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Ring-Opening of Isoxazolidine Nucleus: Competitive Formation of α,β-Enones and Tetrahydro-1,3-Oxazines

Franco Casuscelli,[a] Ugo Chiacchio,[b] Antonio Rescifina,[b] Roberto Romeo,[a] Giovanni Romeo,[a] Silvana Tommasini,[a] and Nicola Uccella[c]

[a]Dipartimento Farmaco-chimico, Università, 98168 Messina, Italy

[b]Dipartimento di Scienze Chimiche, Università, 95125 Catania, Italy

[c]Dipartimento di Chimica, Università, 87036 Arcavacata di Rende, Italy

Abstract: Treatment of isoxazolidine derivatives with methyl iodide, followed by simple heating with aqueous NaOH, gives rise to a competitive formation of α,β-enones and tetrahydro-1,3-oxazines. The ring-opening process is controlled by the stereochemistry of H_5 which represents the driving factor of two competitive reaction routes.

Isoxazolidines, readily available via 1,3-dipolar cycloaddition of nitrones to variously substituted alkenes, represent valuable synthons for simple and complex molecules of natural and biological interest.[1-4]

This powerful approach towards the formation of new C-C and C-O bonds requires the ring-opening of these saturated heterocycles to give access to a variety of functionalized intermediates, in many cases with multiple stereogenic centers introduced during the cycloaddition process.

The most important of these transformations is the hydrogenolytic cleavage of the N-O bond in the isoxazolidine ring system, leading to a *N*-substituted 1,3-aminoalcohol with defined stereochemistry.[5]

However, a large range of different synthetic pathways have been disclosed based on the activation of the nucleus through quaternization of the nitrogen atom. Of definite synthetic usefulness is the oxidative cleavage of *N*-methyl isoxazolidines with MCPBA to yield *N*-hydroxy-1,3-tetrahydrooxazines or nitrones.[6,7] Furthermore, isoxazolidinium salts, obtained by independent procedures, undergo chemical modifications leading to α,β-enones,[8] *N*-substituted hydroxylamines,[9] tetrahydro-1,3-oxazines,[10] 1,3-aminoalcohols,[11] 1,3-aminoketones,[8a,11] polysubstituted allylic alcohols.[8a,12]

In particular, it has been reported that treatment with bases of 5,5-disubstituted isoxazolidinium salts affords, via ring enlargement, the corresponding tetrahydro-1,3-oxazines, while 5-monosubstituted derivatives give rise to α,β-unsaturated ketones, as the only obtained products, via a Hofmann-like elimination process.[7]

In a preliminary report[10a] we indicated that this clear-cut distinction between the behaviour of 5,5-disubstituted and 5-monosubstituted derivatives should be reconsidered: in the presence of a hydrogen atom at

C_5 of the heterocyclic nucleus, both reaction routes are competing.

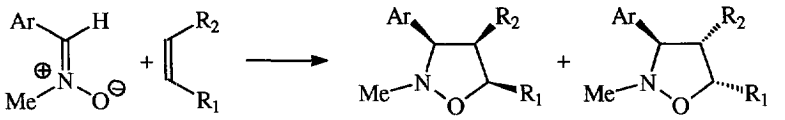
We have also suggested that the ring-opening reaction of 5-monosubstituted isoxazolidinium salts with bases could be controlled by the stereochemical features of the reacting system.

In this paper we would like to give experimental support to this hypothesis and we present the results obtained for a series of pure epimeric 5-monosubstituted compounds. One of the most compelling inputs for our studies follows from the recognition that, on the basis of a complete development and understanding of the suitable and varied methods of conversion of the isoxazolidine ring system, convenient synthetic schemes would be available. We report here in detail on the scope and mechanism of this useful ring-opening reaction.

RESULTS AND DISCUSSION

Reactions of the *C*-aryl-*N*-methylnitrones **1** and **2** with monosubstituted alkenes **3-10** were carried out in refluxing toluene and gave rise to 5-substituted isoxazolidines **11-26** as epimeric mixtures (Table 1). ^{1}H NMR analysis of the crude thermolizate allowed the determination of the amount of two stereoisomers present in the original reaction mixture. The crude residue was separated by flash-chromatography (diethyl ether/petrol ether 40:60 as eluent) and each cycloadduct could be obtained in pure form.

Table 1. Reaction of Nitrones **1,2** with Alkenes **3-10** in Refluxing Toluene.



1,2 **3-10** **11-18** **19-26**

Ar	R_1	R_2	*Cis* adduct (Yield %)	*Trans* adduct (Yield %)	*Cis/Trans* ratio
Ph	Ph	H	**11** (61.2)	**19** (28.8)	68:32
Ph	*p*-Me-C_6H_4	H	**12** (54.4)	**20** (30.6)	64:36
Ph	*p*-MeO-C_6H_4	H	**13** (50.8)	**21** (31.2)	62:38
Ph	*p*-Cl-C_6H_4	H	**14** (55.4)	**22** (32.6)	63:37
Ph	$(CH_2)_4CH_3$	H	**15** (38.2)	**23** (39.8)	49:51
Ph	$(CH_2)_5CH_3$	H	**16** (40.0)	**24** (37.0)	52:48
Ph	$-(CH_2)_6-$		**17** (40.0)	**25** (40.0)	50:50
p-MeO-C_6H_4	Ph	H	**18** (58.2)	**26** (23.8)	71:29

The stereochemistry of the not yet reported cycloadducts **12-18** and **20-26** has been determined by analysis of NMR coupling constants and by NOEDS. In particular, the ^{1}H NMR of *cis* adducts **11-14, 18** showed for two

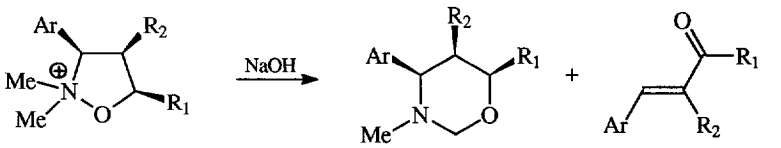
methylene protons at C_4 two well distinct multiplets centred at 3.05 δ and 2.36 δ; the downfield resonances correspond to the C_4 proton in a *cis* position with respect to phenyl substituents at C_3 and C_5, because of the additive deshielding effects of two aromatic substituents on the same side of the pentatomic ring. Conversely, analogous methylene protons in compounds **19-22**, **26** showed a nearly identical chemical shift and appeared as an indistinct multiplet centred at 2.65 δ, which overlaps the *N*-CH_3 signal (2.67 δ).

The configurational assignment for all the obtained compounds **11-26** has been accomplished by NOEDS. For derivatives **11-18**, irradiation of the H_5 resonances resulted in the observation of a signal enhancement for H_3; similarly, when the resonance for H_3 was irradiated, comparable NOE was observed for H_5. These results are in agreement with the structure of stereoisomers *cis* **11-18**, which show H_3 and H_5 in a *syn* relationship. On the contrary, in **19-26** a positive NOE was observed for the ortho protons of the phenyl substituent at C_3, when irradiating H_5, in accord with the *trans* structure, which has the ortho protons and H_5 on the same side of the pentatomic ring.

The pure epimers **11-26** were methylated to give the corresponding methiodides **27-42** (80-99 % yields), which have been fully characterized by NMR analysis and fast atom bombardment mass spectometry (see Experimental).

The isoxazolidinium salts **27-42** were then treated with aqueous 10% NaOH solution at reflux temperature. The *cis* epimers **27-34** lead to a mixture of tetrahydro-1,3-oxazines **43-50** and α,β-enones **51-58** (Table 2), while *trans* epimers **35-42** gave exclusive formation of α,β-enones **51-58** (88-95% yields) (see experimental).

Table 2. Reaction of *Cis* Isoxazolidinium Salts **27-34** with NaOH.



27-34 **43-50** **51-58**

Isoxazolidinium Salt	Oxazine (Yield %)	Enone (Yield %)
27	**43** (80)	**51** (15)
28	**44** (86)	**52** (11)
29	**45** (82)	**53** (15)
30	**46** (80)	**54** (12)
31	**47** (90)	**55** (5)
32	**48** (92)	**56** (4)
33	**49** (92)	**57** (5)
34	**50** (84)	**58** (8)

The structures of all the isolated products have been assigned on the basis of their spectrometric data. In particular, the molecular formula of tetrahydroxazines **43-50** follows from an exact mass determination.

The ^{1}H NMR spectra show two doublets at 3.80-4.30 and 4.41-4.79 ppm for diastereotopic protons at C_2, a multiplet resonating in the range 1.02-2.55 ppm for methylene protons at C_5, one doublet of doublets at 3.02-3.41 for protons at C_4 and a multiplet at 3.30-4.60 ppm for protons at C_6.

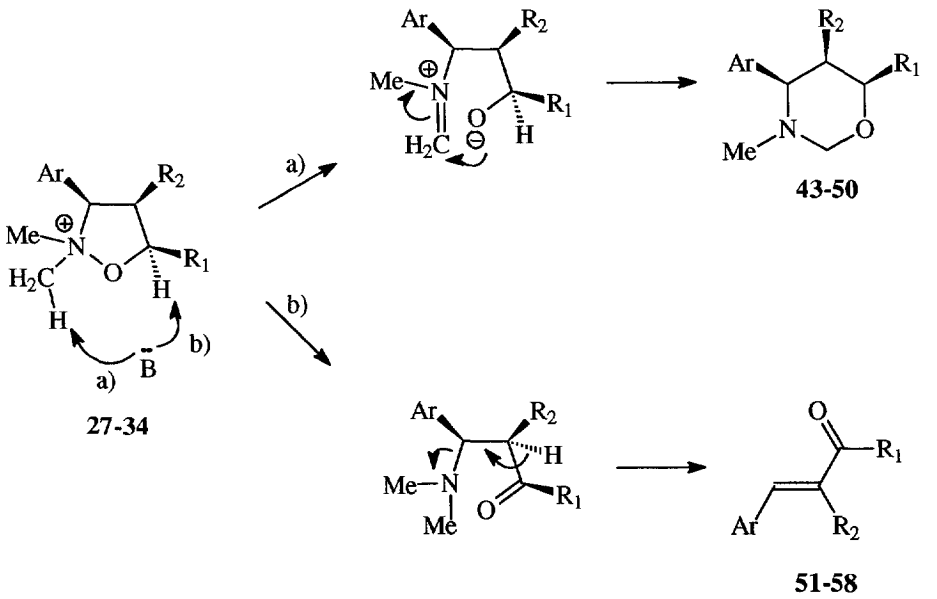
The stereochemical features of isoxazolidine precursors were maintained in the obtained tetrahydro-1,3-oxazines. The configurational assignments to compounds **43-50** as the *cis* isomers have been performed on the basis of the vicinal coupling constants and confirmed by NOE experiments. In fact, ^{1}H NMR decoupling experiments indicated that the pentatomic ring adopts a chair conformation with phenyl groups at C_4 and C_6 in equatorial positions (J = 10.0-12.5 Hz and J = 2.5-4.0 Hz for H_4; J = 10.0-12.5 Hz and J = 2.5-3.5 Hz for H_6). Furthermore, irradiation of the resonance of H_4 induces a positive NOE enhancement (12-15%) of the H_6 resonance and *viceversa*; these results in conjunction with the values of the coupling constants are only compatible with these protons in a *cis* position.

Structures of α,β-enones **51-58** have been established by comparison with authentic samples.

Formation of tetrahydro-1,3-oxazines and α,β-enones from *cis* epimers **27-34** clearly indicates that two competing ring-opening reaction pathways may operate:

- the attack of the base at the *N*-methyl hydrogens which probably proceeds with formation of a β-hydroxyiminium intermediate which undergoes cyclization with ring expansion (path a);

- the abstraction of the hydrogen atom at C_5 which gives rise to a Hofmann-like reaction towards α,β-enones with elimination of the positively charged nitrogen atom (path b). Such ring-opening eliminations have been already observed in the treatment of isoxazolidinium salts with bases[7] (Scheme 1).



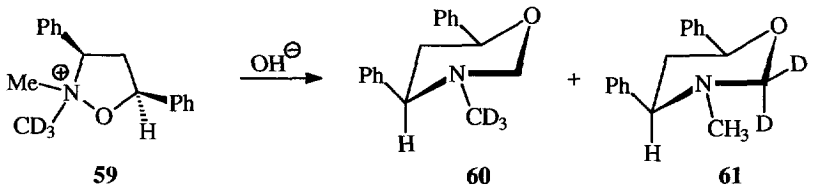
Scheme 1

The mechanism proposed for the formation of tetrahydro-1,3-oxazines has been further investigated.

The removal of the *N*-methyl hydrogens constitutes the rate-determining step in the reaction pathway a)

(Scheme 1). This assumption is supported by the observation of a primary isotopic effect when the *N*-methyl-*N*-trideuteromethyl isoxazolidinium salt **59** was treated with NaOH (Fig. 1). The ratio between the obtained compounds **60** and **61**, determined by ^{1}H NMR and MS analysis, clearly points out that the fission of C-H or C-D bonds occurs in a slow step of the global process.

The obtained value K_H/K_D = 2.5 is the one expected for rate-determining base catalyzed attack (see Experimental).



59 **60** **61**

Figure 1

Furthermore, the E_2 character of the β-hydroxyiminium-forming step has been demonstrated on the basis of the lack of isotopic exchange when the same reaction was performed on **27** with CH_3O^- in CH_3OD. The absence of deuterium atoms in the obtained compounds, when the reaction is stopped before completion, allows to rule out the involvement of a E_{1cb} mechanism.

Both structural and stereochemical features of the substrate deeply affect two competing ring-opening pathways of the isoxazolidinium salts by treatment with bases. The exclusive formation of enones is the general feature for *trans* isomers: in these compounds the *trans*-periplanar arrangement of the C-H and O-N bonds around the C-O bonds is quite readily accessible, on the basis of the consideration that the pseudorotation of the pentatomic ring is only few kcal·mol^{-1}. This favours stereoselectively the formation of the ketoderivatives **51-58**.

The elimination process is drastically suppressed by changing the configuration at C_5 of the isoxazolidinium salt. This is the case of *cis* epimers **27-34**: here, formation of tetrahydro-1,3-oxazines is the preferred reaction pathway. In fact, as reported,[10] the conformational preference of *cis* derivatives, rationalizable as the result of the release of steric interactions between the substituents at C_3 and C_5, is such that the electronic requirements for the *trans* periplanar elimination process E_2 cannot be easily reached.

In conclusion, in the ring-opening reaction of 5-monosubstituted isoxazolidinium salts with bases, the appropriate stereochemistry of H_5 represents the driving factor of two competitive routes leading to α,β-enones and tetrahydro-1,3-oxazines.

EXPERIMENTAL

Mp were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 377 instrument. ^{1}H NMR spectra were measured on a Bruker WP 200 SY instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-

resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. Mass spectra were taken at 70eV on a Varian Math CH-5 DF spectrometer and GC-MS HP 5859 A instruments. FAB Mass spectra were recorded in glycerol solutions on a VG ZAB 2F mass spectrometer equipped with a MSSCAN stearable gun operated with xenon gas at 9.5 KeV at resolution 1000. Merck silica gel 60H was used for preparative short-column chromatography. Isoxazolidines **11**, **19**, isoxazolidinium salts **27**, **33**, **35** and oxazines **43-50** have been already reported in literature.[8a,13]

*Reaction of Nitrones **1**, **2** with Alkenes **3-10**.*

General procedure. A solution of nitrone (10 mmol) and alkene (30 mmol) in anhydrous toluene (50 ml) was heated at 120° C, under stirring, until tlc showed the disappearance of the starting nitrone. The solvent was removed and the residue subjected to flash chromatography on silica gel column with hexane/ether 60/40 as eluent.

*Reaction of **1** with 4-methylstyrene **4**.* First eluted product was (3RS,5SR)-2-methyl-3-phenyl-5-(4-methyl)-phenyl-isoxazolidine **12**, 54.4% yield. Light yellow oil; ν_{max} 3090-2800, 1610, 1460, 1250, 1005, 770 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.34 (s, 3H), 2.37 (ddd, 1H, H_4, J = 11.4, 9.1 and 7.3 Hz) 2.67 (s, 3H, N-CH_3) 3.04 (ddd, 1H, H_4, J = 11.4, 9.1 and 7.4 Hz), 3.70 (dd, 1H, H_3, J = 9.1 and 9.1 Hz), 5.20 (dd, 1H, H_5, J = 7.4 and 7.3 Hz), 7.03-7.45 (m, 9H, Ar-H). Exact mass calculated for $C_{17}H_{19}NO$: 253.1466. Found: 253.1463. Further elution gave (3RS,5RS)-2-methyl-3-phenyl-5-(4-methyl)-phenyl-isoxazolidine **20**, 30.6% yield. Yellow oil; ν_{max} 3085-2800, 1610, 1465, 1245, 1005, 770 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.39-2.81 (m, 2H, H_4), 2.46 (s, 3H) 2.68 (s, 3H, N-CH_3), 3.79 (dd, 1H, H_3, J = 8.2 and 8.0 Hz), 5.12 (dd, 1H, H_5, J = 7.6 and 7.4 Hz), 7.00-7.38 (m, 9H, Ar-H). Exact mass calculated for $C_{17}H_{19}NO$: 253.1466. Found: 253.1462.

*Reaction of **1** with 4-methoxystyrene **5**.* First eluted product was (3RS,5SR)-2-methyl-3-phenyl-5-(4-methoxy)-phenyl-isoxazolidine **13**, 50.8% yield. Yellow oil; ν_{max} 3060-2760, 1610, 1455, 1300, 1245, 1175, 1035, 830 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.36 (ddd, 1H, H_4, J = 11.7, 9.1 and 7.2 Hz), 2.67 (s, 3H, N-CH_3) 3.05 (ddd, 1H, H_4, J = 11.7, 9.1 and 7.3 Hz), 3.70 (dd, 1H, H_3, J = 9.1 and 9.1 Hz), 3.78 (s, 3H, O-CH_3), 5.23 (dd, 1H, H_5, J = 7.3 and 7.2 Hz), 6.82-7.48 (m, 9H, Ar-H). Exact mass calculated for $C_{17}H_{19}NO_2$: 269.1415. Found: 269.1419. Further elution gave (3RS,5RS)-2-methyl-3-phenyl-5-(4-methoxy)-phenyl-isoxazolidine **21**, 31.2% yield. Yellow oil; ν_{max} 3060-2750, 1605, 1510, 1450, 1310, 1245, 1175, 1005, 830 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.55-2.70 (m, 2H, H_4), 2.72 (s, 3H, N-CH_3), 2.78 (s, 3H, O-CH_3), 3.89 (dd, 1H, H_3, J = 7.6 and 7.3 Hz), 5.20 (dd, 1H, H_5, J = 7.4 and 7.3 Hz), 6.85-7.50 (m, 9H, Ar-H). Exact mass calculated for $C_{17}H_{19}NO_2$: 269.1415. Found: 269.1418.

*Reaction of **1** with 4-chlorostyrene **6**.* First eluted product was (3RS,5SR)-2-methyl-3-phenyl-5-(4-chloro)-phenyl-isoxazolidine **14**, 55.4% yield. Oil; ν_{max} 3055-2775, 1600, 1400, 1255, 1090, 1015, 830, 755, 699 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.35 (ddd, 1H, H_4, J = 12.4, 8.6 and 7.7 Hz), 2.67 (s, 3H, N-CH_3) 3.06 (ddd, 1H, H_4, J = 12.4, 8.5 and 7.5 Hz), 3.70 (dd, 1H, H_3, J = 7.7 and 7.5 Hz), 5.19 (dd, 1H, H_5, J = 8.6 and 8.5 Hz), 7.18-7.49 (m, 9H, Ar-H). MS: 275 (M^++2, 4), 273 (M^+, 12), 227 (44), 192 (10), 135 (59), 134 (100), 115 (22), 91 (11), 77 (26). Exact mass calculated for $C_{17}H_{16}ClNO$: 285.0920. Found: 285.0913. Further elution gave (3RS,5RS)-2-methyl-3-phenyl-5-(4-chloro)-phenyl-isoxazolidine **22**, 32.6% yield. Yellow oil; ν_{max} 3090-2780,

1490, 1310, 1095, 1015, 960, 890, 755, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.56 (m, 1H, H_4), 2.71 (s, 3H, N-CH_3), 2.74 (m, 1H, H_4), 3.70 (t, 1H, H_3, J = 7.6 Hz), 5.23 (dd, 1H, H_5, J =9.5 and 7.2 Hz), 7.24-7.66 (m, 9H, Ar-H). MS: 275 (M^++2, 5), 273 (M^+, 15), 229 (13), 227 (40), 192 (9), 135 (58), 134 (100), 115 (22), 91 (13), 77 (25). Exact mass calculated for $C_{17}H_{16}ClNO$: 285.0920. Found: 285.0922.

Reaction of ***1*** *with 1-heptene* ***7***. First eluted product was (3RS,5SR)-2-methyl-3-phenyl-5-pentyl-isoxazolidine **15**, 38.2% yield. Light yellow oil; ν_{max} 3100, 2810, 1615, 1510, 1461, 1410, 1260, 1040, 758, 703 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.97 (t, 3H, J = 6.9 Hz), 1.54 (m, 8H), 2.49 (m, 2H, H_4), 2.57 (s, 3H, N-CH_3), 3.56 (m, 1H, H_3), 3.98 (m, 1H, H_5), 7.16-7.45 (m, 5H, Ar-H). MS: 233 (M^+, 68), 136 (100), 135 (16), 134 (31), 121 (22), 120 (32), 91 (27), 77 (21). Exact mass calculated for $C_{15}H_{23}NO$: 233.1779. Found: 233.1775. Further elution gave (3RS,5RS)- 2-methyl-3-phenyl-5-pentyl-isoxazolidine, **23**, 39.8% yield. Yellow oil; ν_{max} 3100, 2815, 1610, 1500, 1450, 1420, 1255, 1010, 750, 680 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.01 (t, 3H, J= 6.9 Hz), 1.57 (m, 8H), 2.50 (m, 2H, H_4), 2.26 (s, 3H, N-CH_3), 3.55 (m, 1H, H_3), 4.00 (m, 1H, H_5), 7.10-7.47 (m, 5H, Ar-H). MS: 233 (M^+, 55), 136 (100), 135 (10), 134 (41), 121 (12), 91 (35), 77 (28). Exact mass calculated for $C_{15}H_{23}NO$: 233.1779. Found: 233.1781.

Reaction of ***1*** *with 1-octene* ***8***. First eluted product was (3RS,5SR)-2-methyl-3-phenyl-5-hexyl-isoxazolidine **16**, 40% yield. Yellow oil; ν_{max} 3080, 2930, 2910, 1610, 1520, 1472, 1230, 1020, 764, 713 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.95 (t, 3H, J = 7.0 Hz), 1.46 (m, 2H, H_4), 1.67 (m, 10H), 2.58 (s, 3H, N-CH_3), 3.53 (m, 1H, H_3), 4.10 (m, 1H, H_5), 7.04-7.43 (m, 5H, Ar-H). MS: 247 (M^+, 58), 270 (12), 136 (100), 135 (22), 134 (41), 121 (25), 120 (35), 91 (33), 77 (16). Exact mass calculated for $C_{16}H_{25}NO$: 247.1936. Found: 247.1941. Further elution gave (3RS,5RS)-2-methyl-3-phenyl-5-hexyl-isoxazolidine, **24**, 37% yield. Yellow oil; ν_{max} 3075, 2932, 2905, 1610, 1500, 1470, 1230, 1025, 760, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.99 (t, 3H, J = 7.0 Hz), 1.45 (m, 2H, H_4), 1.69 (m, 10H), 2.63 (s, 3H, N-CH_3), 3.53 (m, 1H, H_3), 4.11 (m, 1H, H_5), 7.15-7.50 (m, 5H, Ar-H). MS: 247 (M^+, 55), 270 (13), 136 (100), 135 (20), 134 (43), 121 (35), 120 (35), 91 (30), 77 (10). Exact mass calculated for $C_{16}H_{25}NO$: 247.1936. Found: 247.1932.

Reaction of ***1*** *with cyclooctene* ***9***. First elution gave (1RS,4RS,5RS)-3-methyl-2-oxo-4-phenyl-3-azabiciclo-[6.3.0]-undecane **17**, 40% yield. Yellow oil; ν_{max} 3080, 3055, 2985, 2980, 1610, 1500, 1400, 1290, 1200, 1100, 980, 850, 770, 650 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.57 (m, 12H), 2.40 (m, 1H, H_5), 2.71 (s, 3H, N-CH_3), 2.90 (d, 1H, H_4, J = 8.0 Hz), 4.27 (m, 1H, H_1), 7.26-7.42 (m, 5H, Ar-H). MS: 217 (M^+, 84), 136 (25), 135 (27), 134 (100), 121 (13), 118 (22), 91 (25), 77 (16). Exact mass calculated for $C_{16}H_{23}NO$: 245.1779. Found: 245.1779. Further elution gave (1RS,4SR,5SR)-3-methyl-2-oxo-4-phenyl-3-azabiciclo-[6.3.0]-undecane **25**, 40% yield. Yellow oil; ν_{max} 3090, 3060, 2980, 2970, 1600, 1490, 1450, 1390, 1350, 1300, 1200, 1110, 1050, 1000, 850, 750 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.44 (m, 12H), 2.72 (m, 1H, H_5), 2.76 (s, 3H, N-CH_3), 4.00 (d, 1H, H_4, J = 7.0 Hz), 4.43 (m, 1H, H1), 7.20-7.40 (m, 5H, Ar-H). MS: 217 (M^+, 77), 173 (10), 136 (62), 135 (86), 134 (100), 121 (16), 120 (11), 118 (18), 91 (20), 77 (12). Exact mass calculated for $C_{16}H_{23}NO$: 245.1779. Found: 245.1780.

Reaction of ***2*** *with styrene* ***3***. First elution gave (3RS,5SR)-2-methyl-3-(4-methoxy-phenyl)-5-phenyl-isoxazolidine **18**, 58.2% yield. Yellow oil. ν_{max} 3060, 3020, 2980, 2840, 1609, 1510, 1460, 1730, 1032, 836,

703 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.39 (ddd, 1H, H_4, J = 11.8, 9.3 and 7.2 Hz), 2.67 (s, 3H, N-CH_3), 3.03 (ddd, 1H, H_4, J = 11.8, 9.3 and 7.2 Hz), 3.72 (dd, 1H, H_3, J = 7.2 and 7.2 Hz), 3.77 (s, 3H, O-CH_3), 5.25 (dd, 1H, H_5, J = 9.3 and 9.3 Hz) 6.76-7.62 (m, 5H, Ar-H). MS: 259 (M^+, 43), 223 (34), 165 (100), 164 (55), 148 (13), 135 (22), 134 (20), 116 (12), 77 (18). Exact mass calculated for $C_{17}H_{19}NO_2$: 269.1415. Found: 269.1421. Further elution gave (3SR,5RS)-2-methyl-3-(4-methoxy-phenyl)-5-phenyl-isoxazolidine **26**, 23.8% yield. Yellow oil. ν_{max} 3060, 3020, 2975, 2850, 1600, 1510, 1450, 1160, 1000, 820, 750, 700, 670 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.37-2.78 (m, 1H, H_4), 2.72 (s, 3H, N-CH_3), 3.78 (dd, 1H, H_3, J = 7.3 and 7.2 Hz), 4.00 (s, 3H, O-CH_3), 5.21 (dd, 1H, H_5, J = 7.4 and 7.3 Hz) 6.98-7.59 (m, 5H, Ar-H). MS: 259 (M^+, 50), 223 (30), 165 (100), 164 (45), 148 (9), 135 (25), 134 (20), 116 (15), 77 (15). Exact mass calculated for $C_{17}H_{19}NO_2$: 269.1415. Found: 269.1418.

Preparation of Isoxazolidinium Salts.

General procedure. A solution of isoxazolidine (1 mmol) and iodomethane (4 ml) in anhydrous THF (10 ml) was stirred at room temperature for 24 h. The solvent was removed at reduced pressure and the residue, a yellow sticky oil was used with no further purification.

*Reaction of isoxazolidine **12** with iodomethane.* First elution gave *cis* (3RS,5SR)-2,2-dimethyl-3-phenyl-5-(4-methyl)-phenyl-isoxazolidinium iodide **28**. ^1H NMR: δ ($CDCl_3$) 2.87 (m, 1H, H_4), 3.15 (s, 3H, N-CH_3), 3.17 (m, 1H, H_4), 3.99 (s, 3H, N-CH_3), 6.38 (t, 1H, H_5, J = 8.2 Hz), 6.74 (t, 1H, H_3, J = 8.2 Hz), 7.03-7.95 (m, 9H, Ar-H). FAB: *m/z* 268 (M^+ - I).

*Reaction of isoxazolidine **13** with iodomethane.* First elution gave *cis* (3RS,5SR)-2,2-dimethyl-3-phenyl-5-(4-methoxy)-phenyl-isoxazolidinium iodide **29**. ^1H NMR: δ ($CDCl_3$) 2.94 (m, 1H, H_4), 3.43 (s, 3H, N-CH_3), 3.78 (s, 3H, O-CH_3), 3.80 (s, 3H, N-CH_3), 4.05 (m, 1H, H_4), 6.65 (t, 1H, H_5, J = 7.3 Hz), 6.71 (t, 1H, H_3, J = 7.1 Hz), 6.82-8.13 (m, 9H, Ar-H). FAB: *m/z* 284 (M^+ - I).

*Reaction of isoxazolidine **14** with iodomethane.* First elution gave *cis* (3RS,5SR)-2,2-dimethyl-3-phenyl-5-(4-chloro)-phenyl-isoxazolidinium iodide **30**. ^1H NMR: δ ($CDCl_3$) 2.92 (m, 1H, H_4), 3.49 (s, 3H, N-CH_3), 3.80 (s, 3H, N-CH_3), 4.03 (m, 1H, H_4), 6.23 (t, 1H, H_5, J = 7.0 Hz), 6.41 (t, 1H, H_3, J = 7.3 Hz), 7.02-8.10 (m, 9H, Ar-H). FAB: *m/z* 290 (M^+ +2 - I), 288 (M^+ - I).

*Reaction of isoxazolidine **15** with iodomethane.* First elution gave *cis* (3RS,5SR)-2.2-dimethyl-3-phenyl-5-pentyl-isoxazolidinium iodide **31**. ^1H NMR: δ ($CDCl_3$) 0.98 (t, 3H, J = 6.9 Hz), 1.56 (m, 8H), 2.64 (m, 2H, H_4), 3.28 (s, 3H, N-CH_3), 3.72 (s, 3H, N-CH_3), 4.21 (m, 1H, H_3), 5.81 (dd, 1H, H_5, J = 10.1 and 7.3 Hz), 7.20-8.10 (m, 5H, Ar-H). FAB: *m/z* 248 (M^+ - I).

*Reaction of isoxazolidine **16** with iodomethane.* First elution gave *cis* (3RS,5SR)-2,2-dimethyl-3-phenyl-5-hexyl-isoxazolidinium iodide **32**. ^1H NMR: δ ($CDCl_3$) 0.98 (t, 3H, J = 7.0 Hz), 1.67 (m, 10H), 2.85 (m, 2H, H_4), 3.09 (s, 3H, N-CH_3), 3.31 (s, 3H, N-CH_3), 4.23 (m, 1H, H_3), 5.92 (dd, 1H, H_5, J = 10.2 and 7.2 Hz), 7.35-8.15 (m, 5H, Ar-H). FAB: *m/z* 262 (M^+ - I).

*Reaction of isoxazolidine **18** with iodomethane.* First elution gave *cis* (3RS,5SR)-2,2-dimethyl-3-(4-methoxy)-phenyl-5-phenyl-isoxazolidinium iodide **34**. ^{1}H NMR: δ ($CDCl_3$) 2.82-2.95 (m, 1H, H_4), 3.43 (s, 3H, N-CH_3), 3.78 (s, 3H, O-CH_3), 3.82 (s, 3H, N-CH_3), 4.05 (m, 1H, H_4), 6.10 (dd, 1H, H_5, J = 10.2 and 7.4 Hz), 6.30 (dd, 1H, H_3, J = 10.4 and 7.2 Hz), 7.28-8.15 (m, 9H, Ar-H). FAB: *m/z* 284 (M^+ - I).

*Reaction of isoxazolidine **20** with iodomethane.* First elution gave *trans* (3RS,5RS)-2,2-dimethyl-3-phenyl-5-(4-methyl)-phenyl-isoxazolidinium iodide **36**. ^{1}H NMR: δ ($CDCl_3$) 3.15-3.27 (m, 2H, H_4), 3.44 (s, 3H, N-CH_3), 3.79 (s, 3H, N-CH_3), 6.03 (dd, 1H, H_3, J = 10.8 and 8.5 Hz), 6.24 (dd, 1H, H_5, J = 10.2 and 5.5 Hz), 7.05-8.10 (m, 9H, Ar-H). FAB: *m/z* 268 (M^+ - I).

*Reaction of isoxazolidine **21** with iodomethane.* First elution gave *trans* (3RS,5RS)-2,2-dimethyl-3-phenyl-5-(4-methoxy)-phenyl-isoxazolidinium iodide **37**. ^{1}H NMR: δ ($CDCl_3$) 3.22-3.51 (m, 2H, H_4), 3.78 (s, 3H, O-CH_3), 3.81 (s, 3H, N-CH_3), 3.94 (s, 3H, N-CH_3), 6.22 (dd, 1H, H_3, J = 11.2 and 7.8 Hz), 6.34 (dd, 1H, H_5, J = 10.3 and 5.6 Hz), 6.82-8.13 (m, 9H, Ar-H). FAB: *m/z* 284 (M^+ - I).

*Reaction of isoxazolidine **22** with iodomethane.* First elution gave *trans* (3RS,5RS)-2,2-dimethyl-3-phenyl-5-(4-chloro)-phenyl-isoxazolidinium iodide **38**. ^{1}H NMR: δ ($CDCl_3$) 2.84-3.42 (m, 2H, H_4), 3.50 (s, 3H, N-CH_3), 3.80 (s, 3H, N-CH_3), 6.12 (dd, 1H, H_3, J = 10.2 and 7.4 Hz), 6.22 (t, 1H, H_5, J = 7.2 Hz), 6.92-8.10 (m, 9H, Ar-H). FAB: *m/z* 290 (M^+ +2 - I), 288 (M^+ - I).

*Reaction of isoxazolidine **23** with iodomethane.* First elution gave *trans* (3RS,5RS)- 2,2-dimethyl-3-phenyl-5-pentyl-isoxazolidine, **39**. ^{1}H NMR: δ ($CDCl_3$) 1.03 (t, 3H, J = 6.9 Hz), 1.60 (m, 8H), 2.78 (m, 2H, H_4), 3.03 (s, 3H, N-CH_3), 3.88 (s, 3H, N-CH_3), 4.12 (m, 1H, H_3), 6.41 (t, 1H, H_5, J = 7.1 Hz), 7.18-8.05 (m, 5H, Ar-H). FAB: *m/z* 248 (M^+ - I).

*Reaction of isoxazolidine **24** with iodomethane.* First elution gave *trans* (RS3,5RS)-2,2-dimethyl-3-phenyl-5-hexyl-isoxazolidinium iodide **40**. ^{1}H NMR: δ ($CDCl_3$) 1.02 (t, 3H, J = 7.0 Hz), 1.71 (m, 10H), 2.98 (m, 2H, H_4), 3.07 (s, 3H, N-CH_3), 3.92 (s, 3H, N-CH_3), 4.15 (m, 1H, H_3), 6.48 (dd, 1H, H_5, J = 10.3 and 7.2 Hz), 7.25-8.10 (m, 5H, Ar-H). FAB: *m/z* 262 (M^+ - I).

*Reaction of isoxazolidine **26** with iodomethane.* First elution gave *trans* (3RS,5RS)-2,2-dimethyl-3-(4-methoxy)-phenyl-5-phenyl-isoxazolidinium iodide **42**. ^{1}H NMR: δ ($CDCl_3$) 3.10-3.43 (m, 2H, H_4), 3.16 (s, 3H, N-CH_3), 3.78 (s, 3H, O-CH_3), 4.02 (s, 3H, N-CH_3), 6.46 (m, 1H, H_5), 6.76 (m, 1H, H_3), 7.36-7.96 (m, 9H, Ar-H). FAB: *m/z* 284 (M^+ - I).

*Reaction of Isoxazolidinium Salts **27-42** with 10% aqueous NaOH.*

General procedure. A solution of isoxazolidinium iodide (3 mmol) and 20 ml of aqueous NaOH (10%) was stirred at reflux temperature for 3 h. The solution was then cooled and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was subjected to silica gel chromatography, using an cyclohexane/ethyl acetate 9/1 mixture as eluent.

Reaction of isoxazolidinium iodide 27 with NaOH. First fractions gave *cis* (4RS,6SR)-3-methyl-4,6-diphenyltetrahydro-1,3-oxazine **43**, 80% yield.[10] Further elution gave *trans* 1,3-diphenylpropenone **51**, 15% yield.[10]

Reaction of isoxazolidinium iodide 28 with NaOH. First fractions gave *cis* (4RS,6SR)-3-methyl-4-phenyl-6-(4-methyl)-phenyltetrahydro-1,3-oxazine **44**, 86% yield.[10] Further elution gave *trans* 1-phenyl-3-(4-methyl)-phenylpropenone **52**, 11% yield.[10]

Reaction of isoxazolidinium iodide 29 with NaOH. First fractions gave *cis* (4RS,6SR)-3-methyl-4-phenyl-6-(4-methoxy)-phenyltetrahydro-1,3-oxazine **45**, 82% yield.[10] Further elution gave *trans* 1-phenyl-3-(4-methoxy)-phenylpropenone **53**, 15% yield.[10]

Reaction of isoxazolidinium iodide 30 with NaOH. First fractions gave *cis* (4RS,6SR)-3-methyl-4-phenyl-6-(4-chloro)-phenyltetrahydro-1,3-oxazine **46**, 80% yield.[10] Further elution gave *trans* 1-phenyl-3-(4-chloro)-phenylpropenone **54**, 12% yield.[10]

Reaction of isoxazolidinium iodide 31 with NaOH. First fractions gave *cis* (4RS,6RS)-3-methyl-4-phenyl-6-pentyltetrahydro-1,3-oxazine **47**, 90% yield; yellow oil. ν_{max} 3040-2700, 1465, 1455, 1400, 1330, 1260, 1225, 1110, 1075, 990, 765 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.02-1.57 (m, 13H), 1.85 (s, 3H, N-CH_3), 3.03 (dd, 1H, H_4, J = 9.0 and 5.5 Hz), 3.30 (m, 1H, H_6), 3.82 (d, 1H, H_2, J = 8.5 Hz), 4.41 (d, 1H, H_2, J = 8.5 Hz), 6.80-7.58 (m, 5H, Ar-H). MS: 247 (M^+, 22), 246 (33), 176 (24), 149 (44), 148 (100), 120 (32), 119 (36), 118 (56), 105 (32), 104 (40), 91 (24). Exact mass calculated for $C_{16}H_{25}NO$: 247.1936. Found: 247.1944. Further elution gave *trans* 1-phenyl-3-pentylpropenone **55**, 5% yield.[8a]

Reaction of isoxazolidinium iodide 32 with NaOH. First fractions gave *cis* (4RS,6RS)-3-methyl-4-phenyl-6-hexyltetrahydro-1,3-oxazine **48**, 92% yield; yellow oil. ν_{max} 3040-2710, 1465, 1450, 1430, 1400, 1220, 1110, 1075, 985, 790 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.13-1.62 (m, 15H), 1.82 (s, 3H, N-CH_3), 3.02 (dd, 1H, H_4, J = 9.0 and 5.5 Hz), 3.30 (m, 1H, H_6), 3.81 (d, 1H, H_2, J = 8.4 Hz), 4.43 (d, 1H, H_2, J = 8.4 Hz), 6.70-7.41 (m, 5H, Ar-H). MS: 261 (M^+, 29), 260 (31), 176 (29), 149 (42), 148 (100), 129 (21), 120 (45), 118 (71), 105 (48), 104 (50), 91 (33), 77 (29). Exact mass calculated for $C_{17}H_{27}NO$: 261.2092. Found: 261.2098. Further elution gave *trans* 1-phenyl-3-hexylpropenone **56**, 4% yield.[10]

Reaction of isoxazolidinium iodide 33 with NaOH. First fractions gave *cis* (1RS,5RS,6RS)-4-methyl-2-oxo-5-phenyl-4-azabiciclo-[6.4.0]-dodecane **49**, 92% yield. Yellow oil; ν_{max} 3060-2940, 1490, 1465, 1250, 1200, 1105, 1090-1060, 990, 760, 705 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.24-1.32 (m, 12H), 1.89 (s, 3H, N-CH_3), 2.55 (m, 1H, H_6), 3.32 (d, 1H, H_5, J = 9.4 Hz), 4.30 (d, 1H, H_3, J = 8.6 Hz), 4.74 (m, 1H, H_1), 4.69 (d, 1H, H_3, J = 8.6 Hz), 7.38-7.69 (m, 5H, Ar-H). MS: 259 (M^+, 38), 258 (16), 150 (22), 149 (70), 148 (100), 134 (24), 120 (45), 119 (39), 118 (55), 91 (31), 77 (28). Exact mass calculated for $C_{17}H_{25}NO$: 259.1936. Found: 259.1930. Further elution gave *(E)*-2-benzylidene-cyclooctanone **57**, 5% yield.[8a]

Reaction of isoxazolidinium iodide 34 with NaOH. First fractions gave *cis* (4RS,6SR)-3-methyl-4-(4-methoxy)-phenyl-6-phenyltetrahydro-1,3-oxazine **50**, 84% yield.[10] Further elution gave *trans* 1-(4-methoxy)-

phenyl-3-phenylpropenone **57**, 8% yield.[10]
Isotopic effect.

A solution of isoxazolidine **11** and 2 ml of CD_3I in ether (5 ml) was stirred at room temperature for 24 h. The solvent was removed and the resulting solid [FAB: *m/z* 257 (M^+ - I)] was heated with 5 ml of aqueous NaOH (10%) for 3 h. After usual work-up the crude NMR showed the presence of oxazines **60**, **61** in the ratio 71:29.

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