

# Electron-impact Mass Spectral Fragmentation Patterns of Isoxazolines

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Electron-impact mass spectra of 32 isoxazolines, viz. monocyclic, bicyclic and tricyclic isoxazolines are reported. The major fragmentation pattern for the isoxazolines with alkyl, aryl, methoxycarbonyl, (methylthio)methyl substituents at C-5 is  $\alpha$ -cleavage while there is a competition between the groups at C-5 for elimination in the case of 5,5-disubstituted isoxazolines. Bicyclic and tricyclic isoxazolines undergo ring fission to afford (isoxazole + allyl radical cation) and (isoxazole + cyclopentane radical cation) respectively, to reduce the ring strain present in the parent isoxazolines. In the case of 5-(2-methylphenyl)-isoxazolines, the isoxazole cation is observed as the base peak arising out of  $\text{CH}_3$  loss followed by H-migration.

Isoxazolines have emerged as potential building blocks for a number of bifunctional compounds such as  $\beta$ -hydroxy-ketones,  $\gamma$ -amino-alcohols etc., because of the facile ring cleavage under mild conditions<sup>1</sup>. The isoxazoline-reduction methodology has been successfully employed to accomplish the synthesis of several complex biomolecules. We have been involved in the synthesis of biochemically active  $\beta$ -chiral ketols through isoxazolines and during the course of this programme, we have examined the mass spectral fragmentation patterns of isoxazolines with varying functionalities. In the present communication, we report the

generalised mass spectral fragmentation pattern of these isoxazolines under electron-impact which will be of value in structure determinations though few monosubstituted isoxazolines have already been studied<sup>2</sup>.





## Results and Discussion

The isoxazolines (1–32) has been grouped into four major classes based on the complexity in their structural arrangements. The relative abundance of various fragments in the mass spectra of the isoxazolines are presented in Tables 1 and 2.

TABLE 1—RELATIVE ABUNDANCE OF VARIOUS FRAGMENTS IN THE MASS SPECTRA OF ISOXAZOLINES (1–24)

Compd. no.	R <sup>1</sup>	R	R <sup>2</sup>	% Abundance				
				M <sup>+</sup>	RCNO	$\begin{matrix} \text{R}^1 \\ \diagdown \\ \text{C} = \text{CH}_2\text{CH}^+ \\ \diagup \\ \text{R}^2 \end{matrix}$	R <sup>1</sup> CO <sup>+</sup>	(M-R <sup>1</sup> ) <sup>+</sup>
1	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	1	19	100	1	73
2	CH <sub>3</sub> CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	H	30	0	100	29	3
3	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	42	0	100	13	5
4	4ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	H	61	11	100	24	5
5	4ClC <sub>6</sub> H <sub>4</sub>	COOCH <sub>3</sub>	H	25	11	0	0	100
6	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COOCH <sub>3</sub>	H	6	10	0	9	100
7	CH <sub>3</sub>	nBu	H	21	6	100	3	100
8	CH <sub>3</sub> CH <sub>2</sub>	nBu	H	11	2	0	0	0 <sup>a</sup>
9	C <sub>6</sub> H <sub>5</sub>	nBu	H	29	17	0	3	100
10	4ClC <sub>6</sub> H <sub>4</sub>	nBu	H	34	24	0	0	100
11	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	nBu	H	11	13	0	0	100
12	4ClC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> SCH <sub>3</sub>	H	8	10	4	0	100 <sup>b</sup> (100)
13	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> SCH <sub>3</sub>	H	4	6	4	0	49 <sup>b</sup> (100)
14	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	12	20	68	100 <sup>c</sup>	0 (86 <sup>d</sup> )
15	CH <sub>3</sub> CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	15	0	100	100 <sup>c</sup>	0 (100 <sup>d</sup> )
16	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	40	7	53	100 <sup>c</sup>	0 (42 <sup>d</sup> )
17	4ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	7	4	21	50 <sup>c</sup>	0 (5 <sup>d</sup> )
18	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	4	0	53	100 <sup>c</sup>	0 (6)
19	4ClC <sub>6</sub> H <sub>4</sub>	COOCH <sub>3</sub>	CH <sub>3</sub>	7	7	0	0	17 <sup>e</sup>
20	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COOCH <sub>3</sub>	CH <sub>3</sub>	3	7	0	0	100
21	CH <sub>3</sub>	2CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	3	0	72	100 <sup>f</sup> (0)	3 <sup>g</sup> (74)
22	CH <sub>3</sub> CH <sub>2</sub>	2CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	8	0	62	100 <sup>f</sup> (0)	8 <sup>g</sup> (48)
23	C <sub>6</sub> H <sub>5</sub>	2CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	40	7	54	100 <sup>f</sup> (7)	40 <sup>g</sup> (38)
24	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	2CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	60	0	45	100 <sup>f</sup> (0)	66 <sup>g</sup> (100)

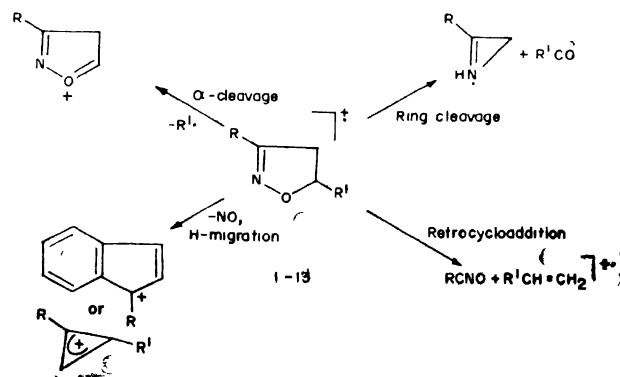
<sup>a</sup>Base peak at  $m/z$  70. <sup>b</sup>Value in parenthesis is for  $\text{CH}_3\text{SCH}_2$ . <sup>c</sup>Abundance of  $\text{PhCO}^+$  ion; in 17, base peak is due to  $4\text{ClC}_6\text{H}_4\text{CNO}$ . <sup>d</sup>Abundance of  $(\text{M}-\text{CH}_3)^+$  ion. <sup>e</sup>Base peak is due to  $\text{CH}_3\text{CO}^+$  ion. <sup>f</sup>Abundance of  $\text{PhCO}^+$  ion; the value in parenthesis is for  $2\text{CH}_3\text{C}_6\text{H}_4\text{CO}^+$  ion. <sup>g</sup>Abundance of  $(\text{M}-2\text{CH}_3\text{C}_6\text{H}_4)^+$  ion; the value in parenthesis is for  $(\text{M}-\text{CH}_3)^+$  ion.

Compd. no.*	R	R <sup>1</sup> R <sup>2</sup>	% Abundance		
			M <sup>+</sup>	RCNO	Alkene $\dot{\gamma}^+$
25	CH <sub>3</sub>	-(CH <sub>2</sub> ) <sub>3</sub> -	97	0	100
26	C <sub>6</sub> H <sub>5</sub>	-(CH <sub>2</sub> ) <sub>3</sub> -	100	12	20
27	CH <sub>3</sub>	-(CH <sub>2</sub> ) <sub>4</sub> -	8	8	120
28	CH <sub>3</sub> CH <sub>2</sub>	-(CH <sub>2</sub> ) <sub>4</sub> -	0	0	78 <sup>a</sup>
29	CH <sub>3</sub>		58 <sup>b</sup>	12	5 <sup>c</sup> (8)
30	CH <sub>3</sub> CH <sub>2</sub>		194 <sup>b</sup>	12	0 <sup>c</sup> (23)
31	C <sub>6</sub> H <sub>5</sub>		100	0	0 <sup>c</sup> (13)
32	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		67 <sup>b</sup>	0	0 <sup>c</sup> (6)

\*R<sup>2</sup> = R<sup>4</sup> = H  
<sup>a</sup>Base peak at *m/z* 67. <sup>b</sup>Base peak is due to cyclopentenyl cation. <sup>c</sup>Value in parenthesis is for (M-C<sub>2</sub>H<sub>4</sub>)<sup>+</sup> ion.

**3-Alkyl- and 3-aryl-5-monomosubstituted-isoxazolines (1–13):** The stabilities of the isoxazolines towards electron-impact is found to increase when the substituent at C-3 is changed from alkyl to aryl group as evidenced by the observed higher abundance of M<sup>+</sup> ion for the latter than for the former. Retrocycloaddition<sup>2</sup>, i.e. ring-opening of the isoxazolines to afford the nitrile oxide and the alkene, is not a favourable fragmentation path for the molecular ion as can be seen from the low abundance of the nitrile oxides. However, the abundance of alkene radical cations are found to be higher than those of the molecular ion and in certain cases the alkene radical cations are observed as base peak. This suggests that prior to retrocycloaddition of the molecular ion, loss of the group attached to the nitrile oxide moiety might take place and subsequent retrocycloaddition leads to alkene radical cation and other low molecular weight fragments. Another important fragmentation path favourable for the 5-monomosubstituted isoxazolines is the cleavage of C(5)–R' bond, known as  $\alpha$  cleavage<sup>3</sup>. This process is facile when the C-5 substituent is alkyl (7–11) or COOCH<sub>3</sub> (5, 6) or CH<sub>2</sub>SCH<sub>3</sub> (12, 13) groups whereas it is not favourable when the C-5 substituent is an aryl group (1–4). Thus in the case of 5-[(methylthio)methyl]isoxazolines, the base peak is observed due to the daughter ion of  $\alpha$ -cleavage namely  $\cdot\text{CH}_2\text{SCH}_3$ . In isoxazoline 12, the base peak is due to  $\cdot\text{CH}_2\text{SCH}_3$  and isoxazole cation, both of them arising out of  $\alpha$ -cleavage. In the case of isoxazoline 13, the base peak is due to  $\cdot\text{CH}_2\text{SCH}_3$ , while the isoxazole cation is observed in 49% abundance only. On the other hand, ring-cleavage of the isoxazolines to afford the azirine and the carbonyl compound is found to occur when the C-5 substituent is an aryl group (Scheme 1). This is quite evident from the occurrence of PhCO<sup>+</sup>/ArCO<sup>+</sup> ions in 100%

abundance in the case of 5-aryl-substituted-isoxazolines. It is also interesting to note the elimination of a molecule of NO followed by H-migration in the case of 5-aryl isoxazolines which leads to the formation of cyclopropenium or indenyl cation as shown in Scheme 1. Similar type of indenyl cation was proposed in the mass spectral fragmentation of 2-arylthiophenes<sup>4</sup>.

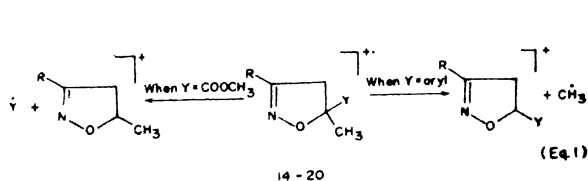


Scheme 1

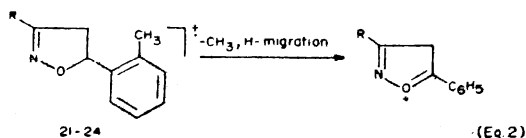
**3-Alkyl- and 3-aryl-5-methyl-5-phenylisoxazoline and 3-aryl-5-methoxy carbonyl-5-methylisoxazolines (14–20):** These geminal disubstituted compounds provide an opportunity to compare the relative ease of elimination of alkyl groups over aryl and methoxycarbonyl groups under electron-impact.

The relative abundances of molecular ion are found to be less compared to those of the corresponding 5-monomosubstituted-isoxazolines, suggesting that the additional substitution leads to a facile elimination of one of the two groups at C-5 under electron-impact. The abundance of the alkene radical cation in these 5,5-disubstituted-isoxazolines is more or less similar to those observed in the case of 5-monomosubstituted-isoxazolines. The abundance of PhCO<sup>+</sup> ion is found to be 100% in the case of 5-methyl-5-phenylisoxazolines. However CH<sub>3</sub>CO<sup>+</sup> ion is not observed in these compounds which indicates that the loss of CH<sub>3</sub> and not Ph occurs in these geminal disubstituted compounds. This observation may be explained on the basis of the relative conjugating abilities of the methyl and phenyl groups of which the latter is expected to exhibit more conjugating abilities than the former. The abundance of (M-COOCH<sub>3</sub>)<sup>+</sup> ion is found to be 100% in the case of 5-methoxycarbonylisoxazolines (5, 6). In the case of 5-methoxycarbonyl-5-methylisoxazolines (19, 20), the abundances of (M-COOCH<sub>3</sub>)<sup>+</sup> ions are found to be 17% and 100% respectively. In the geminal disubstituted isoxazoline, viz. 5-methoxycarbonyl-5-methylisoxazoline, (M-CH<sub>3</sub>)<sup>+</sup> peaks are not observed (equation 1). Therefore it is evident that when two groups compete for elimination under electron-impact, the bulkier the group more

facile is the elimination. However, when the bulkier group is capable of stabilising positive charges (e.g. aryl groups), the smaller group is eliminated.

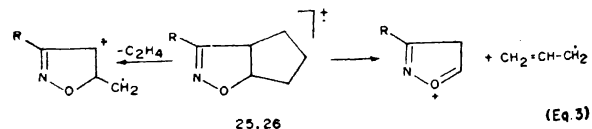


**3-Alkyl- and 3-aryl-5-(2-methylphenyl)isoxazolines (21–24):** These compounds are similar in their structural arrangement to compounds 1–13 discussed earlier except that a  $\text{CH}_3$  group is present in the C-5 phenyl ring (in *ortho*-position) which makes all the difference. The abundance of the molecular ion increases as the C-3 substituent is changed from alkyl to aryl group indicating that the 3-alkyl-substituted-isoxazolines are less stable to electron-impact than the 3-aryl-substituted-isoxazolines. It is found that the abundance of the nitrile oxide is very low while those of the alkene radical cation vary from 45 to 72%. The abundance of  $\text{PhCO}^+$  ions are observed to be 100% while those of the  $2\text{-CH}_3\text{C}_6\text{H}_4\text{CO}^+$  ions are found to be in the range 0–7%. This suggests that prior to ring-cleavage, loss of  $\text{CH}_3$  might occur which on further cleavage gives rise to the  $\text{PhCO}^+$  ion in high abundance. Support for this kind of methyl loss is derived from the observation of  $(M-\text{CH}_3)^+$  ions in relative abundance of 38, 48, 74 and 100% in the mass spectra of 5-(2-methylphenyl)isoxazolines. The higher abundance of  $(M-\text{CH}_3)^+$  ions is visualised as an outcome of  $\text{CH}_3$  loss followed by H-migration as shown in equation (2). Abundance of  $[M-(2\text{-CH}_3\text{C}_6\text{H}_4)]^+$  ions are observed in 3, 8, 40 and 66%.

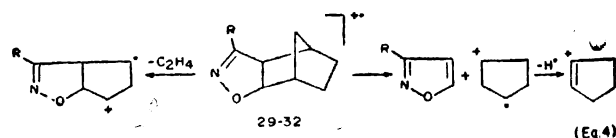


**Bicyclic and tricyclic isoxazolines (25–32):** The bicyclic isoxazolines derived from the nitrile oxide cycloaddition with cyclopentene and cyclohexene are stable to electron-impact as revealed by their high abundant molecular ions (Table 2). Elimination of a molecule of ethylene or allyl radical are favoured in the case of isoxazoline fused to five-membered ring (equation 3). The alkene radical cation, i.e. cyclopentene radical cation is observed in 100% abundance in the case of methyl-substituted-isoxazoline. Loss of a molecule of NO is also favoured in these compounds. In the case of isoxazolines derived from cyclohexene, the prominent peak is due to cyclohexenyl radical

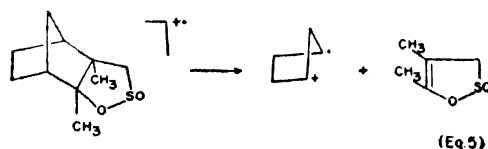
cation presumably formed by retrocycloaddition of the molecular ion.



The tricyclic isoxazolines are also found to be stable to electron-impact as can be seen from their intense molecular ion peaks. Both the nitrile oxide and norbornene radical cation are either absent or weak in the mass spectra of these tricyclic isoxazolines. A significant fragmentation path for the tricyclic isoxazolines is the formation of isoxazole and cyclopentane radical cation through ring cleavage (equation 4). Similar kind



of ring-cleavage in tricyclic compounds of the type 33 has been proposed by Dimmel and Wolinsky (equation 5)<sup>6</sup>. Elimination of a molecule of ethylene from the molecular ion may be responsible for the occurrence of the  $(M-28)^+$  ion which is then transformed to the isoxazole cation via the elimination of allyl radical. The driving force for the ring fission and elimination of ethylene from the tricyclic isoxazolines is that the ring strain is reduced in going from the tricyclic to the bicyclic systems.



Thus it is possible to conclude that elimination of C-5 substituent, i.e.  $\alpha$ -cleavage is a predominant fragmentation path for 5-monosubstituted-isoxazolines. When there is competition between the groups as in the case of 5,5-disubstituted-isoxazolines, the bulkier group, unless it is capable of stabilising a positive charge, gets eliminated in preference to the smaller group. In the case of 5-(2-methylphenyl)isoxazolines, a methyl group from the C-5 phenyl group is eliminated followed by H-migration which gives rise to isoxazole cation. Bicyclic and tricyclic isoxazolines undergo facile ring-fission.

### Experimental

All the isoxazolines were prepared by the 1,3-dipolar cycloaddition of nitrile oxide with the corresponding alkenes<sup>6</sup>. The *cis*-fusion in the case of bicyclic isoxazolines as well as the *exo*-fusion in the case of tricyclic isoxazolines have been established with the help of <sup>1</sup>H nmr data of these compounds. The electron-impact mass spectra were recorded at 70 eV ionising source.

### Acknowledgement

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### References

1. D. P. CURRAN, "Advances in Cycloaddition", JAI Press, New York, 1988 ; K. B. G. TORSELL, "Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis", Verlag Chemie, New York, 1988 ; P. CARAMELLA and P. GRUNANGER, "1,3-Dipolar Cycloaddition Chemistry", ed. A. PADWA, Wiley, New York, 1984, Vol 1 ; S. A. LANG and Y. LIN in "Comprehensive Heterocyclic Chemistry", eds. A. R. KATRITZKY and C. W. REES, Pergamon, London, 1984, Vol 6.
2. Q. N. PORTER, in "Mass Spectrometry of Heterocyclic Compounds", 2nd ed., eds. E. C. TAYLOR and A. WEISSBERGER, Wiley-Interscience, New York, 1985.
3. J. L. COTTOR, *J. Chem. Soc. (B)*, 1967, 6842.
4. C. NOLDE, *J. Chem. Soc. (B)*, 1967, 616.
5. D. R. DIMMEL and J. WOLINSKY, *J. Org. Chem.*, 1967, 32, 2725.
6. A. NAGARAJAN, Ph.D. Thesis, Bharathidasan University, Tiruchirapalli, 1991.