ORGANIC LETTERS

2004
Vol. 6, No. 10
1653−1656

2-*tert*-Butyl-3-methyl-2,3-dihydroimidazol-4-one-*N*-oxide: A New Nitrone-Based Chiral Glycine Equivalent

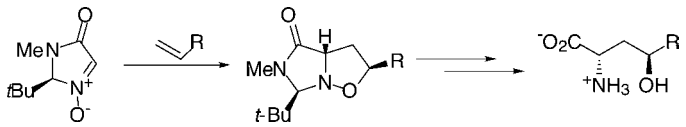
Steven W. Baldwin* and Alan Long

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27708-0346

steven.baldwin@duke.edu

Received March 16, 2004

ABSTRACT

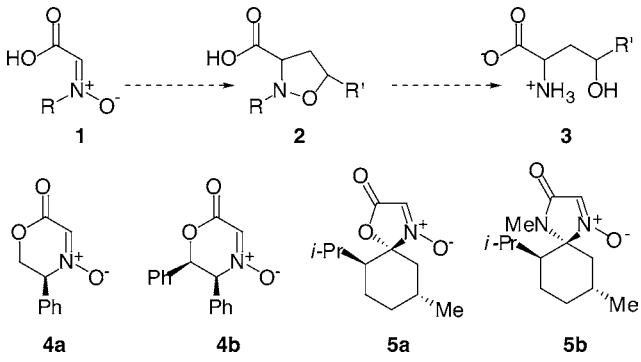


Cycloaddition reactions between a new homochiral imidazolone-derived nitrone afford cycloadducts in high yield and with high stereoselectivity. Subsequent cycloadduct elaboration affords the γ-lactones of γ-hydroxy-α-amino acids as well as the optically pure amino acids themselves.

The known number of naturally occurring α-amino acids has increased dramatically from the twenty (or twenty-one) that make up most proteins to well over 700 at this time.[1] The nonproteinaceous amino acids are those amino acids that are not found in protein main chains, either for lack of a specific transfer RNA and codon triplet, or because they do not arise from protein amino acids by posttranslational modification. Many of these compounds are the end products of secondary metabolism. Their origins are as diverse as their functions, although for most, only little is known on both accounts. Many others arise as intermediates of metabolic pathways or originate from the metabolism or detoxification of foreign compounds.

These compounds are of diverse structural type, often bearing unusual side chains that display varying degrees of hydroxylation and unsaturation. Many of these amino acids have important biological roles, being found in such important materials as cyclosporins and mushroom toxins, among others. Others,[2] such as those containing β,γ- or γ,δ-unsaturation,[3] profoundly perturb the biological properties of certain natural amino acids, converting them from enzyme substrates to irreversible inhibitors with potential therapeutic activity.

While considering possible routes to α-amino acids bearing unusual side chains, we were attracted to the possibility of using a glycine-derived nitrone such as **1** in 1,3-dipolar cycloaddition reaction with alkenes. If successful, the isoxazolidine products **2** would possess the necessary structural features to permit the preparation of amino acids bearing a hydroxyl group at the γ-position, i.e., **3**. Depending on the particular amino acid target, the hydroxyl group would either be left intact or suitably manipulated to yield alternative functionality such as side chain unsaturation. In the case of isoxazolidines derived from styrene derivatives, the final result could also be amino acids with no side chain oxygenation.



(1) (a) Ogura, K.; Inaba, T. *J. Synth. Org. Chem.* **1991**, *49*, 575−583. (b) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; pp 55−139. (c) Wagner, I.; Musso H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816−828.

(2) Ottenheijm, H. C. J.; Herscheid, J. D. M *Chem. Rev.* **1986**, *86*, 697−707.

(3) Williams, R. M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5431−5440, and refs 1−4 therein.

10.1021/ol049505a CCC: $27.50
Published on Web 04/16/2004

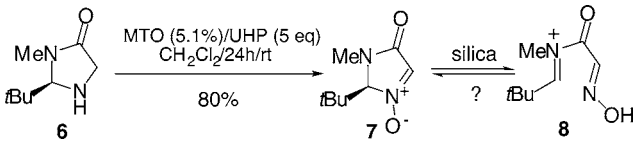
Consideration of several features of nitrones and their cycloaddition reactions leads to the conclusion that the above reaction would be best conducted using a nitrone that was constrained within a ring.[4] To this end we have previously reported the preparation and reactions of two chiral oxazinone-derived nitrones, **4a** and **4b**.[5] Tamura and co-workers have independently reported some related chemistry of nitrone **4a**.[6] In addition, a homochiral lactone-derived five-membered ring acyl nitrone based on menthone has been reported by Katagiri, **5a**,[7] while a lactam-centered homochiral acyl nitrone derived from menthone has also been reported, **5b**.[8]

We describe here the preparation and evaluation of a new chiral five-membered ring nitrone as a chiral glycine equivalent. As indicated in the following discussion, nitrone **7** is a versatile cycloaddition partner with a wide range of alkenes. Furthermore, the isoxazolidine cycloadducts derived from **7** can be converted to useful products by several hydrogenolytic techniques.

Nitrone **7** is conveniently prepared from Seebach's *tert*-butyl-substituted imidazolidinone **6**[9] by direct oxidation with one of several different reagents. In our hands the most successful oxidation method employs catalytic methyltrioxorhenium (MTO) in the presence of a urea/hydrogen peroxide (UHP) complex.[10] In a typical experiment, nitrone **7** (*S* configuration) was obtained from (*R*)-**6** in 80% purified yield as a white crystalline solid, mp 89−90 °C, $[\alpha]_D = +224°$ (*c* 1.04, $CHCl_3$). Diagnostic ^1H and ^{13}C NMR resonances for **7** include a singlet for the imine proton at $\delta = 7.06$ and a signal for the imine carbon at $\delta = 94.9$, respectively. Nitrone **7** prepared in this manner can be refrigerated and used as needed. Because both enantiomers of **6** are available from the same resolution procedure, both enantiomers of nitrone **7** are also readily available.[11]

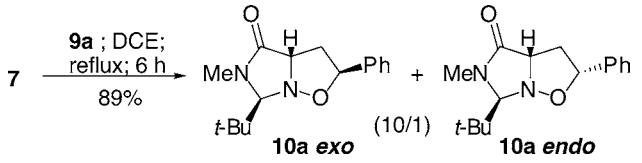
Although optically pure nitrone **7** could be recovered essentially unchanged after heating for 12 h at reflux in $CHCl_3$, it was found that passing **7** through a silica gel column, eluting with ethyl acetate/petroleum ether, led to its complete racemization. One possible explanation for this observation involves the intermediacy of an acyl iminium species such as **8** followed by recyclization.

Scheme 1



Nitrone **7** undergoes ready cycloaddition reactions with a wide range of alkenes. The reactions, which are somewhat slower than the corresponding reactions with nitrone **4**, occur with the normal regiochemical outcome expected for cycloadditions of this kind. In all cases studied, the stereochemical outcome of the cycloaddition reaction is the result of reaction from the less hindered α-face of nitrone **7** and places the isoxazolidine 5-alkyl/aryl substituent of the major stereoisomer in the *exo* position as indicated for the reaction of **7** with styrene (**9a**) (Scheme 2).[12] Stereochemical ratios

Scheme 2



(*exo/endo*) ranged from 5:1 to >20:1. Table 1 shows the results of the cycloaddition of nitrone **7** with five different alkenes, **9a**−**e**. In all cases, the yields of the crude products were excellent. For cycloadducts **10b**−**e** the major isomer was isolated in pure form after simple crystallization or flash chromatography.[13]

The conversion of cycloadducts **10a**−**e** to the corresponding γ-hydroxy-α-amino acids, isolated either as their γ-lactones or the free amino acids, involves initial N−O bond hydrogenolysis followed by imidazolidinone hydrolysis. For the two styrene-derived cycloadducts **10a** and **10b**, N−O bond cleavage was accomplished using Zn/HOAc/Ac_2O (Scheme 3). This reductive method avoids unwanted hydrogenolysis of the benzylic oxygen. The derived diacetates **11a** and **11b** were then converted to the free amino alcohols **12a** and **12b** by reaction with MeOH/K_2CO_3 (Method A).

The other three non-aryl-derived cycloadducts **10c**−**e** were converted to the free amino alcohols **12c**−**e** directly under

(4) For a recent review of nitrones and their cycloaddition reactions, see: Jones, R. C. F.; Martin, J. N. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley: New York, 2002; 59, 1, pp 1−81.

(5) (a) Long, A.; Baldwin, S. W. *Tetrahedron Lett.* **2001**, *42*, 5343−5346. (b) Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819−6822.

(6) (a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun.* **1996**, 1861−1862. (b) Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett*. **1999**, *40*, 895−898. (c) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Mayumi, K.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem*. **2000**, *65*, 8544−8551,

(7) (a) Katagiri, N.; Sato, H.; Kurimoto, A.; Okada, M.; Yamada, A.; Kaneko, C. *J. Org. Chem.* **1994**, *59*, 8101−8106. (b) Katagiri, N.; Okada, M.; Kaneko, C.; Furuya, T. *Tetrahedron Lett.* **1996**, *37*, 1801−1804. (c) Katagiri, N.; Sato, H.; Okada, M.; Morishita, Y.; Kaneko, C. *Chem. Commun.* **1996**, 2137−2138. (d) Katagiri, N.; Sato, H.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997**, *53*, 5727−5746.

(8) (a) Westermann, B.; Walter, A.; Flörke, U.; Altenbach, H.-J. *Org. Lett.* **2001**, *3*, 1375−1378. (b) Vogt, A.; Altenbach, H.-J.; Hahn, M.-G.; Matthaus, M. S. P.; Hermann, A. R. U.S. Patent No. 6,121,487 (issued Sept 19, 2000).

(9) (a) Naef, R.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 135−143. (b) Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622−2632. (c) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277−5292.

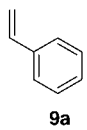
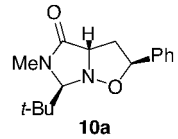
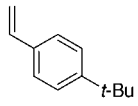
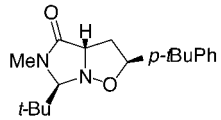
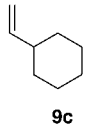
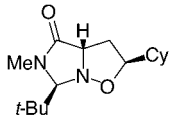
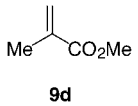
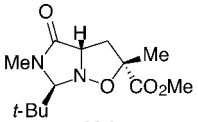
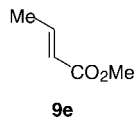
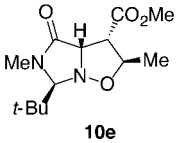
(10) (a) Goti, A.; Nanelli, L. *Tetrahedron Lett*. **1996**, *37*, 6025−6028. (b) Murray, R.; Iyanar, K. *J. Org. Chem*. **1996**, *61*, 8099−8102.

(11) Specific rotation of (*R*)-**7** similarly prepared from (*S*)-**6** was $[\alpha]_D = -221°$ (*c* 0.520, $CHCl_3$).

(12) In one experiment, careful chromatography of the crude product from the reaction of **7** with styrene afforded a minor amount (1.4%) of a third isomer that apparently had arisen from reaction syn to the *tert*-butyl group. This conclusion was reached on the basis of an 8.4% NOE enhancement between the aminal and α-protons in the NMR spectrum.

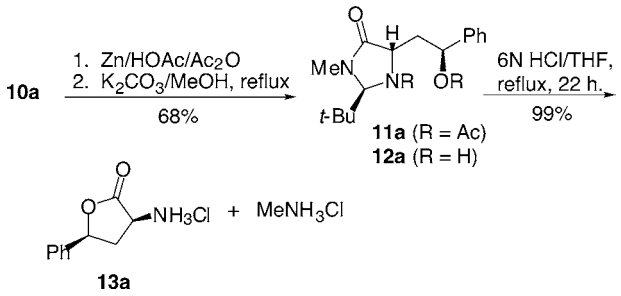
(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

Table 1. Isoxazolidine Derivatives **10a**−**e** Obtained from the 1,3-Dipolar Cycloaddition of **7** to Alkenes **9a**−**e**

alkene	cycloadduct[a]	yield[b]; *exo/endo*[c]
 **9a**	 **10a**	89%;[d] 10:1
 **9b**	 **10b**	95% (91%); >20:1
 **9c**	 **10c**	86% (76%);10:1
 **9d**	 **10d**	98% (93%); >20:1
 **9e**	 **10e**	98% (88%);>20:1

[a] Reactions were performed with 2−10 equiv alkene in $ClCH_2CH_2Cl$ at reflux for 5−52 h. The structure of the major isomer is shown. [b] Total yield of *exo* and *endo* isomers (purified major isomer). [c] *Exo* refers to 5-alkyl or aryl substituent; determined by integration of ^1H NMR spectra of unpurified reaction mixture. [d] Major isomer not isolated in pure form.

Scheme 3

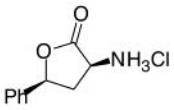
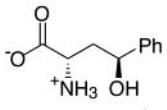
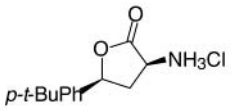
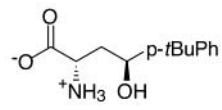
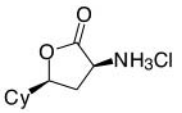
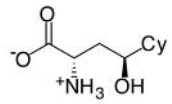
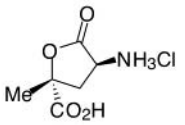
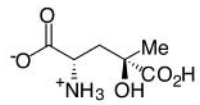
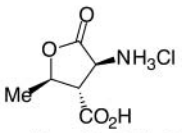


transfer hydrogenolysis conditions using ammonium formate in the presence of palladium (Method B).[14] As shown in Table 2, the yields of purified products for the N−O cleavage process ranged from 68 to 97%. Treatment of the amino alcohols **12a**−**e** with aqueous 6 N HCl then afforded the amino γ-lactone hydrochloride salts **13a**−**e** in excellent yield. Scheme 3 illustrates the conversion of **10a** to lactone **13a**.

The lactones prepared by these processes were admixed with 1 equiv of $MeNH_3Cl$, which for most purposes posed

(14) Johnstone, R. A. W.; Wilby, A. H. *Chem. Rev.* **1985**, *85*, 129−170.

Table 2. γ-Hydroxy-α-amino Acids and Lactones Derived from Cycloadducts **10a**−**e**

cyclo-adduct	lactone (method;[a] yields[b])	α-amino acid (yield[c])
10a	 **13a** (A; 68%, 99%)	 **14a** (75%)[d]
10b	 **13b** (A; 83%, 99%)	 **14b** (50%)
10c	 **13c** (B; 87%, 99%)	 **14c** (62%)
10d	 **13d** (B; 85%, 97%)	 **14d** (94%)[e]
10e	 **13e** (B; 97%, 92%)	[f]

[a] Method A: (1) Zn/HOAc/Ac_2O; (2) K_2CO_3/MeOH; (3) 6 N HCl, reflux. Method B: (1) Pd/C, ammonium formate/MeOH; (2) 6 N HCl, reflux. [b] Amino alcohol, lactone. [c] After basic hydrolysis, neutralization, ion exchange chromatography, and lyophilization. [d] Reference 15. [e] Reference 20. [f] Extensive decomposition during hydrolysis step.

no significant problem. If pure lactone (free of $MeNH_3Cl$) was required, it could be obtained after recrystallization. For instance, recrystallization of lactone **13e** from methanol afforded the pure lactone hydrochloride, mp 240−242 °C. Optically active lactone **13a** has been previously prepared by Hegedus.[15] Melting point, NMR spectra (^1H and ^{13}C), and specific rotation are in accord with those previously reported.

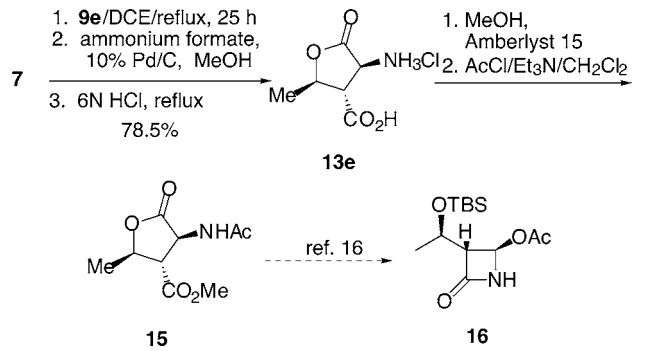
It is worth noting that lactone **13e**, obtained in optically pure form in three steps from methyl crotonate in 78.5% overall yield, contains all of the connectivity and stereochemical information found in important β-lactam antibiotics such as thienomycin (Scheme 4). In fact, lactone **13e**, as its methyl ester acetamide **15**, has been previously used as an intermediate for the synthesis of β-lactam **16**. In our hands, when **15** was prepared from **13e** ($MeOH/H^+$, then AcCl/Et_3N), the physical properties of the material obtained were in complete accord with those reported previously.[16]

Lactones **13a**−**d**, were either admixed with $MeNH_3Cl$ or, after purification, conveniently converted to the ring-opened

(15) Hegedus, L.; Schmeck, C. *J. Am. Chem. Soc.* **1994**, *116*, 9927−9934.

(16) Ohtake, H.; Imada, Y.; Murahashi, S. I. *J. Org. Chem.* **1999**, *64*, 3790−3791, and references therein.

Scheme 4



γ-hydroxy-α-amino acids by careful base hydrolysis followed by ion exchange chromatography on DOWEX 50W-X8 and lyophilization (Table 2). A similar hydrolysis of lactone **13e**, in an attempt to prepare the open chain amino acid, afforded considerable decomposition of starting material. Given the particular arrangement of functional groups in **13e**, this result is not altogether surprising.

Two of these amino acids have been previously reported. Of particular interest is the glutamic acid derivative **14d**. Both (2*S*,4*S*)-amino acid **14d** and its (2*S*,4*R*)-isomer are natural products, the former occurring in *Pandanus veitchii*[17] and the latter in *Ledenbergia roseo-aena*.[18] Both diastereoisomers occur in *Phyllitis scolopendrium*.[19] Recent studies by Bolte have clarified some earlier confusion associated with various spectral data.[20] Spectral information and the specific rotation for **14d** prepared by the method described herein (four steps, 72.1% yield) are in complete accord with that for the authentic material. Data for amino acid **13a** have also been previously reported[15] and are in complete accord with that determined in the context of this study.

In conclusion, nitrone **7** has been shown to be a versatile 1,3-dipole. The cycloaddition reactions are regiochemically regular and proceed with high stereoselectivity. The isoxazolidine cycloadducts can be readily transformed into α-amino-γ-lactones, which are then easily transformed into γ-hydroxy-α-amino acids. Further applications of this efficient methodology to other products of biological interest are currently in progress.

Acknowledgment. We acknowledge NSF (CHE 95 22580) for assistance in the purchase of the 400 MHz NMR instrument used in this work. A.L. thanks the Burroughs Wellcome Foundation for a graduate fellowship. Partial financial support by the Research Corporation (RA0305) is also acknowledged.

Supporting Information Available: Typical experimental procedures and structural characterization data for compounds **10a**−**h**, **12a**−**e**, **13a**−**e**, and **14a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049505A

(17) Alderweireldt, F.; Jadot, J.; Casimir, J.; Loffet, A. *Biochim. Biophys. Acta* **1967**, *136*, 89−94.
(18) Jadot, J.; Casimir, J.; Loffet, A. *Biochim. Biophys. Acta* **1967**, *136*, 79−88.
(19) Meier, L. K.; Sorensen, J. *Phytochemistry* **1979**, *18*, 1173−1175.
(20) (a) Hélaine, V.; Rossi, J.; Gefflaut, T.; Alaux, S.; Bolte, J. *Adv. Synth. Catal*. **2001**, *343*, 692−697. (b) Hélaine, V.; Bolte, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3855−3861.