THE FORMATION OF SUBSTITUTED INDOLES BY ACID CATALYZED REARRANGEMENTS OF 4-ISOXAZOLINES

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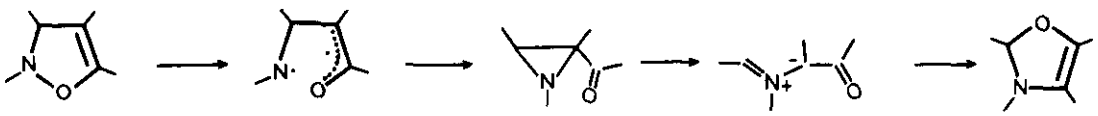
Abstract - Thermal rearrangements of 4-isoxazolines from C,N-diphenylnitrone and substituted alkynes have been directed towards the formation of substituted indoles. Detection and isolation of the intermediates of the process elucidate the reaction pathway. The appropriate choice of substituents and experimental conditions has allowed the control of the single steps involved in the total process.

The primary product of nitrones cycloaddition to alkynes is represented by thermally labile 4-isoxazolines[1] . The known reactivity of the N-O functional group flanked by a π system[2-5] induces the formation of a number of rearranged products from the initial cycloadducts[1-4,6-15] , via one of the possible intermediates 2-4 reported in Scheme 1. A suitable choice of both experimental conditions and degree of substitution at the initial cycloadduct 1 may allow the control of some of the steps involved in the rearrangement of the primary adduct, thus providing a powerful tool for the synthesis of target compounds.



1 2 3 4

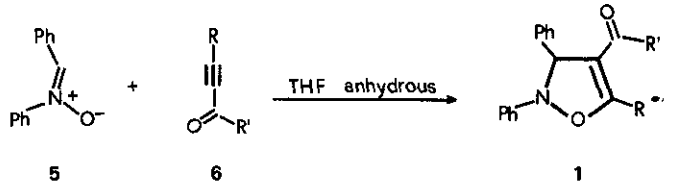
- Scheme 1 -

C,N-diphenylnitrone 5 meets all the requirements to serve as versatile dipole when the synthetic approach above described has to be applied. In fact, it is available in bulk quantities by a straightforward procedure[16] and the phenyl ring at the nitrogen atom provides a good stabilization of the positive charge which develops in the azomethine ylid 3 (Scheme 1) eventually formed. The choice of the

dipolarophile, moreover, allows the control of the equilibrium reported in Scheme 1. It has been clearly established, in fact, that the relative stability of isomers 1-4 is controlled by the nature of the substituent at C-4 of both heterocyclic compounds[17].

RESULTS AND DISCUSSION

C,N-diphenylnitrone 5 and ethyl phenylpropiolate 6a afforded high yield of 4-carboxyethyl-2,3,5-triphenyl-4-isoxazoline 1a when they were allowed to react in a 1:1 ratio at room temperature, in dry tetrahydrofuran, for 48 h. Similarly, good yields of 4-isoxazolines 1b-d were obtained by cycloaddition of nitrone 5 to alkynes 6b-d[4] (Scheme 2); the regiochemistry of the cycloaddition process has been determined in terms of FMO approach[4]. The cycloadduct 1a bears a substituent in the position 4 of the nucleus and this accounts for the relative stability of the otherwise reactive five-membered ring. However, it should be possible to induce the rearrangements reported in Scheme 1 either by changing the experimental conditions of the cycloaddition reaction or by proper treatment of the 4-isoxazoline 1a-d itself.



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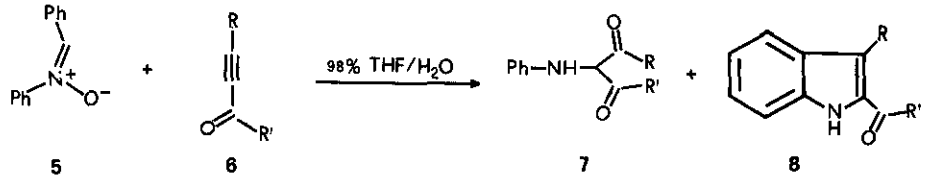
a) R = Ph; R' = OEt
b) R = H , R' = OMe
c) R = H ; R' = OEt
d) R = H ; R' = Me

-Scheme 2-

Furthermore, recent literature data[13] suggest that it could be possible to induce reaction pathways alternative to those reported in Scheme 1 by conducting the cycloaddition or the rearrangement of the system 1 in wet solvents.

When 5 and 6a were allowed to react in 98% tetrahydrofuran-water (v/v) for 6 h at 65°C, the anilino-ketone 7a was obtained in a yield of 95% together with traces of the substituted indole 8a (Scheme 3).

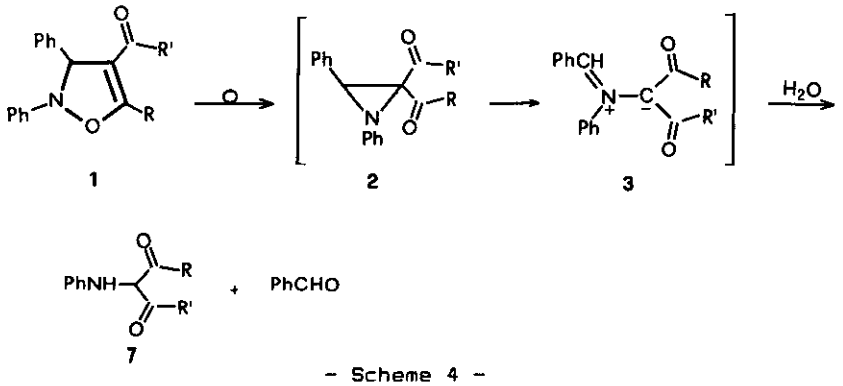


5 6 7 8

- Scheme 3 -

Compounds 7a and 8a could derive from one of the stable intermediates which characterize the well-accepted synthetic cycle reported in Scheme 1. While it was not possible to isolate the eventually formed aziridine 2a[18], the initial cycloadduct 1a was quantitatively converted, by refluxing in tetrahydrofuran for 2 h, into the ylid 3a. The latter afforded the same product 7a and 8a reported in Scheme 3, with similar isolated yields, after refluxing for 3 h at 60 °C in 98% tetrahydrofuran/water. The rearrangement of 1a was clearly accelerated by addition of catalytic amounts of HCl; the conversion to 7a in this case was nearly complete in 2 h.

These results suggest therefore that the rearrangement process starting from the initial 4-isoxazoline cycloadduct can be controlled and directed towards the novel route. The formation of 7a and 8a, in the reaction reported in Scheme 3, can likely be explained by taking into account that at 60 °C, in the adopted experimental conditions, the 4-isoxazoline 1a is a transient intermediate which, by thermal effect, isomerizes via valence rearrangement to the not isolated 2-acylaziridine; this compound gives ring opening to the ylid 3a, which, in the presence of water,



- Scheme 4 -

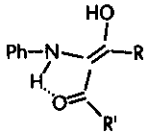
undergoes hydrolytic fragmentation to the amine 7a (Scheme 4), with removal of benzaldehyde also detected in the reaction mixture.

The reaction pathway has been examined with other 4-isoxazolines; compounds 1b-d gave in similar conditions, with different reaction times, the above described rearrangement starting from the initial cycloadduct and leading to the corresponding ylids 4b-d and amino derivatives 7b-d.

Literature precedents[6,19] indicate a sequence of thermal reactions, available to 4-isoxazolines 1 , which leads to 4-oxazolines through aziridine derivatives. With the present compounds aziridines were detected only in traces as intermediates[18] , but further reactions of ylids 3a-d to give 4-oxazolines 4a-d was not observed.

The structures of isolated products were assigned on the basis of analytical and spectroscopic data (see Experimental). In particular, for ylids 3, the strong absorption bands near 1580 cm^{-1}, assignable to enolate ion[20-22], together with the positive color reaction with ferric chloride, suggest the proposed structures. Ms and nmr data further confirmed the attribution. Structures were also unequivocally established on the basis of chemical data; in fact ylids 3 showed 1,3-dipolar activity towards alkynes with formation of 1:1 cycloadducts[23].

Compounds 7 exist in the enolic structure 9 stabilized by the hydrogen bonds, as



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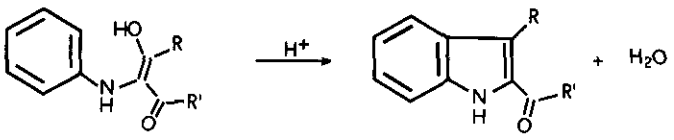
confirmed by the resonance in the range 6.70-6.95 δ of the methine proton as a doublet (J=11 Hz) for the coupling with the hydroxylic proton at 6.27-6.50 δ. By exchange with D_2O, the same proton resonates as a singlet. Ir and Ms data support the structure: besides the molecular ion, the interested fragmentation was observed from the molecular ion by loss of the radical COR. Moreover the presence of the intense fragments at m/z 104, for the $PhN^{+}{\equiv}CH$ ion, evidently confirms the assigned structure[11,30].

The formation of the indole nucleus (Scheme 3) could be of synthetic interest since this heterocyclic ring characterizes the core of many natural products such as the indole alkaloids[24]. The 1,3-dipolar cycloaddition route to indole has been exploited with alkynes[10,25] and substituted allenes[25,26]; in the case here reported, the formation of the heteroaromatic nucleus should occur by acid catalyzed condensation of the keto-aniline 7a, according to Scheme 5.



7 8

- Scheme 5-

The very low yields of 8a, obtained during the cycloaddition process described in Scheme 3, have to be ascribed therefore to the acidity of the reaction medium,

which controls the preequilibrium of the condensation reaction described in Scheme 4. This proposed mechanism was experimentally proved; in fact, the amine 7a gave after 20 h 60% isolated yields of indole 8a, by refluxing in tetrahydrofuran in the presence of catalytic amounts of 98% sulfuric acid.

The results discussed above show that a very simple entry to indoles can be devised by 1,3-dipolar cycloadditions. In fact, when the 4-isoxazolines 1a-d were refluxed in tetrahydrofuran containing a catalytic amount of H_2SO_4 for 24-32 h, good isolated yields of the expected indole were obtained. Moreover, the synthesis of the indole nucleus, according to the Scheme here proposed, can be carried out in a one-pot reaction. In a typical experiment, in fact, the cycloaddition of C,N-diphenylnitrone 5 and ethyl phenylpropiolate 6a (Scheme 3) was performed at room temperature in dry tetrahydrofuran. After the disappearance of the nitrone, monitored by tlc, the resulting solution was treated with a catalytic amount of 98 % sulfuric acid. Tlc analysis showed that approximatively 80% of amine 7a and 20% of indole 8a were present after 10 h of refluxing, while 60% isolated yields of 8a were obtained after 28 h, in the same experimental conditions.

The applicability of this synthetic procedure was checked with other different alkynes. Good conversions to indoles have been obtained, as reported in Table 1.

Compound	R	R'	Reaction Time (h)	Yield (%)
8a	Ph	OEt	28	60
8b	H	OMe	32	58
8c	H	OEt	32	59
8d	H	Me	29	65

Table 1

CONCLUSION

The thermal rearrangements of 4-isoxazolines (Scheme 1) can be controlled in the direction of producing good yields of target compounds. The hydrolytic quenching of the ylid intermediate 3 (Scheme 1) allows the obtainment of quantitative yield of aminoketones of type 7 (Scheme 3) and, more interestingly, good yield of 2-substituted indoles (Scheme 4). The cycloaddition route to indoles here reported

differs from that recently published[26], where the presence of a sulphonyl group in the reacting intermediates markedly affect the observed rearrangement.

EXPERIMENTAL

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were recorded for nujol mulls in the case of solids or for thin films in the case of liquids, using a Perkin-Elmer 225 spectrophotometer. Nmr spectra were measured with a Bruker WP 80 SY spectrometer in $CDCl_3$ solutions with TMS as internal standard. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. Mass spectra were determined with a Varian Mat CH-5 DF instrument. Reaction mixtures were monitored by tlc on silica gel GF 254 (Merck) and analyzed by GC-Ms measurements, using a HP 5890 A instrument.

4-Isoxazolines 1b-d were obtained by cycloaddition reaction of nitrone 5 to alkynes 6b-d [30].

3,5-Diphenyl-4-ethoxycarbonyl-4-isoxazoline (1a).

A solution of C,N-diphenylnitrone 5 (0.985 g, 5 mmol) and ethyl phenylpropiolate (6a) (1.05 g, 6 mmol) in anhydrous THF (30 ml) was stirred at room temperature for 48 h until tlc on silica gel in 7:3 hexane/ether indicated the disappearance of the starting nitrone. The reaction mixture was then evaporated and the residue triturated with ether to give the isoxazoline 1d (85 % yield) as white crystals, mp 87-88° C (from ether); ν max 1700, 1640, 1600, 1560, 1490, 1450, 1390, 1370, 1330, 1300, 1280, 1240, 1080, 1030 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.02 (t, 3H, CH_3, J=7.05), 4.02 (q, 2H, CH_2, J=7.05), 5.72 (s, 1H, CH), 7.02-8.10 (m, 15H, aromatic protons); m/z 371 (M^+,10), 298 (5), 294 (10), 280 (10), 279 (27), 266 (12), 251 (3), 248 (3), 238 (3), 223 (3), 220 (3), 208 (3), 205 (3), 194 (9), 193 (23), 192 (8), 191 (3), 190 (3), 180 (5), 178 (3), 167 (12), 166 (5), 165 (18), 152 (5), 135 (9), 116 (6), 115 (3), 107 (12), 106 (9), 105 (100), 91 (4), 90 (10), 89 (40), 79 (6), 78 (6), 77 (64). (Found: C, 77.5; H, 5.8; N, 3.80 % . $C_{24}H_{21}NO_3$ requires C, 77.61; H, 5.70; N, 3.77 %).

Ethyl 2-anilino-3-hydroxy-3-phenylacrilate 7a.

A solution of C,N-diphenylnitrone 5 (0.98 g, 5 mmol) and ethyl phenylpropiolate 6a (1.05 g, 6 mmol) in 98% THF/H_2O (30 ml) was refluxed (65° C) for 10 h until tlc on silica gel (hexane/ether 7:3 as eluent) indicated the disappearance of the starting nitrone. After the removal of the solvent, the crude reaction mixture was subjected to chromatography on a silica gel column, using hexane/ether 7:3 as

eluent. The first fractions gave 7a as white crystals (90 % yield), mp 93-95° C (from ether); ν max 3420, 3380, 1740, 1695, 1605, 1585, 1535, 1510, 1455, 1440, 1400, 1375, 1290, 1230, 1180, 1160, 1100 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.08 (t, 3H, CH_3, J=6.90 Hz), 4.04 (q, 2H, CH_2, J=6.90 Hz), 5.03 (b, 1H, exchangeable NH), 5.63 (s, 1H, exchangeable OH), 6.40-8.20 (m, 10H, aromatic protons); m/z 283 (M^+, 30), 210 (15), 209 (11), 193 (28), 180 (5), 179 (18), 178 (100), 150 (5), 133 (3), 132 (4), 122 (50), 121 (6), 120 (32), 119 (10), 106 (15), 105 (98), 104 (60), 93 (18), 92 (10), 91 (3), 88 (3), 78(16), 77 (95). (Found: C, 72.2; H, 5.9; N, 5.0 %. $C_{17}H_{17}NO_3$ requires C, 72.07; H, 6.05; N, 4.94 %).

Further elution gave 8a (8 % yield) as a white solid, mp 137-138° C (from methanol), which was identified by comparison with an authentic sample[27].

Rearrangements of isoxazoline 1a.

A solution of isoxazoline 1a (0.371 g, 1 mmol) in anhydrous THF (20 ml) was refluxed for 2 h. After the removal of the solvent, ether was added to the residue to give azomethine ylid 3a as a yellow solid, mp 105-107° C; ν max 1740, 1690, 1605, 1585, 1500, 1450, 1430, 1390, 1370, 1280, 1220, 1180, 1160, 1100, 1020 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.17 (t, 3H, CH_3, J=7.20 Hz), 4.25 (q, 2H, CH_2, J=7.20 Hz), 6.64 (s, 1H, CH), 6.80-8.30 (m, 15H, aromatic protons). (Found: C, 74.5; H, 5.8; N, 3.6 %. $C_{24}H_{21}NO_3$ requires C, 74.37; H, 5.70; N, 3.77 %).

A solution of isoxazoline 1a (1 mmol) in THF (20 ml) containing a catalytic amount of HCl 1:1 was refluxed for 2 h. In these experimental conditions, the residue obtained after the removal of the solvent, triturated with ether, gave the amino derivative 7a with a yield of 95 %.

Direct conversion of azomethine ylid 3a into compound 7a was performed by heating a THF solution of 3a additionated of a catalytic amount of HCl 1:1. The hydrolysis was nearly quantitative in 2 h.

2-Ethoxycarbonyl-3-phenylindole 8a

A solution of C,N-diphenylnitrone 5 (0.197 g, 1 mmol) and ethyl phenylpropiolate (0.194 g; 1 mmol) in 10 ml of THF was refluxed for 6 h until tlc monitoring showed the disappearance of starting nitrone. Then a catalytic amount of 98% sulfuric acid (0.5 ml) was added and the solution further refluxed for 20 h. After the removal of the solvent, the crude mixture was triturated with ether to give the indole 9a (62% yield) as white solid, mp 137-138° C; ν max 3380, 1740, 1695, 1605, 1585, 1510, 1450, 1430, 1400, 1370, 1280, 1230, 1180, 1100 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.40 (t, 3H, CH_3, J=7.0 Hz), 4.46 (q, 2H, CH_2, J=7.0 Hz), 7.10-7.80 (m, 9H, aromatic protons),

8.10 (s, 1H, NH); m/z 265 (M^+, 43), 237 (11), 236 (6), 221 (19), 220 (100), 194 (9), 193 (56), 191 (21), 190 (16), 180 (4), 166 (7), 165 (43), 164 (11), 163 (8), 152 (3), 140 (3), 139 (4), 115 (3), 110 (4), 95 (10), 89 (6), 87 (3), 77 (10).

The residue chromatographed on a silica gel column (hexane/ether 7:3 as eluent), gave amine 6a (10 % yield).

Indole 8a was also obtained in a similar yield by refluxing for 20 h a THF solution of amine 7a to which a catalytic amount of 98% H_2SO_4 had been added. 8a was isolated after the normal work-up of the residue obtained after the removal of the solvent.

Similarly, the isoxazoline 1a in acidic THF solution (0.5 ml of 98% H_2SO_4) at reflux for 24 h was converted into indole 8a with an isolated yield of 60 %.

2-Methyl 2-anilino-3-hydroxyacrilate 7b.

A solution of C,N-diphenylnitrone 5 (5 mmol) and methyl propiolate 6b (5 mmol) in 98% THF/H_2O (30 ml) was refluxed (65° C) for 30 h. After the removal of the solvent, the crude reaction mixture was chromatographed on a silica gel column. First eluted fractions gave 7b as white crystals (90 % yield), mp 71-74°C (from ether); ν max 3410, 3340, 1730, 1680, 1640, 1600, 1530, 1500, 1460, 1380, 1345, 1270, 1240, 1200, 1155, 1120, 1080 cm^{-1}; ^1H nmr δ ($CDCl_3$) 3.81 (s, 3H, CH_3), 5.34 (b, 1H, NH), 6.54 (d, 1H, OH, J=11.0 Hz), 7.16 (d, 1H, CH, J=11.0 Hz), 6.67-7.70 (m, 5H, aromatic protons); m/z 193 (M^+, 29), 163 (3), 162 (5), 134 (4), 133 (46), 116 (3), 106 (11), 105 (68), 104 (100), 79 (4), 78 (22), 77 (38). (Found: C, 62.3; H, 5.8; N, 7.4 % . $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25 %).

Further eluted fractions gave, after the removal of the solvent, indole 8b as a white solid, (9 % yield), mp 151-152° C (from methanol), identified by comparison with an authentic sample[28].

Rearrangements of isoxazoline 1b.

A solution of isoxazoline 1b (0.281 g, 1 mmol) in anhydrous THF (20 ml) was refluxed for 22 h. The solvent was removed by evaporation at reduced pressure, then the addition of ether to the residue gave azomethyne ylid 3b as a yellow solid, mp 78-81° C; ν max 2840, 2720, 1735, 1695, 1630, 1600, 1580, 1500, 1455, 1430, 1245, 1195, 1160, 1130, 1100 cm^{-1}; ^1H nmr δ ($CDCl_3$) 3.91 (s, 3H, CH_3), 6.50-8.02 (m, 11H, CH and aromatic protons), 10.13 (s, 1H, aldehydic proton). (Found: C, 72.4; H, 5.3; N, 5.1 % . $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.38; N, 4.98 %).

A solution of isoxazoline 1a (1 mmol) in THF (20 ml) was additionated of a catalytic amount of HCl 1:1 and refluxed for 6 h. After the removal of the solvent,

the residue was triturated with ether to give the aminoderivative 7b with a yield of 95 %.

Azomethyne ylid 3b was directly converted into 7b by refluxing for 6 h a THF solution of ylid, acidified with a catalytic amount of HCl 1:1 (95 % yield).

2-Methoxycarbonylindole 8b.

A solution of C,N-diphenylnitrone (1 mmol) and methyl propiolate 6b (1 mmol) in 30 ml of aqueous THF was refluxed for 8 h until TLC indicated the disappearance of the starting nitrone. After addition of a catalytic amount of 98 % H_2SO_4 (0.5 ml), the solution was maintained at reflux for 26 h. Then the solvent was removed and the residue treated with ether to afford indole 8b (60 % yield); mp 151-152°C; ν max 3480, 1695, 1612, 1530, 1375, 1340, 1250, 1200, 1152, 1119, 1105, 1005 cm^{-1}; ^1H nmr δ ($CDCl_3$) 3.96 (s, 3H, CH_3), 7.05-7.85 (m, 5H, aromatic protons), 9.20 (s, 1H, NH); m/z 175 (M^+, 37), 163 (3), 146 (5), 145 (12), 144 (100), 117 (9), 116 (28), 115(6), 114 (4), 103 (5), 100 (5), 98 (6), 91 (5), 89 (25), 88 (6), 85 (4), 78 (4), 77 (6). The same yield of indole 8b was obtained by refluxing for 26 h a THF solution of amino derivative 7b, additionated of a catalytic amount of 98 % H_2SO_4, after the normal work-up.

Similarly, indole 8b was obtained (62 % yield) by refluxing an acidic solution of isoxazoline 1b for 30 h.

Ethyl 2-anilino-3-hydroxyacrilate 7c.

The cycloaddition reaction of 5 and ethyl propiolate 6c, performed as previously indicated (30 h of reflux), gave, after chromatographic separation, compound 7c (92 % yield) in the first eluted fractions; white crystals, mp 95-98° C (from ether); νmax 3440, 3340, 1680, 1660, 1605, 1535, 1510, 1465, 1430, 1380, 1350, 1270, 1240, 1210, 1170, 1120 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.24 (t, 3H, CH_3, J=7.0 Hz), 4.20 (q, 2H, CH_2, J=7.0 Hz), 5.20 (b s, 1H, NH), 6.27 (d, 1H, OH, J=11.0 Hz), 6.95 (d, 1H, CH, J=11.0 Hz), 6.73-7.54 (m, 5H, aromatic protons); m/z 207 (M^+, 15), 178 (4), 177 (3), 162 (3), 134 (3), 133 (31), 106 (8), 105 (53), 104 (100), 79 (3), 78 (16), 77 (47). (Found: C, 63.6; H, 6.4; N, 6.7 % . $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76 %).

Indole 8c was eluted successively, (8 % yield); mp 125-126° C (from methanol), identified by comparison with an authentic sample[28].

Rearrangements of isoxazoline 1c.

A solution of isoxazoline 1c (1 mmol) in 20 ml of anhydrous THF was heated at reflux for 24 h. After the removal of the solvent, addition of ether to the residue

gave azomethine ylid 3c as a yellow-orange solid, mp 80-82°C; ν max 2820, 2740, 1730, 1670, 1600, 1580, 1500, 1460, 1410, 1380, 1370, 1240, 1205, 1100, 1030 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.25 (t, 3H, CH_3, 6.9 Hz), 4.22 (q, 2H, CH_2, J=6.9 Hz), 6.60-7.98 (m, 11H, CH and aromatic protons), 9.93 (s, 1H, aldehydic proton). (Found: C, 73.0; H, 5.9; N, 4.9 % . $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74 %).

A solution of isoxazoline 1c (1 mmol) in 20 ml of THF, additionated of HCl 1:1 (1 ml) was refluxed for 6 h to give, after removal of the solvent and treatment with ether, amino derivative 7c (88 % yield).

Direct conversion of 3c into 7c was performed by refluxing for 6 h a THF solution of isoxazoline acidified with a catalytic amount of HCl 1:1.

2-Ethoxycarbonylindole 8c.

An equimolar solution of nitrone 5 and ethyl propiolate 6c in aqueous THF was refluxed for 8 h. The reaction was monitored by tlc up to disappearance of the starting nitrone. 98 % H_2SO_4 (1 ml) was then added and the mixture was refluxed for 24 h. By the usual work-up, indole 8c was obtained (65 %) as white crystals, mp 125-126° C (from methanol); ν max 3460, 1705, 1630, 1600, 1545, 1395, 1380, 1320, 1270, 1240, 1190, 1150, 1130, 1100, 1020 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.40 (t, 3H, CH_3, J=7.4 Hz), 4.43 (q, 2H, CH_2, J=7.4 Hz), 6.95-7.82 (m, 5H, aromatic protons), 9.60 (s, 1H, NH); m/z 189 (M^+, 29), 174 (4), 161 (15), 145 (11), 144 (100), 132 (3), 117 (11), 116 (22), 115 (5), 114 (3), 90 (3), 89 (19), 88 (3), 77 (3).

From the residue amine 7c was separated (9 % yield), after the chromatographic treatment.

The same yield of indole 8c was obtained by heating at reflux for 24 h a THF solution of amino derivative 8b, acidified with a catalytic amount of 98 % H_2SO_4.

Similarly, indole 8c was obtained by refluxing an acidic solution of isoxazoline 1c for 30 h. The normal work-up gave 8c with a 60 % yield.

2-Anilino-1-hydroxy-3-buten-2-one 7d.

An equimolar solution of 5 and 6d in 30 ml of 98 % THF/H_2O was heated at reflux for 30 h. After the chromatographic separation, amino derivative 7d was obtained in the first eluted fractions (90 % yield), white solid, mp 122-125° C (from ether); ν max 3375, 3310, 1690, 1600, 1585, 1545, 1520, 1500, 1460, 1445, 1400, 1380, 1350, 1340, 1280, 1250, 1210, 1155, 1090, 1030 cm^{-1}; ^1H nmr δ ($CDCl_3$) 2.45 (s, 3H, CH_3), 6.46 (b, 2H, exchangeable NH and OH), 7.27 (d, 1H, CH, J=12.0 Hz), 6.94-7.67 (m, 5H, aromatic protons); m/z 177 (M^+, 48), 162 (3), 148 (3), 134 (22), 133 (3), 130 (4), 116 (5), 107 (8), 106 (100), 104 (37), 93 (21), 79 (10), 78 (12), 77 (38). (Found: C, 67.9; H, 6.4; N, 7.8 % . $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.90 %).

Indole 8d was the successively eluted product (6% yield), mp 120-3° C (from ether).

Rearrangements of isoxazoline 7d.

Thermal treatment of isoxazoline 1d in anhydrous THF solution, for 24 h at reflux, gave azomethine ylid 3d, as yellow solid, mp 77-80° C; νmax 2820, 2720, 1705, 1670, 1600, 1580, 1530, 1460, 1380, 1355, 1330, 1290, 1270, 1215, 1180, 1160, 1140, 1095, 1070, 1030 cm^{-1}; ^1H nmr δ ($CDCl_3$) 2.39 (s, 3H, CH_3), 6.73-8.00 (m, 11H, CH and aromatic protons), 10.40 (s, 1H, aldehydic protons). (Found: C, 77.10; H, 5.60; N, 5.4 % . $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28 %).

Rearrangement of isoxazoline 1d in THF solution acidified with 1 ml of HCl 1:1, at reflux for 8 h, gave the aminoderivative 7d (95 % yield).

Direct conversion of ylid to aminoderivative was nearly quantitative after 8 h of reflux of an acidic solution of 3d.

2-Acetylindole 8d.

The cycloaddition reaction between 5 and 6d was performed in aqueous THF at reflux for 8 h. After the addition of 1 ml of 98% H_2SO_4, the mixture was refluxed for 28 h to give, after the usual work-up, indole 8d, as white crystals (62 % yield), 120-123° C (from ether); ν max 3420, 1730, 1690, 1610, 1550, 1400, 1370, 1320, 1260, 1180, 1120, 1080, 1020 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.52 (s, 3H, CH_3), 7.0-7.85 (m, 5H, aromatic protons), 9.93 (s, 1H, NH); m/z 159 (M^+, 15), 144 (80), 117 (8), 116 (45), 115 (6), 114 (3), 98 (7), 94 (3), 93 (4), 91 (5), 77 (3). (Found: C, 75.6; H, 5.8; N, 8.8 % . $C_{10}H_9NO$ requires C, 75.45; H, 5.70; N, 8.79 %).

Indole 8d was also obtained by refluxing for 22 h an acidic THF solution of amino derivative 8c.

Similar yield (62 %) was obtained by direct conversion of isoxazoline 1d in acid THF solution at reflux for 32 h.

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18) Aziridines were detected as intermediates in the reaction mixture by monitoring by GC/Ms the rearrangement process of the original 4-isoxazoline cycloadducts; the M -1 peak was diagnostic for the structure attribution .
2a: m/z 371 (M^+, 8), 370 (10), 267 (12), 266 (54), 265 (6), 237 (10), 223 (22), 221 (14), 220 (32), 194 (86), 193 (48), 165 (28), 159 (20), 144 (22), 105 (100), 77 (48); 2b: m/z 281 (M^+, 29), 280 (30), 222 (40), 196 (6), 195 (15), 194 (100), 193 (39), 167 (23), 165 (21), 164 (8), 152 (14), 144 (8), 117 (13), 116 (13), 104 (34), 91 (11), 90 (14), 89 (20), 77 (19); 2c: m/z 295 (M^+, 14), 294 (30), 265 (13), 249 (23), 247 (10), 222 (45), 221 (12), 194 (100), 148 (10), 146 (24), 144 (30), 130 (22), 128 (22), 118 (10), 117 (20), 116 (13), 104 (35), 102 (10), 94 (30), 93 (20), 91(10), 78(12), 77 (50); 2d: m/z 265 (M^+,10), 264 (12), 222 (18), 194 (100), 193 (20), 183 (10), 182 (30), 167 (15), 165 (10), 116 (10), 104 (19), 91 (11), 90 (14), 83 (13), 77 (26).

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