*Tetrahedron* Vol. 48, No. 43, pp. 9473-9482, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00


# Ring-Opening of Isoxazolidine System: Homologation of 3-Aryl into 3-Styryl Nitrones Via Intermediate 5-Hydroxy-Isoxazolidines.[1]

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(*Received in UK* 7 *August* 1992)

***Abstract:*** *High yield conversion of 3-aryl-5-ethoxy-isoxazolidines into 3-styryl nitrones has been achieved by 1,5 h refluxing in aq.* $H_2SO_4$ *or catalytic p-toluensulfonic acid/ethanol media. The rearrangement pathway is interpretable on the basis of the ring-opening process of intermediate 5-hydroxy-isoxazolidines. Formation of a masked 5-OH function has been also developed by basic or acid treatment of 5-acetoxy-isoxazolidines.*

The otherwise stable isoxazolidines nucleus, obtained by 1,3-dipolar cycloadditions of nitrones to alkenes,[2-6] can be converted into powerful synthons by cationization of the nuclear nitrogen atom.

The ring opening of N-methylated isoxazolidinium cations can be controlled by a proper choice of the experimental conditions.[7-15] A reaction channel widely explored corresponds to the base catalyzed conversion of N,N-dimethyl isoxazolidinium salts into chalcones, driven by a N-O bond dissociation followed by an Hofmann type elimination.[12, 16, 17]

We wish to report here a conceptually different approach based on the introduction at the position 5 of the heterocyclic ring of a labile functionality, which affords the structural situation suitable for the subsequent rearrangement of isoxazolidine nucleus towards open-chain molecules. This paper documents the exploitation of this synthetic design.

## RESULTS AND DISCUSSION

Nitrones **1-4** have been reacted with ethyl vinyl ether in the absence of solvent at 80 °C, using a 1:10 relative ratio of dipole-dipolarophile, at different times, until t.l.c. showed the disappearance of the starting nitrone. The reaction of nitrone **1** has been already reported in literature.[18]

As indicated in Table 1, the investigated 1,3-dipolar cycloadditions were found to be regiospecific, with the 5-ethoxy-isoxazolidines **5-11** as the only obtained adducts.

The molecular structure of the reaction products was assigned on the basis of analytical and spectroscopic data (see Experimental).

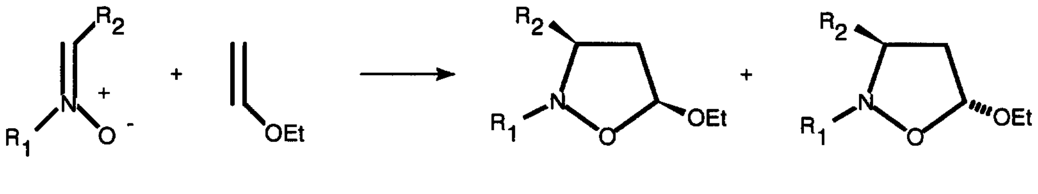
The regiochemistry of the cycloaddition process was readily deduced from the $^1$H NMR data. In each case, there was a one proton signal at δ 5.15-5.28 which corresponded to the C-5 acetal proton in compounds **4-8**; the alternative regioisomers are not reported to show a resonance at this chemical shift value.[18]

As expected, the reaction of C-aryl-N-methyl nitrones **1-3** resulted in the observation of a poor stereoselectivity leading to the formation of a mixture of epimeric isoxazolidines **5, 9** ; **6, 10** and **7, 11** respectively. The product ratios of *cis* epimer/*trans* epimer was estimated from the integrals of the $^1$H NMR resonances.

On the contrary, C,N-diphenyl nitrone **4** showed a high stereoselectivity which gave rise to the single isoxazolidine **8** (*cis*-adduct).

The relative configurational assignment of compounds **5-11** were attributed by correlation of their [1]H NMR

**Table 1.** Reaction of Nitrones **1-4** with ethyl vinyl ether




**1-4** **5-8** **9-11**

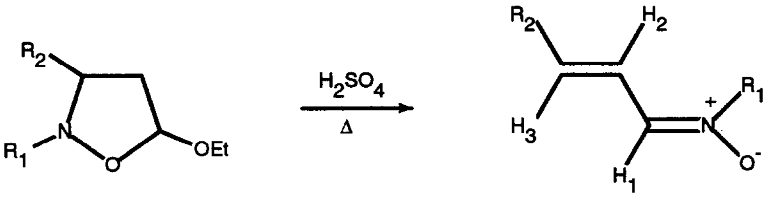
| Nitrone | $R_1$ | $R_2$ | Reaction time | Yield | Epimeric ratio *cis/trans* |
|---|---|---|---|---|---|
| 1 | $CH_3$ | Ph | 72 | 61 | 5:9 (50:50) |
| 2 | $CH_3$ | *p*-$CH_3C_6H_4$ | 72 | 82 | 6:10 (68:32) |
| 3 | $CH_3$ | *p*-$CH_3OC_6H_4$ | 60 | 70 | 7:11 (55:45) |
| 4 | Ph | Ph | 240 | 62 | 8 |

chemical shifts and J $_{1,2}$ coupling constants with those of compounds **5** and **9**, already reported in literature,[18,19] and by NOE experiments.[18, 20]

Isoxazolidines **5-11** were reacted at reflux with 20% aqueous $H_2SO_4$: α,β-unsaturated N-methyl- and N-phenylnitrones **12-15** were obtained in a nearly quantitative yield (Tab. 2).

Substituted C-styrylnitrones **12-15** were characterized by IR, NMR and MS spectroscopic methods. The [1]H

**Table 2.** Reaction of isoxazolidines **5-11** with 20% $H_2SO_4$




**5-11** **12-15**

| Isox (epimers mix.) | $R_1$ | $R_2$ | Reaction time (min) | Yield | Nitrones |
|---|---|---|---|---|---|
| 5,9 | $CH_3$ | Ph | 105 | 100 | 12 |
| 6,10 | $CH_3$ | *p*-$CH_3C_6H_4$ | 105 | 95 | 13 |
| 7,11 | $CH_3$ | *p*-$CH_3OC_6H_4$ | 110 | 95 | 14 |
| 8 | Ph | Ph | 110 | 100 | 15 |

NMR spectrum of **12**, taken as model system, showed for H-2 a doublet of doublets at 6.85 δ with coupling constants of 14.0 and 14.2 Hz, so suggesting that nitrone assumes the *E* configuration of substituens around the styryl double bond.

The mass spectrum was highly diagnostic of the original structure. The molecular ion of **12** (M=161, 53%), after the electron impact, dissociates by loss of the aromatic substituent giving rise to the fragment at m/z 84, as the most abundant peak. The other competitive process, originated from the molecular ion, leads to the ion at m/z $M^+$ - 46 by transfer of one proton to the nitrogen atom (Fig. 1). Analogous parameters characterize the $^1H$ NMR and MS spectra of nitrones **13-15**.

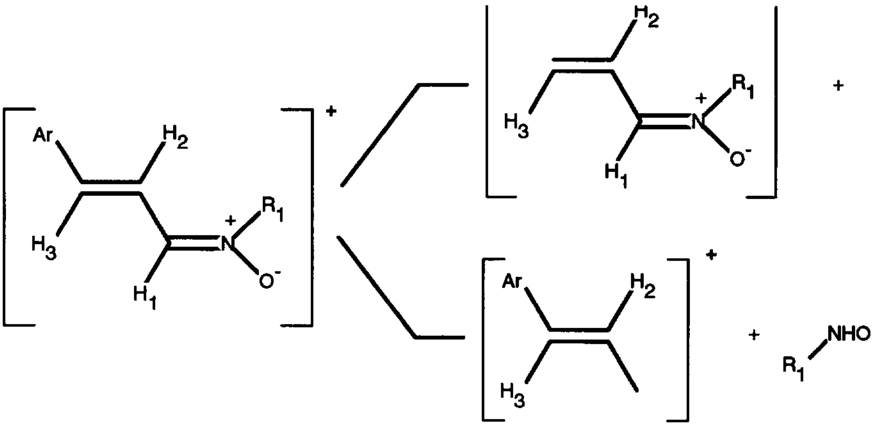
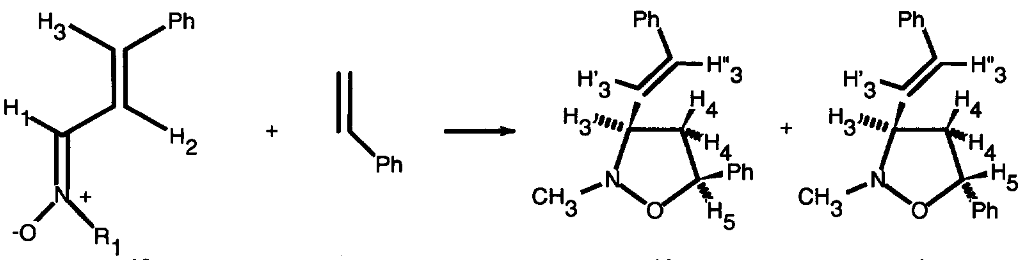


**Figure 1**

Unequivocal proof of the structural assignment was achieved by the identity of physico-chemical data between **12** and the nitrone obtained from the reaction of cinnamaldehyde with N-methyl hydroxylamine.

Chemical behaviour of nitrone **12** as 1,3-dipole was tested: 1,3-dipolar cycloaddition to styrene afforded a diastereomeric mixture of 2-methyl-3-styryl-5-phenylisoxazolidines **16** and **17** (Scheme 1).

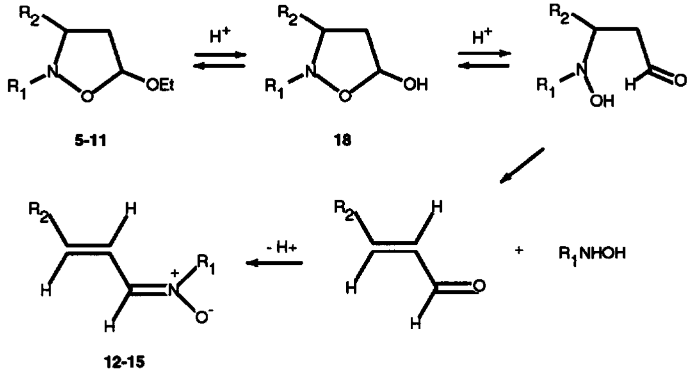


**12** **16** **17**

**Scheme 1**

The epimeric ratio *cis/trans*, established from the integrals in the $^1H$ NMR was 69:31. The value of $J_{3',3''}$ (14 Hz) in both compounds **16** and **17** confirmed the assigned configuration of the styryl double bond in nitrones **12-15**.

Conversion of isoxazolidines **5-11** into nitrones **12-15** under acidic medium can evolve through a sequence of equilibrium steps, with a 5-hydroxy-isoxazolidine **18** as the key intermediate (Scheme 2) which allows to rationalize the observed reaction route. In fact, the acetal moiety present in the five-membered ring rapidly induces the formation of the intermediate, not isolated 5-hydroxy-isoxazolidines: the so unmasked emiacetal functionality drives the N-O bond dissociation towards open-chain β–hydroxylamino-aldehydes. The subsequent Hofmann type elimination gives rise to cinnamaldehyde and N-methyl- or N-phenyl-hydroxylamines, which, in the adopted experimental conditions, afford the isolated nitrones.



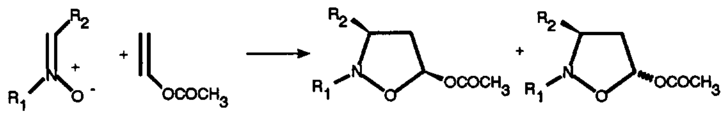

**Scheme 2**

The reaction of substituted aldehydes with N-methylhydroxylamine hydrochloride constitutes, in fact, a classical route to the formation of nitrones.[21]

A different approach was evaluated to induce the formation of the key 5-hydroxy-isoxazolidine intermediates: a masked 5-OH function has been developed by cycloaddition of nitrones **1-4** to vinylacetate.

The obtained products are reported in Table 3. Isoxazolidines **19-25** have been characterized on the basis of analytical and spectroscopic data (Experimental); compound **22** has been already reported in literature.[18]

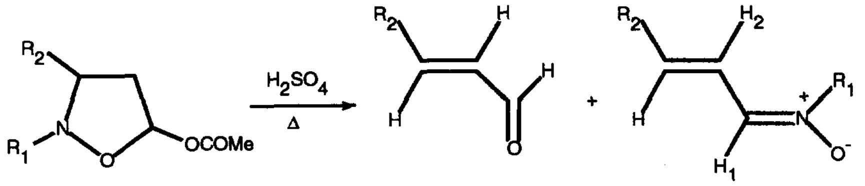
**Table 3.** Reaction of Nitrones **1-4** with vinyl acetate




| Nitrone | $R_1$ | $R_2$ | Reaction time (h) | Yield | Epimeric ratio *cis/trans* |
|---|---|---|---|---|---|
| 1 | $CH_3$ | Ph | 72 | 61 | 19:23 (70:30) |
| 2 | $CH_3$ | *p*-$CH_3C_6H_4$ | 72 | 82 | 20:24 (67:33) |
| 3 | $CH_3$ | *p*-$CH_3OC_6H_4$ | 240 | 62 | 21:25 (43:57) |
| 4 | Ph | Ph | 240 | 62 | 27 |

Compounds **19-25** were reacted with 20% aqueous $H_2SO_4$ at reflux: the nitrones **12-15** were isolated in 58-98% yields, together with variable amounts of cinnamaldehydes **26-28** (Table 4).

**Table 4.** Reaction of isoxazolidines **19-25** with 20% $H_2SO_4$.



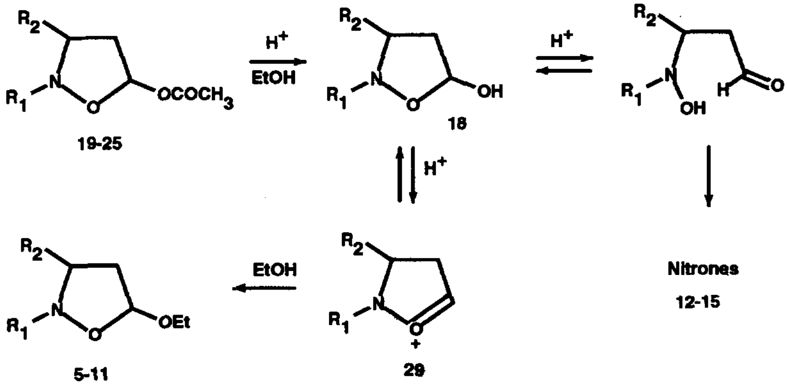

**19-25** **26-28** **12-15**

| Isox (epimers mix.) | $R_1$ | $R_2$ | Reaction time (min) | Nitrones (yield) | Aldehydes (yield) |
|---|---|---|---|---|---|
| 19,23 | $CH_3$ | Ph | 60 | 12 (58%) | 26 (17%) |
| 20,24 | $CH_3$ | $p$-$CH_3C_6H_4$ | 30 | 13 (76%) | 27 (12%) |
| 21,25 | $CH_3$ | $p$-$CH_3OC_6H_4$ | 15 | 14 (74%) | 28 (19%) |
| 22 | Ph | Ph | 60 | 15 (85%) | |

Analogous results were obtained in basic conditions: compounds **19-25** by treatment at reflux with methanolic KOH gave the corresponding nitrones in 78-84% yields.

Isolation of cinnamaldehydes constitutes a good support to the suggested overall process: the observed rearrangements in acid and basic conditions are both amenable to the intermediate 5-hydroxy-isoxazolidine **18**, unmasked by acidic or basic hydrolysis of corresponding 5-acetoxy-derivatives.

As further support to the reaction mechanism, isoxazolidines **19-25** have been heated in ethanolic solution containing catalytic amount of p-toluenesulphonic acid (Scheme 3).




**Scheme 3**

The reaction afforded, besides nitrones **12-15** in 49-50% yields, an epimeric mixture of 5-ethoxy-isoxazolidines **5-11** in 40-62% yields.

These findings can be easily explained according to two competiting reaction channels. Transesterification of isoxazolidines **14-18** releases the 5-hydroxy-isoxazolidines **18** which evolve through the ring-opening of heterocyclic nucleus into styryl nitrones. However the hemiacetal **18** in the acidic medium is in equilibrium with the species **29** arising form $H_2O$ removal assisted by the lone pair of the nuclear oxygen atom (Scheme 3).

The subsequent reaction of **29** with ethanol produces the 5-ethoxy-isoxazolidines, whose formation constitues an indirect proof of the existence of **18** in the reaction medium.

In conclusion, the observed ring transformation, induced by acid or basic treatments of 5-ethoxy-isoxazolidines, opens new possible synthetic applications exploiting the uniqueness of the regio- and stereospecificity of 1,3-dipolar cycloaddition processes.

## 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 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 5859 A instruments. Reaction mixtures were analyzed by t.l.c. on silica gel GF 254 (Merck) and the spots were detected under UV light (254 nm). Flash chromatography was carried out with Kieselgel 60 (Merck).

### Preparation of isoxazolidines 5-11, and 19-25.

*General procedure.* Isoxazolidines **5-11** were prepared from nitrones **1-4** (8.7 mmol) and ethyl vinyl ether (87 mmol). The reaction mixtures were sealed in a thick-walled glass reaction tube and heated at 80° C, under stirring, until t.l.c. showed the disappeareance of the starting nitrone. The excess of vinyl ethyl ether was removed by evaporation under high vacuum and the residues subjected to flash-chromatography on silica gel column with hexane-ethyl acetate 10:1 as eluent. Following the above procedure, isoxazolidines **16** and **17** were prepared from C-styril-N-methylnitrone **12** and styrene, while isoxazolidines **19-25** were obtained from nitrones **1-4** and vinyl acetate. Compounds **5**, **9** and **22** have been already obtained by the same procedure.[18]

*Reaction of C-p-tolyl-N-methylnitrone* **2** *with ethyl vinyl ether.* Reaction time 72 h. First fractions gave *(3R, 5S)-2-methyl-3-p-tolyl-5-ethoxyisoxazolidine* **6**, 55.8% yield; white solid, m.p. 144-146°C; $\nu_{max}$ 2980, 2930, 1510, 1440, 1295, 1210, 1020, 895 $cm^{-1}$; $^1H$ NMR: $\delta$ ($CDCl_3$) 1.28 (t, 3H, $CH_3$-$CH_2O$, J= 7.5 Hz), 2,32 (ddd, 1H, $H_4$, J=3, 9 and 14 Hz), 2.36 (s, 3H, $CH_3$-$C_6H_4$), 2.57 (s, 3H, $CH_3$-N), 2.87 (ddd, 1H, $H_4$, J=6, 9 and 14 Hz), 3.38 (t, 1H, $H_3$, J=10 Hz), 3.50 (dq, 1H, $CH_2O$, J= 7.5 and 14 Hz), 5.18 (dd, 1H, $H_5$, J= 3 and 6 Hz), 7.10-7.32 (m, 4H, aromatic protons); MS: *m/z* 221 ($M^+$, 11%), 148 (100). (Found: C, 70.41; H, 8.75; N, 6.11 %. Calc. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.30 %). Further fractions gave *(3R, 5R)-2-methyl-3-p-tolyl-5-ethoxyisoxazolidine* **10**, 26.2% yield; white solid, m.p. 148-150 °C; $\nu_{max}$ 2985, 2930, 1510, 1450-1420, 1355, 1295, 1210, 1020, 895 $cm^{-1}$; $^1H$ NMR: $\delta$ ($CDCl_3$) 1.27 (t, 3H, $CH_3$-$CH_2O$, J= 7.5 Hz), 2.35 (s, 3H, $CH_3$-$C_6H_4$), 2.47 (ddd, 1H, $H_4$, J=5, 9 and 13 Hz), 2.57 (dd, 1H, $H_4$, J= 6 and 13 Hz), 2.80 (s, 3H, $CH_3$-N), 3.50 (dq, 1H, $CH_2O$, J= 7.5 and 12 Hz), 3.88 (dq, 1H, $CH_2$, J= 7.5 and 12 Hz), 4.03 (dd, 1H, $H_3$, J=6 and 9 Hz), 5.20 (d, 1H, $H_5$, J= 5 Hz), 7.12-7.35 ( m, 4H, aromatic protons.); MS: *m/z* 221 ($M^+$, 16%), 175 (100). (Found: C, 70.47; H, 8.72; N, 6.08 %. Calc. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.30 %).

*Reaction of nitrone* **3** *with ethyl vinyl ether.* Reaction time 60 h. First eluted product was *(3R, 5S)-2-methyl-3-p-methoxyphenyl-5-ethoxyisoxazolidine* **7**, 38.5% yield, pale light oil; $\nu_{max}$ 2960, 2940,2900, 2820, 1610, 1510, 1240, 1100, 1080, 1030, 980, 840, 730 $cm^{-1}$; $^1H$ NMR: $\delta$ ($CDCl_3$) 1.28 (t, 3H, $CH_3$-$CH_2O$, J= 7.0 Hz), 2,33 (ddd; 1H $H_4$, J=3.2, 10.1, and 13.2 Hz), 2.56 (s, 3H, $CH_3$-N), 2.87 (ddd, 1H, $H_4$, J=6.4, 10.1 and 13.2 Hz), 3.38 (t, 1H, $H_3$, J=10.1 Hz), 3.51 (dq, 1H, $CH_2O$, J= 4.5 and 14 Hz), 3.81(s, 3H, $OCH_3$), 3.94 (dq, 1H, $CH_2O$, J=4.5 and 14 Hz) 5.17 (dd, 1H, $H_5$, J= 3.2 and 6.4 Hz), 6.87 (d, 2H, J=8.6 Hz aromatic protons), 7.33 (d, 2H, J=8.6 Hz); MS: *m/z* 237 ($M^+$, 10%), 191 (100). (Found: C, 65.79; H, 8.16; N, 5.95 %. Calc. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90 %). Further fractions gave *(3R,5R)-2-methyl-3-p-methoxyphenyl-5-ethoxyisoxazolidine* **11**, 31.5% yield; white oil; $\nu_{max}$ 2960, 2940, 2920, 2860, 1610, 1510, 1300, 1240, 1170, 1090, 1030, 935, 890, 870 $cm^{-1}$; $^1H$ NMR: $\delta$ ($CDCl_3$) 1.27 (t, 3H, $CH_3$-$CH_2O$, J= 7.0 Hz), 2.43 (ddd, 1H, $H_4$, J=4.4, 9.5 and 13 Hz), 2.58 (dd, 1H, $H_4$, J= 6 and 13 Hz), 2.78 (s, 3H, $CH_3$-N), 3.53 (dq, 1H, $CH_2O$, J= 7.0 and 10.0 Hz), 3.79 (s, 3H, $OCH_3$), 3.89 (dq, 1H, $CH_2$, J= 7.0 and 10.0 Hz), 3.98 (dd, 1H, $H_3$, J=6 and 9.5 Hz), 5.19 (d, 1H, $H_5$, J= 4.4 Hz), 6.87 (d, 2H, J= 8.6 Hz aromatic protons), 7.3 (d, 2H, J=8.6 Hz aromatic protons); MS: *m/z* 232 ($M^+$, 165), 201 (100). (Found: C, 65.75; H, 8.18; N, 5.92 %. Calc. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90 %).

*Reaction of nitrone* **4** *with ethyl vinyl ether.* Reaction time 240 h. Column chromatography gave *(3R,5S)-2,3-diphenyl-5-ethoxyisoxazolidine* **8**, 62% yield; white solid, m.p. 74-76 °C; $\nu_{max}$ 2990, 2870, 1600, 1470, 14,90, 1390, 1360, 1340, 1250, 1150, 1090, 1000, 920, 760, 710, 690, 620 $cm^{-1}$; $^1H$ NMR: $\delta$ ($CDCl_3$) 1.24 (s, 3H, $CH_3$-$CH_2O$, J=7.5 Hz), 2.38 (ddd, 1H, H-4, J=2, 7, and 14 Hz), 2.96 (ddd, 1H, H-4, J=6, 10, and 14 Hz), 3.50 (dd, 1H, H-3, J=7 and 10 Hz), 5.4 (dd, 1H, H-5, J=2 and 7 Hz), 7.05-7.40 (m, 10H, aromatic protons); MS: m/z 269 ($M^+$, 20), 161 (100). (Found: C, 76.11; H, 7.10; N, 5.09%. Calc. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%).

*Reaction of nitrone* **12** *and styrene.* Reaction time 240 h. First eluted product was *(3R, 5S)-2-methyl-3-styryl-5--phenylisoxazolidine* **16**, 57.6% yield; light yellow oil; $\nu_{max}$ 3060, 3040, 2980, 2960, 2860, 2835, 1650, 1580, 1480, 1435, 1340, 1085, 1065, 1020, 960, 745, 695 $cm^{-1}$; $^1H$ NMR: $\delta$ ($CDCl_3$) 2.24-2.75 (m, 1H, $H_4$), 2.85 (s, 3H, $CH_3$-N), 3.2-3.5 (m, 1H, $H_4$), 5.11 (m, 1H, $H_3$), 6.15 (dd, 1H, $H_5$, J= 4 and 8 Hz), 6.6 (d, 1H, $H'_3$, J= 14 Hz), 7.2-7.5 (m, 11H, $H''_3$ and aromatic protons), MS: *m/z* 265 ($M^+$, 18), 84 (100). (Found: C, 81.62; H, 7.17; N, 5.34 %. Calc. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22 ; N, 5.28 %). Further eluted product was *(3R, 5R)-2-methyl-3-styryl-5-phenylisoxazolidine* **17**, 25.7% yield; light yellow oil; $\nu_{max}$ 3040, 3020, 2980, 2960, 2860, 2830, 1650, 1580, 1480, 1435, 1340, 1090, 1060, 1020, 960, 745, 690 $cm^{-1}$ ; $^1H$ NMR: $\delta$ ($CDCl_3$) 2.70 (s, 3H, N-$CH_3$), 2.8-3.2 (m, 1H, $H_4$), 3.85-4.2 (m, 1H, $H_4$), 4.25 (m, 1H, $H_3$), 6.10 (dd, 1H, $H_5$, J= 4 and 8 Hz), 6.40 (d, $H'_3$, J= 14 Hz), 7.2-7.5 (m, 11H, $H''_3$ and aromatic protons), MS: *m/z* 265 ($M^+$, 18), 84 (100). (Found: C, 81.51; H, 7.19; N, 5.31 %. Calc. for $C_{18}H_{19}NO$:C, 81.47; H, 7.22; N, 5.28 %).

*Reaction of nitrone* 1 *and vinyl acetate.* Reaction time 72 h. First fractions gave *(3R, 5S)-2-methyl-3-phenyl-5-acetoxyisoxazolidine* **19**, 43% yield; m.p. 65-67 °C; $\nu_{max}$ 2990, 2960, 2860, 1715, 1485, 1450, 1360, 1225, 1125, 1100, 1060, 1010, 900, 850, 760, 695 $cm^{-1}$; $^1H$ NMR: $\delta$ ($CDCl_3$) 2.18 (s, 3H, $CH_3CO_2$), 2.46 (ddd, 1H, $H_4$, J=3, 7 and 14 Hz), 2.65 (s, 3H, $CH_3$-N), 3.06 (ddd, 1H, $H_4$, J=6, 9 and 14 Hz),3.35 (dd, 1H, $H_3$, J=7 and 9 Hz), 6.35 (dd, 1H, $H_5$, J=3 and 6 Hz), 7.2-7.5 (m, 5H, aromatic protons); MS: *m/z* 221 ($M^+$, 21), 105 (100). (Found: C, 66.23; H, 7.30; N, 6.08%. Calc. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95 %. Further elution gave *(3R, 5R)-2-methyl-3-phenyl-5-acetoxyisoxazolidine* **23**, 18% yield; m.p. 72-74 °C; $\nu_{max}$ 3050, 2950, 2900, 1715, 1480, 1355, 1220, 1060, 1005, 965, 900, 850 and 755 $cm^{-1}$. $^1H$ NMR: $\delta$ ($CDCl_3$) 2.14 (s, 3H, $CH_3CO_2$), 2.50 (ddd, 1H, $H_4$, J=5, 9 and 14 Hz), 2.60 (s, 3H, N-$CH_3$), 3.01 (ddd, 1H, $H_4$, J=3, 6 and 14 Hz), 3.58 (dd, 1H, $H_3$, J=6 and 9 Hz), 6.40 (dd, 1H, $H_5$, J=3 and 5 Hz), 7.18-7.55 (m, 5H, aromatic protons); MS: *m/z* 221 ($M^+$, 15), 105 (100).(Found: C, 66.32; H, 7.30; N, 6.10 %. Calc. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95 %).

*Reaction of nitrone* 2 *and vinyl acetate.* Reaction time 72 h. First eluted product was *(3R, 5S)-2-methyl-3-p-tolyl-5-acetoxyisoxazolidine* **20**, 55% yield; m.p. 78-80 °C; $\nu_{max}$ 2970, 1710, 1420, 1360, 1225, 1060, 1010, 965, 900, and 850 $cm^{-1}$. $^1$H NMR: δ ($CDCl_3$) 2.18 (s, 3H, $CH_3CO_2$), 2.36 (3H, s, $CH_3$-$C_6H_4$), 2.44 (ddd, 1H, $H_4$, J=2, 6 and 14 Hz), 2.65 (s, 3H, N-$CH_3$), 3.08 (ddd, 1H, $H_4$, J=5, 8, and 14 Hz), 3.40 (dd, 1H, $H_3$, J=6 and 8 Hz), 6.32 (dd, 1H, $H_5$, J=2 and 6 Hz), 7.12-7.38 ( m, 4H,aromatic protons).MS: *m/z* 225 ($M^+$, 19), 119 (100). (Found: C, 67.30; H, 7.76; N, 5.81 %. Calc. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62 %). Further elution gave *(3R, 5R)-2-methyl-3-p-tolyl-5-acetoxyisoxazolidine* **24**, 27% yield; m.p. 81-83°C; $\nu_{max}$ 2960, 2860, 1700, 1510,1425, 1350, 1230, 1060, 1020, 980, 920, and 850 $cm^{-1}$. $^1$H NMR: δ ($CDCl_3$) 2.16 (s, 3H, $CH_3CO_2$), 2.35 (3H, s, $CH_3$-$C_6H_4$), 2.50 (ddd, 1H, $H_4$, J=3, 7 and 14 Hz), 2.62 (s, 3H, N-$CH_3$), 3.02 (ddd, 1H, $H_4$, J=4, 8, and 14 Hz), 3.60 (dd, 1H, $H_3$, J= 7 and 8 Hz), 6.35 (dd, 1H, $H_5$, J=3 and 4 Hz), 7.12-7.38 ( m, 4H,aromatic protons).MS: *m/z* 235 ($M^+$, 15), 146 (100).(Found: C, 69.32; H, 5.05; N, 5.61 %. Calc. for $C_{14}H_{12}NO_3$: C, 69.41; H, 4.99; N, 5.78 %).

*Reaction of nitrone 3 and vinyl acetate.* Reaction time 240h. Flash chromatography gave a not resolved mixture of epimeric *cis* and *trans* isoxazolidines **21** and **25** in 62 % yield . The epimeric ratio, evaluated by NMR spectroscopy was 43:57; $\nu_{max}$ 2960, 2940, 2820, 1710, 1585,1495, 1450, 1400,1350, 1285, 1165, 1015, 965, 845, and 825 $cm^{-1}$. $^1$H NMR: δ ($CDCl_3$) 2.05 (s, 3H, $CH_3CO_2$), 2.15 (s, 3H, $CH_3CO_2$), 2.30-2.45 (1H,m, $H_4$), 2.60 (3H, s, $CH_3$-N), 2.90-3.20 (dt, 1H, $H_4$,), 3.43-3.58 (dd, 1H, $H_5$), 3.75 (3H, s, $CH_3O$-$C_6H_4$), 6.20-6.40 (dd, 1H, $H_5$, J=3 and 6 Hz), 7.80-7.40 (m, 4H,aromatic protons).MS: *m/z* 251 ($M^+$, 20), 163 (100).

**Rearrangement Reactions of Isoxazolidines 5-11 and 19-25 with 20% Aqueous $H_2SO_4$.**

*General procedure.* A solution of isoxazolidine (6 mmol.) and 20 ml of aqueous $H_2SO_4$ (20%) was stirred at reflux temperature, for 15-110 minutes, according to the substituents (see tables 2 and 4). The solution was then cooled and extracted with ether. The organic layer was washed with saturated aqueous sodium carbonate solution, dried over $MgSO_4$ and concentrated under reduced pressure to give a residue which was subjected to silica gel chromatography using a ethyl ether/hexane 40:60% mixture as eluent.

*Reaction of isoxazolidines* **5** and **9** *with $H_2SO_4$.* Reaction time 105 min. First fractions gave *C-styryl-N-methyl nitrone* **12**, 100% yield; mp 83-85 °C; $\nu_{max}$ 3020-3000, 2960, 1605, 1560, 1495, 1390, 1180, 1140, 980, 945, 755, 690, 600 $cm^{-1}$. $^1$H NMR: δ ($CDCl_3$) 3.75 (s, 3H, N-$CH_3$), 6.85 (dd, 1H, $H_2$, J=14 and 14.2 Hz), 7.19-7.62 (m, 7H, aromatic and vinylic protons). MS: m/z 161 ($M^+$, 53), 160, 144, 127, 116, 115, 105, 103, 91, 84, 78, 77, 51, 42, 32.

*Reaction of isoxazolidines* **6** and **10** *with $H_2SO_4$.* Reaction time 105 min. First fractions gave *p-methylcinnamaldehyde* **27**, 5% yield. Further elution gave *C-p-methylstyryl-N-methyl nitrone* **13**, 95% yield; $\nu_{max}$ 2850, 1590, 1305, 1290, 1125, 1090, 975, 850, 800, 600 $cm^{-1}$. $^1$H NMR: δ ($CDCl_3$) 2.30 (s, 3H, $CH_3$-$C_6H_4$), 3.73 (s, 3H, N-$CH_3$), 6.87 (dd, 1H, $H_2$, J=14 and 16 Hz), 7.<03-7.60 (m, 6H, aromatic and vinylic protons). MS: m/z 175 ($M^+$, 67), 174, 158, 131, 130, 129, 116, 105, 91, 84, 42, 32.

*Reaction of isoxazolidines* **7** and **11** *with $H_2SO_4$.* Reaction time 110 min. First fractions gave *C-p-methoxystyryl-N-methyl nitrone* **14**, 95% yield; $\nu_{max}$ 2980, 2960, 2840, 1575, 1500, 1450, 1410, 1380, 1285, 1245, 1165, 1135, 1020, 965, 940, 820, 790 $cm^{-1}$. $^1$H NMR: δ ($CDCl_3$) 3.70 (s, 3H, $CH_3O$-$C_6H_4$), 3.80 (s, 3H, N-$CH_3$), 6.84 (dd, 1H, $H_2$, J=14 and 16 Hz), 7.7-7.60 (m, 6H, aromatic and vinylic protons). MS: m/z 191 ($M^+$, 100), 190, 174, 162, 146, 145, 135, 131, 103, 91, 84, 77.

*Reaction of isoxazolidine* **8** *with $H_2SO_4$.* Reaction time 110 min. First fractions gave *C-styryl-N-phenyl nitrone* **15**, 100% yield; $\nu_{max}$ 3060-3020, 1590, 1380, 1120, 970, 850, 810, 610 $cm^{-1}$; $^1$H NMR: δ ($CDCl_3$) 3.85 (s, 3H, N-$CH_3$), 7.05 (dd, 1H, $H_2$, J=14.2 and 16 Hz), 7.3-7.89 (m, 12H, aromatic and vinylic protons). MS: m/z 223 ($M^+$, 100), 222, 206, 146, 145, 103, 77.

*Reaction of isoxazolidines* **19** and **23** *with $H_2SO_4$.* Reaction time 60 min. First fractions gave *cinnamaldehyde* **26**, 17% yield. Further elution gave *C-styryl-N-methyl nitrone* **12**, 58%.

*Reaction of isoxazolidines* **20** and **24** *with $H_2SO_4$.* Reaction time 30 min. First fractions gave *p-methylcinnamaldehyde* **27**, 12% yield. Further elution gave *C-p-methylstyryl-N-methyl nitrone* **13**, 76% yield.

*Reaction of isoxazolidines* **21** and **25** *with $H_2SO_4$.* Reaction time 15 min. First fractions gave *p-methoxycinnamaldehyde* **28**, 19% yield. Further elution gave *C-p-methoxystyryl-N-methylnitrone* **14**, 74% yield.

*Reaction of isoxazolidine* **22** *with $H_2SO_4$.* Reaction time 60 min. Chromatographic separation gave *C-styryl-N-phenyl-nitrone* **15**, 85% yield.

*Alternative synthesis of C-styryl-N-methyl nitrone* **12**. In a 50 mL Erlenmeyers flask, kept to 0 °C, cinnamaldehyde (3 mL), N-methylhydroxylamine (3.0 g) NaOH (13 mL), were mixed for 4 h. The solution was extracted with chloroform. The organic layer was dried on anhydrous sodium sulfate, filtered and concentrated under reduced pressure, to give a residue which was chromatographed to give 68% yield of **12**.

**Rearrangement Reactions of Isoxazolidines 19-25 with KOH.**

*General procedure.* A solution of isoxazolidine (4 mmol) and KOH (16 mmol) in 15 mL of methanol was refluxed for 3.5 h under stirring; the solvent was then removed under reduced pressure. The residue was treated with a solution of 10% HCl and extracted with chloroform. The organic layer was dried over $Mg_2SO_4$ and concentrated under reduced pressure to give an oil, which was subjected to silica gel chromatography using a 3% methanol-ether mixture as eluent.

*Reaction of isoxazolidines* **19** and **23** *with KOH.* Reaction time 3.5 h. First eluted product was *C-styryl-N-methyl nitrone* **12**, 84% yield.

*Reaction of isoxazolidines* **20** and **24** *with KOH.* Reaction time 3.0 h. First fractions gave *C-p-methylstyryl--N-methyl nitrone* **10**, 78% yield.

*Reaction of isoxazolidines* **21** and **25** *with KOH.* Reaction time3.0 h. First fractions gave *C-p-methoxystyryl--N-methyl nitrone* **14**, 85% yield

*Reaction of isoxazolidine* **16** *with KOH.* Reaction time 3.0 h. First fractions gave *C-styryl-N-phenyl-nitrone* **15**, 83% yield.

**Rearrangement Reactions of Isoxazolidines 19-25 with p-Toluenesulphonic Acid.**

*General procedure.* A solution of isoxazolidine (4 mmol) was heated in ethanolic solution (5 mL) with 5 mg of p-toluensulphonic acid for 2 h, and extracted with chloroform. The organic layer was dried over $Mg_2SO_4$ and concentrated under reduced pressure to give an oil which was subjected to silica gel chromatography using a 3% methanol-ether mixture as eluent.

*Reaction of isoxazolidines* **19** and **23** *with p-Toluenesulphonic Acid.* Reaction time 2 h. First fractions gave epimeric mixtures of isoxazolidines **5**, **9**, 62% yield. Second fraction gave *C-stiryl-N-methyl nitrone* **12**, *3 4% yield.*

*Reaction of isoxazolidines* **20** and **24** *with p-Toluenesulphonic Acid* . Reaction time 2 h. First fractions gave epimeric mixtures of isoxazolidines **6**, **10**, 46% yield. Further elution gave *C-p-methylstyryl-N-methyl nitrone* **13**, 53% yield.

*Reaction of isoxazolidines* **21** and **25** *with p-Toluenesulphonic Acid* . Reaction time 5 h. First fractions gave epimeric mixtures of isoxazolidines **7**, **11**, 56% yield. Further elution gave *C-p-methoxystyryl-N-methyl nitrone* **14**, 43% yield.

*Reaction of isoxazolidine* **22** *with p-Toluenesulphonic Acid*. Reaction time 2 h. First fractions gave isoxazolidine

**8**, 41% yield. Further fractions gave *C-styryl-N-phenyl nitrone* **12**, 45% yield.

**Acknowledgements**.: This work was supported by C.N.R. and M.U.R.S.T., project of national interest -40%.

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