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A selective catalytic side chain oxidation of lysine and ornithine derivatives ☆

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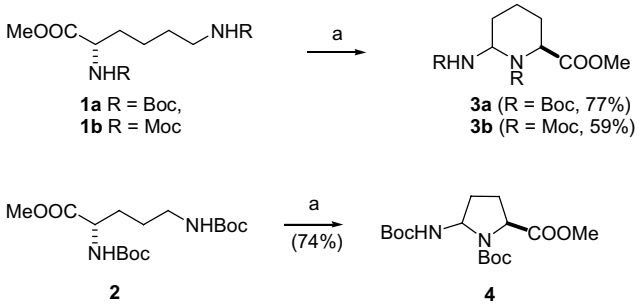
Abstract—The fully protected derivatives of the diamino acids lysine and ornithine ($n = 1, 2$) can be oxidized selectively in the side chain using a $Mn(OAc)_2$/peracetic acid/NaOAc system. The ε or γ carbon, respectively, is converted to the aldehyde oxidation state, protected as the cyclic *N*,*N*-acetal.

The natural α-amino acids are important building blocks not only for proteins, but their ready availability in both enantiomeric forms makes them useful starting materials for the synthetic and medicinal chemist. Consequently, the synthesis and modification of amino acids is an important topic in organic chemistry. We now report on novel uses of the amino acids L-lysine, which is prepared by fermentation on a very large scale as a feed additive, and ornithine, also readily available. The oxidation of the ε-amino residue of lysine to the aldehyde in proteins is catalyzed by enzymes belonging to the large group of lysyl oxidases and this oxidation has an important biological function in the crosslinking of proteins, in aging and is implicated in various diseases.[1] In spite of its biological importance and significant advances in the understanding of the mechanism of several lysyl oxidases, the organic chemistry of this transformation is largely undeveloped. To the best of our knowledge, no catalytic oxidation of lysine or a lysine derivative to an aldehyde has been reported in the literature, which prompted us to examine this reaction for bis-carbamate protected lysine and ornithine methyl esters. In general, oxidations of amines and protected amines fall into one of three classes: (a) a biomimetic oxidation via Schiff base formation and subsequent tautomerizaton,[2] (b) direct oxidation by converting the amine to the N-halo or N-oxide[3] or using electrochemical methods[4] and most importantly (c) oxidation using a metal catalyst and an oxidizing agent.[5] The latter category is exemplified by the elegant work of Murahashi et al.[6] in the manufacture of a key carbapenem intermediate.

We prepared various α,ϖ bis-carbamate protected derivatives of lysine and ornithine methyl esters in two straightforward high yielding steps from the free amino acids. A variety of oxidation conditions were initially examined without success. Manganese is used in oxidases and we decided to follow up Nature's suggestion by combining the catalyst $Mn(OAc)_2$ with NaOAc buffered peracetic acid. Indeed, the desired ε or γ aldehyde derivatives of lysine and ornithine were obtained in good yield as *N*,*N*-acetals **3a**[7] (77%), **3b** (59%) and **4** (74%) (Scheme 1).



Scheme 1. Reagents and conditions: (a) $Mn(OAc)_2 \cdot 4H_2O$ (7 mol%), AcOOH (4.5 equiv), AcONa, AcOH.

Keywords: Amino acids and derivatives; Amino aldehydes; Catalysis; Cyclization; Manganese and compounds; Oxidation; Piperidines.

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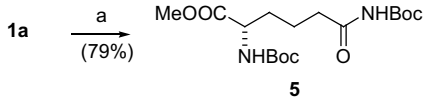
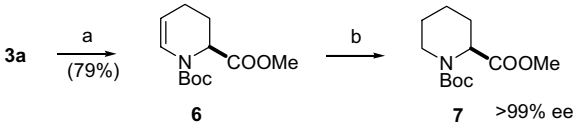
Optimized reaction conditions use 7 mol% of $Mn(OAc)_2$ in a saturated solution of NaOAc in HOAc with the slow addition of 4 equiv of commercial peracetic acid over 4 h at 22 °C. The key to a high yield is the use of hexane to extract the product away from the reaction mixture. As a result, **3a**, **3b**, and **4** are obtained essentially pure as crystalline solids by a simple concentration. By contrast, a standard aqueous work-up leads to significant decomposition. While both **3a** and **4** had been reported in the literature,[8] they were obtained as minor by-products from complex reaction mixtures. For example, subjecting **1** to different variants of the Murahashi oxidation (Ru/C, $RuCl_2(PPh_3)$ or $RuCl_3{\cdot}xH_2O$ with peracetic acid) gave a complex reaction mixture from which some of the desired **3a** as well as the product of elimination, **6**, could be isolated after a lengthy chromatography in less than 10% yield. Remarkably, the use of an alternative oxidant $NaIO_4$ with Ru completely altered the reaction course, leading instead to **5** in good yield (Scheme 2).[9]



Scheme 2. Reagents and conditions: (a) $RuO_2{\cdot}xH_2O$, $NaIO_4$, AcOEt, H_2O.

Our new simple oxidation conditions make **3a**, **3b**, and **4** readily available to be used as useful starting materials for the preparation of various amino acid derivatives.

Initially, we had used a large excess of peracetic acid in overnight reactions, and the result was inevitably a mixture of **3a** and its elimination product **6**. Indeed, **3a** is converted cleanly to the enamide **6** by using slightly acidic reaction conditions (Scheme 3). A simple hydrogenation of **6** to the corresponding pipecolic derivative **7** confirmed that no racemization had occurred under the buffered oxidation conditions (Scheme 3).



Scheme 3. Reagents and conditions: (a) AcOH (2 equiv); (b) H_2, Pd/C (5%).

Commercial peracetic acid is a mixture of peracetic acid in acetic acid containing 3% H_2O and a catalytic amount of H_2SO_4. Consequently, the function of the NaOAc in the reaction mixture could be that of a drying agent or as a buffer. To this end we examined the reaction with the neutral drying agent $MgSO_4$. Surprisingly, a completely different reaction course was observed and **8a**[10] and **8b** were formed as the only products in quantitative yield (Scheme 4).

In essence, we have converted a lysine derivative to a glutamic acid derivative through a novel formal removal

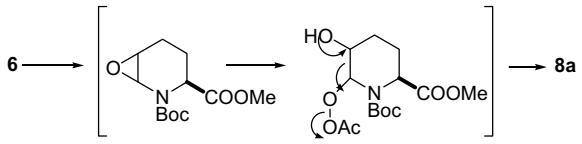
Scheme 4. Reagents and conditions: (a) $Mn(OAc)_2{\cdot}4H_2O$ (7 mol%), AcOOH (7 equiv), $MgSO_4$ (3 equiv), AcOH.

of the carbon alpha to an amine. While the synthetic utility may appear limited on first sight as glutamic acid is readily available, the protected glutamic acid derivatives **8a** and **8b** are challenging synthetic targets. We assume that the mechanism of the reaction starts from **6**, which results from elimination of *tert*-butylcarbamate under the more acidic reaction conditions, followed by epoxidation of the enecarbamate **6** and opening of the epoxide with excess peracetic acid and subsequent fragmentation and oxidation (Scheme 5).

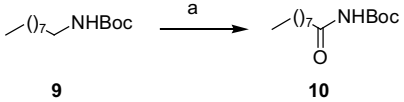
To probe the generality of the reaction *N*-Boc-nonylamine **9** was subjected to the standard reaction conditions. Remarkably, an amide **10** was formed in essentially quantitative yield, that is the oxidation of the amine carrying carbon did not stop at the aldehyde oxidation state but went on to the oxidation state of an acid (Scheme 6).

This result indicates that the $Mn(OAc)_2$ catalyzed peracetic oxidation is not general, but is specific to the lysine and ornithine derivatives **1** and **2**. Two possible explanations can be proposed: the facile formation of five- and six-membered *N*,*N*-acetals serves to protect the intermediate of the aldehyde. Additionally, it is very conceivable that the protected α-amino acid enters the coordination of the Mn generating a catalytic center with new steric and electronic properties resulting in a novel chemoselectivity of the oxidation.

Further work will probe the mechanistic aspects of this novel oxidation reaction. Additionally, the simple preparative access to the highly functionalized amino acid derivatives **3a**, **b**, and **4** will make them useful starting materials for further syntheses. We will report on this in due time.



Scheme 5.



Scheme 6. Reagents and conditions: (a) $Mn(OAc)_2{\cdot}4H_2O$ (7 mol%), AcOOH (3 equiv), AcONa, AcOH.

Supplementary Material

Characterization of compounds **3a**, **3b**, **4**, **6**, and **8a**.

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7. Representative procedure for **3a**. $Mn(OAc)_2{\cdot}4H_2O$ (7 mol%, 119 mg) was dissolved in a saturated solution of NaOAc in AcOH (30 mL) followed by **1** (2.5 g, 6.94 mmol, 1 equiv). Peracetic acid (5.5 mL, 4 equiv 39% in acetic acid) was added dropwise with vigorous stirring over a period of 4 h. The reaction mixture was poured into 50 mL of *n*-hexane and 50 mL of water. After separation of the organic phase, the aqueous one was extracted with *n*-hexane (2×50 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL) and concentrated under vacuum to give **3a** as a colorless solid (1.91 g, 77% yield).
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10. Representative procedure for **8a**. $Mn(OAc)_2{\cdot}4H_2O$ (5 mol%, 222 mg) was dissolved in AcOH (30 mL), followed by **1** (18.1 mmol, 5.0 g) and $MgSO_4$ (3 equiv, 6.54 g). AcOOH (7 equiv, 21.6 mL) was added dropwise over a period of 4 h. TLC analysis (AcOEt) indicated a complete and clean conversion. The reaction mixture was poured into 150 mL of AcOEt, 70 mL of water was added and after separation of the organic phase the aqueous one was extracted with AcOEt (2×100 mL). The combined organic layers were washed with brine (50 mL) and water (50 mL), dried over $MgSO_4$ and concentrated under vacuum, which resulted in the isolation of a pale-yellow oil (quantitative yield).