ORGANIC LETTERS

2004
Vol. 6, No. 3
449−452

Synthesis of β-Substituted α-Amino Acids via Lewis Acid Promoted Radical Conjugate Additions to α,β-Unsaturated α-Nitro Esters and Amides

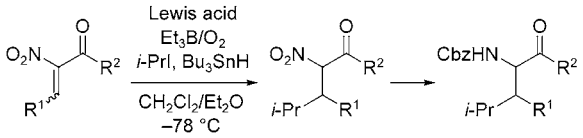
G. S. C. Srikanth and Steven L. Castle*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602

scastle@chem.byu.edu

Received December 18, 2003

ABSTRACT



R¹ = aryl, R² = OMe or NHBn

β-Substituted α,β-unsaturated α-nitro esters and amides undergo radical conjugate additions when treated with an appropriate Lewis acid. Deuterium studies revealed that the acidic α-stereocenter of the α-nitro ester products does not racemize under strictly controlled workup conditions. The α-nitro amides did racemize significantly during chromatography, but this could be greatly minimized by subjecting the crude adducts to subsequent transformations. The conjugate addition products can be elaborated into β-substituted α-amino acids in two simple steps.

β-Substituted α-amino acids are present in several peptidic natural products;[1] additionally, they are of interest as conformationally constrained analogues of α-amino acids.[2] Accordingly, several methods have recently been devised for their preparation,[3] including some that employ conjugate additions to α,β-unsaturated amino acid precursors.[3h−j] We were attracted to this strategy but mindful of the fact that the organometallic reagents normally employed in these reactions would be incompatible with complex peptides such as the projected intermediates in our synthesis of the antimitotic natural product Celogentin C.[4] Thus, we turned our focus to radical conjugate additions, which have been skillfully used by Sibi to construct β-unsubstituted α-amino acids.[5] Herein, we report that β-substituted α,β-unsaturated α-nitro esters and amides are viable substrates in Lewis acid promoted radical conjugate additions.[6] Significantly, we have discovered that racemization of the labile α-stereocenter of the resulting adducts[7] can be prevented in many cases. This result suggests the possibility of using this method in a

(1) (a) Suzuki, H.; Morita, H.; Iwasaki, S.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 5307. (b) Kobayashi, J.; Suzuki, H.; Shimbo, K.; Takeya, K.; Morita, H. *J. Org. Chem.* **2001**, *66*, 6626. (c) Leung, T.-W. C.; Williams, D. H.; Barna, J. C. J.; Foti, S.; Oelrichs, P. B. *Tetrahedron* **1986**, *42*, 3333.

(2) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585.

(3) (a) O'Donnell, M. J.; Cooper, J. T.; Mader, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2370. (b) Bull, S. D.; Davies, S. G.; Garner, A. C.; Mujtaba, N. *Synlett* **2001**, 781. (c) Soloshonok, V. A.; Tang, X.; Hruby, V. J.; Van Meervelt, L. *Org. Lett.* **2001**, *3*, 341. (d) Burtin, G.; Corringer, P.-J.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3451. (e) Tamura, O.; Yoshida, S.; Sugita, H.; Mita, N.; Uyama, Y.; Morita, N.; Ishiguro, M.; Kawasaki, T.; Ishibashi, H.; Sakamoto, M. *Synlett* **2000**, 1553. (f) Medina, E.; Moyano, A.; Pericàs, M. A.; Riera, A. *Helv. Chim. Acta* **2000**, *83*, 972. (g) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (h) Han., G.; Lewis, A.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 4601. (i) Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353. (j) Liang, B.; Carroll, P. J.; Joullié, M. M. *Org. Lett.* **2000**, *2*, 4157.

(4) Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611.

(5) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew Chem., Int. Ed.* **2001**, *40*, 1293.

(6) For a review of Lewis acid promoted radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. For a comprehensive treatise on the uses of radicals in organic synthesis, see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: New York, 2001.

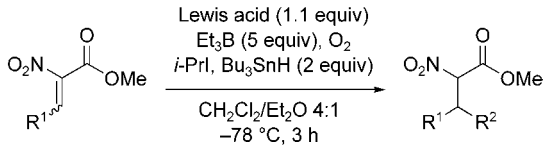
(7) The pK_a of ethyl nitroacetate has been measured as 5.62. For discussions of the chemistry of these acidic compounds, see: Shipchandler, M. T. *Synthesis* **1979**, 666.

10.1021/ol036461h CCC: $27.50
Published on Web 01/14/2004

diastereo- and enantioselective synthesis of β-substituted α-amino acids.

Our initial investigations of radical conjugate additions to α,β-unsaturated α-nitro esters (**1**)[8] are summarized in Table 1. We employed *p*-methoxyphenyl-substituted nitro ester **1a** as our test substrate for isopropyl radical addition under reaction conditions developed by Sibi for α,β-unsaturated *N*-acyl oxazolidinones.[9] We found that 1,4-reduction[10] product **3a**[11] was formed in reactions employing $MgBr_2 \cdot OEt_2$ as the Lewis acid promoter. Reduction was also observed with $ZnCl_2$ and $Yb(OTf)_3$, but the conjugate addition product **2a** could be obtained by increasing the amount of *i*-PrI from 5 to 12 equiv. Radical conjugate addition products were also obtained with phenyl- and *p*-fluorophenyl-substituted nitro esters **1b** and **1c**. Substrate **1c** provided a mixture of conjugate addition adduct **2c** and reduction product **3c** when $MgBr_2 \cdot OEt_2$ was employed as the Lewis acid, whereas **2c** was the sole product with $ZnCl_2$. Compounds **1a**−**c** were used as ca. 2:1 mixtures of olefin isomers, and adducts **2a**−**c** were formed as 1:1 mixtures of diastereomers. Although isomerically pure *Z*-**1a**−**c** could be obtained via recrystallization,[12] use of this material in the radical conjugate additions also provided **2a**−**c** as 1:1 diastereomeric mixtures. Finally, attempted radical conjugate additions to nitro ester **1d** bearing an aliphatic β-substituent resulted in complex mixtures.

Table 1. Radical Conjugate Additions of Ester Substrates



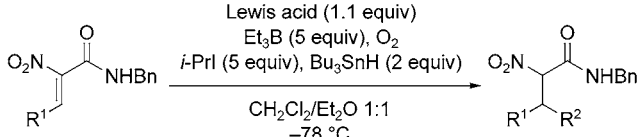
1a, R^1 = *p*-OMePh **1c**, R^1 = *p*-FPh **2a–d**, R^2 = *i*-Pr
1b, R^1 = Ph **1d**, R^1 = *i*-Pr **3a–d**, R^2 = H

substrate	Lewis acid	equiv *i*-PrI	product	yield (%)[a]
1a	$MgBr_2 \cdot OEt_2$	25	**3a**	60
1a	$ZnCl_2$	5	**3a**	60
1a	$ZnCl_2$	12	**2a**	85
1a	$Zn(OTf)_2$	25	**2a**	85
1a	$Yb(OTf)_3$	5	**3a**	60
1a	$Yb(OTf)_3$	12	**2a**	70
1a	$Cu(OTf)_2$	12	**2a**	80
1b	$MgBr_2 \cdot OEt_2$	5	nr[b]	
1b	$ZnCl_2$	5	**2b**	85
1b	$La(OTf)_3$	5	**2b**	58
1b	$Sm(OTf)_3$	5	**2b**	65
1b	$Yb(OTf)_3$	5	nr[b]	
1c	$ZnCl_2$	15	**2c**	85
1c	$MgBr_2 \cdot OEt_2$	15	**2c**,**3c**	7,49
1d	$MgBr_2 \cdot OEt_2$	5	nr[b]	
1d	$ZnCl_2$	5	nr[b]	

[a] For reactions of **1a**, yields were calculated from ^{1}H NMR because of persistent tin byproducts. All other yields are for isolated materials. [b] Neither product observed.

Having established the viability of esters **1a**−**c** as substrates in radical conjugate additions, we next examined the performance of the corresponding α,β-unsaturated α-nitro amides **4**[13] in this reaction. Amides **4a**−**c** were each obtained as a single olefin isomer of undetermined configuration; the *Z*-isomers are arbitrarily depicted in Table 2. The solvent was changed to CH_2Cl_2/Et_2O 1:1 in order to facilitate solubility of the substrate−Lewis acid complexes, and the amount of *i*-PrI was held constant at 5 equiv. $Zn(OTf)_2$ was the superior Lewis acid for all three substrates, affording adducts **5** as the major products along with minor amounts of reduced compounds **6**. In contrast, $Cu(OTf)_2$-mediated reactions delivered roughly equimolar amounts of **5** and **6**, whereas the use of lanthanide triflates provided **6** as the major product. The increased levels of reduction of amides **4** relative to esters **1** may be attributed to tighter binding of the amides to Lewis acids creating more electrophilic complexes.[14] Sibi has observed similar reductions when strong Lewis acids were employed in radical conjugate addition studies.[9] Additionally, all amides **5** were obtained

Table 2. Radical Conjugate Additions of Amide Substrates



4a, R^1 = *p*-OMePh **5a–c**, R^2 = *i*-Pr
4b, R^1 = Ph **6a–c**, R^2 = H
4c, R^1 = *p*-FPh

substrate	Lewis acid	time (h)	**5**:**6**	yield (%)[a]
4a	$MgBr_2 \cdot OEt_2$	2	0:100	82
4a	$Zn(OTf)_2$	1	86:14	92
4a	$Cu(OTf)_2$	1	52:48	70
4a	$Yb(OTf)_3$	1	28:72	62
4a	$Sm(OTf)_3$	1	25:75	54 (64)
4a	$La(OTf)_3$	1	25:75	50 (64)
4b	$Zn(OTf)_2$	3	84:16	84
4b	$Cu(OTf)_2$	3	44:56	52
4b	$Yb(OTf)_3$	3	25:75	58
4c	$Zn(OTf)_2$	4	89:11	80
4c	$Cu(OTf)_2$	4	44:56	46
4c	$Yb(OTf)_3$	4	25:75	30

[a] Sum of the isolated yields of **5** and **6**. Yields in parentheses are based on recovered **4**. Adducts **5a**−**c** were obtained as a 1:1 mixture of diastereomers.

(8) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528.
(9) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517.
(10) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2585.
(11) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 5282.
(12) The olefin stereochemistry of *Z*-**1a** was determined by X-ray crystallography. We thank Dr. John F. Cannon for this experiment.
(13) Preparation of these compounds is detailed in Supporting Information. The synthesis was based on the following report: Fenk, C. J. *Tetrahedron Lett.* **1999**, *40*, 7955.
(14) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576.

as 1:1 mixtures of diastereomers despite the fact that a single olefin isomer of **4** was used in each reaction, an observation identical to our findings with esters **2**.

The nitro moieties of adducts **2** and **5** can be transformed into protected amines **7** and **8** via a simple two-step sequence (Scheme 1). Thus, radical conjugate addition to α,β-unsaturated α-nitro esters **1** and amides **4** is a useful method for the synthesis of β-substituted α-amino acid derivatives. Moreover, the successful use of amides **4** as substrates suggests that the reaction could be carried out on a peptide. However, application of this protocol to natural product or complex molecule synthesis necessitates development of a diastereo- and enantioselective version. A requirement for such a reaction is inhibition of racemization of the sensitive α-stereocenters of **2** and **5**. To determine if this is possible, we performed radical conjugate additions to **1** and **4** with Bu_3SnD to see if deuterium would be retained in **2** and **5** (Table 3).

Scheme 1. Conversion of Adducts into Protected Amino Acids

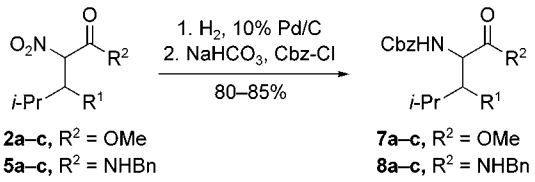
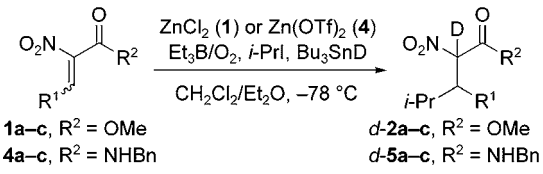


Table 3. Incorporation and Retention of Deuterium in **2** and **5**



substrate	time (h)	workup	H incorporation (%)[a]
1c	3	H_2O	10
1c	3	0.25 N HCl	4
1b	3	0.25 N HCl	nd[b]
1a	3	0.25 N HCl	nd[b]
4a	1	1 N HCl	4
4b	3	1 N HCl	nd[b]
4c	3	1 N HCl	11

[a] Measured by ^{1}H NMR of *d*-**2a**−**c** or *d*-**8a**−**c** (see text). [b] Not detected.

When we conducted this experiment with electron-poor ester substrate **1c**, we observed modest levels of hydrogen incorporation (10%) at the α-center when water was used in the workup. Fortunately, when the same reaction was worked up with 0.25 N HCl instead of water, the amount of D−H exchange dropped significantly. With nitro esters **1b** and **1a**, α-protons were not observed in the ^{1}H NMR spectra of *d*-**2b** and *d*-**2a**. Thus, racemization of acidic α-nitro esters **2** can be prevented in most cases and minimized in others by simply conducting the workup with dilute acid.

On the other hand, radical conjugate additions to amides **4a**−**c** with Bu_3SnD were characterized by extensive D−H exchange (32−57%). Use of more concentrated acid in the workup failed to decrease hydrogen incorporation. NMR studies implicated the amide hydrogen in this exchange.[15] Additionally, examination of the ^{1}H NMR spectra of crude *d*-**5a**−**c** revealed that the D−H exchange was taking place during SiO_2 chromatography. Accordingly, we removed this step from our procedure and subjected the adducts to hydrogenation followed by *N*-Cbz protection immediately after workup.[16] We were pleased to discover that this greatly attenuated the D−H exchange, as α-protons were not detected in the ^{1}H NMR spectrum of *d*-**8b** and were observed at low levels (4% and 11%) in the spectra of *d*-**8a** and *d*-**8c**. Therefore, of the six substrates examined in this study, only one (**4c**) exhibited >4% D−H exchange.

These deuterium studies indicate that the lack of diastereoselectivity in radical conjugate additions to isomerically pure **1** and **4** is not due to epimerization at the α-stereocenter of the products. Rather, it appears that the initially formed β-stereocenter does not exert any influence over the subsequent hydrogen atom abstraction step. Although the lack of substrate stereocontrol limits the current utility of our method, it actually bodes well for the discovery of a chiral Lewis acid controlled, diastereo- and enantioselective synthesis of β-substituted α-amino acids via this protocol. In addition to setting the β-stereochemistry, a suitable chiral Lewis acid would be expected to control the configuration at the α-position without interference from the newly established β-stereocenter.[17]

In summary, we have demonstrated that α,β-unsaturated α-nitro esters and amides undergo Lewis acid promoted radical conjugate additions, affording β-substituted α-amino acid derivatives. Competitive reduction is more pronounced with amides, presumably as a result of the tighter substrate−Lewis acid complexes. Importantly, we have discovered workup conditions that prevent or minimize deprotonation of the extremely acidic α-center of nitro esters **2** and amides **5**, thereby indicating the feasibility of asymmetric radical conjugate additions to these substrates provided a suitable chiral Lewis acid can be identified. Furthermore, we note that in some instances selective epimerization of the α-nitro amide stereocenter in a complex peptide adduct could be used advantageously to obtain a thermodynamic product. Consequently, we envision a variety of applications for these

(15) ^{1}H NMR spectra recorded immediately after isolation of *d*-**5a**−**c** exhibited amide N−H signals attenuated by an amount consistent with the extent of hydrogen incorporation at the α-position. Over time, the nitrogen-bound deuterium exchanged with protons derived from trace moisture and the amide signals returned to their normal levels of intensity. Unfortunately, attempts to block this exchange by performing radical conjugate additions on protected or tertiary amides have been unsuccessful. The *N*-Boc derivative of **4a** afforded reduction product exclusively, whereas *N*-PMB and *N*-Me versions were unreactive.

(16) Reductions of crude *d*-**5a**−**c** were sluggish as a result of the presence of tin byproducts, requiring ca. 3 wt equiv of 10% Pd/C.

(17) Sibi has successfully used a chiral Lewis acid to control the stereochemistry at both the α- and β-positions in radical conjugate additions to α,β-unsaturated *N*-acyl oxazolidinones: Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472.

radical conjugate additions in amino acid and peptide synthesis. Studies to delineate the full scope of this method are in progress and will be reported in due course.

Acknowledgment. We thank Brigham Young University for support of this work.

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

OL036461H