Pergamon

Tetrahedron Letters 39 (1998) 6819–6822

TETRAHEDRON LETTERS

Preparation and Evaluation of a Cyclic Acyl Nitrone as a Synthon for Stereospecific α-Amino Acid Synthesis

Steven W. Baldwin,* Bruce G. Young, and Andrew. T. McPhail

Department of Chemistry, Duke University, Box 90346, Durham, N.C. 27708-0346, USA

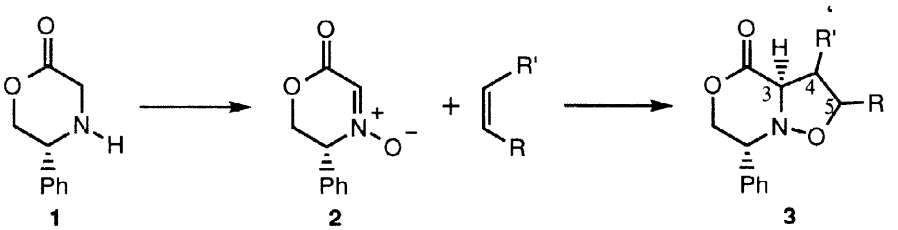
Received 28 May 1998; accepted 7 July 1998

Abstract: The preparation and characterization of cyclic optically active (5R)-3,4,5,6-tetrahydro-5-phenyl-2H-1,4-oxazin-2-one-N-oxide (**2**) is described. This nitrone, which is viewed as a template for the synthesis of γ-oxygenated α-amino acids, reacts with alkenes efficiently and with high stereospecificity.

Keywords: Nitrones; Cycloadditions; Stereoselection; X-Ray crystal structures

The nitrone-olefin 1,3 dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centers in a single step. Based on an evaluation of the nitrone cycloaddition,[1] it was felt that the stereochemistry of these new centers could be controlled both relatively and absolutely if the reaction system were properly designed. With the goal of developing a simple route to enantiomerically pure, unusually substituted α-amino acids, we have designed and prepared chiral cyclic acyl nitrone **2** as a template for olefin cycloadditions, (**Fig. 1**). The three structural features which can influence the stereochemical outcome of nitrone/alkene cycloadditions (E/Z isomerization about the C=N bond, nitrone facial selectivity, and *endo/exo* preferences) are all addressed with **2**, the expectation being unusually high levels of stereochemical control.

Figure 1

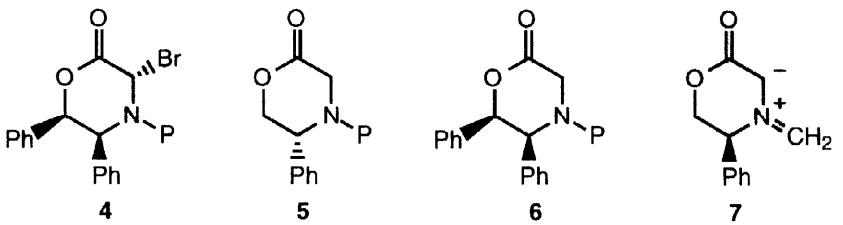


Substituted chiral 1,4-oxazin-2-ones have been successfully employed by others in a variety of ways, (**Fig. 2**). For instance, Williams has employed bromide **4** as an acyliminium

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01474-9

electrophile precursor in a broad range of alkylation reactions.[2] Dellaria[3] and Williams[4] both found that the enolates, derived from **5** and **6**, respectively, were good nucleophiles for reaction with traditional alkylating agents. Finally, azomethine ylid **7** has been employed by Harwood in 1-3-dipolar cycloaddition reactions with alkenes.[5] In the context of this communication the latter reactions proceeded with only modest efficiency and stereoselectivity.

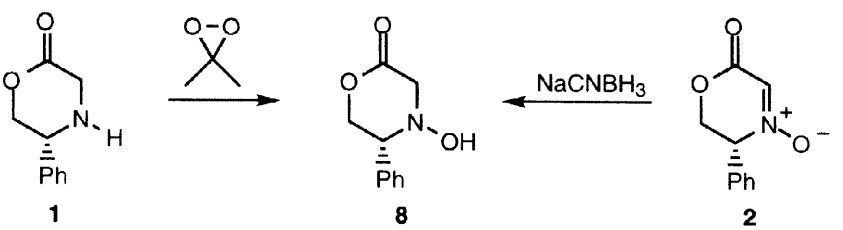
Figure 2



After considerable experimentation, it was found that nitrone **2** could be most conveniently prepared by direct oxidation of oxazinone **1**, the product of the reaction between phenyl glycinol and phenyl bromoacetate.[3] Treatment of **1** with 3-4 equivs of *in situ* generated dimethyl dioxirane, in a procedure modified from that of Curci,[6,7] produced **2** smoothly and in good (70-80%) yield.

Before proceeding it was necessary to establish that nitrone **2** was optically pure, given the likely acidity of the C-5 benzylic proton. To this end, the specific rotation of hydroxylamine **8**, prepared by partial oxidation of **1**, was compared with that of **8** obtained by controlled reduction of **2**, (**Fig 3**). The concordance of the two values (α= -73.08° and -73.36°, respectively) established that **2** was, in fact, enantiomerically pure.

Figure 3



With the nitrone template in hand we began a preliminary study of its cycloaddition reactions. Three simple alkene substrates (cyclopentene, 1-octene and ethylene) were initially chosen to provide information about the reactivity and cycloaddition facial selectivity of the nitrone. Methyl crotonate was selected because of its different electronic characteristics and as a rigorous test of the regio- and stereoselectivity of the cycloaddition process.

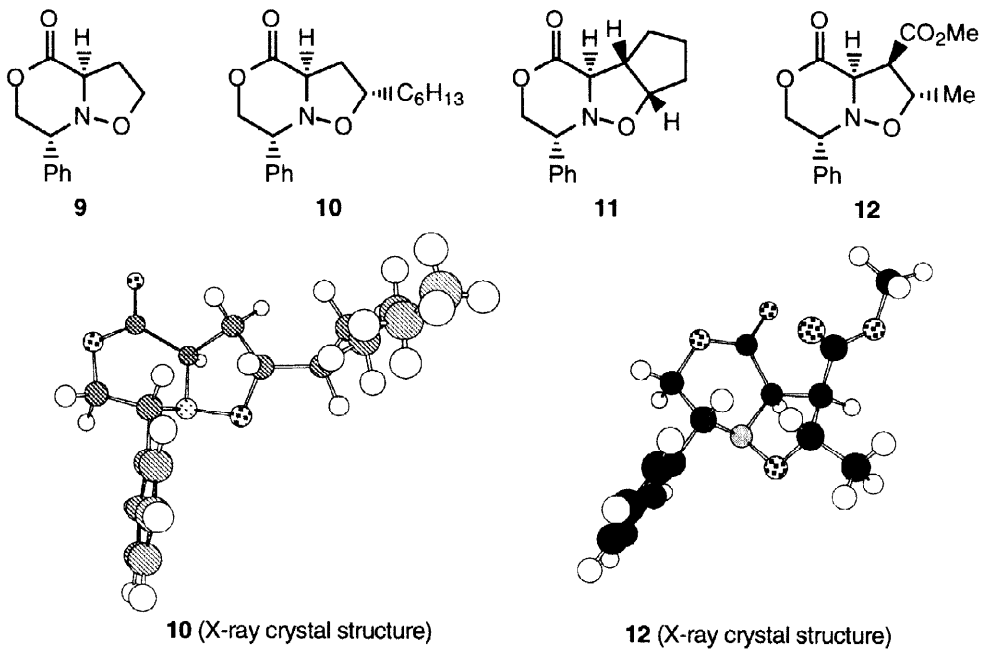
As expected the three simple alkenes reacted slowly with nitrone **2** at room temperature. Stirring a $CHCl_3$ solution of nitrone and 2-3 equivs of either cyclopentene or 1-octene for 13-20 h led to complete consumption of **2**. An ethylene-saturated $CHCl_3$ solution of **2** in a sealed tube led to nearly complete reaction after 7 days at 25°C. After removal of solvent and excess

alkene under vacuum, the three pure crystalline cycloadducts (**9-11**) were each isolated in >90% yield.

The results of these experiments were very encouraging. In each case only a single cycloadduct was formed,[8] confirming the key assumption that the template phenyl group would effectively shield the bottom face of the nitrone. The regio- and stereochemistry of the addition to 1-octene were proven through x-ray crystallographic analysis of cycloadduct **10**, (**Fig. 4**).[9] In addition to verifying that the reaction had occurred at the nitrone β-face, the x-ray results confirmed that the pendant hexyl group was at the isoxazolidine 5-position with α-stereochemistry. This stereochemistry is the result of an *exo* cycloaddition as expected for a non-conjugating substituent. A similar *exo* assignment was made for cyclopentene cycloadduct **11** on the basis of ^{1}H NMR comparisons.

Reaction of **2** with methyl crotonate (2-3 equivs) was complete in 3 hours to produce a single crystalline product **12** in 96% yield. The expected regiochemistry and stereochemistry (C-4 *endo* CO_2Me; C-5 *exo* CH_3) were confirmed by single crystal x-ray analysis, (**Fig. 4**).[9]

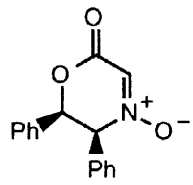
Figure 4



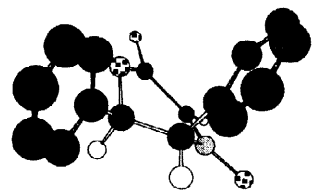
In contrast to the smooth cycloaddition reactions of **2**, diphenyl nitrone **13**, (**Fig. 5**), prepared in a similar fashion by oxidation of the corresponding amine,[2] behaved quite differently. First, cycloaddition reaction times for **13** were considerably longer than for **2** (cyclopentene, 240 vs 13 h; 1-octene, 120 vs 20 h; methyl crotonate, 72 vs 3 h). Moreover, the reactions between cyclopentene and methyl crotonate and **13** each led to nearly equal amounts of two stereochemically distinct cycloadducts rather than the stereochemically homogeneous isoxazolidine products seen with **2**. We suspect that this mixture of products is due to loss of facial selectivity during the cycloadditions. It is tempting to ascribe both the decreased reaction rates and stereoselectivities of **13** to an energetically unfavorable

interaction between the adjacent phenyl groups in the cycloaddition transition states as the oxazinone ring adopts the conformation of the product. Regardless, these results led us to abandon further development of nitrone **13** in favor of **2**.[10]

Figure 5



13



X-ray crystal structure

In summary, the encouraging results described here for nitrone **2** suggest that the initial goals of this study have been realized. A subsequent communication will describe the further development of **2** as a chiral glycine equivalent for the preparation of novel amino acids.

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7. To minimize dimerization of the oxazinone, oxidation is carried out immediately upon completion of chromotographic purification. The oxazinone is dissolved in $CHCl_3$ to which a phosphate/water buffer and a phase transfer catalyst have been added. Acetone is added to the mixture and then Oxone® added dropwise as an aqueous solution. The Oxone® oxidizes acetone to dimethyl dioxirane which is then consumed by its reaction with **1**. Additional buffer is added periodically to keep the pH at a constant 7.5. The reaction takes approximately 1h per gram of amine, can be scaled to any size, and purification involves simple chloroform extraction. The reaction proceeds smoothly in good (70-80%) yield.
8. All substances described herein gave spectroscopic data in accord with assigned structures. Selected spectroscopic data:
   -(5R)-3,4,5,6-tetrahydro-5-phenyl-2H-1,4-oxazin-2-one-N-oxide (**2**). Orange oil HRMS calculated for $C_{10}H_{10}O_3N$: m/z=192.0661, found: m/z=192.0660; ^{1}H NMR (300MHz, $CDCl_3$), δ 4.79 (qd, 2H, COOCH2), 5.08 (t, 1H, COCH), 7.45 (m, 5H, Ph); ^{13}C NMRδ 158.6, 131.3, 129.3, 127.5, 125.2, 71.3, 67.7; $[\alpha]_D$=-56.30 (CH_2Cl_2).
   -(5S,6R)-5,6-diphenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one-N-oxide (**13**). Yellow solid HRMS calculated for $C_{16}H_{14}O_3N$: m/z=268.0974, found: m/z=268.0973; ^{1}H NMR (300MHz, $CDCl_3$), δ 5.09 (d, 1H, NCH), 6.08 (m, 1H, CO_2CH), 7.33 (s, 1H, N=CH); ^{13}C NMR δ 159.0, 127.0-131.0, 124.4, 78.2, 77.3, 76.6, 75.9.
   -(2R, 6R, 7R, 8S)-2-phenyl-8-methyl-1-aza-4,9-dioxa[4.3.0]bicyclononan-5-one-7-carboxylic acid, methyl ester (**12**). White solid Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.8; H, 5.9. Found: C, 62.0; H, 6.0. ^{1}H NMR (300MHz, $CDCl_3$), δ 7.4 (m, 5H, Ph), 4.70 (d, 1H, COCH, J=10.0 Hz), 4.44 (m, 1H, MeCH), 4.37 (m, 2H, CO_2CH_2), 4.11 (t, 1H, CHPh), 3.77 (s, 3H, CO_2Me), 3.50 (dd, 1H, COCHCH, J=7.6, 10.2 Hz), 1.50 (d, 3H, Me, J=6.0 Hz); ^{13}C NMR δ 175.4, 170.0, 130–132, 80.5, 73.9, 69.5, 62.9, 62.3, 55.9,21.3.
9. Crystallographic data for **10**, **12**, and **13** have been deposited at the Cambridge Crystallographic Data Center.