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Anodic Substitution Reaction of Proline Derivatives Using the 2,4,6-Trimethoxyphenyl Leaving Group

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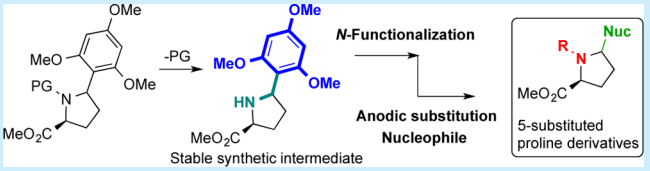
Supporting Information

ABSTRACT: An efficient method for modifying a proline moiety through anodic carbon−carbon bond cleavage is developed. Use of the 2,4,6-trimethoxyphenyl (TMP) moiety as a leaving group at the 5-position allows the incorporation of various functional groups for modification in both the *N*- and *C*-terminal direction due to the stability of the N1−C5−C linkage. This approach also enables anodic substitution reactions using reactants with lower oxidation potential compared to *N*-carbonyl bonds.



Electrochemical synthetic methods provide versatile and straightforward strategies to access valuable organic molecules by triggering anodic and/or cathodic electron transfer. Of these, anodic oxidation of N−C bonds in pyrrolidine and proline moieties allows the efficient functionalization of the α-position including the postsynthetic modification using Lewis/Brønsted acid. Yoshida and Suga's group have developed methodologies for this modification, such as the cation pool[1] and electroauxiliaries[2] to construct a variety of *N*-containing heterocycles. Moeller and co-worker have developed the anodic site-elective reaction[3] to the synthesis of proline and other peptide derivatives. We have also shown anodic modification of proline moieties using a lithium perchlorate/nitromethane (LPC/NM) system.[4] This reaction system enables the generation and accumulation of reactive intermediates derived from *N*-protected proline derivatives under mild conditions, resulting in the incorporation of various nucleophiles such as thiols and nucleobases.

Although the anodic *N*-α C−H activation of *N*-carbonyl bonds is attractive for the synthesis of artificial proline analogues, there are significant limitations for further diversification in both the *N*-terminal and *C*-terminal directions. These limitations arise from the relatively high oxidation potential of *N*-carbonyl bonds, and the structural vulnerability associated with leaving groups at the 5-position of proline. The electrochemical method cannot often be directly applied to proline derivatives including the competitive oxidation potential peptide side chain, protecting group and other functional units as compared with that of *N*-carbonyl bonds. Furthermore, replacement reactions in the *N*-terminal direction involving the deprotection of a *N*-protected proline possessing a 5-methoxy, trifluoroethoxy, or acetoxy group generate unstable intermediates containing the hemiaminal ether (HN1-C5-OR) bond; these intermediates decompose before they can engage in the subsequent reaction. Indeed, when using 5-phenylthio-Boc-Pro-OMe, the HN1−C5-S linkage generated by Boc deprotection was not tolerated in the conditions used, and the desired reaction did not proceed.

To address these problems, we explored viable electrochemical strategies for diversifying 5-substituted proline derivatives. Specifically, considering aspects of the oxidation potential and the lack of the stability, we sought to introduce a phenyl group as the leaving moiety: this intermediate should be stable as it avoids the *germinal* diheterolytic linkage. As shown in Figure 1, we assumed that anodic oxidation of 5-trimethoxyphenyl proline would transiently form the radical cation, thus triggering C−C bond cleavage[5] to deliver the *N*-acyl iminium cation and the phenyl radical. The resulting cation

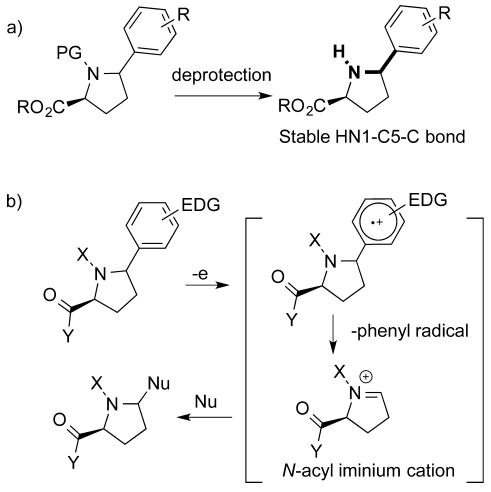


Figure 1. Schematic view of proline derivatization based on a stable and cleavable C−C linkage. PG: protective group. EDG: electro-donating group.

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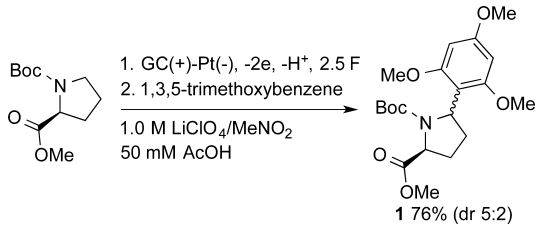
would couple with nucleophiles to provide 5-substituted proline derivatives. Furthermore, incorporation of electron-donating substituents into the phenyl group would lower the oxidation potential, thus enabling the use of various nucleophiles.

Herein, we describe anodic modification reactions of proline derivatives using the 2,4,6-trimethoxyphenyl (TMP) moiety as a leaving group. TMP at the 5-position of proline is stable during deprotection of the *N*- and *C*- termini and the subsequent modification reaction. Furthermore, the anodic substitution reaction proceeded via carbon−carbon bond cleavage at a lower oxidation potential due to the electron-donating property of the trimethoxy substituents.

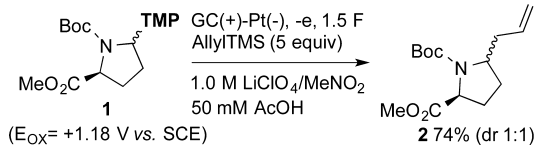
Initially, we synthesized TMP substituted proline derivative **1**, as previously reported (Scheme 1). The addition of 1,3,5-trimethoxybenzene as the nucleophile gave the desired product in 76% yield. The compound **1** was obtained as a mixture of syn- and anti-isomers and its configuration was not determined. The oxidation potential of compound **1** was measured by cyclic voltammetry; the oxidation peak was observed at +1.18 V vs Ag/AgCl, which is significantly lower than that of *N*-Boc-Pro-OMe (E_{ox}= +1.86 V vs Ag/AgCl). This result suggested that the TMP group lowered the oxidation potential of the proline derivative, and thus might support selective oxidation in the presence of nucleophiles. Cleavage of the TMP moiety by anodic oxidation was tested by conducting electrolysis of **1** in the presence of allyltrimethylsilane (5 equiv) under LPC/NM conditions (Scheme 2).

Scheme 1. Introduction of a TMP Leaving Group[a]



[a]TMP = 2,4,6-trimethoxyphenyl, AllylTMS = allyltrimethylsilane.

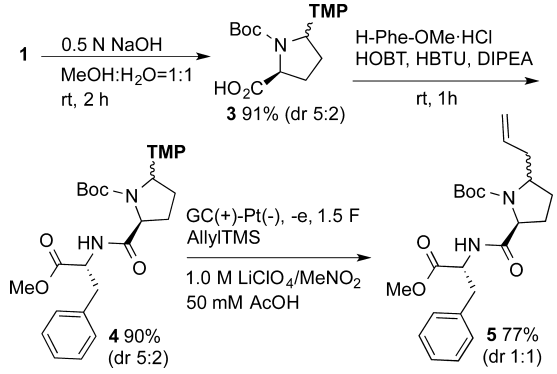
Scheme 2. Anodic Substitution Reaction via C−C Bond Cleavage



The reaction was carried out in 1.0 M $LiClO_4$/$MeNO_2$-50 mM AcOH using a GC anode/Pt cathode undivided cell under constant current conditions (1.0 mA/cm^2) at room temperature. The target reaction occurred and provided the allylated compound **2** in 74% yield and compound **1** was consumed when 1.5 F of electricity was passed. Moderate amounts of allylated trimethoxybenzene (ca. 14% yield) and oligomers (dimer, tetramer) of trimethoxybenzene were also produced. These results indicate that 5-TMP proline would be selectively oxidized to form the phenyl radical cation, and that this cation induces C−C bond cleavage to afford the *N*-acyl iminium cation and the phenyl radical species. Subsequently, the coupling reaction proceeded to give the desired 5-substituted proline. On the other hand, the phenyl radical would be further oxidized to generate the cation intermediate, resulting in the production of the allylated benzene moiety. In addition, the formation of this product might involve an addition of the aryl radical to the double bond of the allylsilane followed by the second oxidation, formation of a cation beta to the silane, and then elimination of the trimethylsilyl group. And the tetramer would be formed via the oxidative coupling of the dimer, because the oxidation potential of the dimer (+1.15 V) was nearly equal to that of substrate **1**.

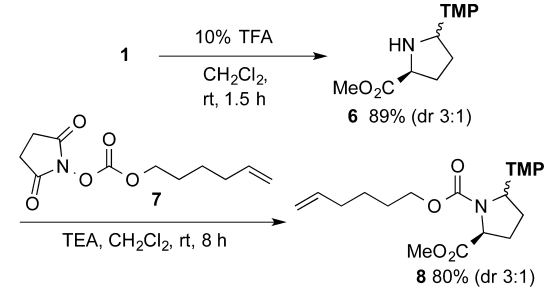
A model peptide containing a proline with a 5-substituent which allows a lower oxidation potential than the *N*-carbonyl bond were prepared to evaluate the viability of this approach. Specifically, proline derivative **4** was prepared from compound **1** using classical peptide chemistry (Scheme 3). As expected, the TMP group is stable toward basic deprotection and incorporation processes in the *C*-terminal direction. Using similar electrochemical conditions, allylated compound **5** was obtained in high yield. The anodic substitution reaction occurred effectively even when the reactant was derivatized with an oxidation potential lowering moiety.

Scheme 3. Chemical Modification of Proline Derivative 1 at the *C*-Terminal and 5-Position with the TMP Leaving Group



Finally, functionalization for the *N*-terminal direction and subsequent anodic substitution reaction were examined. As described in Scheme 4, Boc deprotection of **1** with TFA smoothly proceeded to give the corresponding synthetic intermediate **6**, with no decomposition of the TMP leaving group or the generated C−C bond under the acidic conditions. The olefin-containing lipophilic activated ester **7** was used as the functional group because proline residues are extensively used in linkers for constructing bioconjugated molecules such

Scheme 4. Chemical Modification of Proline Derivative 1 at the *N*-Terminal



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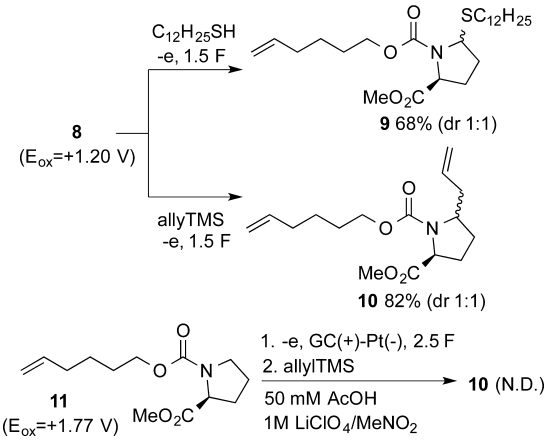
as lipophilic nucleotides and peptides.[6] The anodic substitution reaction of compound **8** using 1-dodecanethiol or allylTMS as the nucleophile afforded the desired product **9** or **10**, in 68% and 82% yield, respectively (Scheme 5). The anodic oxidation

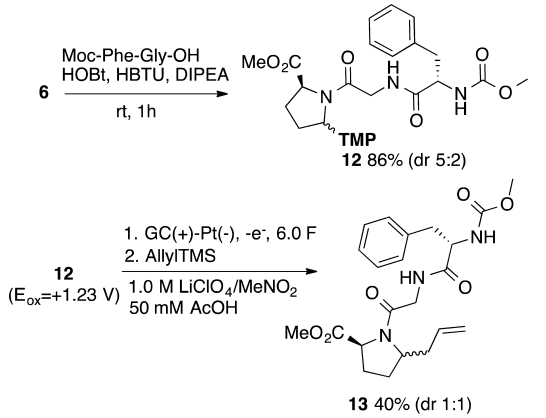
Scheme 5. Anodic Oxidation Reactions of Compounds 8 and 11



of compound **11** did not give product **10** due to the higher oxidation potential of carbamate (E_{ox} = +1.86 V) compared to the hexenyl moiety (E_{ox} = +1.77 V). The allylated product could be constructed by another route, i.e., *N*-functionalization using an allylated synthetic intermediate containing a stable C−C bond. In contrast, the electrochemical thiol-substitution reaction of **8** is extremely effective, considering the oxidation potential and the instability of the N−C−S linkage. This approach might allow effective assembly of proline-based lipid-bilayer motifs using various alkyl thiols.[7]

To apply the method for the functionalization of peptide derivatives containing the 5-TMP proline residue at *C*-terminal, tripeptide **12** was prepared as shown in Scheme 6. The

Scheme 6. Anodic Modification of Tripeptide 12



oxidation potential of the tripeptide **12** (E_{ox} = +1.23 V) was nearly equal to carbamate **8** (E_{ox} = +1.20 V). However, under the similar condition, the target reaction did not efficiently proceed to afford the corresponding product **13** in a low (10%) yield along with 70% recovered starting material. In this reaction, allylated product on the TMP aromatic ring of substrate **12** was also observed (19%). To avoid the competition between the allylation on the TMP aromatic ring and the C−C bond cleavage, we conducted anodic oxidation of compound **12** in the absence of allylTMS, which was added into the reaction mixture after the completion of oxidation. When 3.0 F/mol, 6.0 F/mol electricity were passed, the desired product was obtained in 22%, 40% yield, respectively. It was found with increasing electricity the approach improved the yield albeit with low current efficiency. Although further examination is needed, the present results reveal the usefulness of this methodology for the modification of proline peptide derivatives.

In conclusion, we have demonstrated that 1,3,5-trimethoxybenzene can be used as a 5-substituted leaving group for proline moieties under LPC/NM conditions. This leaving group is tolerant of deprotection conditions for *N*- and *C*-terminal modification of 5-substituted proline derivatives. TMP can also be activated by anodic oxidation to form the *N*-acyl iminium cation via C−C bond cleavage to effectively provide the corresponding proline analogue.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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