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THE REGIOCHEMISTRY OF INTRAMOLECULAR N-ALKENYLNITRONE ADDITIONS: PREPARATIVE AND MECHANISTIC IMPLICATIONS

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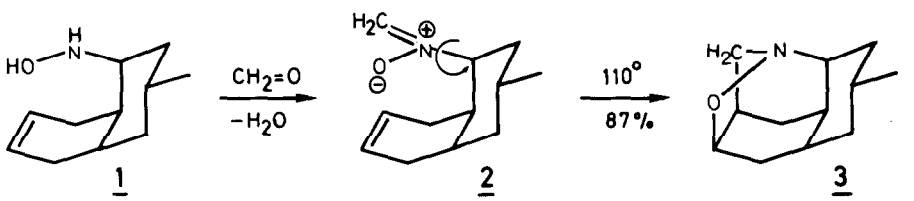
Summary. The opposite regiochemistry, observed for the reactions 7a → 8a and 7d → 8d, as compared with additions 7b → 9b, 7c → 9c and 7e → 9e, supports the hypothesis that in the transition state of nitrone-olefin additions the new C,C bond is more advanced than the C,O bond. Further examples show the superimposition of substituent effects on this intramolecular control.

Recently we have reported an efficient synthesis of luciduline,[1] based on the unidirectional 1,3-dipolar addition[2] 2 → 3 with exclusive attack of the dipole-carbon at the nearer centre



1 2 3

of the non-polarized olefinic bond. In contrast, highly selective C,C bond formation with the more remote olefinic carbon was described for the conversion 7 → 9, n=1, R^1=R^2=H, R^3=Ph.[3] We now present a systematic study of intramolecular N-alkenylnitrone additions with the aim to understand and to predict their regiochemistry. In order to exclude secondary steric and electronic factors the thermolyses of straight chain N-3-butenyl-, N-4-pentenyl- and N-5-hexenyl-nitrones 7a to 7e, containing a "symmetric" olefinic bond, were first investigated (Table 1). The nitrones 7 were readily obtained *in situ* by condensation of the hydroxylamines 6[4] with aldehydes. In order to avoid the cyclizations of 6 to N-hydroxy pyrrolidines, (*e.g.* the smooth reaction 6i → 10[5]), the hydroxylamines 6 were liberated from their stable hydrogenoxalates at 0° under argon and condensed immediately with the requisite aldehyde (*e.g.* by introducing a stream of gaseous formaldehyde at 0°) in toluene in the presence of anhydrous Na_2SO_4; the resulting nitrone solutions were then heated at reflux for several hours. Under these conditions 6a furnished 9a as the sole adduct *via* the non-isolated nitrone 7a, whereas the addition of the higher homologue 7b proceeded with completely reversed regioselectivity. Increasing the distance between the dipole and the dipolarophile by yet another methylene group led *via* 7c to a 3:1 mixture of 8c and 9c. No interconversion of 8c and 9c occurred on heating the isolated regioisomers in boiling toluene for 3h, thus indicating the observed regiochemistry to result from kinetic control.[6] Opposite regioselectivity was also displayed by the intramolecular additions of the C-*p*-nitrophenyl nitrones 7d → 9d and 7e → 8e.

In order to understand this apparent kinetically controlled,[6] bridge length-dependent reversal of regioselectivity[7] transition state geometries were examined using appropriate models.

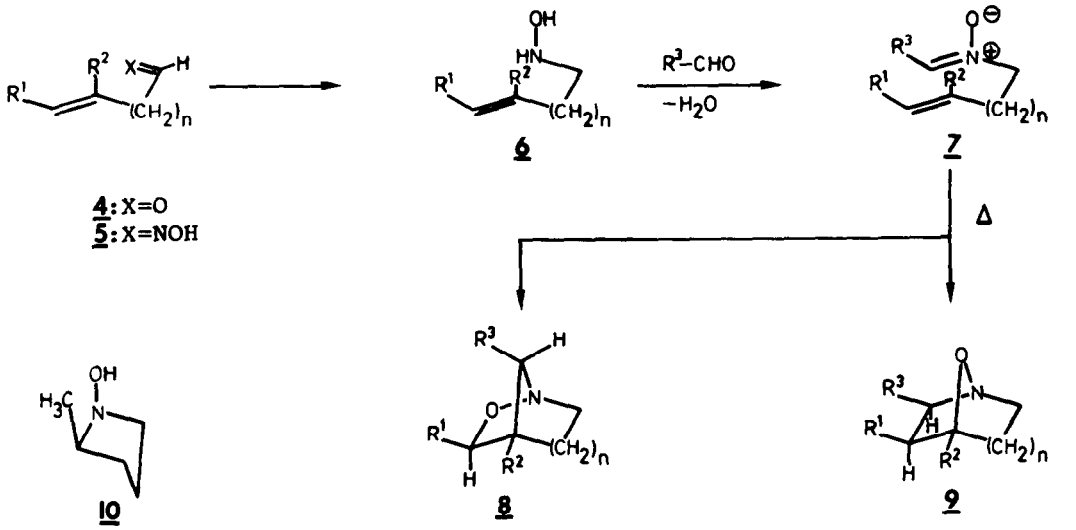
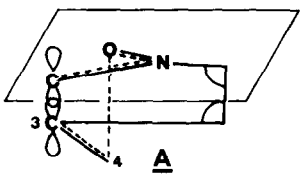


Table 1. Intramolecular Cycloadditions of the N-Alkenyl Nitrones 7 formed *in situ* from 6.[a]

Entry	n	R^1	R^2	R^3	Reaction time/110°	Yield of 8	Yield of 9	m.p.°C of 8[b]	m.p.°C of 9[b]
a	1	Me	H	H	6h	0%	76%	-	116-118
b	2	Me	H	H	3h	95%	0%	158-160	-
c	3	Me	H	H	3h	68%	23%	104-106	108-111
d	1	Me	H	pNO_2Ph	1.5h/180°[d]	0%	85%	-	117-118[c]
e	2	Me	H	pNO_2Ph	18h	69%	0%	110-112[c]	-
f	1	Ph	H	H	2h	9%	56%	122-123	147-148
g	2	Ph	H	H	3h	87%	0%	74-76[c]	-
h	2	Ph	H	pNO_2Ph	11h	95%	0%	144-146[c]	-
i	2	H	H	H	3h	47%	23%	127-129	148-151
j	2	H	Me	H	2.5h	10%	77%	oil	127-130
k	2	H	Ph	H	6h	0%	82%	-	73-74[c]

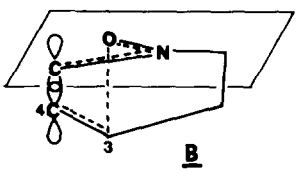
[a]The hydroxylamines 6 and the products 8 and 9 showed IR, ^{1}H-NMR, and mass spectra in full agreement with the assigned structures. Mixtures of regioisomers 8 and 9 were analyzed by GC, ^{1}H-NMR or HPLC and separated either by fractional crystallization of their hydrogenoxalates (c, i), or by chromatography on SiO_2 (f), or by prep. GC (j). [b]m.p. of hydrogenoxalate. [c]m.p. of free base. [d]Heating the dimers of 7d in refluxing *o*-dichlorobenzene.

Considering coplanarity of the nitrone unit and the first bridge carbon atom[8] the observed regiochemistry can only be explained on the assumption that the new C,C bond is more developed than the C,O bond in the corresponding transition state.[9] Thus, comparing the possible orienta-



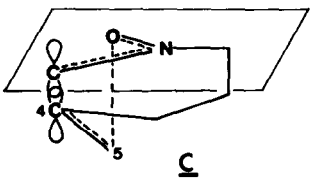
A

Angle Strain



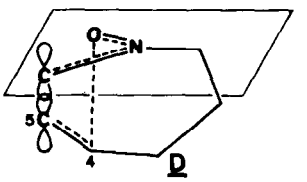
B

Preferred



C

6-Ring Formation
Preferred



D

7-Ring Formation

tions for N-3-alkenyl nitrone additions, C,C bond formation to the nearer olefinic centre C(3) implies a strained transition state A, whereas the exclusively observed C,C(4) bond formation corresponds to the unstrained transition state B.[10] With regard to N-4-alkenyl nitrone additions, both orientations C and D do not exhibit strain. However, the observed preference of the transition state C over D may be ascribed to an entropically favoured 6-ring closure as compared with 7-ring formation. An analogous argument (preferred cyclization to a 7- rather than an 8-membered ring) applies to the less selective cyclization of 7d to 8d. We then studied the competition of these intramolecular-derived orientational effects with those of dipolarophile substituents.[11] Thus, a phenyl group on the terminal olefinic centre diminishes the predominance of the transition state B over A during the N-3-alkenyl nitrone addition 7f → 8f + 9f (1:6), whereas in the higher homologues 7g and 7h both influences cooperate to give exclusively the products 8g and 8h. Similarly, substituents on the nearer olefinic centre C(4) of N-4-alkenyl nitrones may counteract the intramolecular favouring of the transition state C over D. Thus, with no terminal olefinic methyl group the regioselectivity is reduced (7i → 8i + 9i (2:1)) while a methyl group at C(4) leads already to a reversal of regiochemical control (7j → 8j + 9j (1:8)), which becomes complete when replaced by a phenyl substituent (7k → 9k). Intramolecular cycloadditions thus provide a valuable mechanistic tool for the study of orientational substituent effects and in particular the geometry of transition states which are subject to controversy;[12] moreover, the above findings may prove of value in the synthesis of complex alkaloids.[4,10]

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5) Cyclization of free 6i to 10 already proceeded at 40°/2h with 50% conversion; this reaction was not further studied after publication of independent analogous findings: H.O. House, D.T. Manning, D.G. Melillo, L.F. Lee, O.R. Haynes & B.E. Wilkes, *J. Org. Chem.* 41, 855 (1976).

6) The general operation of kinetic control in the examples reported here is further supported by the non-interconvertibility (GC, TLC or NMR evidence) of the isomer pairs 8f/9f, 8i/9i and 8j/9j in boiling toluene within 3h; the isoxazolidines 8c, 8i, 9i and 9j were recovered as pure, recrystallized hydrogenoxalates in 84 to 87% yield.

7) This applies also to N-alkenylazomethinimines: W. Oppolzer, *Tetrahedron Letters* 1972, 1707.

8) For calculations in support of a planar nitrone geometry see: P. Caramella, R.W. Gandour, J.A. Hall, C.G. Deville & K.N. Houk, *J. Am. Chem. Soc.* 99, 385 (1977); R. Grée & R. Carrié, *Bull. Soc. Chim. France* 1975, 1319.

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