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ANODIC AMIDE OXIDATIONS: CONFORMATIONALLY RESTRICTED PEPTIDE BUILDING BLOCKS FROM THE DIRECT OXIDATION OF DIPEPTIDES

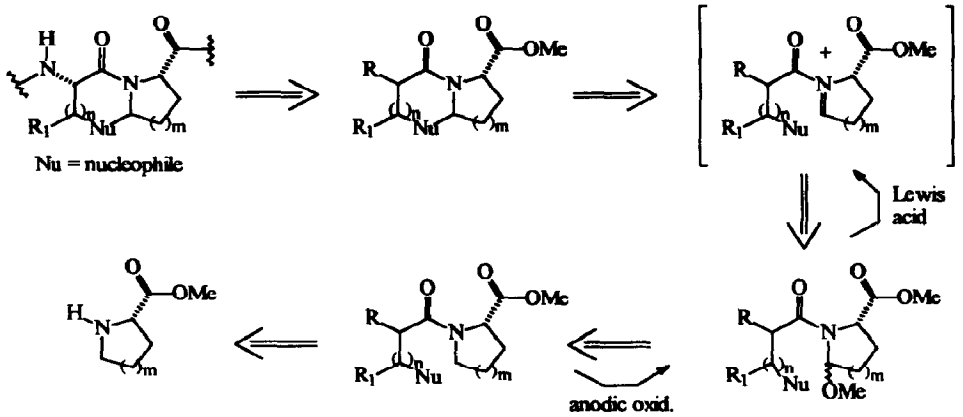
Fabrice Cornille,[1] Yvette M. Fobian,[2] Urszula Slomczynska,[1] Denise D. Beusen,[3] Garland R. Marshall,[1,3]* and Kevin D. Moeller[2]*

[1]Department of Molecular Biology and Pharmacology, [2]Department of Chemistry, and [3]Center for Molecular Design, Washington University, St. Louis, MO 63130

Abstract: A pair of bicyclic lactam based conformationally restricted peptide mimetics have been synthesized in good yield by the direct anodic oxidation of dipeptides. This work highlights the simplicity of using electrochemistry to construct peptide mimetics and serves to further define the nature of the substituents that are compatible with an electrochemical procedure for annulating rings onto amino acid derivatives.

Recently, we have been investigating the use of anodic amide oxidations for constructing bicyclic lactam based peptide building blocks.[1] This work has focused on the utility of electrochemistry for functionalizing amino acid derivatives and annulating rings onto amines and amino acid derivatives.[2,3] A general approach is outlined in Scheme 1.

Scheme 1

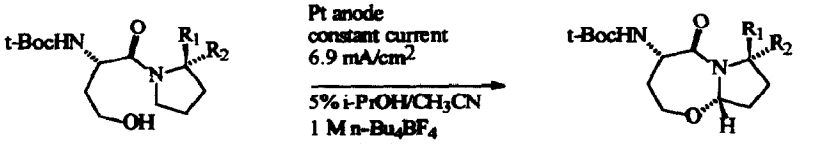


One of the chief strengths of this synthetic route is that it makes use of starting materials derived from proline and pipecolic acid. In addition, a variety of other cyclic amines, like the decahydroisoquinoline derivatives found in a number of the more potent HIV-protease inhibitors,[4] should be compatible with this annulation procedure. The use of amino acid derived starting materials allows for the rapid incorporation of key stereogenic atoms into the non-lactam ring of the bicyclic amino acid derivatives. However, to date no effort has been made to address the chirality of the lactam ring. Ideally, the stereogenic atom alpha to the amide carbonyl could again be derived from an amino acid starting material (Scheme 1, R=NHBoc). Such an approach would allow for the use of easily synthesized dipeptides as substrates. However, such an

approach would also require the selective oxidation of a tertiary amide in the presence of a secondary amide. We report here that the selective oxidation of a proline moiety in a dipeptide is possible and that the success of this oxidation can lead to the rapid construction of bicyclic peptide analogs.

Initially, the readily synthesized *t*-BocHseProMe substrates **1a** and **1b** were chosen for study.[5]

Scheme 2



1a. R_1=H; R_2=CO_2Me
1b. R_1=CO_2Me; R_2=H

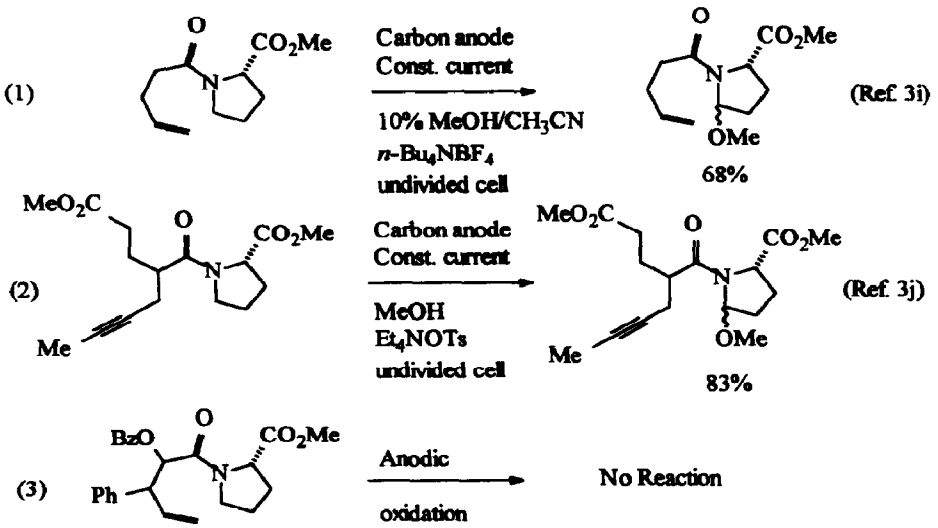
2a. R_1=H; R_2=CO_2Me 48%
2b. R_1=CO_2Me; R_2=H 52%

Both substrates were electrolyzed (Scheme 2) in an undivided cell using a 1 M tetra-*n*-butylammonium tetrafluoroborate in 5% isopropanol/acetonitrile electrolyte solution, platinum foil electrodes, and a constant current of 138 mA (current density = 6.9 mA/cm^2). In the case of **1a** (*L*-proline), 40 mmole of the starting material was oxidized using 3.8 F/mole in order to form 6.3 g (48%) of the desired bicyclic building block **2a**. Both the oxidation and cyclization steps occured during the electrolysis. The cyclization reaction was highly diastereoselective and led to only the bridgehead isomer having an *S*-configuration.[6] No other diastereomer was observed by NMR. The oxidation of **1b** (*D*-proline) also led directly to the formation of the desired bicyclic building block. In this case, a 52% isolated yield of **2b** was obtained. The cyclization led to the same high preference for formation of the *S*-stereochemistry at the bridgehead. Clearly, the bridgehead stereochemistry was dictated by the stereochemistry of the homoserine moiety.

Several aspects of these reactions deserve further comment. First, the use of isopropanol was important for the cyclization reaction. When methanol was used as the solvent for the electrolysis, the *N*-α-methoxyalkyl amide was obtained. Second, the reactions benefited from the use of a platinum anode. Carbon anodes were not as effective. Finally, the success of the reactions was found to depend strongly on the current density. When the current density was raised to 19.5 mA/cm^2, the yield dropped to 21% over the two steps. For this reason, the current density of the electrolysis was carefully maintained during "scale ups" of the oxidation-cyclization sequence.

In addition to affording good yields of the bicyclic building blocks, these reactions have also served to refine our view of the anodic amide oxidation. At the start, it was not clear that the oxidation of a proline based dipeptide would be successful. Several anodic oxidations of peptides had been reported. However, these oxidations had involved either the formation of an iminium ion utilizing a Kolbe decarboxylation reaction[2c-e] or the indirect oxidation of secondary amide with Cl^+.[2f-h] To our knowledge, the selective oxidation of a proline moiety in a peptide had not been attempted. In addition, preliminary results from our laboratories offered no clear precedent for the required oxidation. Although the oxidation of proline derived amides having either no substituent (Scheme 3/ equation 1) or a carbon substituent on the carbon alpha to the amide carbonyl (Scheme 3/ equation 2) did proceed smoothly, the anodic oxidation of proline derived amides having an oxygen substituent at this position routinely met with failure (for example: Scheme 3/ equation 3).[7] In these cases, an excellent yield of starting material was recovered. The difficulties encountered were due to a combination of both the oxygen substituent on the alpha carbon and the substituent on the five-membered ring. Removal of either substituent led to a substrate that could be readily

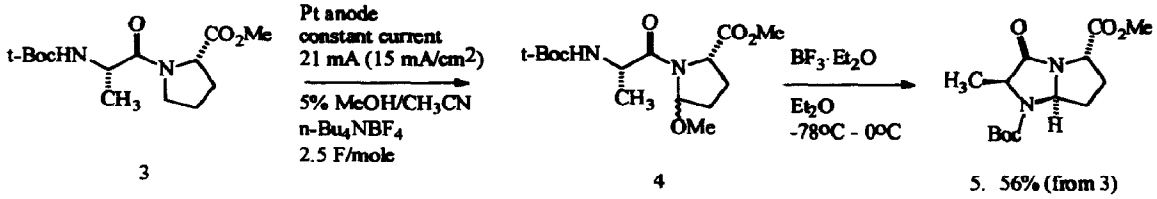
Scheme 3



oxidized. Apparently, the substituents combined to raise the oxidation potential of the substrate to a point where it no longer competed succesfully with solvent oxidation. From the current reactions, we now know that the dividing line separating successful oxidations from reactions that lead to exclusive recovery of starting material lies between a *t*-Boc protected nitrogen and an oxygen substituent alpha to the amide carbonyl. Understanding dividing lines of this nature provides a critical guide for designing future syntheses.

The direct electrolysis of a dipeptide could also be used to synthesize α-amino cyclized building blocks (Scheme 4). For example, when the *t*-BocAlaProMe substrate 3 was oxidized using an undivided cell, a 0.1 M

Scheme 4



3 4 5. 56% (from 3)

tetra-*n*-butylammonium tetrafluoroborate in 5% methanol/acetonitrile electrolyte solution, platinum foil electrodes, and a constant current of 21 mA (15 mA/cm^2) a 71:29 mixture (by NMR) of methoxylated product and recovered starting material was obtained. The crude product was treated directly with a -78°C solution of BF_3-Et_2O (3 equiv.) in ether. The reaction was stirred at -78°C for one hour and then raised to 0°C for 30 min before quenching to afford the desired bicyclic product 5 in a 56% isolated yield over the two steps. Only the product having a *R*-configuration (as illustrated) was obtained.[6]

As earlier, several aspects of the electrolysis reaction deserve further comment. First, the oxidation of 3 was strongly influenced by the choice of electrolyte. When tetraethylammonium tosylate was used, the yield of the methoxylated product dropped dramatically. The mass balance of the reaction remained high, but the conversion of starting material to the methoxylated product was greatly reduced. Second, the oxidation

reaction was compatible with the use of water as a cosolvent and led to the hydroxylated product in a fashion that was directly analagous to the formation of methoxylated product in oxidations using methanol. Finally, the direct formation of the bicyclic product **5** in the electrolysis cell has not been successful to date.

In conclusion, the anodic oxidation of proline based dipeptides can rapidly lead to multigram quantities of bicyclic lactam peptide mimetics. In addition, the oxidation reactions reported serve to help define the nature of the substituents that are compatible with anodic amide oxidations. For *N*-acylproline derivatives, the line separating when an oxidation will work and when it will not for a substituent on the carbon alpha to the amide carbonyl now lies in between a *t*-Boc protected nitrogen and an oxygen. Efforts to generalize these oxidations, to utilize the oxidation-cyclization sequence to construct carbocyclic lactam derivatives, and to examine the effect of bicyclic lactam groups on the secondary structure of peptides are currently underway.

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5. The syntheses of substrates **1a**, **1b**, and **3** were accomplished using standard peptide chemistry.
6. The bridgehead stereochemistry was assigned using a combination of NOE data and molecular modeling. The details of this anaylsis will be published as part of the full account of this work.
7. Unpublished results with Mr. Scott L. Rothfus.

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