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Reduction of 2,3-Dihydroisoxazoles to β-Amino Ketones and β-Amino Alcohols

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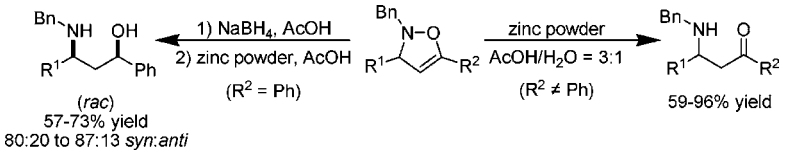
ABSTRACT

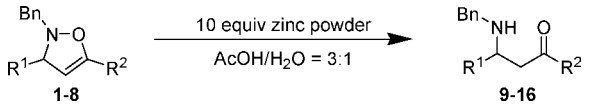


We report the reduction of 2,3-dihydroisoxazoles to β-amino ketones and β-amino alcohols. The latter are obtained in high diastereoselectivity with preference for the *syn* isomer.

We have recently developed a novel cyclization reaction of propargyl *N*-hydroxylamines[1] to 2,3-dihydroisoxazoles under mild conditions in the presence of catalytic amounts of ZnI_2 and DMAP.[2] This approach complemented extant methods, providing regioselective access to 3,5-disubstituted 2,3-dihydroisoxazoles. The reductive opening of these can provide access to versatile building blocks for the preparation of pharmaceuticals and natural products.[3] In this paper, we describe our investigations concerning the conversion of these heterocycles into β-amino ketones[4] and β-amino alcohols.[5,6]

The most common methods for the reductive ring opening of dihydroisoxazoles include $LiAlH_4$ and catalytic hydrogenation with Raney nickel.[7] Our initial screening with these methods proved unsuccessful in providing the desired β-amino ketones or β-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 suspension of Zn powder (5 equiv) in glacial acetic acid. The formation of β-amino ketone **13** and the corresponding α,β-unsaturated ketone was observed within less than 1 h. Optimal conditions were found to be the use of an excess

Table 1. Dihydroisoxazole Reduction to β-Amino Ketones



isoxazoline	R^1	R^2	β-amino ketone	yield (%) (range for three runs)
1	Me	*n*Bu	**9**	74−81
2	Me	*t*Bu	**10**	77−82
3	*i*Pr	*n*Bu	**11**	86−91
4	*i*Pr	*t*Bu	**12**	88−90
5	*t*Bu	*n*Bu	**13**	91−96
6	*t*Bu	*t*Bu	**14**	88−92
7	Ph	*n*Bu	**15**	59−73
8	Ph	*t*Bu	**16**	65−78

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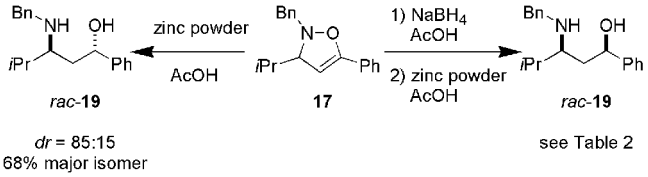
(10 equiv) of activated zinc powder added in two portions to a solution of substrate in 3:1 AcOH/H_2O. Thus, the desired β-amino ketone **5** was obtained, with only trace amounts of the undesired α,β-unsaturated ketone being observed.

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 α,β-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 β-amino ketones, the corresponding *anti*-β-amino alcohols were obtained in moderate to good diastereoselectivities (Scheme 1). However, this observation did not prove

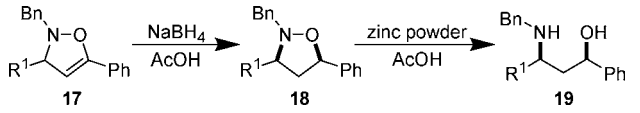
Scheme 1. Reduction to β-Amino Alcohols



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*-β-amino alcohols as confirmed by NOE measurements. This observation proved to be general.

To examine the scope of this process, various 2,3-dihydroisoxazoles with R^2 = Ph were subjected to the reaction conditions ($NaBH_4$/AcOH then Zn/AcOH, Table 2). In the $NaBH_4$-promoted reduction of the 3-methyl-substituted

Table 2. Preparation of *syn*-β-Amino Alcohols



		18		19
entry	R^1	yield (%)[a]	dr[b]	yield (%) (*syn*)
1	Me	59[c]	80:20	96[d]
2	*i*Pr	89	91:9	72
3[e]	*i*Pr			63
4	Cy	85	89:11	79
5	Ph	79	87:13	75

[a] Combined yield of *syn*- and *anti*-isoxazolidines **18**. [b] Diastereomeric ratios were determined by ^{1}H NMR of the crude products. [c] Yield for the *syn*-isoxazolidine **18**. [d] Yield observed using *syn*-isoxazolidine **18** as starting material for the N−O bond cleavage reaction. [e] One-pot procedure.

2,3-dihydroisoxazole **17** (R^1 = Me), 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 NO-bond cleavage with zinc powder in AcOH proceeded with no stereochemical degradation, thus furnishing the diastereomerically pure *syn*-β-amino alcohol **19** (R_1 = Me). 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 β-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 β-amino ketones or β-amino alcohols depending on their substitution pattern. The desired β-amino ketones can be obtained in preparatively useful yields. Additionally, a borohydride reduction followed by ring opening reaction provided a general entry to *syn*-β-amino alcohols in high selectivities. These versatile building blocks may find further synthetic applications, in particular when derived from unusually substituted 2,3-dihydroisoxazoles.

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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.

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