# Electrolytic Cyclization of Dipeptides Involving Proline-Moiety for Construction of Conformation-Constrained Peptidomimetics

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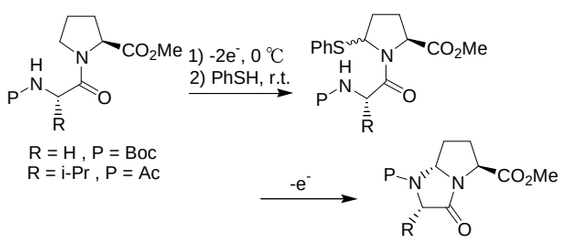
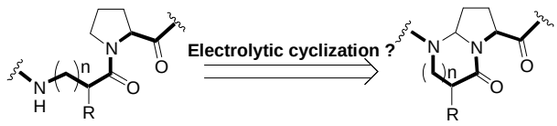
There has been considerable interest in the synthesis of unnatural and/or conformationally constrained amino acids, peptidomimetics, and small peptide fragments encompassing these residues. Of all common α-amino acids, proline plays a particular role in peptide secondary structure formation. Furthermore, the importance of peptidomimetics involved proline in the design of new catalysts or in the chemical synthesis of pharmacologically or biologically interesting molecules is well recognized. From a synthetic standpoint, electrochemical means are among the most useful methods for the modification of iminium cation intermediates of proline derivatives. Moeller and co-workers developed new routes to construct functionalized, conformation-constrained peptido-mimetics[1] by introducing sily-groups as electron-auxiliaries to lower the oxidation potentials.[2] Yoshida, Suga and co-workers reported a “cation-pool” method that can electrochemically generate and stabilize iminium caitons of carbamates to introduce functional groups on the carbon α to nitrogen.[3]

Recently we found that N-acyliminium cations of proline dierivatives can be generated to give functionalized proline derivatives using undivided cell in a lithium perchlorate / nitromethane electrolyte solution.[4] In this reaction media, iminium cation of proline-based peptides can be generated and accumulated in the electrolyte solution. This gave us the incentive to develop an electrolytic method to accomplish intramolecular cyclization of proline-based pepeides to construct conformation-constrained peptidemimetics involving proline moiety.

Initially, it was performed an introduction of a phenylsulfanyl group in the α-position of the proline moiety as a electrolytic substrate of aimed intramolecular cyclization with its lowered oxidation potential for the generation of iminium cation intermediates of proline derivatives.[2] Finally, anodic oxidation of the sulfides gave cyclized dipeptides in good yield in lithium perchlorate / nitromethane using undivided cell at room temperature. On the other hand, the desired reaction was not successful in other usual electrolytic conditions.




In conclusion, a practical new pathway to the synthesis of conformationally constrained dipeptides has been developed. The intramolecular amide or carbamate nitrogen atom attacked to the prolyl iminium cation under mild, electrooxidative conditions. In the sequential electrolytic reaction system, the reaction medium should work to stabilize iminium cation to assist the generation and accumulation of the intermediates *via* direct electrooxidation of proline moiety or anodic C-S bond cleavage.

**References**

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