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Interesting Behavior of α,β-Unsaturated Oximes in Intramolecular [4 + 2] Cycloaddition Reactions

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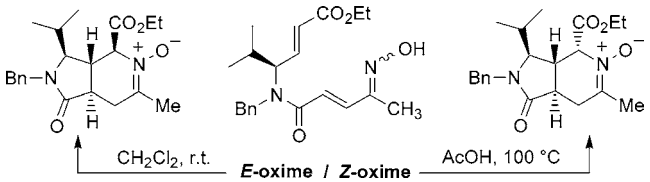
ABSTRACT



Intramolecular [4 + 2] cycloaddition using α,β-unsaturated oximes was explored. The reactions proceeded under unusually facile conditions to furnish the nitrones. The latter were subsequently reacted with DMAD to afford [3 + 2] cycloaddition products.

The intramolecular Diels−Alder (IMDA) reaction has proven to be useful in the regio- and stereoselective construction of highly substituted bicyclic and polycyclic ring systems.[1] The advantages of an intramolecular reaction over its intermolecular counterpart are well documented.[2] Over the past 15 years, considerable effort has gone into the development of the Diels−Alder reaction of 1-azadienes.[3] The latter, unlike their counterpart 2-azadienes, are known for their reluctance to undergo [4 + 2] cycloaddition reactions. The introduction of a nitrogen atom at position 1 of the diene creates an electron-deficient π-system and explains why 1-azadienes are characteristically poor dienes in the normal [$HOMO_{diene}$-controlled] Diels−Alder reaction with electron-deficient dienophiles. Important contributions by several groups have shown that this problem can be circumvented by introducing either electron-donating[4] or -withdrawing[5] substituents on the imine nitrogen. Considerable difficulties have been encountered in the extension of those approaches to α,β-unsaturated oximes[4,5a,e] because of their reduced thermodynamic driving force compared to typical dienes and also due to possible rearrangements to conjugated enamines or to 2-azadienes.[6,7]

Accordingly, this particular class of 1-azadienes has drawn very little attention, and to date, only one example of an α,β-unsaturated oxime involved in an intermolecular Diels−Alder reaction has been reported; but the authors do not report spontaneous isomerization to a nitrone.[8]

It would be anticipated that the substitution of an α,β-unsaturated imine with an electron-donating substituent such as an alcohol group would accentuate the electron-rich nature of the heterodiene and thus preferentially promote a

(1) For reviews on Diels−Alder reaction, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (b) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550.

(2) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295.

(3) For a general discussion of Diels−Alder reactions of 1-azadienes, see: (a) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 9.

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$HOMO_{diene}$-controlled Diels−Alder reaction with an electron-deficient dienophile (Figure 1).

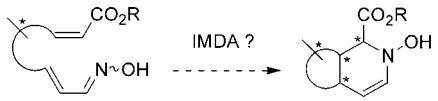
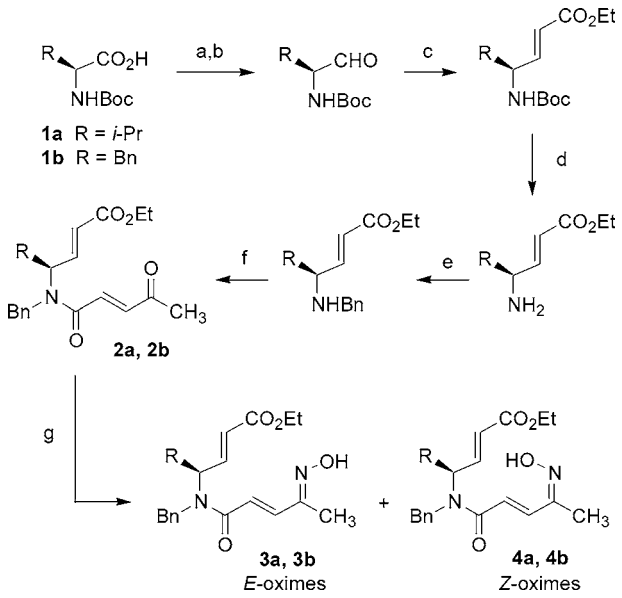


Figure 1. Proposed Aza-Diels−Alder Reaction of α,β-Unsaturated Oximes.

As part of our ongoing program to expand the synthetic utility of optically active amino acid-derived trienes in IMDA reactions,[9] we set out to study the behavior of four chiral nonracemic 1-azadienes, namely, the valine- and phenylalanine-derived precursors **3a**,**b** and **4a**,**b** (Scheme 1). The presence of a stereocenter in these triene precursors at the allylic position of the dienophile should allow for discrimination of the diastereotopic faces of the reacting diene and dienophile. Moreover, in IMDA reactions, the nature of the tether linking the diene and dienophile often influences the reactivity of the substrate and the structure of the transition state and, thus, the stereochemical outcome. In this preliminary communication, we disclose the first examples of α,β-unsaturated oximes involved in IMDA reactions to produce bicyclic nitrones. In our studies, no trace of the expected allylic hydroxylamines were found. These IMDA reactions apparently occur via the enamine intermediate (Figure 1) and rearrange to the nitrone. This facile rearrangement, due to an interaction between the lone pair of the nitrogen atom and the π system, is well documented, particularly when no enamine-stabilizing group is present.[10]

Scheme 1. Synthesis of Four New Chiral Nonracemic 1-Azadienes[a]



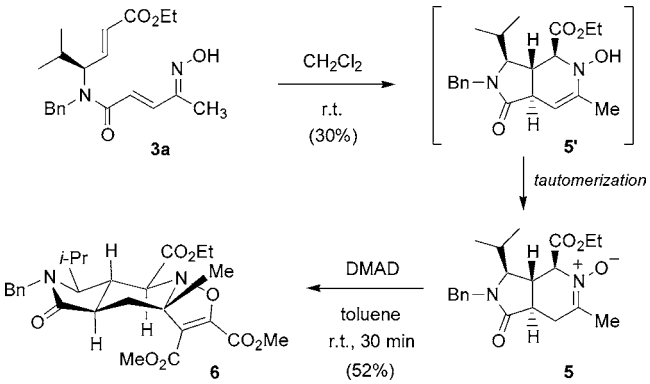
[a] Reagents and conditions: (a) isobutyl chloroformate, 4-methylmorpholine, MeNH(OMe)·HCl, CH_2Cl_2, 87%; (b) LAH, THF, −78 °C, 82%; (c) $(EtO)_2P(O)CH_2CO_2Et$, *t*-BuOK, THF, 0 °C to rt, 70%; (d) 50% TFA in CH_2Cl_2, rt then $NaHCO_3$, 95%; (e) PhCHO, $NaBH_4$, EtOH, 0 °C, 86%; (f) EDCI, HOAT, 3-acetyl acrylic acid, DMF, 0 °C to rt, 80%; (g) NH_2OH·HCl, $NaHCO_3$, EtOH 50% aq, 0 °C to rt, 76%.

The requisite starting materials **2a**,**b** were readily obtained from the corresponding NH−Boc-protected L-amino acids **1a**,**b** as described previously (Scheme 1).[11] Formation of the corresponding α,β-unsaturated oximes took place upon condensation of hydroxylamine hydrochloride with **2a**,**b** to give, in moderate yields, a separable mixture of (*E*)-oximes **3a**,**b** as the minor isomers and (*Z*)-oximes **4a**,**b** as the major isomers. The *E*/*Z* stereochemistry of these oximes was determined by one-dimensional difference NOE experiments in DMSO-d_6.

Surprisingly, while the (*Z*)-oximes **4a** and **4b** were stable indefinitely when stored at room temperature, the (*E*)-oximes **3a** and **3b** were exceptionally reactive and underwent a cycloaddition reaction within a few hours, even at 0 °C. Only storage at −78 °C prevented these compounds from reacting and allowed us to carry out ^1H, ^{13}C, and one-dimensional NOE experiments. The transformation, which occurred either in solution in CH_2Cl_2 or neat at room temperature, did not lead to the anticipated formation of a Δ^2-piperidine product.

Instead, starting from **3a**, an unexpected product was formed in 30% yield. This product was identified as the nitrone **5** through NMR studies. This presumably proceeds through the formation of an unstable endocyclic Δ^2-piperidine enamine **5′** that undergoes tautomerization to furnish the nitrone **5** (Scheme 2). Related bicyclic nitrones have been reported in the literature.[12]

Scheme 2. [4 + 2]/[3 + 2] Sequence with the (*E*)-Oxime **3a**



The optically active nitrone presents numerous opportunities for synthetic manipulations. At this point, we decided to subject the diastereomerically pure nitrone **5** to 1,3-dipolar cycloaddition[13] in order to both chemically prove the structure of the nitrone moiety and evaluate the reactivity of the asymmetric nitrone. Reaction of **5** with dimethyl

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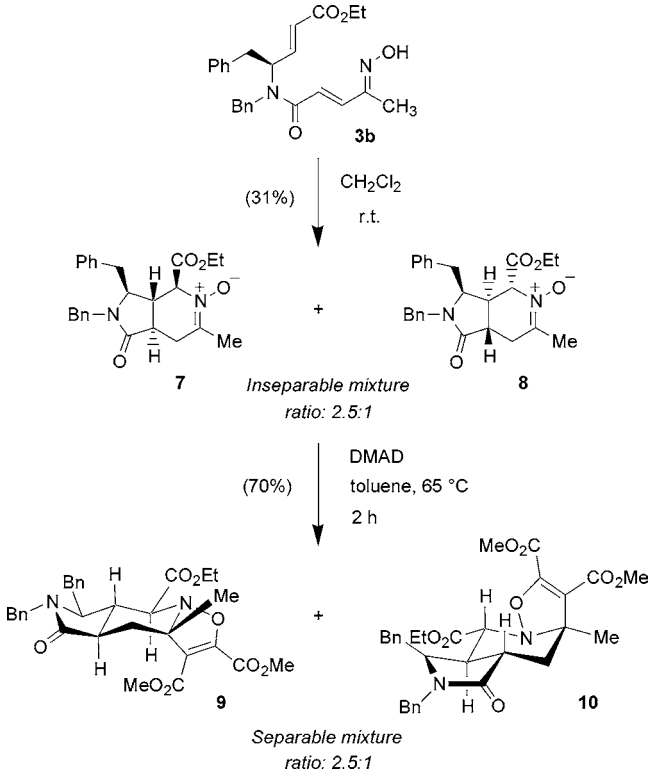
acetylenedicarboxylate (DMAD) afforded isoxazoline **6** as the only identifiable compound in 52% yield.

As previously observed for **3a**, the phenylalanine-derived precursor **3b** spontaneously cyclized at room temperature either in CH_2Cl_2 solution or neat. ^1H NMR showed the existence of a mixture of two isomers **7** and **8** (ratio 2.5:1), which could not be separated by either flash chromatography or HPLC. We found the mixture of nitrones to be relatively unstable at room temperature, and they had to be derivatized soon after isolation. The structural conformation and the relative stereochemistry of **7** and **8** were established by derivatization of their mixture with DMAD. This led to the formation of two separable and characterizable isoxazolines **9** and **10** (ratio 2.5:1) in 70% yield and allowed us by analogy to establish the stereochemistry of nitrones **7** and **8** (Scheme 3).

Scheme 3. [4 + 2]/[3 + 2] Sequence with the (*E*)-Oxime **3b**



It appears that 1,3-dipolar cycloaddition of **7** and **8** takes place with complete stereoselectivity. This result is analogous to that of **5** in terms of stereoselectivity. As a consequence, a single stereoisomer resulted from each of these bicyclic nitrones **5**, **7**, and **8**. These structures have a rigid conformation, leading to efficient shielding of one of the nitrone faces. The high π-facial selectivity of these cycloaddition reactions seems to be dictated by the ester group adjacent to the dipole. The dipolarophile thus approaches preferentially the less hindered face (opposite face to the ester group), which for **5** and **7** is the *re* face and for **8** is the *si* face (Figure 2).

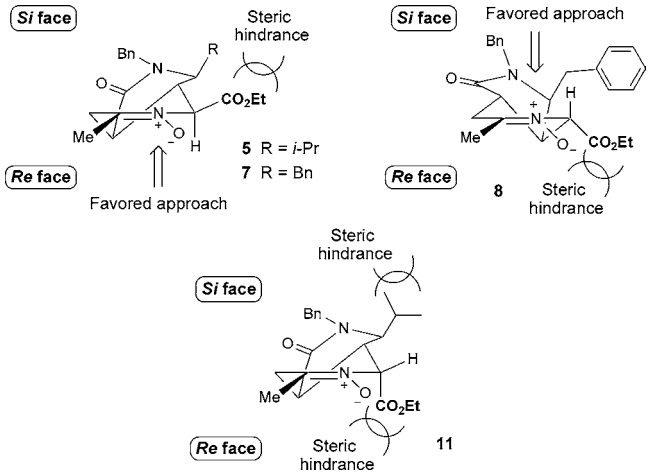
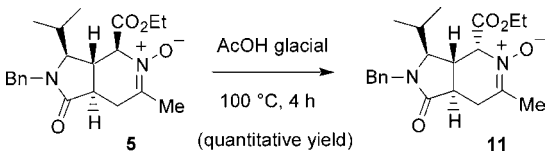


Figure 2. π-Facial Selectivities Accounting for the Formation of Isoxazolines **6**, **9**, **10**, **12**, and **13**.

Although (*Z*)-oximes exhibit a less pronounced intrinsic reactivity at room temperature, we observed, in the case of **4a**, that heating in acetic acid at 100 °C cleanly provided the [4 + 2] cycloadduct **11** as a single diastereomer in 77% yield.[14] Surprisingly, the stereochemistry of the ester group in **11** is inverted compared with that of nitrone **5**. When compound **5** was subjected to acetic acid at 100 °C for 4 h, nitrone **11** was recovered in quantitative yield (Scheme 4).

Scheme 4. Epimerization of **5** in Acidic Medium



This could indicate an initial isomerization of **4a** to **3a**, cycloaddition, and subsequent epimerization.

The thermal cycloaddition between **11** and DMAD leads to the formation of two stereoisomers **12** and **13** in 76% yield

(10) (a) Wright, S. W.; Harris, R. R.; Kerr, J. S.; Green, A. M.; Pinto, D. J.; Bruin, E. M.; Collins, R. J.; Dorow, R. L.; Mantegna, L. R.; Sherk, S. R.; Covington, M. B.; Nurnberg, S. A.; Welch, P. K.; Nelson, M. J.; Magolda, R. L. *J. Med. Chem.* **1992**, *35*, 4061. (b) Padwa, A.; Wong G. S. K. *J. Org. Chem.* **1986**, *51*, 3125. (c) Reamer, R. A., Sletzinger, M., Shinkai, I. *Tetrahedron Lett.* **1980**, *21*, 3447.

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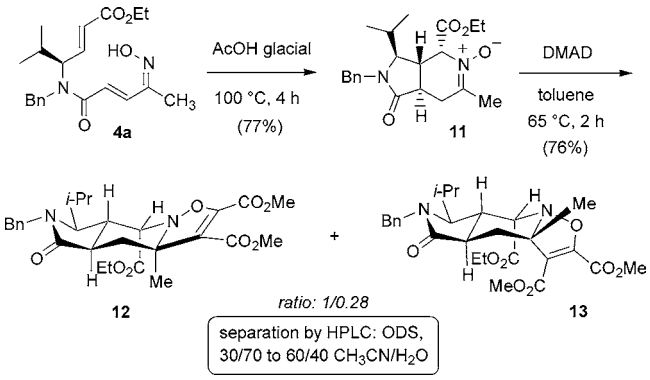
(14) It is worth noting that a simple treatment of **4a** in acetic acid at room temperature does not produce any cycloadduct.

Scheme 5. [4 + 2]/[3 + 2] Sequence with the (*Z*)-oxime **4a**



(ratio 1/0.28) (Scheme 5). The poor stereoinduction achieved with cyclic nitrone **11** is in contrast with all of our examples described herein. It is reasonable to justify this low π-facial selectivity with steric hindrance on both sides due to the isopropyl and ester groups.

Although the isopropyl group is remote from the reactive center, its bulk tends to partially block the upper face (*si* face). This presumably explains why cycloadduct **13** was formed through an approach of DMAD on the *re* face. It is interesting to note the subtle difference of behavior between the two nitrones **8** and **11**. The dipolarophile is not able to efficiently differentiate between the *si* and *re* faces of the nitrone **11**, whereas it does for the nitrone **8**. This observation indicates that, when the ester group is positioned on the face opposite to the benzyl group or isopropyl group, changing from a benzyl group to a sterically more hindered isopropyl group decreases the stereofacial selectivity (Figure 2).

These new polycycles, encompassing the piperidine ring, could allow rapid access into building blocks and/or biologically active compounds. Much attention has been focused on unnatural pipecolic acid derivatives substituted on the piperidine ring as useful building blocks for the synthesis of enzyme inhibitors[15] or NMDA receptor antagonists.[16] Interestingly, all of the final cycloadducts **6**, **9**, **10**, **12**, and **13** could open a direct route to highly substituted pipecolinic acid esters via N−O bond breaking.

This IMDA/1,3-dipolar cycloaddition sequence gives access to complex functionalized azapolycyclic systems. The reaction proceeds through the formation of three carbon−carbon bonds and four stereogenic centers in a process that is unprecedented in the chemistry of α,β-unsaturated oximes and in their proficiency in aza Diels−Alder reactions.

The above results demonstrate that the stereochemical outcome of the IMDA reactions is governed by a combination of factors: (1) the reaction conditions and (2) the nature of the starting amino acid. As we observed in earlier work,[17] a better diastereofacial selectivity for the IMDA was observed with the isopropyl group than with the benzyl group presumably due to subtle steric effects in the transition structures inherent to the size difference of these two groups. As for the [3 + 2] cycloaddition reactions, the high degree of facial discrimination observed is governed by the ester function adjacent to the reacting center.

In summary, we have shown the first examples of IMDA reactions of α,β-unsaturated oximes. Theoretical calculations to gain insight into the differences of reactivity between the (*Z*)- and (*E*)-oximes are underway and will be reported in due course as well as a full account of other cycloadditions.

Supporting Information Available: Complete experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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