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Type 2 Intramolecular Nitroso Diels–Alder Reaction. Synthesis and Structure of Bridgehead Oxazinolactams

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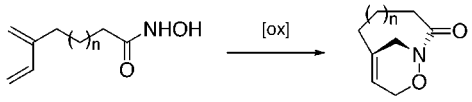
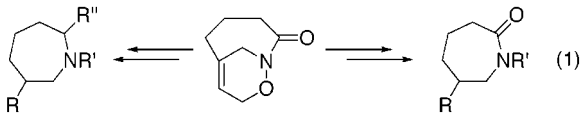
ABSTRACT



The type 2 intramolecular Diels–Alder cycloaddition utilizing *N*-acylnitroso dienophiles provides an efficient entry into bridged oxazinolactams. In contrast to the bimolecular counterpart, the reaction is completely regioselective. Structural characterization of the cycloadducts allows for evaluation of the olefin distortion and the degree of pyramidalization of the bridgehead oxazinolactam.

Diels−Alder reactions with heterodienophiles have provided entry into a number of important ring systems. The early studies of Kirby established that the use of *N*-acylnitroso dienophiles offer an efficient entry into the 3,6-dihydro-1,2-oxazine ring system.[1] These adducts have been elaborated into pyrrolidines, piperidines, and tropanes as well as a number of amino alcohol derivatives. The extension of this methodology to include the intramolecular *N*-acylnitroso Diels−Alder reaction has been used as a key step in the synthesis of a number of alkaloid natural products including members of the pyrrolizidine and indolizidine families.[2]

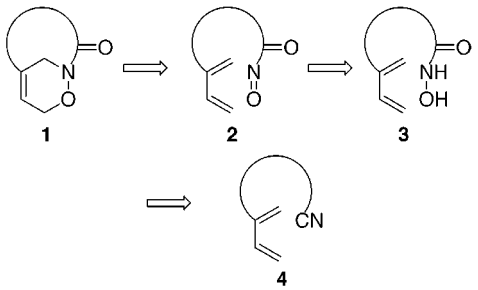
The utility of oxazinolactams as key intermediates in the synthesis of heterocycles has prompted our study of the type 2 variant of the intramolecular nitroso Diels−Alder reaction. Type 2 intramolecularity provides an opportunity to control the regiochemistry of the cycloaddition, a factor that has restricted applications of this reaction in more complex settings. Attachment of the hydroxamic acid to the two position of the diene would allow for the synthesis of bridged oxazinolactams, which, after the appropriate manipulations, could be elaborated to medium ring amines or lactams (eq 1). We now report the first examples of a type 2 intramolecular *N*-acylnitroso Diels−Alder reaction for the synthesis of bridged oxazinolactams.



(1)

Our strategy for the synthesis of [*n*.3.1] bridgehead olefin/oxazinolactams anticipated a Diels−Alder cycloadduct **1** that would arise from the corresponding 2-substituted-*N*-acylnitroso-1,3-diene **2** which in turn would be generated in situ by oxidation of the requisite hydroxamic acid **3** (Scheme

Scheme 1



(1) Kirby, G. W.; *Chem. Soc. Rev.* **1977**, *6*, 1−24.

(2) For reviews of nitroso Diels−Alder reactions, see: (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348. (b) Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873−879. (c) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107−1117. (d) Boger, D. L.; Weinreb, S. M. *Hetereo Diels−Alder Methodology in Organic Synthesis*; Pergamon: Oxford, 1987. (e) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087−3128.

(3) Shea, K. J.; Pham, P. Q. *Tetrahedron Lett.* **1983**, *24*, 1003.

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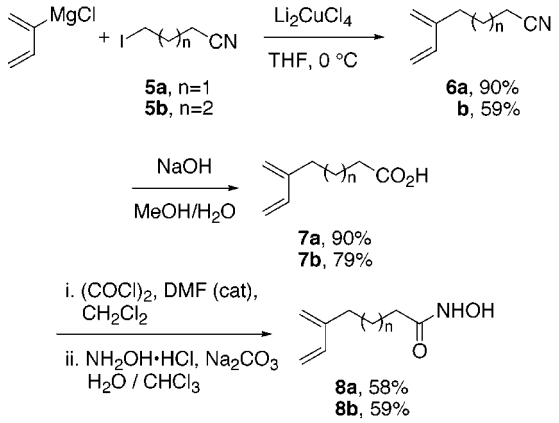
1). The hydroxamic acid can be derived from a carboxylic acid that would ultimately come from nitrile **4**.

The diene nitriles **6a**,**b** needed for the synthesis of the Diels−Alder precursors were prepared by coupling the iodonitriles **5a**,**b** with chloroprene Grignard in the presence of Li_2CuCl_4 (Scheme 2).[3] Basic hydrolysis of the resulting

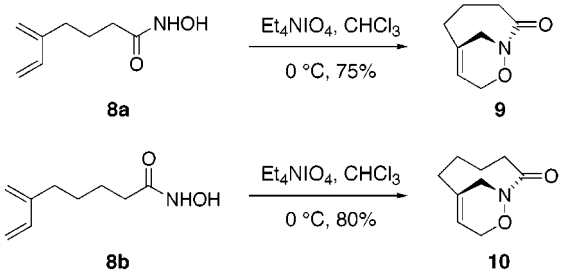
Scheme 2



nitriles afforded the carboxylic acids **7a**,**b**. The acids were converted to the corresponding hydroxamic acids **8a**,**b** by treatment with oxalyl chloride followed by addition of hydroxylamine hydrochloride under biphasic conditions.

The bridgehead olefin/oxazinolactams were prepared by the type 2 intramolecular nitroso Diels−Alder cycloaddition of hydroxamic acids **8a** and **8b** (Scheme 3). The Diels−

Scheme 3



Alder precursors were treated with Et_4NIO_4 in $CHCl_3$ at 0 °C under dilute conditions (0.01 M) to afford the corresponding cycloadducts **9** and **10** in 75 and 80% yield, respectively. Each Diels−Alder reaction gave a single product. The reactions occurred with complete regiochemical control to provide the 1,3-bridged cycloadducts exclusively. The intermediacy of the *N*-acylnitroso compounds is inferred from the structure of the cycloadducts, and no attempt was made to observe the intermediates. Compounds **9** and **10** were crystalline and were analyzed by X-ray crystallography.[4]

(4) Experimental details of the X-ray crystallography can be found in the Supporting Information.

The X-ray structures verify the regiochemistry of the cycloaddition. In addition, the structures reveal the bridgehead double bond and bridgehead oxazinolactam are significantly distorted from planarity (Figure 1).[5] The extent

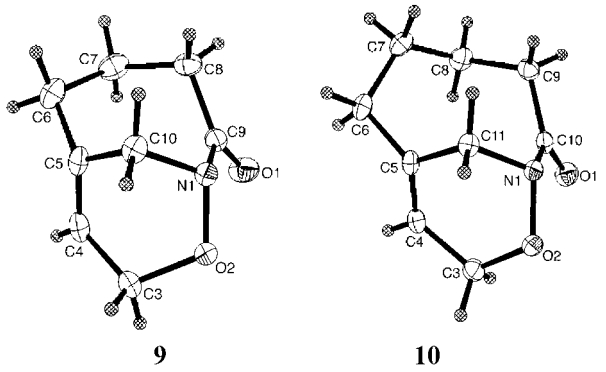


Figure 1. ORTEP plot of **9** and **10** at the 50% probability level.

of the distortions can be quantified by the torsion angle τ between the p-orbitals of the double bond and nitrogen−carbonyl π systems and the pyramidalization angles χ of the constituent atoms of the two functional groups. The method used to measure the distortions observed in unsymmetrically deformed π systems is shown in Figure 2.[6]

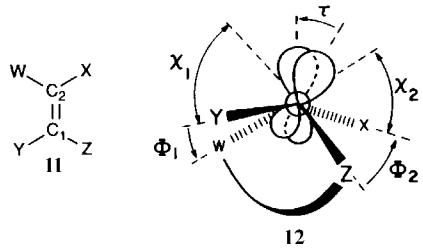


Figure 2. Definitions of distortional parameters χ and τ.

The view along the C_1-C_2 axis of π system **11** is represented by **12** (Figure 2). Rotation of C_1 relative to C_2 produces a misalignment of the π bond p-orbitals. This deformation causes the two atoms of the π-system to rehybridize independently. The torsional deformation is quantified by the angle τ between the axes of the two p-orbitals. The torsion angle τ is not directly measurable but may be determined by summing the four atom torsion angles YC_1C_2W (Φ_1) and ZC_1C_2X (Φ_2) and dividing the result by 2 ($\tau = (\Phi_1 + \Phi_2)/2$). The p-orbital alignment is presumed to be optimal for a double bond with $\tau = 0.0$ °.

(5) For similar studies of bridgehead olefins, see: (a) Lease, T. G.; Shea, K. J. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, CT, 1992; Vol. 2, pp 79−112. (b) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248−2260. (c) Shea, K. J.; Lease, T. G.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 8627−8629.

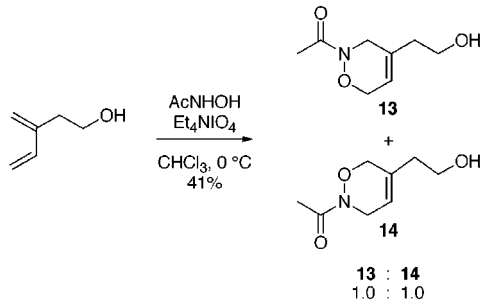
(6) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169−182.

The degree of pyramidalization of each atom is quantified by the pyramidalization angle χ, defined as the acute angle formed by the projection of one substituent (Z) across the atom onto the geminal substituent (Y). For an $sp^{2.00}$ atom, $\chi = 0.0°$, while, for an $sp^{3.00}$ atom, $\chi = 60.0°$.

At the bridgehead C−C double bond, the torsion angles τ_{C4-C5} are 6.83(9)° for **9** and 3.53(9)° for **10**. The pyramidalization angle of the bridgehead carbons χ_{C5} is 20.3° for **9** and 13.5° for **10** whereas χ_{C4} is 9.0° for **9** and 6.0° for **10**. The C=C bond distances, 1.3331(18) Å for **9** and 1.3323(14) Å for **10** are within error of the value for cyclohexene (1.335(3) Å)[7] and reveal the bond distance is not a sensitive function of the olefin distortions.

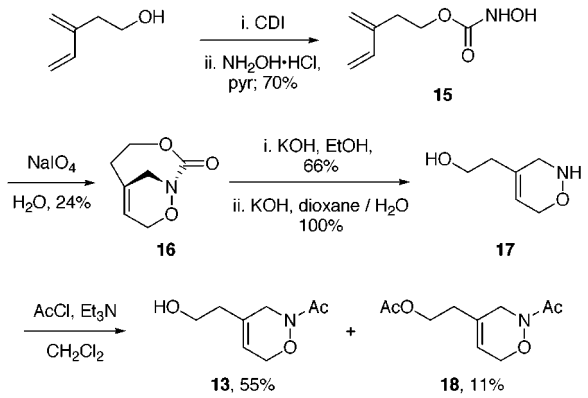
A soft bending potential at nitrogen and a weak torsion potential about the C−N bond result in a more extensive distortion of the bridgehead oxazinolactam. Pyramidalization of the bridgehead nitrogen is essentially complete: $\chi_{N1} = 54.8°$ for **9** and 52.6° for **10**. This is in contrast to the carbonyl carbons which undergo almost no pyramidilization: $\chi_{C7} = 0.4°$ for **9** and 1.5° for **10**. The torsion angle τ_{N1-C9} is 3.53(10)° for **9** and τ_{N1-C10} is 10.35(8)° for **10**. It is interesting to note that the torsion angle of the bridgehead oxazinolactam **10** is greater than that of cycloadduct **9**. This may be a consequence of relief of transannular interactions in cycloadduct **10** that could result in a greater distortion of the bridgehead oxazinolactam. The crystal structure of **10** reveals two close contacts between hydrogens at C-7 and C-9 with the syn hydrogen at C-11. Only one such contact is observed in **9**.

Scheme 4



In addition to providing access to novel bridged bicyclic oxazinolactams, type 2 intramolecularity provides a strong regiochemical bias for formation of the meta or 1,3-regioisomer. To establish the unencumbered regiochemical preference of the corresponding intermolecular reaction, the Diels−Alder reaction of 3-methylene-4-penten-1-ol with acetohydroxamic acid was carried out.[8] Addition of acetohydroxamic acid to a 0 °C solution of Et_4NIO_4 in $CHCl_3$ led to a 1:1 mixture of inseparable regioisomers. The diagnostic peaks in the ^1H NMR of the mixture included two vinyl proton resonances at 5.68 and 5.64 ppm. The identity of the 1,3-substituted isomer was verified by its independent synthesis via a type 2 nitroso Diels−Alder reaction containing a cleavable tether.[9] Diels−Alder precursor **15** was prepared from 3-methylene-4-penten-1-ol by condensation with carbonyldiimidazole followed by displacement with hydroxylamine. Oxidation of **15** with $NaIO_4$ in water led to cycloadduct **16**. Tether cleavage with ethanolic potassium hydroxide afforded the ethyl carbamate which was hydrolyzed with potassium hydroxide in water/dioxane. Acylation with acetyl chloride provided isomerically pure **13** in 55% along with 11% of acetate **18**. Conformation of

Scheme 5



the structure of **13** was verified by correlation of the ^1H NMR spectra to the regioisomeric mixture. The vinyl proton resonance at 5.68 ppm for the 1,3-regioisomer **13** matched that seen in the spectra of the mixture of regioisomers.

In summary, the type 2 nitroso Diels−Alder reaction has been developed for the synthesis of bridged oxazinolactams. The reaction provides complete control over the regiochemistry of the cycloaddition to furnish the 1,3-substituted regioisomer exclusively. Structural characterization of the bridged compounds has allowed for quantification of the distortions of the bridgehead double bond and oxazinolactam functional groups. Bridgehead oxazinolactams are currently being developed for the stereoselective synthesis of medium ring amides and amines.

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Supporting Information Available: Crystallographic data for compounds **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005811M

(7) Determined by electron diffraction: Chiang, J. F.; Bauer, S. H. *J. Am. Chem. Soc.* **1969**, *91*, 1898−1901.

(8) For earlier studies of the regiochemistry of intermolecular acyl nitroso Diels−Alder reactions, see: (a) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397. (b) Boger, D. L.; Patel, M. *J. Org. Chem.* **1984**, *49*, 4098. (c) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911.

(9) Davies, G.; Russel, A. T.; Sanderson, A. J.; Simpson, S. J. *Tetrahedron Lett.* **1999**, *40*, 4391.