Synthesis of Proline Derivatives as Peptide Building Block Designed for Selective Electrochemical Modification

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In recent years, there has been great interest in the synthesis of unnatural and/or conformationally constrained amino acids, peptidomimetics, and small peptide fragments emcompassing these residues. Of all the common alpha amino acids, proline plays important role in peptide secondary structure formation. And many kinds of peptides can be readily prepared by coupling Fmoc amino acids in sequence using combinatorial techniques. Therefore, modifying proline residue in peptide should be reasonable method for preparing conformationally constrained peptide.

Electrochemical means are the most useful methods for the modification of proline derivatives. It has been revealed that an amide or carbamate is oxidized to generate an iminium cation and react with nucleophiles. It is, however, difficult to oxidize the proline residue without affecting other residues in peptide because the oxidation potentials of amino acids including aromatic ring are usually lower than that of proline. In this regard, it is known that introduction of hetero atoms on the carbon alpha to nitrogen lowers oxidation potential than that of other amino acids like phenylalanine. This gave us incentive to develop Fmoc-proline derivatives containing hetero atom on the carbon alpha to nitrogen.

This paper describes synthesis and application of Fmoc-proline derivatives as peptide building blocks that can be easily modified by electrochemical method.

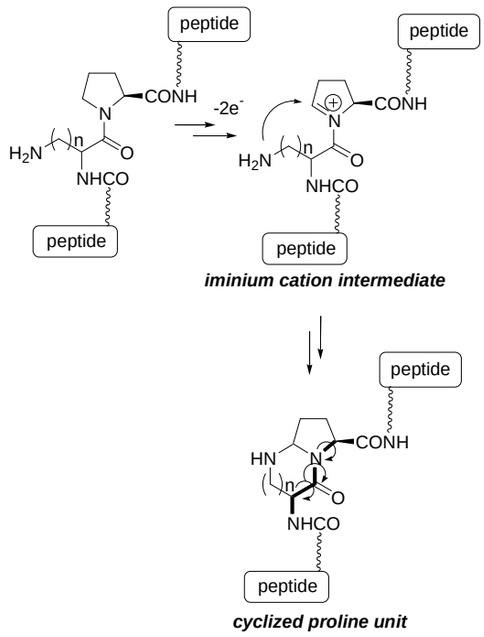

Fig. 1 Synthetic strategy for conformation-constrained peptides

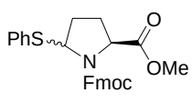

Fig. 2 Proline derivatives containing hetero atoms on carbon alpha to nitrogen as peptide building blocks