Tetrahedron Letters,Vol.23,No.31,pp 3123-3126,1982 0040-4039/82/313123-04$03.00/0
Printed in Great Britain

Methods for the Conversion of Isoxazolines to β-Hydroxy Ketones

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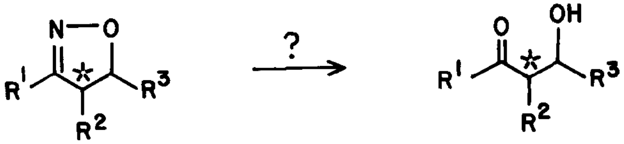
Summary: Two methods have been developed for converting isoxazolines to β-hydroxy ketones in a stereospecific manner.

In some of our more recent efforts to explore the use of isoxazolines in natural product synthesis, we have had the need to develop procedures through which one can efficiently unmask this heterocyclic nucleus to reveal a β-hydroxy ketone (an aldol fragment).[1] It was essential that the unmasking operation be performed under conditions which did not epimerize a neighboring α-asymmetric center.



We have devised currently two procedures through which such an operation can be performed with essentially complete stereospecificity. The first method is based on a catalytic hydrogenation procedure using W-2 Raney nickel. While several reports are to be found in the literature for the hydrogenolytic cleavage of the N-O bond of isoxazolines (W-2 Raney nickel, acetic acid[2] and Pd/C, acetic acid[3]) these reduction systems (even with large amounts of acetic acid) when applied to **1** led to a chromatographically separable mixture (50:50-70:30) of the cis- and trans-isomers of 2-acetylcyclopentanol [cis: ^{1}H NMR ($CDCl_3$, 300 MHz) 4.47-4.55 (m, 1 H), 3.32 (br s, 1 H), 2.74-2.84 (m, 1 H), 2.23 (s, 3 H), 1.60-2.10 (m, 6 H); trans: ^{1}H NMR ($CDCl_3$, 300 MHz) 4.33-4.43 (m, 1 H), 2.74-2.86 (m, 1 H), 2.22 (s, 3 H), 1.56-2.15 (m, 6 H)]. Since the pure cis-isomer was found *not* to undergo epimerization in the presence of acetic acid, it was reasoned that epimerization must occur at the β-hydroxy imine stage via the tautomeric enamine. By employing a stronger mineral acid (weaker conjugate base) in the hydrogenation brew, it would seem that rapid protonation of the imine with addition of water would lead to a carbinolamine that could break down to β-hydroxy ketone without epimerization.[4] Alternatively, the isoxazoline might first be hydrated, and then N-O bond cleavage to carbinolamine occur. The hydrogenation reaction of **1** was thus repeated with W-2 Raney nickel, and four equivalents of concentrated HCl in 5:1 methanol-water.

The reaction was complete within 30 min, and within the limits of TLC and 300 MHz ^1H NMR analysis reduction had occurred with complete specificity. *None of the trans-isomer was detectable and the isolated yield was nearly quantitative.*

Since aluminum(III) is known to catalyze imine hydrolysis, and since aluminum chloride undergoes hydrolysis to release HCl, we have furthermore examined in greater detail a catalyst system comprised of W-2 Raney nickel and $AlCl_3$ (4 equiv) in methanol and water (5:1). Reduction occurred cleanly and in high yield with all seven isoxazolines displayed in the Table.[5] *We thus suggest that the present catalyst system should be one of the first to be considered when the conversion of isoxazoline to β-hydroxy ketone is required.*[6]

Our second method for the unmasking of isoxazolines recognizes the structural relationship of these heterocycles to oximes. Oximes can generally be converted in moderate to good yield to the corresponding carbonyl compounds by ozonolysis.[7] The various isoxazolines indicated in the accompanying table were thus dissolved in methylene chloride and exposed to a stream of ozone/oxygen at -78°C until a persistent blue color was obtained (∿3 h). After an additional 3 h at -78°C, the reaction mixture was quenched with dimethyl sulfide. Upon workup and chromatography, the pure β-hydroxy ketones were isolated in yields of 61 - 74%. *No epimerization was found to occur under these reaction conditions.*

The mechanism of this reaction is probably similar to that proposed for the ozonolytic cleavage of oximes. Initial electrophilic attack of ozone on the C-3 carbon of the isoxazoline is followed by C-N bond rupture to deliver upon further oxidation a keto nitrate or nitrite.

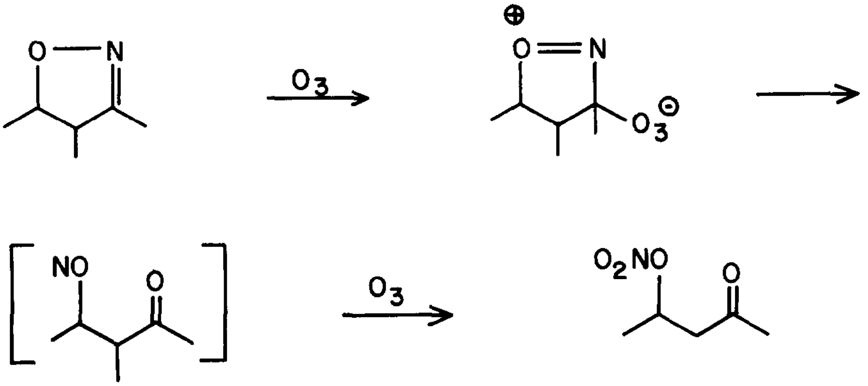
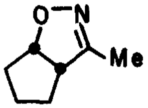
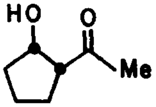
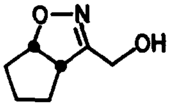
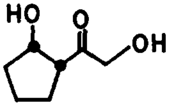
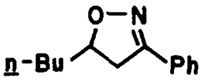
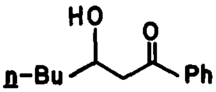
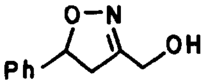
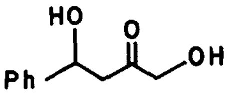
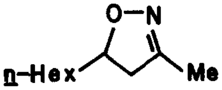
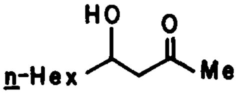
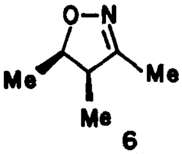
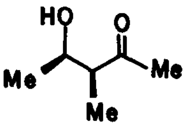
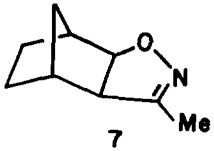
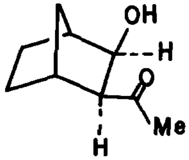


Table. Conversion of Isoxazolines to β-Hydroxy Ketones.

Isoxazoline	β-Hydroxy Ketone	Yield (%) from hydrogenation	Yield (%) from ozonolysis
 1		97	73
 2		98	--
 3		97	61
 4		96	--
 5		98	73
 6		95	74
 7		97	72

Although the isolated yields are lower than obtained for the hydrogenolytic cleavage process, the ozonolysis procedure may nonetheless be useful in cases where hydrogenation conditions are prohibited due to the presence of other reducible functional groups. Of course, neither method may be applicable to molecules which contain additional unsaturation. In such cases, chemical reduction procedures (e.g. Ti^{+3}) may be warranted.[8]

Acknowledgements: We are indebted to the National Institutes of Health (HL-20579), and the Camille and Henry Dreyfus Foundation for support of this work.

References and Notes

1. A. P. Kozikowski and Y. Y. Chen, Tetrahedron Lett., in press; A. P. Kozikowski and P. D. Stein, manuscript submitted; A. P. Kozikowski and M. Adamczyk, manuscript submitted.
2. R. H. Wollenberg and J. E. Goldstein, Synthesis, 757 (1980).
3. M. Asaoka, T. Mukuta and H. Takei, Tetrahedron Lett., **22**, 735 (1981).
4. A. Bruylants and E. Feytmants-de Medicis, in "The Chemistry of the Carbon-Nitrogen Double Bond", S. Patai, Ed., Interscience Publishers, London, 1970, pp. 465-504.
5. Attempts to carry out this reduction with Pd/C-HCl, Raney nickel-$ZnCl_2$, Raney nickel-$SnCl_4$, Raney nickel-$Cu(OAc)_2$, Raney nickel-PPTS, or Raney nickel alone led either to a mixture of isomers or to formation of a metal complex.
6. A reduction system comprised of Raney nickel and boric acid does also appear to be equally effective. We thank Professor Curran for making this information known to us prior to publication.
7. R. E. Erickson, P. J. Andrulis, Jr., J. C. Collins, M. L. Lungle and G. D. Mercer, J. Org. Chem., **34**, 2961 (1969).
8. S. H. Andersen, N. B. Das, R. D. Jorgensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma and K. B. G. Torssell, Acta Chem. Scand. B, **36**, 1 (1982).

(Received in USA 29 April 1982)