ORGANIC LETTERS

2002
Vol. 4, No. 21
3735−3737

Anodic Modification of Proline Derivatives Using a Lithium Perchlorate/ Nitromethane Electrolyte Solution

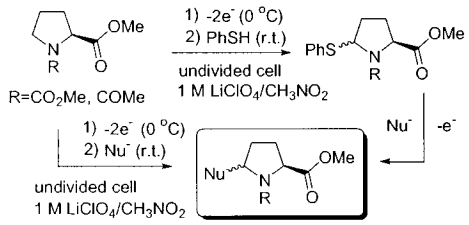
Shokaku Kim, Kanako Hayashi, Yoshikazu Kitano, Masahiro Tada, and Kazuhiro Chiba*

Laboratory of Bio-organic Chemistry, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Fuchu, Tokyo 183-8509, Japan

chiba@cc.tuat.ac.jp

Received August 12, 2002

ABSTRACT



***N*-Acyliminium cation of prolines was efficiently generated to accumulate in an undivided cell at 0 °C by an anodic oxidation of *N*-acylprolines or α′-phenylsulfanylated *N*-acylproline derivatives in a lithium perchlorate/nitromethane solution. The iminium cation intermediates gave modified prolines by a reaction with nucleophiles under mild conditions.**

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.[2] Furthermore, the importance of substituted prolines in the design of new catalysts or in the chemical synthesis of pharmacologically or biologically interesting molecules is well recognized.[3] From a synthetic standpoint, electrochemical means are among the most useful methods for the modification of proline derivatives.[4] It has been revealed that an amide or carbamate is oxidized to generate an iminium cation and that trapping of the iminium cation with the methoxy group leads to a product that has been functionalized on the carbon α to nitrogen.

It is, however, difficult to oxidize the starting material without affecting some nucleophiles because the oxidation potentials of nucleophiles are usually lower than those of the electrolytic substrates. In this regard, Yoshida and co-workers have shown that the introduction of heteroatoms on the carbon α to nitrogen leads to the generation of an iminium cation by anodic oxidation of the heteroatoms (electron auxiliary) followed by a reaction with carbon nucleophiles having lower oxidation potential than that of the amide or carbamate groups.[5] Moeller and co-workers developed new routes to construct functionalized and/or

(1) (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (b) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (c) Long, R. D.; Moeller, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 12394. (d) Li, W.; Moeller, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 10106.

(2) Takeuchi, Y.; Marshall, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 5363.

(3) (a) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122. (b) Hodgson, M.; Parker, D. *J. Organomet. Chem.* **1987**, *325*, C27−C30. (c) Tani, K.; Suwa, K.; Tanigawa, E.; Ise, T.; Yamagata, T.; Tatsuno, Y.; Otsuka, S. *J. Organomet. Chem.* **1989**, *370*, 203. (d) Brunner, H.; Graf, E.; Leitner, W.; Wutz, K. *Synthesis* **1989**, 743. (e) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954. (f) For a review, see: Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

(4) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (b) Shono, T. *Tetrahedron* **1984**, *40*, 811. (c) Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer-Verlag: Berlin, 1984.

(5) (a) Yoshida, J.; Itoh, M.; Isoe, S. *J. Chem. Soc., Chem. Commun.* **1993**, 549. (b) Yoshida, J.; Morita, Y.; Ishichi, Y.; Isoe, S. *Tetrahedron Lett.* **1994**, *35*, 5247. (c) Sugawara, M.; Mori, K.; Yoshida, J. *Electrochim. Acta* **1997**, *42*, 1995.

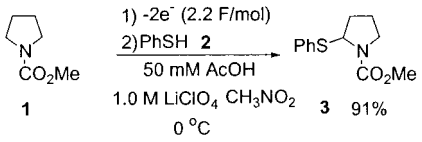
10.1021/ol026713z CCC: $22.00
Published on Web 09/17/2002

conformation-constrained peptidomimetics by introducing silyl groups as electron auxiliaries to lower the oxidation potential that enabled anodic substitution of the silyl group with a methoxy group that worked as a trigger for following Lewis-acid-catalyzed cyclization reactions via *N*-acyliminium cation for the construction of peptidomimetics.[6] On the other hand, Yoshida, Suga, and co-workers reported a "cation-pool" method that can electrochemically generate and stabilize iminium cations of carbamates in divided electrolytic cells at low temperatures (lower than −47 °C) followed by a reaction with nucleophiles in the absence of an electrolytic current.[7]

In anodic oxidation systems, a divided cell is often introduced to avoid cathodic re-reduction of electrogenerated products or their undesired reactions with cathodic products, but the application of higher electrolytic potentials is generally required, and there is an accumulation of electrogenerated acid accompanied by the generation of the products. This gave us the incentive to develop an extended, simple electrochemical method that would enable anodic generation and accumulation of unstable *N*-acyliminium cations of prolines in an undivided system for their diverse functionalization. In this case, an electrolytic medium would play an important role to avoid the re-reduction and decomposition of the reactive intermediates. Furthermore, if we can also introduce an electron auxiliary that converts to the corresponding *N*-acyliminium cation under neutral, lower oxidation potential conditions, it should further open the door for the introduction of varied functional groups in the proline residues of peptides. We herein report a new method for the introduction of nucleophiles on the carbon α′ to nitrogen of proline derivatives including phenylsulfanylated ones as a precursor of the iminium cations.

Initially, an introduction of the phenylsulfanyl group in the α-position of MOC-pyrrolidine **1** was investigated (Scheme 1). Electrolysis of MOC-pyrrolidine **1** was performed in a 1 M lithium perchlorate/nitromethane electrolyte solution[8] in the presence of 50 mM AcOH using an undivided cell, a glassy carbon anode and a platinum cathode. Because of the higher oxidation potential of **1** (E_{ox} 1.9 V vs Ag/AgCl) compared with that of thiols, electrooxidation of **1** in the presence of thiophenols did not give the desired product.

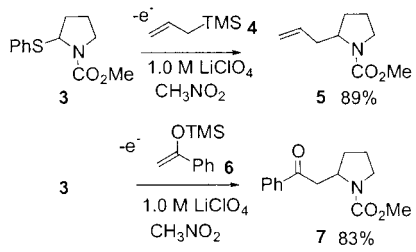
Scheme 1



On the other hand, electrolysis of compound **1** conducted under constant current conditions (2 mA, 2.2 F/mol) at 0 °C followed by the addition of thiophenol **2** (3 equiv) successfully gave the desired product **3** in 91%. On the other hand, the product was scarcely obtained under other typical electrolytic conditions, such as tetralkylammonium tosylate in acetonitrile or in nitromethane. Anodic generation of iminium cation of **1** was confirmed[9] by ^{1}H NMR (δ_H 9.14, C*H*=N$^+$) and ^{13}C NMR (δc 195.0, *C*=N$^+$) spectra in $CDCl_3$/CH_3NO_2 (1:1) in the presence of lithium perchlorate (0.5 M) and acetic acid at 25 °C (electrolyzed solution was diluted with $CDCl_3$ just after electrolysis, TMS as an internal standard at 0 ppm).

This result suggested that the intermediate generated by anodic oxidation of compound **1** was highly stabilized in the reaction media, which also assisted the progress of the following C−S bond-forming reaction. The oxidation potential of **3** was lowered to E_{ox} 1.2 V vs Ag/AgCl, which enabled us to try the oxidative C−S bond cleavage in the presence of electron-rich olefins. As described in Scheme 2, the anodic oxidation of compound **3** allowed the preparation of the alkylated products. Oxidative C−C bond formation of **3** with allyltrimethylsilane **4** (1.2 equiv) in lithium perchlorate/nitromethane resulted in an 89% yield of allylated product **5**; in addition, treatment with 1-phenyl-1-(trimethylsilyloxy)ethylene **6** provided the expected product **7** in an 83% yield.

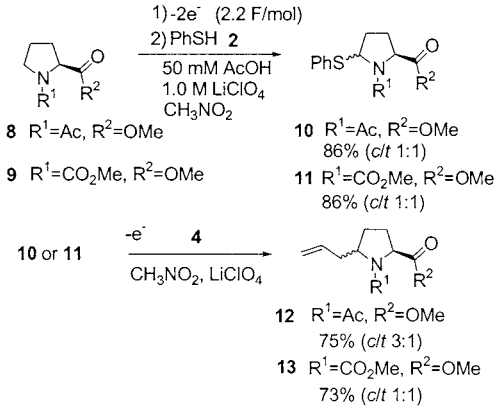
Scheme 2



The introduction reaction of the sulfur atom on the α′-position to the nitrogen of proline derivatives and the C−C bond formation reaction were carried out according to the same conditions (Scheme 3). Anodic oxidation of amide **8** or carbamate **9** led to the formation of the corresponding proline derivatives with the phenylsulfanyl group and afforded the allylated products in high yield. Although it is generally difficult to generate cationic intermediates of *N*-acylprolines followed by C−C bond formation triggered by anodic C−S bond cleavage, the desired reaction successfully occurred in this media system. It was presumed that the lowered oxidation potential based on the introduction of thiophenol to iminium cations and the electrolytic reaction media with moderate Lewis acidity led to the aimed oxidative C−S bond fission followed by a nucleophilic attack of the carbon nucleophile under a mild condition.

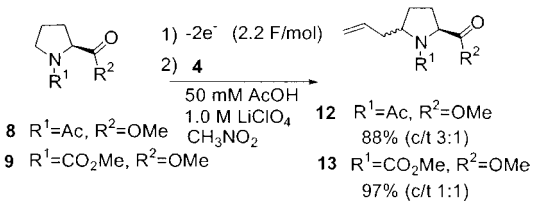
(6) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547.
(7) (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30.
(8) (a) Chiba, K.; Tada, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2485. (b) Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. *J. Am. Chem. Soc.* **2001**, *123*, 11314.
(9) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121 and ref 7a.

Scheme 3



Furthermore, the application of a direct C−C bond formation of iminium cations with **4** was also investigated. After the completion of anodic oxidation of **8** or **9** in lithium perchlorate/nitromethane in the presence of acetic acid (2.2 F/mol) at 0 °C followed by the addition of allyltrimethylsilane at ambient temperature, the desired products **12** or **13** were produced in good yield, respectively (Scheme 4).

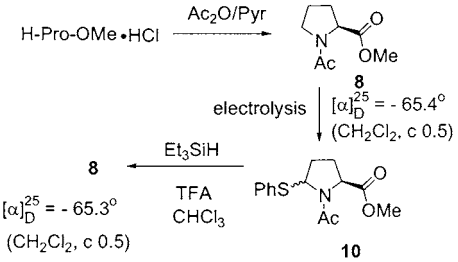
Scheme 4



To elucidate optical purity through the electro-oxidative conversion of proline derivatives, a comparison of two *N*-acetyl-L-proline methyl esters was carried out (Scheme 5).[10] Compound **8** was prepared by treating L-proline methyl ester with acetic anhydride and pyridine, and it was oxidized in lithium perchlorate/nitromethane to give phenylsulfanyl-*N*-acetylproline methyl ester **10** by the addition of thiophenol. Subsequent reduction of **10** with Et_3SiH and TFA in $CHCl_3$ yielded compound **8**. *N*-Acetyl-L-proline methyl ester ob-

(10) Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434.

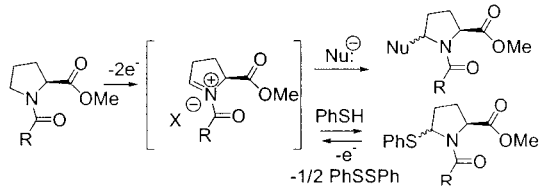
Scheme 5



tained at the first step has a $[\alpha]^{25}_D$ value of −65.4°, while the one derived from phenylsulfanyl-*N*-acetylproline methyl ester **10** has a value of −65.3°. This result showed that no significant racemization occurred in the anodic introduction of thiophenol. Furthermore, it is thought that this electrolytic system has the potential for use in a wide variety of peptides having a pyrrolidine skeleton in a facile way.

In conclusion, a practical new pathway to the synthesis of substituted proline derivatives has been developed. It was found that amides and carbamates of pyrrolidine derivatives were efficiently generated and trapped by nucleophiles in a lithium perchlorate/nitromethane solution (Scheme 6). The

Scheme 6. Proposed Reaction Mechanism



introduction of thiophenol as a nucleophile lowered the oxidation potential of proline derivatives, leading to the oxidative C−S bond fission followed by the intermolecular C−C bond-forming reaction with a nucleophilic attack of carbon nucleophiles under mild conditions.

Supporting Information Available: Experimental procedures, spectroscopic data for compounds **3**, **10**, and **11**, and ^{1}H NMR spectra of compounds **3**, **7**, and **10**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026713Z