

Anodic Modification of Proline Derivatives

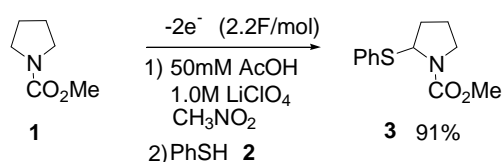
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In recent years, there has been considerable interest in the synthesis of unnatural and/or conformationally constrained amino acids, peptidomimetics, and small peptide fragments encompassing these residues.¹⁾ Of all the common α -amino acids, proline plays a particular role in peptide secondary structure formation. From a synthetic standpoint, the electrochemical means is one of the most useful methods for the modification of proline derivatives. It is revealed that an amide or carbamate is oxidized to generate corresponding iminium cation and trapping of the iminium cation with alkoxy groups leads to product that has been functionalized on the carbon alpha to nitrogen. It is however difficult to oxidize the starting material without affecting some nucleophiles because the oxidation potentials of nucleophiles are usually low. In this regard, Yoshida and coworkers have shown some new method for the introduction easily oxidizable nucleophiles.²⁾ On the other hand, we recently accomplished anodic generation of benzyl cations initiated by benzylic carbon-sulfur bond fission and these intermediates were successfully trapped by some nucleophiles to give the desired compounds³⁾ by using nitromethane-lithium perchlorate solution.⁴⁾ The reaction media was found to promote the oxidative fission of carbon-sulfur (C-S) bonds. It is therefore envisioned that by using this solvent system, C-S bond fission would efficiently occur to generate the iminium cations of proline derivatives followed by new carbon-carbon (C-C) bond formation with carbon nucleophiles in a synthetically useful way. We herein report a new method for the effective introduction of sulfur groups on the carbon alpha to nitrogen and electro-oxidative C-S bond fission to generate iminium cations of the pyrrolidine skeletons.

Initially, an introduction of phenylsulfanyl group in α -position of *N*-methoxycarbonylpyrrolidine **1** was investigated (Scheme 1). Because of higher oxidation potential of **1** (E_{ox} 1.9 V vs. Ag/AgCl) compared with that

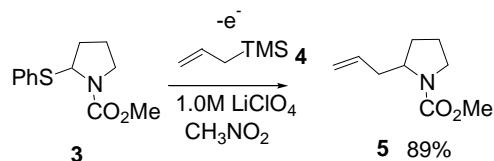
Scheme 1



of thiols, electrooxidation of **1** in the presence of thiophenols gave no desired product. On the other hand, electrolysis of compound **1** conducted under constant current conditions (2 mA, 2.2F/mol) at 0 °C followed by the addition of thiophenol **2** successfully gave the desired product **3** in 91%. This result suggested the intermediate generated by anodic oxidation of compound **1** was highly stabilized in the reaction media with the following C-S bond formation. Oxidation potential of **3** was lowered to E_{ox} 1.2 V vs. Ag/AgCl, which enabled the oxidative C-S bond cleavage even in the presence of electron-rich

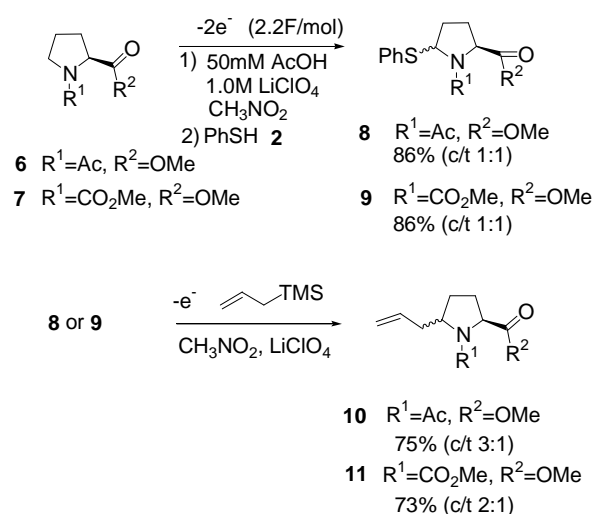
olefins. As shown in scheme 2, anodic oxidation of compound **3** allowed the preparation of the alkylated products. Oxidative C-C bond formation of **3** with allyltrimethylsilane **4** in lithium perchlorate / nitromethane resulted in 89% yield of allylated product **5**.

Scheme 2



On the other hand, introduction of sulfur atom on α' -position to nitrogen of proline derivatives and the C-C bond formation were carried out in the same condition (Scheme 3). Although the electrochemical cleavage of C-S bond adjacent to amide nitrogen is generally difficult in

Scheme 3



mild conditions, anodic oxidation of amide **6** successfully led to the formation of corresponding proline derivatives with phenyl sulfanyl group and to afford the allylated products in high yield, respectively. Furthermore, it was revealed that no significant racemization of the proline took place during the electrolytic substitution reaction.

In conclusion, a practical new pathway to the synthesis of substituted proline derivatives has been developed.

References

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