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Intramolecular cyclisation of *(Z)-N*-4-alkenylnitrones and the effects of alkenyl substituents

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Abstract

The intramolecular 1,3-dipolar cycloaddition reactions of *(Z)-N*-4-alkenylnitrones carrying various alkenyl substituents were investigated, and the regiochemistry of the resulting isoxazolidines was determined. Silyl- and bromo-substituents were found to effect significant regiocontrol on the intramolecular nitrone dipolar cycloaddition reaction.

Keywords: Cycloadditions; Isoxazolidines; Nitrones; Regiochemistry

1,3-Dipolar cycloadditions between nitrones and olefins produce isoxazolidines which are useful intermediates in the synthesis of many natural products [1,2]. Several alkaloids including indolizidines 167B, 205A, 207A, 209B [3] and deoxynojirimycin [4] have been prepared using the intramolecular version of this cycloaddition reaction, and we wanted to extend this methodology to other polyhydroxylated indolizidines and piperidine alkaloids. Previously, we had investigated the effect of a single allylic substituent on the stereochemical outcome of the cycloaddition reaction [5]. This Letter describes how various substituents on the alkene affect the stereochemistry of the isoxazolidine products.

The synthesis of the alkenylnitrones **5a-f** is summarised in Scheme 1. Various α,β-unsaturated aldehydes **1a-f** were treated with the lithium enolate of ethyl acetate to form the β-hydroxyesters **2a-f**. Protection of the resulting alcohols as their *tert*-butyldimethylsilyl ethers **3a-f** and reduction with DIBAL gave the corresponding aldehydes which were converted into the oximes **4a-f** as a 1:1 mixture of geometrical isomers. Reduction of the oximes **4a-f** with sodium cyanoborohydride gave the corresponding hydroxylamines which upon reaction with 4-benzoyloxybutanal gave the alkenylnitrones **5a-f**.

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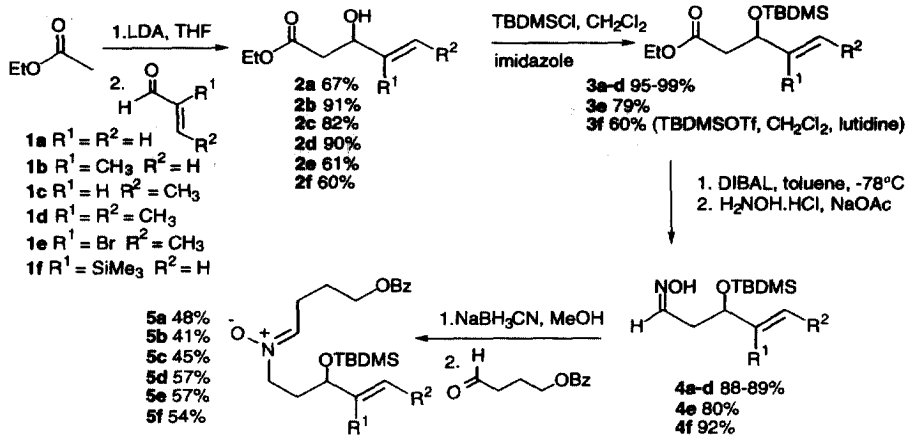
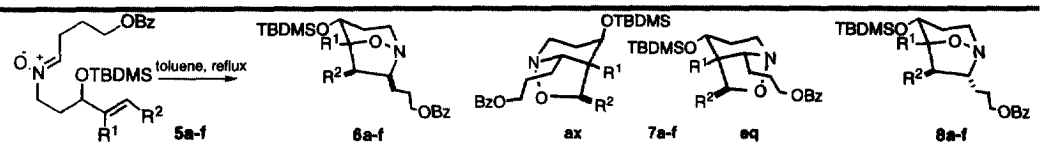


Scheme 1

A dilute toluene solution (~10^{-2} M) of each of the alkenylnitrones **5a-f** was heated under reflux to afford the various bridged (**6a-f, 8a-f**) and fused (**7a-f**) isoxazolidines (Table 1) [6,7]. These were separated by flash chromatography and their relative stereochemistry was determined by ^{1}H NMR, NOE studies and an *X*-ray crystallographic analysis[1] of the axial isomer of **7a** (Figure 1).

Table 1
Cycloaddition reaction of the alkenylnitrones and their isoxazolidine products.[2]



entry				
1	**5a** $R^1 = R^2 = H$	**6a** 10%	**7a** 70% (6:1 ax:eq)	**8a** 13%
2	**5b** $R^1 = CH_3$ $R^2 = H$	**6b** 29%	**7b** 0%	**8b** 41%
3	**5c** $R^1 = H$ $R^2 = CH_3$	**6c** 0%	**7c** 67% (3:1 ax:eq)	**8c** 0%
4	**5d** $R^1 = R^2 = CH_3$	**6d** 5%	**7d** 12% (2:1 ax:eq)	**8d** 63%
5	**5e** $R^1 = Br$ $R^2 = CH_3$	**6e** 0%	**7e** 36% (2:1 ax:eq)	**8e** 25%
6	**5f** $R^1 = SiMe_3$ $R^2 = H$	**6f** 30%	**7f** 0%	**8f** 54%

In such cycloaddition reactions, it is generally assumed that the new C-C bond is more developed in the transition state than the C-O bond [8] and hence for both steric and electronic reasons, the C-C bond is preferably formed at the less substituted alkene position (Figure 2). Thus the alkenylnitrone **5c** which has a terminal methyl substituent (entry 3), gave exclusively the carbon-bridged isoxazolidine **7c** whereas **5b**, possessing a methyl substituent at the R^1 position (entry 2) gave only the oxygen-bridged products **6b** and **8b**.

[1] Crystal data : monoclinic; $P2_1/c$; a = 17.8000(10) Å, b = 10.7410(10) Å, c = 12.791(3) Å, α = 90°, β = 110.89(4)°, γ = 90°; Z = 4; goodness-of-fit on F^2 1.045; final R indices [$I > 2\sigma(I)$] R1= 0.0585, wR2 = 0.1485; R indices (all data) R1 = 0.0987, wR2 = 0.2667. mp 44.5-46 °C. Data deposited in the Cambridge Crystallographic Database.

[2] All new compounds exhibited spectroscopic and analytical HRMS data consistent with the assigned structure. Axial: equatorial ratios of **7a-f** were determined by ^{1}H NMR.

In the absence of substituent effects (entry 1), there is a kinetic preference for the C-C bond to be placed in a six-membered ring. In the case for which both R^1 and R^2 were methyl groups (entry 4), steric considerations in the transition state seemed more important, with the oxygen-bridged isoxazolidines **6d** and **8d** predominating.

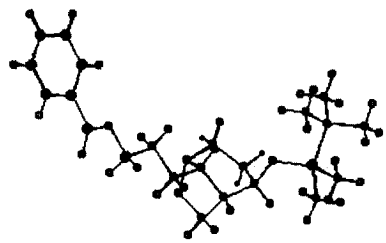


Figure 1 The *X*-ray structure of the axial isomer of **7a** as represented in Chem 3D™.

By incorporating bromine, an electronegative heteroatom, at the R^1 position (entry 5 compared with entry 3) of the alkenylnitrone **5e**, it became apparent that the transition state **9a** was less favourable, resulting in more of the carbon-bridged isoxazolidines **7e**. It was expected that the introduction of Me_3Si at R^1 (entry 6 compared with entry 2) would result in stabilisation of the developing δ+ charge in the transition state **9b**. However, the oxygen-bridged isoxazolidines **6f** and **8f** were the sole products. Clearly, the unfavourable steric demands of the Me_3Si group outweigh the electronic effect.

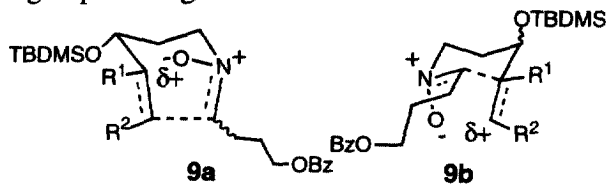
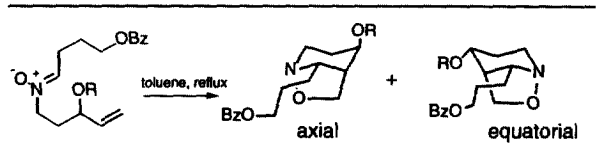


Figure 2 Transition states **9a, 9b** for the intramolecular cycloaddition of **5**.

The axial preference of the OTBDMS group in the fused isoxazolidines, discussed previously [5], arises from the lowering of the HOMO as a result of the interaction between the equatorial C-OR σ* orbital and the π-orbital of the alkene. In order to determine the extent to which the steric bulk of the protecting group influences this axial preference, the alkenylnitrones **5a**, **5g** and **5h** were synthesised and compared (Scheme 2). It was found that as the steric demands of the protecting group increased, the preponderance of the axial cycloadduct decreased, presumably as a result of an increasingly unfavourable 1,3-diaxial interaction in the transition state [5].



5a R = TBDMS	6:1	**7a**
5g R = TIPS	4:1	**7g**
5h R = TPS	2.5:1	**7h**

Scheme 2

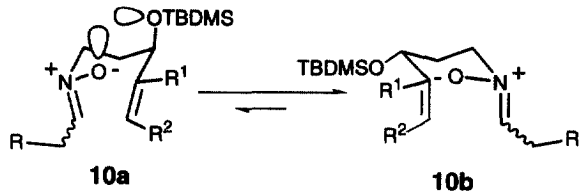


Figure 3 Stereoelectronic effect of OTBDMS group in bridged isoxozolidine adducts.

Interestingly, all the oxygen-bridged isoxazolidines **6a-f** and **8a-f** were formed exclusively as their equatorial OTBDMS isomers. While it is probable that the same π-COR σ* interactions exist, these are apparently overcome by the unfavourable 1,3-diaxial interaction between the lone pairs of electrons (Figure 3).

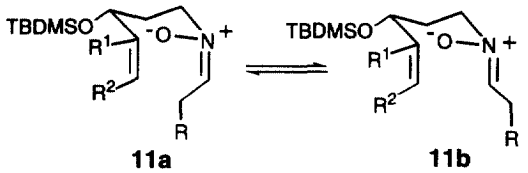


Figure 4

The oxygen-bridged isoxazolidines **6a-6f** were formed from the *Z*-nitrones **11a** and the isomers **8a-8f** apparently arose from the *E*-nitrones **11b** (Figure 4). Only the *Z*-nitrones **5a-5f** were produced from the hydroxylamines. Thus Z/E isomerisation occurred at the elevated temperatures under which the cycloaddition took place.

In conclusion, we have synthesized several *(Z)-N*-4-alkenylnitrones and investigated the steric and electronic influences of various substituents on the transition states of the intramolecular cycloaddition and the regiochemistry of the isoxazolidines that are formed. The bromo- and silyl substituents exhibit stereoelectronic effects which should be applicable to the synthesis of new alkaloids.

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