## Reduction of 2,3-Dihydroisoxazoles to $\beta$ -Amino Ketones and $\beta$ -Amino Alcohols

Patrick Aschwanden, Lisbet Kværnø, Roger W. Geisser, Florian Kleinbeck, and Erick M. Carreira\*

Laboratorium für Organische Chemie, ETH Hönggerberg, CH-8093 Zürich, Switzerland

carreira@org.chem.ethz.ch

Received October 20, 2005

## ABSTRACT



We report the reduction of 2,3-dihydroisoxazoles to  $\beta$ -amino ketones and  $\beta$ -amino alcohols. The latter are obtained in high diastereoselectivity with preference for the syn isomer.

We have recently developed a novel cyclization reaction of propargyl *N*-hydroxylamines<sup>1</sup> to 2,3-dihydroisoxazoles under mild conditions in the presence of catalytic amounts of ZnI<sub>2</sub> and DMAP.<sup>2</sup> This approach complemented extant methods, providing regioselective access to 3,5-disubstituted 2,3dihydroisoxazoles. The reductive opening of these can provide access to versatile building blocks for the preparation of pharmaceuticals and natural products.<sup>3</sup> In this paper, we describe our investigations concerning the conversion of these heterocycles into  $\beta$ -amino ketones<sup>4</sup> and  $\beta$ -amino alcohols.<sup>5,6</sup>

The most common methods for the reductive ring opening of dihydroisoxazoles include LiAlH<sub>4</sub> and catalytic hydrogenation with Raney nickel.<sup>7</sup> Our initial screening with these

(1) Frantz, D. E.; Fässler, R.; Carreira, E. M. J. Am. Chem. Soc. 1999, 121, 11245.

(4) For general methods to prepare  $\beta$ -amino ketones, see: (a) Davies, S. G.; McCarthy, T. D. Synlett **1995**, 700. (b) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. J. Am. Chem. Soc. **2005**, 127, 1313. (c) Kantam, M. L.; Neeraja, V.; Kavita, B.; Neelima, B.; Hussain, S. Adv. Synth. Catal. **2005**, 347, 763. (d) Dondoni, A.; Marra, A.; Boscarato, A. Chem.-Eur. J. **1999**, 5, 3562. (e) Kobayashi, S.; Ishitani, H. Chem. Rev. **1999**, 99, 1069.(b) Arend, M.; Westermann, B.; Risch, N. Angew. Chem., Int. Ed. **1998**, 37, 1045. (f) Hart, D. J.; Ha, D. C. Chem. Rev. **1989**, 89, 1447.

10.1021/oI052540c CCC: \$30.25 © 2005 American Chemical Society Published on Web 11/05/2005

methods proved unsuccessful in providing the desired  $\beta$ -amino ketones or  $\beta$ -amino alcohols, leading us to investigate zinc in acetic acid as an alternative. In preliminary experiments, test substrate **5** (Table 1) was subjected to a

Table 1.	Dihydroisoxazole	Reduction to	$\beta \beta$ -Amino	Ketones
----------	------------------	--------------	----------------------	---------

Bn N-O	10 equiv zinc powder	<sup>Bn</sup> `ŅH Q	
$R^1$ $R^2$	AcOH/H <sub>2</sub> O = 3:1	$R^1  R^2$	
1-8		9-16	

isoxazoline	$\mathbb{R}^1$	$\mathbb{R}^2$	eta-amino ketone	yield (%) (range for three runs)
1	Me	nBu	9	74 - 81
2	Me	tBu	10	77 - 82
3	$i \Pr$	nBu	11	86-91
4	$i \Pr$	tBu	12	88-90
5	tBu	nBu	13	91 - 96
6	tBu	tBu	14	88 - 92
7	$\mathbf{Ph}$	nBu	15	59 - 73
8	$\mathbf{Ph}$	tBu	16	65 - 78

suspension of Zn powder (5 equiv) in glacial acetic acid. The formation of  $\beta$ -amino ketone **13** and the corresponding  $\alpha$ , $\beta$ -unsaturated ketone was observed within less than 1 h. Optimal conditions were found to be the use of an excess

<sup>(2)</sup> Aschwanden, P.; Frantz, D. E.; Carreira, E. M. Org. Lett. 2000, 2, 2331.

<sup>(3) (</sup>a) Kleemann. A.; Lindner, E.; Engel, J. In *Arzneimittel*; VCH: Weinheim 1987. (b) Traxler, P.; Trinks, U.; Buchdunger, E.; Mett, H.; Meyer, T.; Müller, M.; Regenass, U.; Rösel, J.; Lydon, N. *J. Med. Chem.* **1995**, *38*, 2441. (c) Dimmock, J. R.; Siduh, K. K.; Chen, M.; Reid, R. S.; Allen, T. M.; Kao, G. Y.; Truitt, G. A. *Eur. J. Med. Chem.* **1993**, *28*, 313.

(10 equiv) of activated zinc powder added in two portions to a solution of substrate in 3:1 AcOH/H<sub>2</sub>O. Thus, the desired  $\beta$ -amino ketone **5** was obtained, with only trace amounts of the undesired  $\alpha$ , $\beta$ -unsaturated ketone being observed.

We next examined the substrate scope of the reaction with a number of substituted 2,3-dihydroisoxazoles (Table 1). In general, good to excellent yields were obtained. With C3-aryl-substituted substrates (7 and 8), the competing elimination to the  $\alpha$ , $\beta$ -unsaturated ketone led to slightly diminished yields.

When C5-aryl-substituted 2,3-dihydroisoxazoles ( $R^2 = Ph$ ) were subjected to zinc powder in acetic acid, instead of the expected  $\beta$ -amino ketones, the corresponding *anti-\beta*-amino alcohols were obtained in moderate to good diastereoselectivities (Scheme 1). However, this observation did not prove



to be general with respect to substrate scope. In subsequent investigations of various reducing conditions, we observed that reduction with sodium borohydride in acetic acid followed by NO-bond cleavage with zinc in acetic acid provided the corresponding syn- $\beta$ -amino alcohols as confirmed by NOE measurements. This observation proved to be general.

To examine the scope of this process, various 2,3dihydroisoxazoles with  $R^2 = Ph$  were subjected to the reaction conditions (NaBH<sub>4</sub>/AcOH then Zn/AcOH, Table 2). In the NaBH<sub>4</sub>-promoted reduction of the 3-methyl-substituted



Bn, N-O R <sup>1</sup> 17	NaBI `Ph AcO	$\frac{H_4}{H} \rightarrow \frac{Bn}{R^1} \frac{N-O}{18}$	zinc powc Ph AcOH	Bn∖NH OH R <sup>1</sup> ↓↓Ph 19
		18		19
entry	$\mathbb{R}^1$	yield (%) <sup>a</sup>	$\mathrm{d}\mathbf{r}^b$	yield (%) (syn)
1	Me	$59^c$	80:20	$96^{d}$
2	$i \Pr$	89	91:9	72
$3^e$	$i \Pr$			63
4	Су	85	89:11	79
5	Ph	79	87:13	75

<sup>*a*</sup> Combined yield of *syn-* and *anti-*isoxazolidines **18**. <sup>*b*</sup> Diastereomeric ratios were determined by <sup>1</sup>H NMR of the crude products. <sup>*c*</sup> Yield for the *syn-*isoxazolidine **18**. <sup>*d*</sup> Yield observed using *syn-*isoxazolidine **18** as starting material for the N–O bond cleavage reaction. <sup>*e*</sup> One-pot procedure.

2,3-dihydroisoxazole **17** ( $\mathbb{R}^1 = \mathbb{M}e$ ), the resulting intermediate isoxazolidines obtained in 80:20 dr were readily separable by column chromatography affording the pure *syn*-isomer **18** in 59% isolated yield (entry 1). Subsequent reductive NObond cleavage with zinc powder in AcOH proceeded with no stereochemical degradation, thus furnishing the diastereomerically pure *syn*- $\beta$ -amino alcohol **19** ( $\mathbb{R}_1 = \mathbb{M}e$ ). For the *syn*-selective reductions of the remaining substrates, the inseparable diastereomeric mixtures of isoxazolidines **18** were subjected directly to NO-bond cleavage, affording the readily separable  $\beta$ -amino alcohols **19** (entries 2, 4, and 5). As exemplified by entry 3, it was possible to carry this out as a one-pot process transformation.

In summary, we have shown that 2,3-dihydroisoxazoles can serve as precursors for the preparation of either  $\beta$ -amino ketones or  $\beta$ -amino alcohols depending on their substitution pattern. The desired  $\beta$ -amino ketones can be obtained in preparatively useful yields. Additionally, a borohydride reduction followed by ring opening reaction provided a general entry to *syn-\beta*-amino alcohols in high selectivities. These versatile building blocks may find further synthetic applications, in particular when derived from unusually substituted 2,3-dihydroisoxazoles.

Acknowledgment. We thank the Swiss National Science Foundation and F. Hoffmann-LaRoche for generous support. L.K. thanks The Technical University of Denmark for a doctoral fellowship. F.K. thanks the Fonds der Chemischen Industrie for a fellowship.

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

OL052540C

<sup>(5)</sup> For selected examples to prepare  $\beta$ -amino alcohols, see: (a) Pilli, R. A.; Russowsky, D. J. Chem. Soc., Chem. Commun. **1987**, 1053. (b) Pilli, R. A.; Russowsky, D.; Dias, L. C. J. Chem. Soc., Perkin Trans. 1 **1990**, 1213. (c) Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A. L. J. Org. Chem. **1992**, 57, 1219. (d) Keck, G. E.; Truong, A. P. Org. Lett. **2002**, 4, 3131.

<sup>(6)</sup>  $\beta$ -Amino alcohols are also commonly used as chiral ligands; see: (a) *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 1999. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

<sup>(7) (</sup>a) For a review, see: Freeman, J. P. Chem. Rev. 1983, 83, 241. (b) Adachi, T.; Harada, K.; Miyazaki, R.; Kano, H. Chem. Pharm. Bull. 1974, 22, 61. (c) Curran, D. P. J. Am. Chem. Soc. 1983, 105, 5826. (d) Curran, D. P.; Scanga, S. A.; Fenk, C. J. J. Org. Chem. 1984, 49, 3474. (e) Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. Angew. Chem., Int. Ed. 2005, 44, 4036. (f) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. Angew. Chem., Int. Ed. 2001, 40, 2082. (g) Bode, J. W.; Carreira, E. M. J. Am. Chem. Soc. 2001, 123, 3611.