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REGIOSELECTIVE FORMATION OF 4-ISOXAZOLINES FROM N-ARYL NITRONES AND ALKYNES

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Abstract: 4-Regioisomeric 4-isoxazolines are selectively formed by 1,3-dipolar cycloaddition of N-arylnitrones to substituted alkynes. The reactivity and regioselectivity of the addition process are interpreted by the application of FMO principles. Secondary orbital interactions between reactants affect the transition state for the 4- and 5-regioisomeric 4-isoxazolines, while the steric effect is limited as shown by the experiments with N-alkylnitrones.

The N,O-vinyl functional group with the double bond both endocyclic[1] and exocyclic[2] within a five membered heterocyclic framework constitute a novel source of well characterized intramolecular rearrangements leading to deep chemical modification of the original derivatives. The production of the endocyclic N,O-vinyl functionality can be achieved by the 1,3-dipolar cycloaddition of nitrones to triple bonds[3,4], as a mild approach to substituted 4-isoxazolines. The reaction of C-C, C-O and C-N bond formation can be utilized in organic synthesis because of the possible conversion of the initial cycloadducts into different functionalities[5]. Therefore, factors controlling regiochemical preferences in intermolecular cycloadditions of nitrones to dipolarophiles[6] must be clearly understood, in order to allow the prediction of the formation of regioisomeric 4-isoxazolines from substituted nitrones and alkynes, whose chemistry has been experimentally shown to be different[7].

N-Arylnitrones are known to be more reactive than the N-alkyl substituted ones[8], thus providing an easily accessible mode to generate N-aryl-4-isoxazolines[9-13], which undergo facile intramolecular rearrangements[1].

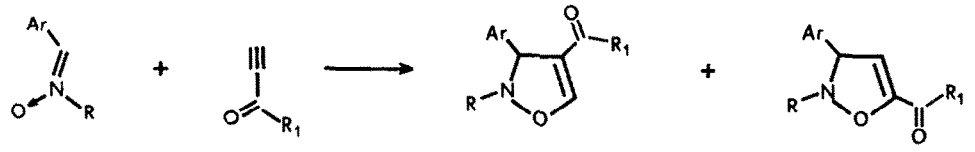
The reactivity and regioselectivity in the 1,3-dipolar cycloaddition has been already rationalized applying the frontier molecular orbital (FMO) approximation of the perturbation theory[3,6]. The careful consideration of FMO interactions permits, in fact, to account for most of the experimental findings. While a significant body of data regarding the regiochemical control of cycloaddition reaction of N-alkylnitrones and alkynes has been acquired[14-17], little detailed information is available for the more reactive N-arylnitrones adding to the same dipolarophiles. The FMO's of parent nitrone, i.e. CH_2NHO, reveal almost a node through the central nitrogen atom, c_N=0,155, in the HOMO of the dipole[18]; thus the change of substituent at this position should preserve at first approximation the shape of the MO considered, while altering the relative energy.

In connection with the evaluation of the 4-isoxazoline chemistry for synthetic application[1,2,4,19], the 1,3-dipolar cycloaddition of N-arylnitrones to some electron-withdrawing

substituted alkynes has been performed. The result of the experiments carried out has been interpreted on the basis of the perturbation molecular orbital treatment with the assistance of SCF-MO calculations[20].

RESULTS AND DISCUSSION

N-Arylnitrones (1-3) have been allowed to react with electron-deficient alkynes (6-8) in refluxing anhydrous THF for several hours, according to the substituents, to yield 4-isoxazoline derivatives (9-15) as stable cycloadducts, as shown in Scheme 1. Using an almost 1:1 ratio of the dipole and dipolarophile, the reaction products were isolated after conventional work-up and purified by short column chromatography under slight pressure.



1 - 5 6 - 8 9 - 15 16 - 21

1)R=Ar=Ph
2)R=p-ClPh;Ar=Ph
3)R=Ph;Ar=p-NO_2Ph
4)R=C_6H_{11};Ar=Ph
5)R=i-Pr,Ar=Ph

6)R_1=OMe
7)R_1=OEt
8)R_1=Me

9)R=Ar=Ph;R_1=OMe
10)R=Ar=Ph;R_1=OEt
11)R=Ar=Ph;R_1=Me
12)R=p-ClPh;Ar=Ph;R_1=OMe
13)R=p-ClPh;Ar=Ph;R_1=OEt
14)R=Ph;Ar=p-NO_2Ph;R_1=OMe
15)R=Ph;Ar=p-NO_2Ph;R_1=OEt
16)R=C_6H_{11};Ar=Ph;R_1=OMe
17)R=C_6H_{11};Ar=Ph;R_1=OEt
18)R=i-Pr;Ar=Ph;R_1=OMe

19)R=C_6H_{11};Ar=Ph;R_1=OMe
20)R=C_6H_{11};Ar=Ph;R_1=OEt
21)R=i-Pr;Ar=Ph;R_1=OMe

SCHEME 1

The isolated 4-isoxazolines (9-15) were analyzed by physico-chemical methods and the data were consistent with the assigned structures. The regiochemical orientation of the dipolarophiles (6-8) used in the reaction with dipoles (1-3) has been derived by the ^{1}H NMR spectra of the N,O-heterocycles formed after the 1,3-dipolar cycloaddition. The 5-H's of the 4-isoxazolines (9-15) resonate in the range 7.3-7.7 ppm, in accordance with the well known absorption at lower field than the 4-H's[1], owing to the deshielding effect of the oxygen atom on the former. The mass spectrum fragmentation pattern of the molecular ion is diagnostic, thus supporting the regiochemical assignment to the isolated 4-isoxazolines. In fact, the ionized species in the case of (9), (11), (12) and (14) expels CHO radical from position 5 of the N,O-five-membered nucleus, thus showing that the substituent group is at C-4.

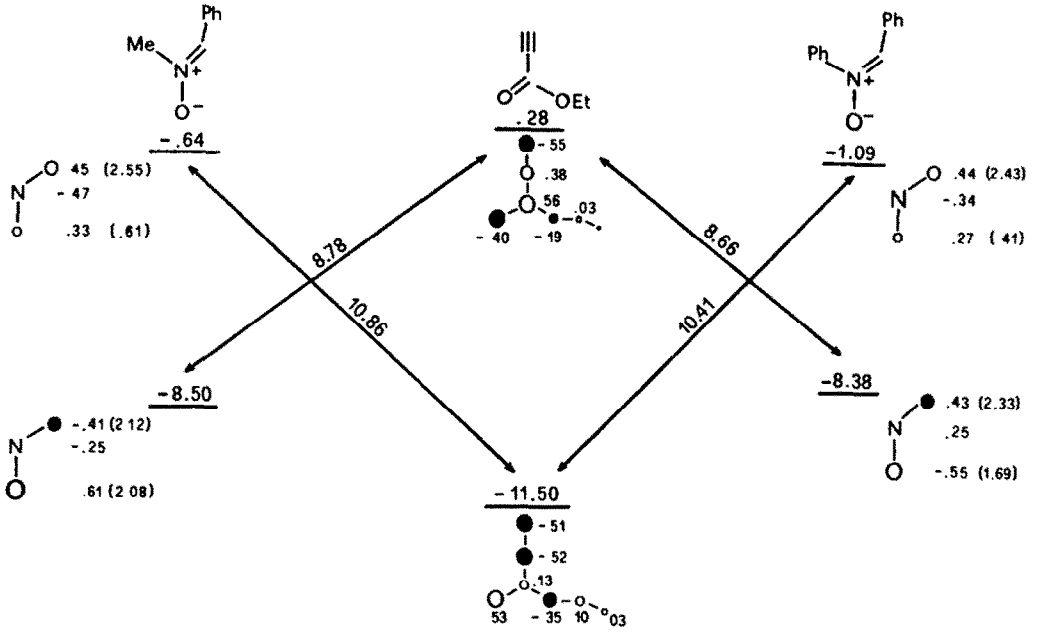
The 4-substituted regioisomeric 4-isoxazolines were the only cycloadduct formed, as was clearly confirmed by NMR analysis of the crude reaction mixture and by TLC check during the reaction procedure, which showed the absence of the 5-substituted regioisomers.

The experiments thus carried out demonstrate the marked influence of the substituent pattern on the regiochemical control of the 1,3-dipolar cycloaddition of N-arylnitrones to the triple bonds used. In fact when C-phenyl-N-methylnitrone (22) undergoes cycloaddition to the alkyne (6), a competitive formation of 4- and 5-substituted regioisomers has been ascertained[7]. This tendency of forming reversed regioisomers has been rationalized by the use of FMO interactions[7].

The enhanced reactivity and the drastic regioselectivity observed for nitrones (1-3) can also be considered in terms of FMO characteristics for the model dipole (1). The change of substituent group from methyl to phenyl one on the nitrogen atom of the 1,3-dipoles raises the HOMO of the nitrone (1) to -8.38 eV as compared to -8.50 eV of the nitrone (22) reported in

Scheme 2, which includes the results of MO calculations, using the MNDO method with complete optimization of structure[4,21]. Similarly, the LUMO level of (1) is lowered to -1.09 eV compared with the same of (22) which lies at -0,64 eV. The resulting stabilization of the transition state, with subsequent increase of reaction rate, can be due to the increment of interaction between the HOMO of (1) and the LUMO of (6), as well as LUMO of (1) and HOMO of (6), both leading to the rate enhancement of the 1,3-dipolar cycloaddition of (1) to (6).

The increase of the reactivity observed for the cycloaddition of nitrones (1-3), as compared with that of (4) and (5) (see Experimental), can be also explained by the conjugative interaction at the nitrogen atom of the related cycloadducts. This is experienced when the iminium ion character of the nitrones (1-3) is suppressed, generating the aniline-type resonance at the nitrogen atom in the 4-isoxazoline adduct[8b]. Furthermore, nitrone (2) experimentally shows a marked decrease of reaction time in the 1,3-dipolar cycloaddition to the alkynes used.



SCHEME 2. Frontier orbitals coefficients and energies for 1,3-dipoles and ethyl propiolate. Figures in brackets refer to $(c\beta)^2$ values.

This can be interpreted on the basis of a larger LUMO-nitrone HOMO-alkyne interaction, because the electron withdrawing effect of the Cl atom on the aryl moiety at the nitrogen atom lowers the LUMO more than the HOMO[21]. The improvement of conjugative interaction in derivatives (12) and (13) can also affect the reaction enthalpy in the case of the addition with dipole (2).

The complete regiochemical control of the cycloaddition process of the N-arylnitrones to the alkynes studied can also be interpreted on the basis of FMO theory[3,6] with comparison to the novel theoretical calculations performed on the N-methyl-substituted nitrone (22).

In the case of reaction of (1) with (6), the dipolar HOMO-dipolarophile LUMO-dipole is the dominant interaction. Therefore, the 4-regioisomeric 4-isoxazoline (9) is the expected reaction product because of the larger coefficient at oxygen than carbon. This favours the transition state leading to the 4-isomer, this interaction being the most stabilizing one. However, since nitrones are 1,3-dipoles characterized by a borderline behavior where both dipole HOMO and dipole LUMO control can be important[3], the dipole LUMO interaction for the addition process of

(1) with (6) cannot affect the regiochemistry of the reaction which leads to an unique isomer. This derives from the consideration that the HOMO coefficients on carbon atoms of the triple bond of (6) are almost identical[4], thus leading to a possible mixture of regioisomers. Moreover, the energy gap difference between the two FMO interactions is larger than 1 eV[22].

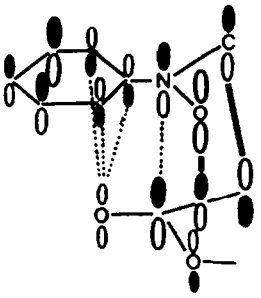
The loss of regioselectivity, experienced in the 1,3-dipolar cycloaddition of (22) to (6), has been already explained on qualitative basis[6,7,22] leading to the conclusion that nitrone (22) must show a greater tendency to 4-regioisomers[7], compared to the parent nitrone, since the phenyl and methyl substituents should alter the difference between carbon and oxygen coefficients[16]. This explanation is confirmed by the MO calculations reported in Scheme 2, where the nitrone (22) shows the HOMO coefficients favouring the 4-regioisomeric 4-isoxazoline, which is, however, 58% of the reaction mixture[8]. The 42% of the 5-regioisomeric 4-isoxazoline experimentally found[8] cannot be easily justified by the dipole LUMO regiochemical control, since the dipolarophile HOMO of (6) is at a low energy level with an energy gap of 2.08 eV and reveals almost identical coefficients at both carbons of the reacting triple bond.

In order to accommodate the apparent discrepancy between the experimental and the theoretical results obtained for the reaction of nitrones (1) and (22) with the alkyne (6), the squares of the product of the MO coefficients[16] of (22) and the resonance integrals, β_{CO}=2.366 and β_{CC}=3.549, calculated at 2.24 Å[23], have been evaluated and are reported in brackets in Scheme 2. Using this more appropriate FMO treatment, the corrected relevant coefficients of (22) become nearly the same, thus explaining the attainment of a mixture of 4- and 5-regioisomeric isoxazolines which is controlled by the dipole HOMO interaction only. The slight tendency towards the formation of the 4-regioisomer can be due to a secondary-orbital attractive interaction between the nitrone C-orbital and the C-carbonyl orbital of the substituted alkyne (6)[24].

The extension of the same FMO treatment as above to the 1,3-dipole (1) involves that the proposed interpretation, previously discussed taking into account the simple coefficients of the dipole HOMO of (1), must be reconsidered. The more correct approach which takes into account the $(c\beta)^2$ values should lead to the conclusion that the dipole HOMO controlled interaction should favour the 5-regioisomer, while the dipole LUMO one should give a mixture of isomers on the basis of the equivalence of coefficients at the dipolarophile (6)[23].

The experimental findings with clear cut results of only one 4-regioisomeric 4-isoxazoline isolated from the reaction of the nitrones (1-3) with alkynes (6-8) can be attributed to long-range bonding interactions between secondary orbitals of the N-aryl substituted 1,3-dipoles and the electron-poor dipolarophiles used. The stabilizing secondary orbital interaction between the C-orbital of the nitrone and the C-carbonyl orbital of the substituted alkynes cited above cannot explain the drastic effect observed in the regioselection in the 1,3-dipolar cycloadditions studied, since it should be also observed for the reaction of (22) with (6). This is also the case for the destabilizing interaction between N-orbital of the nitrones (1) and (22) and the C-orbital of the ester group of the alkyne (6). An additional factor which contributes to the stabilization of the transition state leading to the 4-isomer, in the process of addition of (1) to (6), can be sought in the repulsive secondary orbital interaction between the oxygen orbitals of the ester group of (6) and the π orbitals of the N-aryl group of (1) in the dipole HOMO approach to the dipolarophile LUMO, leading to the formation of the 5-regioisomeric 4-isoxazolines as shown in Scheme 3.

In order to ascertain that a long range bonding interaction can be involved without the possible steric effect encouraging the transition state for the experimentally observed 4-regioisomers, the 1,3-dipolar cycloaddition of nitrones (4) and (5) has been carried out. The isolated products were a mixture of 4- and 5-isoxazolines (16-21), whose composition was in the range of 60% and 40% respectively. This experiment clearly indicates that the regioselection is highly influenced by the aryl substituent group on the nitrogen atom of the 1,3-dipole, while other substituents, i.e. cyclohexyl and isopropyl, demonstrate identical trend with the methyl one of the nitrone (22).



SCHEME 3

CONCLUSION

N-Arylnitrones undergo 1,3-dipolar cycloaddition to electron-poor alkynes showing an increase of reactivity and a high degree of regioselection which can be interpreted by the application of FMO concepts. The careful FMO treatment allows the correct rationalization of the N-alkylnitrone addition to the same substrates, with the dominant dipole HOMO interaction being able to explain the experimental results. On the other hand, the same theoretical approach requires that secondary orbital interactions between the reactants can stabilize the transition state for the 4-regioisomers while destabilizing that for the 5-regioisomers. The value of the steric effect is limited because the N-alkyl nitrones studied give rise to the same reaction mixture of 4- and 5-isomers.

EXPERIMENTAL

M.p.s. were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer. ^{1}H NMR spectra were obtained at 25 ° C for solutions in $CDCl_3$ on Bruker WP 80 and WP 200 SY instruments; chemical shifts were reported in ppm downfield from Me_4Si. IR spectra were recorded on a Perkin-Elmer 225 instrument as nujol mulls. Mass spectra were performed on a Varian Mat CH-5 DF and on a GC-MS HP 5890 A instruments. Reaction mixtures were analysed 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). MNDO calculations were carried out as described elsewhere[24].

Reaction of nitrones (1-5) with alkynes (6-8). General procedure .-
A solution of nitrone (10 mmol) and alkyne (12 mmol) in anhydrous THF (50 ml) was refluxed (65 °C) for 4-12 h until t.l.c. on silica gel in 7:3 hexane/ether indicated the disappearance of starting nitrone. The reaction mixture was evaporated and the residue triturated with ether to give 4-isoxazolines 9-21. Regioisomers were separated by flash-chromatography of the crude reaction mixture (hexane/ether 8:2 as eluent).

Reaction of nitrone (1) with methyl propiolate (6).
2,3-diphenyl-4-methoxycarbonyl-4-isoxazoline (9), reaction time 6 h, 80% yield, light yellow solid, m.p. 154-6 °C (ether); νmax 1695, 1635, 1600, 1585, 1515, 1495, 1465, 1385 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 3.90 (s, 3H, CH_3), 6.90 (s, 1H, 3-H), 7.60 (s, 1H, 5-H), 6.65-7.80 (m, 10H, aromatic protons); m/z 281 (M^+, 44), 266 (4), 252 (6), 223 (18), 222 (100), 220 (8), 204 (22), 195 (12), 194 (74), 193 (39), 192 (8), 189 (7), 180 (3), 167 (3), 166 (6), 165 (18), 164 (3), 152 (9), 144 (4), 118 (59), 117 (10), 116 (23), 105 (10), 104 (36), 92 (3), 91 (38), 90 (17), 89 (28), 78(8), 77 (75). (Found: C, 72.7; H, 5.4; N, 5.1% . $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.37; N, 4.98%).

Reaction of nitrone (1) with ethyl propiolate (7).
2,3-diphenyl-4-ethoxycarbonyl-4-isoxazoline (10), reaction time 6 h, 82% yield, light yellow prisms, m.p. 149-50 ° C (ether); ν max 1690, 1650, 1600, 1580, 1510, 1460, 1420, 1390 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 1.33 (t, 3H, CH_3), 4.27 (q, 2H, CH_2, J=7.4 Hz), 6.80 (s, 1H, 3-H), 7.44 (s, 1H, 5-H), 6.60-7.65 (m, 10H, aromatic protons); m/z 295 (M^+, 40), 266 (7), 223 (15), 222 (100), 220 (13), 218 (13), 203 (4), 195 (9), 194 (60), 193 (29), 191 (3), 190 (7), 181 (3), 180 (7), 178 (4), 177 (4), 175 (4), 167 (7), 166 (4), 165 (17), 163 (3), 152 (9), 151 (4), 145 (3), 144 (5), 118 (5), 117 (7), 116 (22), 115 (4), 106 (8), 105 (16), 104 (37), 91 (28), 90 (13), 89 (20), 78 (7), 77 (55). (Found: C, 73.4; H, 5.7; N, 4.9% . $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%).

Reaction of nitrone (1) with 3-butyn-2-one (8).
4-acetyl-2,3-diphenyl-4-isoxazoline (11), reaction time 6 h, 78% yield, light yellow solid, m.p. 147-9°C ; ν max 1715, 1670, 1600, 1580, 1530, 1495, 1470, 1455 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.27 (s, 3H, CH_3), 6.87 (s, 1H, 3-H), 7.60 (s, 1H, 5-H), 6.70-7.75 (m, 10H, aromatic protons); m/z 265 (M^+, 13), 236 (4), 223 (9), 222 (81), 206 (11), 205 (14), 204 (10), 197 (11), 195 (12), 194(52), 193 (40), 182 (31), 181 (35), 180 (33), 172 (10), 165 (10), 149 (25), 105 (48), 104 (19), 93 (20), 91 (35), 90 (10), 89 (13), 78 (16), 77 (100). (Found: C, 7.5; H, 5.8; N, 5.4% $C_{17}H_{15}NO_2$ requires C, 7.69; H, 5.70; N, 5.28%).

Reaction of nitrone (2) with methyl propiolate (6).
2-p-chlorophenyl-4-methoxycarbonyl-3-phenyl-4-isoxazoline (12), reaction time 4h, 86% yield, white solid, m.p. 158-160 °C (ether); ν max 1695, 1640, 1600, 1585, 1515, 1490, 1470 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 3.75 (s, 3H, CH_3), 6.97 (s, 1H, 3-H), 7.50 (s,1H, 5-H), 6.70-7.80 (m, 10H, aromatic protons); m/z 315 (M^+,38), 314 (6), 286 (5), 280 (4), 259 (5), 258 (34), 257 (19), 256 (100), 254 (8), 240 (5), 238 (14), 231 (3), 230 (19), 229 (13), 228 (57), 227 (19), 220 (5), 214 (3), 194 (4), 193 (24), 191 (6), 190 (5), 189 (14), 178 (4), 166 (8), 165 (29), 164 (5), 163 (3), 152 (6), 151 (4), 150 (5), 144 (4), 140 (14), 139 (7), 138 (38), 125 (3), 121 (4), 118 (5), 117 (6), 116 (14), 115 (3), 114 (4), 113 (10), 112 (3), 111 (28), 106 (3), 105 (9), 102 (4), 95 (3), 92 (4), 91 (48), 90 (15), 89 (25), 82 (3), 78 (3), 77 (15). (Found: C, 64.8; H, 4.6; N, 4.6% . $C_{17}H_{14}Cl\,NO_3$ requires C, 64.65; H, 4.47; N, 4.43%).

Reaction of nitrone (2) with ethyl propiolate (7).
2-p-chlorophenyl-4-ethoxycarbonyl-3-phenyl-4-isoxazoline (13), reaction time 4 h, 84% yield, white solid, m.p. 163-5°C (ether); ν max 1695, 1655, 1605, 1580, 1515, 1470, 1430, 1390 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.30 (t, 3H, CH_3, J=7.2 Hz), 4.23 (q, 2H, CH_2, J=7.2 Hz), 6.98 (s, 1H, 3-H), 7.46 (s, 1H, 5-H), 6.60-7.80 (m, 10H, aromatic protons); m/z 329 (M^+, 33), 328 (3), 300 (7), 284 (3), 259 (5), 258 (31), 257 (17), 256 (100), 254 (14), 252 (7), 231 (3), 230 (15), 229 (11), 228 (45), 227 (14), 224 (3), 220 (4), 216 (3), 214 (3), 203 (7), 194 (3), 193 (19), 192 (7), 191 (6), 190 (4), 166 (6), 165 (22), 164 (4), 163 (3), 152 (4), 151 (3), 150 (4), 144 (4), 140 (13), 139 (7), 138 (41), 125 (4), 118 (4), 117 (5), 116 (8), 115 (3), 114 (3), 113 (10), 112 (3), 111 (28), 105 (7), 102 (3), 96 (3), 91 (33), 90 (9), 89 (19), 77 (11). (Found: C, 65.4; H, 4.7; N, 4.4% . $C_{18}H_{16}ClNO_3$ requires C, 65.55; H, 4.89; N, 4.24%).

Reaction of nitrone (3) with methyl propiolate (6).
4-methoxycarbonyl-3-p-nitrophenyl-2-phenyl-4-isoxazoline (14), reaction time 6.30 h, 75 % yield, white solid, m.p. 208-209 °C; ν max 1700, 1650, 1605, 1585, 1530, 1510, 1500, 1470, 1350 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 3.37 (s, 3H, CH_3), 6.85 (s, 1H, 3-H), 7.66 (s, 1H, 5-H), 6.50-8.26 (m, 9H, aromatic protons); m/z 326 (M^+, 32), 325 (5), 297 (5), 280 (13), 269 (15), 268 (9), 267 (80), 265 (10), 249 (6), 239 (48), 238 (25), 193 (100), 165 (20), 132 (25), 91 (30), 90 (15), 89 (10), 77 (80). (Found: C, 62.5; H, 4.1; N, 8.7% . $C_{17}H_{14}N_2O_5$ requires C, 62.57; H, 4.32; N, 8.58%).

Reaction of nitrone (3) with ethyl propiolate (7).
4-ethoxycarbonyl-3-p-nitrophenyl-2-phenyl-4-isoxazoline (15), reaction time 7 h, 79 % yield, white solid, m.p. 210-2 °C; ν max 1695, 1660, 1590, 1540, 1510, 1500, 1480, 1370 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.32 (t, 3H, CH_3, J=7.15 Hz), 4.28 (q, 2H, CH_2, J=7.15 Hz), 6.83 (s, 1H, 3-H), 7.70 (s, 1H, 5-H), 6.60-8.30 (m, 10H, aromatic protons); m/z 340 (M^+, 40), 339 (4), 312 (7), 311 (12), 296 (8), 294 (15), 269 (16), 268 (11), 267 (100), 265 (15), 242 (11), 239 (48), 238 (16), 193 (50), 165 (15), 138 (10), 111 (15), 91 (32), 90 (12), 89 (9), 77 (60). (Found: C, 63.7; H, 4.6; N, 8.4% . $C_{18}H_{16}N_2O_3$ requires C, 63,52; H, 4.74; N, 8.23%).

Reaction of nitrone (4) with methyl propiolate (6).
2-cyclohexyl-4-methoxycarbonyl-3-phenyl-4-isoxazoline (16), reaction time 12 h, 52 % yield, yellow oil; ν max 1695, 1640, 1610, 1580, 1520, 1480, 1385 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 0.80-2.40 (m, 10H, cyclohexyl CH_2), 2.95 (m, 1H, cyclohexyl CH), 3.67 (s, 3H, CH_3), 5.34 (s, 1H, 3-H), 7.2-7.8 (m, 6H, 5-H and aromatic protons); m/z 287 (M^+, 50), 270 (11), 258 (8), 228 (5), 211 (15), 210 (80), 206 (7), 205 (8), 204 (17), 200 (7), 188 (16), 178 (35), 176 (10), 172 (3), 159 (10), 146 (15), 145 (30), 144 (10), 131 (12), 129 (12), 128 (100), 117 (20), 116 (10), 105 (35), 104 (40), 103 (28), 96 (10), 91 (45), 90 (15), 89 (10), 83 (45), 78 (10), 77 (50).
2-cyclohexyl-5-methoxycarbonyl-3-phenyl-4-isoxazoline (19), 28 % yield, light yellow oil; ν max 1705, 1650, 1615, 1575, 1530, 1490, 1385 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.80-2.40 (m, 10H, cyclohexyl CH_2) 2.95 (m, 1H, cyclohexyl CH), 3.87 (s, 3H, CH_3), 5.26 (d, 1H, 3-H, J=3.10 Hz), 5.87 (d, 1H, 5-H, J=3.10 Hz), 7.2-7.8 (m, 5H, aromatic protons); m/z 287 (M^+, 30), 270 (5), 228 (20), 211 (7), 210 (70), 204 (25), 200 (20), 197 (15), 188 (10), 187 (22), 186 (15), 178 (15), 176 (5), 170 (5), 159 (8), 146 (9), 145 (30), 144 (5), 129 (8), 128 (100), 123 (20), 117 (5), 116 (3), 106 (3), 104 (25), 103 (8), 91 (45), 90 (20), 89 (6), 83 (50), 81 (8), 78 (3), 77 (60).

Reaction of nitrone (4) with ethyl propiolate (7).
2-cyclohexyl-4-ethoxycarbonyl-3-phenyl-4-isoxazoline (17), reaction time 12 h, 48 % yield, oil; ν max 1715, 1655, 1605, 1585, 1510, 1470, 1415 cm^{-1} ; ^1H NMR δ ($CDCl_3$) 1.12 (t, 3H, β-H of ester, J=7.05 Hz), 1.20-2.26 (m, 10H, cyclohexyl CH_2), 3.05 (m, 1H, cyclohexyl CH), 5.13 (s, 1H, 3-H), 4.08 (q, 2H, α-H of ester, J=7.05 Hz), 7.02-8.00 (m, 6H, 5-H and aromatic protons); m/z 301 (M^+, 41), 274 (9), 273 (5), 272 (15), 228 (75), 218 (5), 211 (5), 210 (58), 204 (5), 200 (35), 188 (10), 178 (15), 146 (8), 145 (20), 142 (40), 91 (31), 90 (28), 89 (8), 83 (30), 78 (3), 77 (45).

2-cyclohexyl-5-ethoxycarbonyl-3-phenyl-4-isoxazoline (20), 32 % yield, yellow oil; ν max 1710, 1655, 1600, 1575, 1510, 1470, 1425 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.14 (t, 3H, β-H of ester, J=7.05 Hz), 1.20-2.26 (m, 10H, cyclohexyl CH_2), 3.05 (m, 1H, cyclohexyl CH), 4.13 (q, 2H, α-H of ester, J=7.05 Hz), 5.07 (d, 1H, 3-H, J=3.0 Hz), 5.67 (d, 1H, 5-H, J=3.0 Hz), 7.02-8.00 (m, 5H, aromatic protons); m/z 301 (M^+, 41), 272 (3), 228 (100), 224 (80), 218 (10), 211 (15), 210 (8), 200 (90), 187 (8), 186 (15), 178 (4), 145 (20), 142 (38), 91 (7), 90 (12), 89 (9), 83 (35), 78 (5), 77 (35).

Reaction of nitrone (5) with methyl propiolate (6).
2-isopropyl-4-methoxycarbonyl-3-phenyl-4-isoxazoline (18), reaction time 12 h, 52 % yield, yellow oil; ν max 1700, 1635, 1610, 1590, 1500, 1490, 1380 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.08 (d, 6H, $(CH_3)_3C$, J=10.5 Hz), 3.25 (m, 1H, isopropyl CH), 3.65 (s, 3H, CH_3), 5.30 (s, 1H, 3-H), 7.20-7.75 (m, 6H, 5-H and aromatic protons); m/z 247 (M^+, 42), 232 (6), 219 (5), 218 (7), 204 (12), 188 (100), 170 (30), 160 (30), 159 (12), 127 (30), 91 (20), 90 (5), 77 (70).
2-isopropyl-5-methoxycarbonyl-3-phenyl-4-isoxazoline (21), 33 % yield, yellow oil; ν max 1715, 1660, 1610, 1580, 1520, 1500, 1385 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.10 (d, 6H, $(CH_3)_3C$, J=11.0 Hz), 3.28 (m, 1H, isopropyl CH), 3.80 (s, 3H, CH_3), 5.20 (d, 1H, 3-H, J=3.5 Hz), 5.90 (d, 1H, 5-H, J=3.5 Hz), 7.20-7.80 (m, 5H, aromatic protons); m/z 247 (M^+, 35), 232 (5), 216 (3), 204 (15), 188 (100), 170 (35), 160 (3), 147 (8), 111 (15), 91 (30), 77 (80).

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