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Peracid Induced Ring Opening of Isoxazolidines. A Mechanistic Study.

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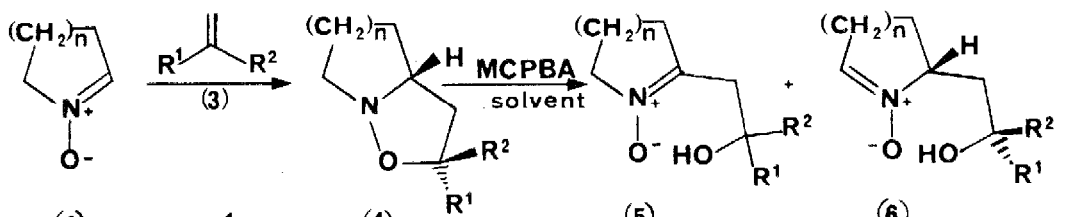
Abstract : Conformational analysis and mechanistic study of peracid induced ring opening of several isoxazolidines have been carried out. The orientation of the nitrogen lone pair dictates the regiochemistry of the ring opening which involves an intramolecular kinetic deprotonation of a nitroxonium ion intermediate.

1,3 Dipolar Cycloaddition of nitrones with alkenes is the best chemical template for constructing isoxazolidines in high yields.[1] Among the nitrones, 1-pyrroline 1-oxide (**1**) and 3,4,5,6-tetrahydropyridine 1-oxide (**2**) have emerged as the most important cyclic nitrones, since their addition reactions have found widespread use in the synthesis of natural products.[2] Nitrones generated by the oxidation of the isoxazolidines with peracids marked the beginning of the utilization of the second generation of nitrones.[3] For example, the isoxazolidine (**4a**), a nitrone (**1**) -styrene (**3a**) addition product,[4] on treatment with m-chloroperbenzoic acid (MCPBA) in dichloromethane, affords the less substituted nitrone (**6a**) as the sole product[3b] (Scheme 1). However, in this work the corresponding nitrone (**2**) -styrene cycloadduct[5] (**7a**) on MCPBA treatment,



(**1**) n = 1 (**4**) (**5**) (**6**)

(**2**) n = 2 (**7**) (**8**) (**9**)

(5a) : (6a) 0 : 100 in CH_2Cl_2 (5b) : (6b) 0 : 100 in CH_2Cl_2

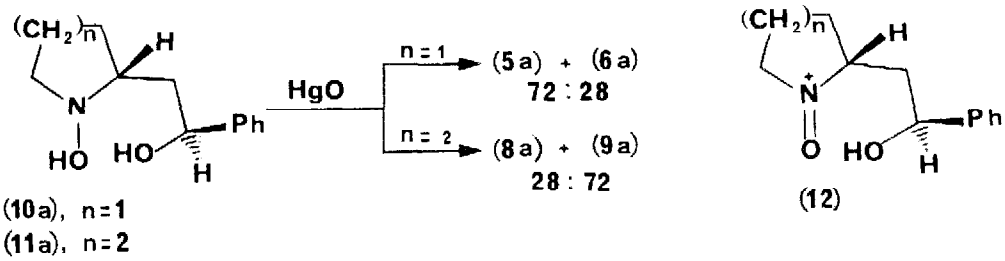
(5a) : (6a) 100 : 0 in CH_3CO_2H (8b) : (9b) 85 : 15 in CH_2Cl_2

a, $R^1 = H$, $R^2 = Ph$; b, $R^1 = CO_2CH_3$, $R^2 = CH_3$

Scheme 1

quite unexpectedly, gave a mixture of nitrones (**8a**) and (**9a**) (See the Table). Similar trends are observed in the peracid induced ring opening of the methyl methacrylate cycloadducts (**4b**) and (**7b**). While the former adduct afforded the less substituted nitrone (**6b**) regiospecifically, the latter gave the more substituted nitrone (**8b**) regioselectively (Scheme1).

It is interesting to note that the N-hydroxy-pyrrolidine (**10a**) and -piperidine derivative (**11a**) (prepared by sodium borohydride reduction of nitrones (**6a**) and (**9a**), respectively) on treatment with HgO in dichloromethane afforded a mixture of nitrones in each case (Scheme 2). It is widely presumed that both the peracid induced ring opening and HgO oxidation involve the intermediacy of a nitrosonium ion intermediate (**12**) which then tautomerizes to the nitrones.[3c] The results so far imply that the tautomerization process is controlled by thermodynamic factors to give the more substituted nitrones as the predominant products in the MCPBA ring opening of the isoxazolidine (**7**).



Scheme 2

In order to understand this differece in regiochemical behaviour observed in the peracid induced ring opening of the isoxazolidines (**4**) and (**7**), we undertook a systematic study of the conformations of several isoxazolidines obtained from nitrone (**2**) -alkene (**3**) cycloadditions.[5] The orientation of the lone pair of electrons on nitrogen probably holds the key for a better understanding of the mechanism of peracid induced ring opening of the isoxazolidines.

Geometric constraints do not permit nitrogen inversion in the isoxazolidine (**4**), which must remain *cis*-fused. However, the 6/5 system as exemplified by (**7**) can exist in three different conformations,[6] the trans conformer (**7 'ee'**) and the *cis* pair (**7'ea'**) and (**7 'ae'**) (**a** and **e** represent axial and equatorial substituents on the six membered ring; see scheme 3). While the *cis* pair is in rapid equilibrium between them by chair inversion (C_i), one of the conformer (**7 'ea'**) is converted to the trans conformer (**7 'ee'**) by a relatively slow nitrogen inversion process (N_i). Our study indicates the *trans* compound as the favoured conformer. Indeed X-ray diffraction study of one such cycloadduct is shown to have the **'ee'** conformation in the solid state.[7] Barrier to nitrogen inversion in (**7a**) was determined by NMR band shape analysis[8] of the C-13 NMR spectral lines, over a temperature range of 60°C, in $CDCl_3$. The free energy of activation for nitrogen inversion

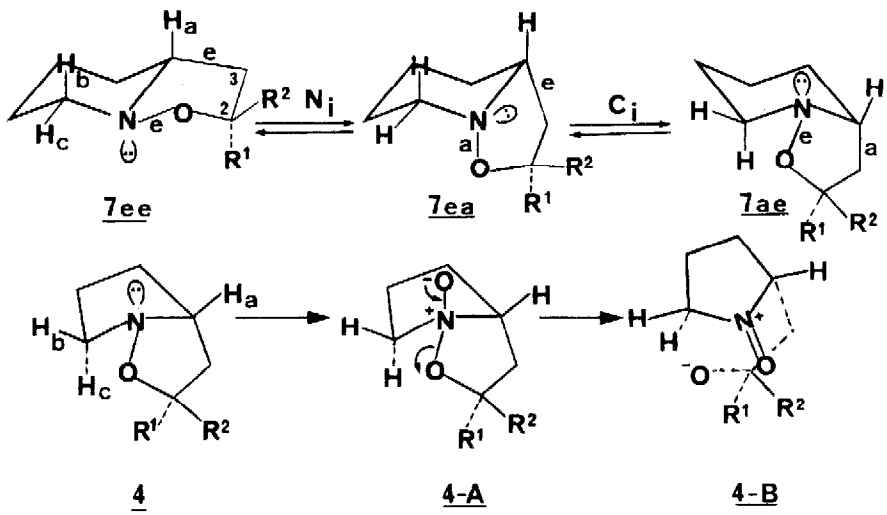
TABLE. Composition of Conformers and regiochemistry of MCPBA induced ring opening of the isoxazolidines (7).

7	% composition of conformers[a]		% composition of the nitrones[b]	
	7'ee'	7'ea'+7'ae'	8	9
a, R^1 = H, R^2= Ph	78	22	65	35
b, R^1 = CO_2Me, R^2= Me	87	13	85 (100)[c]	15 (0)
c, R^1 = H, R^2= CH_2OH	58	42	70	30
d, R^1 = H, R^2= CH_2OAc	71	29	80	20
e, R^1 = CH_2OH, R^2= H	100	0	100	0

[a]in $CDCl_3$ at 25°C; [b]in CH_2Cl_2 at -10°C; [c]in HOAc

is found to be 68.1 kJ mol $^{-1}$; to the best of our knowledge this is the first report of such data for a system where the nitrogen is in the bridgehead position.

As can be seen from the table, the adducts exist in solution as a mixture of *trans* and *cis* conformers.The importance of N: --H-O hydrogen bonding is amply demonstrated in the series of allyl alcohol adducts. While the adduct (**7c**), with *exo* hydroxymethyl group at C(2) can form N:--HO bonding in



Scheme 3

its *cis* conformation, such H-bonding for the adduct (**7e**), with *endo* hydroxymethyl group, is possible only in its *trans* conformation with the result that the latter exists exclusively as the *trans* conformer. It seems that amine oxide intermediate **4-A** obtained by peracid oxidation of the adduct (**4**) would be converted to the nitroxonium salt **4-B** in which the alkoxide ion finds H_c in its immediate vicinity (Scheme 3). Fast kinetic deprotonation thus results in the formation of the less substituted nitrone (**6**) as the sole product. Of the corresponding amine oxide from the adducts (**7**) only the *cis* conformer may lead to the formation of the less substituted nitrone (**9**) and the *trans* conformer to the more substituted isomer (**6**). As expected, the adduct (**7e**),which exists only in its trans conformation, led to the exclusive formation of the nitrone (**8e**). It is evident from the Table that the population ratio of the adduct (**7**) and the ratio of the regiomeric nitrones are similar. The high barrier to nitrogen inversion (68 kJ/mol) and the activation barrier for peracid oxidation may be of comparable magnitude. In such cases, the Curtin-Hammett princple[9] may not apply. As such the ratio of product would very much depend on the population ratio of the starting conformers. In a protic solvent such as acetic acid the alkoxide ion (**4-B**) is protonated fast and the acid catalysed tautomerization of the protonated (**4-B**) results in the formation of the more substituted nitrones as the sole product.

Work is in progress in our laboratory to investigate, in detail, the effects of various substituents in the isoxazolidine ring and a way to make the less substituted nitrone from adduct (**7**) regioselectively.

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