Tetrahedron Letters, Vol. 34, No. 1, pp. 83-86, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

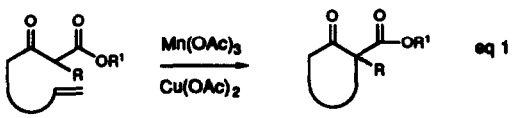
Mn(III) Promoted N-O Bond Reduction of N-Hydroxy-2-Azetidinones

Arun Ghosh and Marvin J. Miller*

Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556 USA.

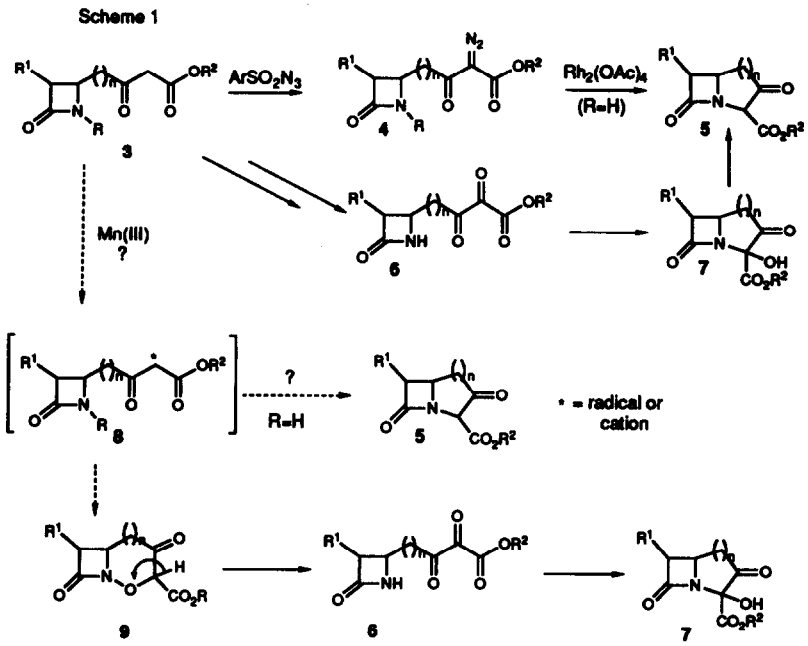
Abstract: Treatment of various N-hydroxy-2-azetidinones with Mn(III) acetate unexpectedly afforded the corresponding reduced N-unsubstituted-2-azetidinones in the presence of hydrogen donor solvents.

Manganese(III) acetate promoted oxidation of ß-dicarbonyl compounds produces electrophilic radicals that have been used extensively for intramolecular cyclization of ω-unsaturated-ß-dicarbonyl compounds (eq 1).[1] ß-Dicarbonyls have also served as sources of electrophilic carbon for the formation of bicyclic ß-lactams but require prior conversion to α-diazo-ß-ketoesters[2,3] or vicinal tricarbonyls[4,5] (Scheme 1). Direct oxidation of a ß-dicarbonyl appended to a monocyclic ß-lactam, **3**, to an intermediate radical or cation (**8**) might facilitate straightforward cyclization to bicyclic ß-lactams (**5**) of current interest for the synthesis of important carbapenems and carbacephems.

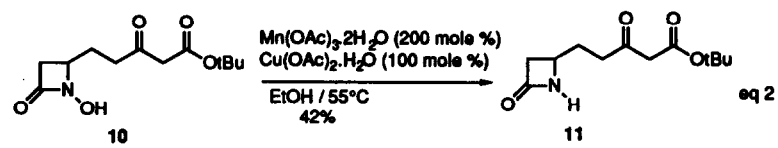


1 **2** eq 1

Our previous studies of substituted-N-hydroxy-ß-lactams[6] suggested that related ß-dicarbonyl-containing N-hydroxy-ß-lactams **3** (R = OH) might be especially interesting substrates for Mn(III) oxidations. Several modes of reaction could be envisioned. Oxidation to **8** (R = OH) might induce intramolecular trapping by the N-hydroxy group to generate the bicyclic oxamazin[7] analog **9**. Based on the precedented intermolecular [1,2]-anionic rearrangement of N-hydroxy substituted ß-lactams,[8] **9** could then be induced to rearrange to tricarbonyl **6** and subsequently recyclize to the corresponding bicyclic ß-lactam **7**. Alternatively, reaction of the ß-lactam nitrogen of an oxidized intermediate might produce bicyclic ß-lactams directly. While we have demonstrated that Ti(III) effectively reduces the N-O bond of N-hydroxy-2-azetidinones,[9] the potential fate of the N-O bond under presumed oxidative Mn(III) conditions was unknown.



Interestingly, when compound **10** was exposed to 200 mole % of $Mn(OAc)_3 \cdot 2H_2O$ and 100 mole % of $Cu(OAc)_2 \cdot H_2O$ in ethanol at 55°C, the N-O reduced product **11** was obtained in 42% yield as the only isolable product (eq 2). While the mechanism of the reaction is not yet clear, Mn-mediated cleavage of the N-O bond, presumably by a homolytic process or by alternative reduction, competes with and excludes the expected oxidation of the ß-dicarbonyl. Substitution of acetic acid for ethanol as the solvent and lowering the temperature to 25°C gave a decreased yield (19%) of the reduced product. The use of the aprotic solvent benzene did not give any characteristic product, but complete destruction of the ß-lactam ring system. The critical role of ethanol as the solvent may be due to its precedented function as a hydrogen atom donor.[1a,10,11] Thus, if Mn(III) first induces homolysis of the N-O bond to give the corresponding nitrogen radical with concommitant generation of a Mn(IV) oxo species, hydrogen atom transfer from ethanol might provide the final reduction product (**11**).



Despite uncertainties about the mechanism and the low yield of this unexpected N-O bond reduction, several other N-hydroxy ß-lactam derivatives were subjected to the reaction to determine its generality and compatibility or incompatibility with other substituents. The results are summarized in the table.[12]

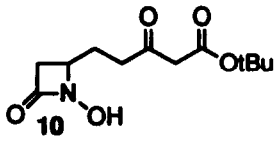
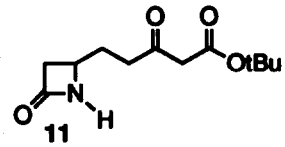
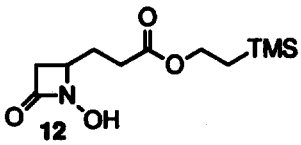
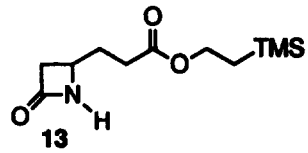
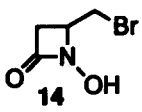
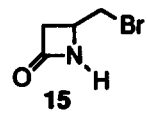
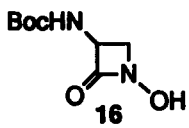
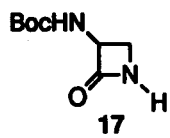
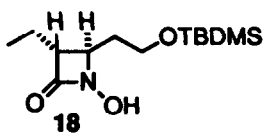
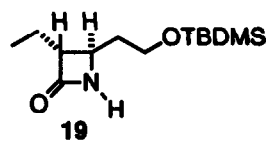
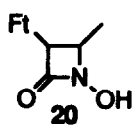
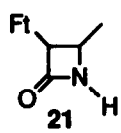
Entry	Substrate	Product[a]	Procedure[b]	Yield (%)[c]
1	 **10**	 **11**	A B	42 19
2	 **12**	 **13**	A B	45 18
3	 **14**	 **15**	A B	53 12
4	 **16**	 **17**	No characteristic product	
5	 **18**	 **19**	A	28
6	 **20**	 **21**	A	22

Table: [a]All unknown compounds showed characteristic spectral data and exact mass spectroscopic data. [b]For procedure A and B, see text. [c]Isolated yields are given.

In contrast to buffered Ti(III)-mediated reduction of N-hydroxy ß-lactams, which is compatible with a variety of sensitive functionality, the Mn(III) process fails with the Boc protected 3-amino substituted-2-azetidinone **16** (entry 4), and gives significantly lower yields in the presence of a silylated hydroxyl group (entry 5) and a phthalimido group (entry 6). Despite these apparent limitations, the unprecedented nature of the Mn(III)-mediated N-O bond reduction merits further mechanistic study.

Experimental procedure:

In a typical reaction (Procedure A), $Mn(OAc)_3 \cdot 2H_2O$ (0.42 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.21 mmol) were dissolved in ethanol (2 mL) and placed in a preheated (55°C) oil-bath. N-Hydroxy-2-azetidinone (0.21 mmol) in ethanol (1 mL) was added to the resulting greenish brown solution. After stirring for 10-15 h at 55°C, the brown reaction mixture was quenched by the addition of 1 mL of water followed by a 100 mM solution of Na_2EDTA (5 mL). The resulting solution was extracted with three 10-mL portions of CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The residue obtained after removal of solvent was purified by either flash or radial chromatography. In procedure B, AcOH was used instead of EtOH, and the reaction was performed at room temperature.

Acknowledgment: We are grateful to Eli Lilly and Co. for partial support of this research.

References:

1. For an authoritative background review and comprehensive list of references, see: a) Snider, B. B.; Meritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544 and references cited therein. b) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607.
2. a) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tet. Lett.* **1980**, *21*, 31. b) Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M., Jr., Nist, R. L.; Prather, D. E.; Sparks, D. L.; Vladuchick, W. C. *Tet. Lett.* **1989**, *30*, 2321. c) Evans, D. A.; Sjogren, E. B. *Tet. Lett.* **1985**, *26*, 3787.
3. Williams, M. A., Hsiao, C.-N.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 2688.
4. Wasserman, H. H.; Han, W. T.-W. *Tet. Lett*, **1984**, *25*, 3743.
5. Gasparski, C.M.; Ghosh, A.; Miller, M. J. *J. Org. Chem.* **1992**, *57*, 3546.
6. Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
7. a) Woulfe, S. R.; Miller, M. J. *Tet. Lett.* **1984**, *25*, 3293. b) Woulfe, S. R.; Miller, M. J. *J. Med. Chem.* **1985**, *28*, 1447.
8. Lee, B. H.; Biswas, A.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 106.
9. Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410.
10. For references on the relative ease of hydrogen atom abstraction from ethanol than from acetic acid: see, a) Gilbert, B. C.; Norman, R. O. C.; Placucci, G.; Sealy, R. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 885. b) Thomas, J. K. *J. Phys. Chem.* **1967**, *71*, 1919.
11. The oxidation of 1-hydroxyethyl radical to acetaldehyde is relatively easy: Asmus, K.-D.; Bonifacic, M. In *Landolt-Bornstein New Series, Group 2;* Fisher, H., Ed.; Spring Verlag: Berlin, 1984; Vol. 13b, pp 311-313.
12. All new compounds gave satisfactory spectroscopic and analytical data.

(Received in USA 18 August 1992; accepted 6 October 1992)