), 92 (4), 91 (34), 90 (10), 89 (6), 78 (9), 77 (98).

Reaction of nitrone with ethyl phenylpropiolate (7). Reaction time 22 h. First fractions gave ethyl 2-benzoyl-3-phenylamino-propenoate (22), in a nearly equimolar and not separable mixture of E- and Z-isomers, (30 % yield); yellow oil; ν max 3380,1710,1670,1640, 1605, 1570, 1500, 1480, 1420, 1370, 1300 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 0.81 and 0.83 (t, 3H, CH_3, J=7.3 Hz), 3.94 and 3.93 (q, 2H, CH_2, J=7.3 Hz), 6.74-7.67 (m, 10H, aromatic protons), 8.12 and 8.37 (d, 1H, vinylic proton, J=12.8 Hz), 10.83 and 11.47 (d,1H, exchangeable NH,J=12.8 Hz); m/z 295 (M^+,8), 294 (13), 248 (10), 225 (5), 220 (3),219 (3),197 (7), 180 (4), 179 (19), 174 (13), 173 (3), 144 (3), 130 (12), 129 (47), 118 (4), 117 (4), 107 (8), 106 (85), 105 (53), 104 (6), 103 (4), 102 (36), 101 (6), 98 (86), 94(33), 93 (100), 92 (48), 91 (8), 88 (20), 86 (95), 85 (6), 84 (100), 83 (5), 79 (5), 78 (12), 77 (53).
Further elution gave 2,5-diphenyl-3-benzoyl-4-ethoxycarbonyl-4-isoxazoline (12) (5 % yield); white crystals, m.p. 92-4 C°(from ether); ν max 3400, 1745, 1690, 1670, 1600, 1585, 1495, 1490, 1470, 1450, 1370 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.13 (s, 3H, CH_3, J=7.20 Hz), 4.29 (q, 2H, CH_2, J=7.20 Hz), 7.38 (s, 1H, 3-H),

6.8-8.10 (m, 15H, aromatic protons); m/z 399 (M^+,12), 370 (4), 354 (8), 326 (7), 309 (8), 301 (6), 296 (4), 295 (15), 294 (100), 291 (5), 285 (3), 283 (6), 281 (15), 278 (6), 266 (6), 249 (3), 248 (8), 225 (5), 221 (5), 209 (6), 205 (7), 198 (5), 197 (15), 193 (10), 190 (3), 184 (3), 179 (5), 178 (15), 174 (13), 173 (6), 172 (10), 162 (3), 146 (8), 145 (10), 144 (20), 129 (8), 122 (20), 118 (5), 117 (5), 116 (5), 106 (20), 105 (70), 104 (13), 93 (8), 91 (30), 90 (5), 86 (14), 85 (35), 77 (90). (Found: C, 74.8; H, 5.5; N, 3.6 % . $C_{25}H_{21}NO_4$ requires C, 75.17; H, 5.30; N, 3.50 %).

Subsequent fractions contained 2,4-diphenyl-3-benzoyl-5-ethoxycarbonyl-4-isoxazoline (17) (25 % yield); white solid, m.p. 95-7°C (from ether); ν max 1740, 1690, 1600, 1580, 1495, 1450, 1390, 1370, 1320, 1250 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 0.99 (t, 3H, CH_3, J=7.15 Hz), 4.10 (q, 2H, CH_2,J=7.15 Hz), 4.86 (s,1H, 3-H), 6.87-8.17 (m, 15H, aromatic protons); m/z 399 (M^+,4), 354 (6), 326 (3), 298 (10), 296 (5), 295 (20), 294 (100), 283 (30), 267 (8), 266 (25), 241 (20), 220 (3), 219 (3), 194 (6), 193 (14), 192 (6), 191 (3), 190 (3), 178 (3), 171 (30), 167 (5), 166 (4), 165 (17), 152 (4), 144 (3), 129 (4), 117 (4), 116 (10), 115 (5), 107 (5), 106 (8), 105 (77), 104 (10), 103 (3), 102 (4), 91 (8), 90 (7), 89 (16), 78 (7), 77 (15), (Found: C, 74.9; H, 5.4; N, 3.6 %).

The last eluted product was 2,3-dibenzoyl-2-ethoxycarbonyl-1-phenylaziridine (24) (40 % yield); white crystals, m.p. 132-4°C (from ether); ν max 1740, 1710, 1675, 1620, 1605, 1595, 1495, 1450, 1395, 1370, 1335, 1320, 1300, 1240 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.10 (t, 3H, CH_3, J=7.3 Hz), 4,20 (q, 2H, CH_2, J=7.3 Hz), 6.67-7.74 (m, 15H, aromatic protons), 8.63 (s, 1H, CH); m/z 399 (M^+, 37), 398 (48), 354 (8), 295 (18), 294 (38), 278 (5), 276 (3), 249 (7), 248 (35), 222 (3), 221 (9), 220 (7), 205 (7), 193 (5), 180 (3), 172 (3), 144 (6), 122 (12), 117 (3), 116 (3), 106 (35), 105 (100), 104 (7), 97 (3), 95 (3), 91 (3), 90 (3), 89 (4), 78 (7), 77 (57). (Found: C, 75.0; H, 5.2; N, 3.4 %).

Reaction of nitrone with 4-phenyl-3-butyn-2-one (8). Reaction time 22 h. First eluted fractions gave ethyl 2-benzoyl-1-phenylamino-1-buten-3-one (23) (30 % yield) in an equimolar mixture of E- and Z-isomers; light yellow oil; ν max 1720, 1685, 1630, 1600, 1580, 1510, 1470, 1420,1385,1310 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 2.42 and 2.38 (s, 3H, CH_3), 6.80- 7.70 (m, 10H, aromatic protons), 8,18 and 8.30 (d, 1H, vinylic proton, J=13.0 Hz), 10.90 and 11.25 (d, 1H, exchangeable NH, J=13.0 Hz); m/z 265 (M^+, 29), 264 (100), 246 (9), 236 (10), 222 (10), 220 (8), 219 (4), 218 (4), 194 (11), 193 (5), 188 (5), 174 (7), 173 (5), 172 (8), 170 (8), 147 (4), 146 (18), 144 (11), 128 (4), 118 (5), 117 (5), 116 (7), 115 (3), 111 (3), 106 (6), 105 (70), 93 (12), 91 (11), 90 (8), 89 (5), 78 (9), 77 (72).

Successively 2,5-diphenyl-3-benzoyl-4-acetyl-4-isoxazoline (13) was obtained (4 % yield); light yellow oil; ν max 3390, 1720, 1680, 1650, 1600, 1590, 1500, 1470, 1385 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 2.66 (s, 3H, CH_3), 7.35 (s, 1H, 3-H), 6.84-7.85 (m, 15H, aromatic protons); m/z 369 (M^+,15), 326 (10), 295 (15), 292 (15), 279 (8), 278 (10), 264 (100), 261 (5), 251 (20), 249 (6), 225 (4), 179 (3), 173 (8), 167 (15), 160 (3), 145 (10), 144 (18), 129 (3), 122 (8), 118 (28), 105 (70), 104 (10), 93 (3), 91 (30), 90 (5), 89 (3), 88 (3), 86 (5), 85 (25), 77 (90).

Further elution afforded 2,4-diphenyl-3-benzoyl-5-acetyl-4-isoxazoline (18) (24 % yield); white crystals, m.p. 68-70°C (from ether); ν max 1720, 1690, 1610, 1590, 1500, 1480, 1430, 1385, 1350, 1320, 1270 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 2.58 (s, 3H, CH_3), 5.00 (s, 1H, 3-H), 6.87-8.27 (m, 15H, aromatic protons); m/z 369 (M^+, 6), 326 (7), 298 (15), 292 (4), 268 (3), 266 (4), 265 (8), 264 (100), 251 (30), 250 (8), 246 (10), 237 (3), 236 (13), 222 (9), 194 (11), 193 (5), 188 (5), 174 (5), 172 (8), 170 (8), 155 (4), 147 (4), 146 (18), 144 (15), 128 (4), 118 (35), 117 (5), 116 (7), 111 (3), 106 (5), 105 (70), 104 (3), 93 (11), 91 (18), 90 (5), 89 (3), 78 (5), 77 (80). (Found: C, 78.3; H, 4.9; N, 3.9 % . $C_{24}H_{19}NO_3$ requires C, 78.03; H, 5.18; N, 3.79 %).

Last fractions gave 2-acetyl-2,3-dibenzoyl-1-phenylaziridine (25) (42% yield); white solid, m.p. 125-7°C; ν max 1730,1710, 1670, 1610, 1600, 1580, 1500, 1460, 1385, 1350, 1310, 1250 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 2.27 (s, 3H, CH_3), 6.87-7.20 (m, 15H, aromatic protons), 8.02 (s, 1H, CH); m/z 369 (M ,20), 368 (29), 326 (10), 322 (5), 298 (35), 265 (4), 264 (25), 116 (4), 115 (3), 106 (10), 105 (100), 94 (3), 91 (4), 89 (3), 78 (6), 77 (48). (Found: C, 77.9; H, 5.3; N,3.9 %).

Rearrangement reactions of isoxazolines (9-13).
To a solution of isoxazoline (1 mmol) in 15 cc of THF, a catalytic amount of HCl 1:1 was added. The mixture was heated at reflux (65°C) for 2 h. After the evaporation of the solvent, enamines (20-23) were obtained in 95-98 % yield.

2-Methoxycarbonyl-3-phenylamino-propenale (19) (96 % yield); yellow oil; ν max 3380, 2810, 2750, 1710, 1690, 1630, 1605, 1570, 1500, 1480, 1410, 1385, 1300 cm^{-1} ; ^1H NMR δ($CDCl_3$) 3.80 (s, 3H, CH_3), 7.15-7.70 (m, 5H, aromatic protons), 8.47 (dd, 1H, vinylic proton, J=13.60 and 3.80 Hz), 9.96 (d,1H, aldehydic

proton, J=3.80 Hz),12.50 (s, 1H, NH, J=13.6 Hz); ^{13}C NMR 48.10 (q), 103.10 (s), 117.12 (d), 126.02 (d), 129.69 (d), 139.02 (s), 151.02 (d), 167.02 (s), 191.10 (d); m/z 205 (M^+, 68), 204 (62), 188 (6), 177 (3), 176 (19), 174 (13), 173 (8), 172 (46), 161 (3), 151 (3), 146 (12), 145 (28), 144 (100), 132 (5), 130 (4), 128 (6), 119 (3), 118 (36), 117 (91), 116 (16), 113 (3), 104 (15), 102 (4), 94 (3), 93 (17), 92 (4), 91 (16), 90 (32), 89 (17), 85 (5), 77 (40).

2-Ethoxycarbonyl-3-phenylamino-propenale (20) (98 % yield); pale yellow crystals, m.p. 56-8°C (from ether); ν max 3360, 2820, 2780, 1700, 1640, 1605, 1580, 1490, 1470, 1420, 1380, 1300 cm^{-1} ; ^{1}H NMR δ ($CDCl_3$) 1.35 (t, 3H, CH_3, J=7.17 Hz), 4.30 (q, 2H, CH_2, J=7.17 Hz), 7.20-7.45 (m, 5H, aromatic protons), 8.47 (dd, 1H, vinylic proton, J=13.43 and 3.51 Hz), 9.95 (d,1H, aldehydic proton, J=3.51 Hz), 12.48 (d, 1H, NH, J=13.43 Hz); ^{13}C NMR 14.34 (q), 59.98 (t), 102.59 (s), 117.67 (d), 125.96 (d), 129.79 (d), 138.37(s),150.77 (d),166.76 (s),191.06 (d); m/z 219 (M^+,100), 218 (42), 202 (3), 190 (14), 174 (23), 173 (10), 172 (51), 161 (10), 149 (6), 146 (20), 145 (41), 144 (92), 135 (4), 130), 119 (6), 118 (42), 117 (93),116 (10), 104 (17), 93 (21), 91 (18), 90 (22), 88 (13), 78 (8), 77 (58). (Found: C, 65.6; H, 5.8; N, 6.5 % . $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39 %).

2-Acetyl-3-phenylamino-propenale (21) (97 % yield); oily product; ν max 3290, 2830, 2790, 1700, 1660, 1605, 1560, 1480, 1410, 1385 cm^{-1} ; ^{1}H NMR δ ($CDCl_3$) 2.35 (s, 3H, CH_3), 7.25-7.75 (m, 5H, aromatic protons), 8.50 (dd, 1H, vinylic proton, J=13.50 and 3.70 Hz), 9.98 (d, 1H, aldehydic proton, J=3.70 Hz), 12.50 (d, 1H, NH, J=13.50 Hz); ^{13}C NMR 23.05 (q), 103.50 (s), 118.05 (d), 125.90 (d), 128.90 (d), 138.50 (s), 150.70 (d), 163.20 (s), 192.10 (d); m/z 189 (M^+,35), 188 (70), 171 (25), 161 (10), 160 (52), 146 (50), 144 (21), 128 (9), 119 (16), 118 (100), 117 (28), 116 (10), 105 (10), 104 (18), 101 (6), 93 (11), 92 (7), 91 (30), 90 (16), 89 (10), 79 (7), 78 (9), 77 (70).

Ethyl 2-benzoyl-3-phenylamino-propenoate (22). By refluxing for 2 h a THF solution of isoxazoline (12),containing a catalytic amount of HCl 1:1, enamine (22) was obtained with a yield of 97 %, as an equimolar mixture of E- and Z-isomers.

2-Benzoyl-1-phenylamino-1-buten-3-one (23). In similar conditions, from isoxazoline (13) an equimolar mixture of E- and Z-isomers was obtained, with a yield of 96 %, after 2 h of reflux.

Rearrangement of isoxazolines (14).

A solution of isoxazoline (14) (0.31 g; 1mmol) in 15 cc of anhydrous THF was refluxed (65°C) for 4.30 h. After the removal of the solvent, the residue was crystallized from ether to afford 2-benzoyl-3-phenyl-5-methoxycarbonyl-4-oxazoline (26) (98 % yield) as colorless crystals; m.p.77-80 °C ; ν max 1715, 1690, 1645, 1605, 1585, 1510,1455,1400, 1380, 1270, 1240 cm^{-1} ; ^{1}H NMR δ ($CDCl_3$) 3.65 (s, 3H, CH_3), 6.70 (s, 1H, 2-H), 6.97 (s, 1H, 4-H), 6.40-8.10 (m, 10H, aromatic protons); m/z 309 (M^+,10), 294 (8), 293 (50), 266 (8), 265 (34), 264 (34), 204 (60), 194 (16), 150 (12), 131 (41), 106 (16), 105 (100), 104 (76), 103 (17), 101 (13), 91 (39), 89 (10), 78 (18), 77 (42). (Found: C, 70.0; H, 4.7; N, 4.7 % . $C_{18}H_{15}NO_4$ requires C, 69.89; H, 4.89; N, 4.53 %).

When a solution of (14) in the same solvent was treated in similar conditions with a catalytic amount of HCl 1:1 for 1 h, methyl 2-oxo-3-phenylamino-propanoate (30) was obtained in a nearly quantitative yield (98 %) as a pale yellow oil; max 3450, 1705, 1670, 1595, 1560, 1480, 1420, 1385 cm^{-1} ; ^{1}H NMR ($CDCl_3$) 3.50 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 3.95 (broad, 1H, NH), 6.50-8.10 (m, 5H, aromatic protons); m/z 193 (M^+, 21), 192 (10), 191 (5), 133 (12), 106 (16), 105 (37), 104 (100), 92 (17), 78 (15), 77 (65).

Rearrangement of isoxazoline (15).

Isoxazoline (15) was converted in oxazoline (27) (98 % yield) by refluxing for 4.30 h a THF solution. 2-benzoyl-3-phenyl-5-ethoxycarbonyl-4-oxazoline (27), white crystals, m.p. 91-3 °C; ν max 1710, 1670, 1640, 1600, 1580, 1500, 1470, 1420, 1370, 1300, 1250 cm^{-1} ; ^{1}H NMR δ ($CDCl_3$) 1.27 (t, 3H, CH_3, J=6.90 Hz), 4.20 (q, 2H, CH_2,J=6.90 Hz), 6.72 (s, 1H, 2-H), 7.04 (s, 1H, 4-H), 6.40-8.20 (m, 10H, aromatic protons); m/z 323 (M^+,4), 250 (7), 222 (14), 220 (4), 219 (30), 218 (100), 191 (14), 190 (70), 165 (3), 146 (4), 144 (6), 118 (6), 117 (27), 116 (9), 105 (25), 104 (12), 91 (23), 90 (6), 89 (7), 78 (5), 77 (70). (Found: C, 70.7; H, 5.5; N, 4.2 % . $C_{19}H_{17}NO_4$ requires C, 70.57; H,5.30; N,4.33 %).

A similar solution, containing a catalytic amount of HCl 1:1, was refluxed for 1 h to give the ethyl 2-oxo-3-phenylamino-propanoate (31) (93 % yield) as an oil; ν max 3450, 1695, 1670, 1590, 1500, 1380 cm^{-1} ; ^{1}H NMR δ($CDCl_3$) 1.27 (t, 3H, CH_3, J=6.90 Hz) 4.27 (q, 2H, CH_2, J=6.90 Hz), 4.50 (s, 2H, CH_2),6.54-8.07

(m, 5H, aromatic protons); m/z 207 (M^+,5), 206 (18), 205 (3),178 (5), 133 (15), 106 (18), 105 (30), 104 (100), 92 (20), 78 (13), 77 (70),

Rearrangement of isoxazoline (16).
Thermal treatment for 4 h of a solution of isoxazoline (16) in THF gave, after removal of the solvent, 2-benzoyl-3-phenyl-5-acetyl-4-oxazoline (28) (94 % yield) as an oil; ν max 1690,1670,1625,1590, 1520, 1470, 1430, 1385, 1310 cm^{-1} ; ^1H NMR δ($CDCl_3$) 2.35 (s, 3H, CH_3), 6.62 (s, 1H, 2-H), 6.89 (s, 1H, 4-H), 6.25-7.92 (m, 10H, aromatic protons); m/z 293 (M^+, 15), 251 (22), 250 (100), 222 (22), 221 (5), 194 (7), 193 (9), 180 (6), 167 (9), 166 (5), 165 (8), 146 (6), 145 (5), 117 (10), 116 (5), 115 (4), 106 (5), 105 (45), 104 (23), 103 (5), 102 (12), 101 (4), 97 (3), 94 (4), 92 (3),91 (13),90 (10),89 (5), 78 (6), 77 (84). By refluxing for 2 h a THF solution of (16) containing a catalytic amount of HCl 1:1, 4-phenylamino-2,3-dioxo-butane (32) was obtained (97 % yield) as a yellow oil; ν max 3450, 1685 1450, 1380, 1300, 1245 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 2.28 (s, 3h, CH_3), 3.80 (broad, 1H, NH), 4.10 (s, 2H, CH_2), 6.70-7.80 (m, 5H, aromatic protons); m/z 177 (M^+, 28), 176 (15), 175 (10), 162 (3), 134 (20), 133 (13), 106 (12), 105 (72), 104 (100), 92 (15), 91 (5), 86 (7), 78 (15), 77 (70).

Rearrangement of isoxazoline (17).
A solution of 0.4 g (1 mmol) of isoxazoline (17) in 15 cc of THF was refluxed for 5 h to give 2-benzoyl-3,4-diphenyl-5-ethoxycarbonyl-4-oxazoline (29) (97 % yield) as a white crystals; m.p. 97-9 °C ; ν max 1710, 1630, 1600, 1580, 1495, 1450, 1400, 1385, 1330, 1300 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.04 (t, 3H, CH_3,J=7.0 Hz), 4.14 (q, 2H, CH_2, J=7.0 Hz), 6.48 (s, 1H, 2-H), 6.94-8.30 (m, 15H, aromatic protons); m/z 399 (M^+; 3), 354 (3), 296 (4), 295 (21), 294 (100), 267 (5), 266 (26), 223 (5), 219 (3), 194 (4), 193 (11), 192 (5), 191 (4), 190 (3), 167 (5), 166 (4), 165 (13), 152 (4), 129 (4), 117 (5), 116 (8), 115 (3), 106 (5), 105 (52), 104 (9), 103 (4), 102 (3), 91 (10), 90 (6), 89 (15), 79 (3), 78 (5), 77 (60). (Found: C, 74.9; H, 5.4; N, 3.7 % . $C_{25}H_{21}NO_4$ requires C, 75.17; H, 5.30; N, 3.50 %).
A similar solution additionated of a catalytic amount of HCl 1:1, was refluxed for 2 h to yield the ethyl 3-phenyl-3-phenylamino-propanoate (33) (98 % yield) as a light yellow oil; ν max 3430,1710,1550,1580, 1520, 1490, 1410, 1370 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.07 (s, 3H, CH_3, J=7.20 Hz), 4.13 (q, 2H, CH_2, J=7.20 Hz), 4.70 (broad, 1H, NH), 5.63 (s, 1H, CH), 6.55-7.75 (m, 5H, aromatic protons); m/z 283 (M^+,14), 282 (15), 281 (12), 211 (4), 210 (8), 209 (11), 179 (12), 178 (52), 150 (8), 132 (7), 130 (6), 107 (4), 106 (18), 105 (61), 104 (100), 101 (3), 92 (15), 91 (3), 89 (3), 80 (5), 79 (3), 78 (10), 77 (70).

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