Anodic Carbon-Carbon Bond Formation in Lithium Perchlorate/Nitromethane Electrolyte Solution

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Anodic processes in the lithium perchlorate/nitromethane (LPC/NM) electrolyte system provide a wide variety of carbon-carbon bond formation. The electrolyte solution exhibits markedly accelerated properties as a Lewis acid catalyst that even enable intermolecular reactions between unactivated alkenes and anodically generated intermediates to form unique products. The properties of the electrolyte solution and application to electrochemical reactions are reviewed.

Key Words : Lithium Perchlorate, Nitromethane, Organic Synthesis, Carbon-carbon Bond Formation

1 Introduction

It has recently been shown that electrochemical reactions provide an efficient means of carbon-carbon bond formation.1) Anodic electrochemistry is used to generate extremely useful carbocation intermediates for the construction of a wide variety of carbon skeletons under mild conditions.2) In the course of our research on the effect of electrolyte solution media, we have found that a simple undivided lithium perchlorate/nitromethane (LPC/NM) electrolytic system provides acceleration and intermediate-stabilizing properties to achieve a wide variety of carbon-carbon bond formation. The electrochemical method might allow for the selective polarity inversion of electron-rich substrates and open the door for the construction of carbon frameworks by new combinations of carbon nucleophiles, even under neutral conditions. Recent efforts towards such reactions based on this unique electrochemical medium are introduced.

2 Function of LPC/NM Electrolyte Solution

Previously, we reported that an electrolyte solution composed of LPC/NM exhibits marked acceleration of the Diels-Alder reaction (Fig. 1).3) Among a wide variety of usual organic solvents, the combination of NM and LPC has shown remarkable acceleration of the Diels-Alder reaction between 4-benzoquinone and α-terpinene. The function of the solution has been investigated and applied to several organic reactions.4) The electrolyte medium was then applied to the Diels-Alder reaction of electrogernated quinones in the presence of dienes (Fig. 2). Quinones are widely employed as dienophiles in the Diels-Alder reaction; however, unstable quinones possessing electron- withdrawing groups are difficult to isolate and readily decompose under the standard conditions of Lewis acid catalysis. In the presence of a small amount of acetic acid for the stabilization of electrogernated quinones, the anodic oxidation of hydroquinones followed by in-situ Diels-Alder reaction with dienes successfully afforded the corresponding cycloadduct in good yield.

3 Intermolecular C-C Bond Formation via Electrooxidative Desulfurization

The anodic oxidation of heteroatom compounds often leads to the formation of a carbocation adjacent to the heteroatom, and the cation reacts with the heteroatom or with an activated carbon nucleophile. For example, anodic oxidation of α-heteroatom-substituted organotin compounds produced α-heteroatom-substituted carbocations via cleavage of the C-Sn bond.5) It has been further revealed that α-heteroatoms assist in lowering oxidation potentials and in cleaving the C-Sn bonds.6) Organosulfur compounds are attractive in that they can also secure anodic intermolecular C-C bond formation initiated by oxidative C-S bond fission.7) In the LPC/NM electrolyte solution, direct anodic oxidation of 2-(phenylthiomethyl)phenols yielded corresponding α-quinomethanes that were immediately trapped by unactivated alkenes (Fig. 3). In this case, the LPC/NM solu-
Fig. 2 Anodic Diels-Alder reactions in the LPC/NM electrolyte solution.

Fig. 3 Chromatic synthesis by the anodic intermolecular cycloaddition between electrogenerated o-quinomethanes and unactivated alkenes in the LPC/NM electrolyte solution.

Fig. 4 Structures of naturally occurring euglobals and robustadials and proposed biosynthesis pathway.

tion assisted fission of the C-S bond triggered by the electrooxidation of sulfides and also accelerated nucleophilic attack, even by unactivated alkenes. The intermolecular cycloaddition between o-quinomethane generated in-situ and unactivated alkenes provided the incentive to attempt the electrochemical synthesis of naturally occurring euglobal skeletons. Euglobals and robustadials, strong inhibitors of Epstein-Barr virus activation, have been isolated from the juvenile leaves of Eucalyptus grandis (Myrtaceae) (Fig. 4). It has been presumed that these naturally occurring compounds are biologically synthesized via the intermolecular hetero-Diels Alder reaction between corresponding o-quinomethanes and olefin moieties of terpenes (unactivated alkenes). The anodic synthesis of euglobal skeletons was attempted first. Electrooxidative desulfurization followed by a hetero
Diels-Alder reaction yielded various chroman frameworks, including naturally occurring euglobal skeletons (Fig. 5) and with a NM solution system, various naturally occurring euglobals were successfully synthesized.\textsuperscript{10,11}

\textit{o}-Quinodimethanes also play a very important role in the organic synthesis of polycyclic compounds. To date, various methods have been reported for the generation of \textit{o}-quinodimethane intermediates, including metal,\textsuperscript{12} anion,\textsuperscript{14} or acid-induced,\textsuperscript{15} thermal, or photochemical elimination reactions\textsuperscript{16} of the corresponding precursors. On the other hand, it was also anticipated that the electrochemical method has the potential to play an important role in the generation of unstable \textit{o}-quinodimethanes followed by cycloaddition with dienophiles. This method is further expected to proceed under quantitative control of the chemical reaction by regulating the applied charge. Previously, cathodic generation and Diels-Alder reaction of \textit{o}-quinodimethanes has been accomplished using 1,2-bis-(bromomethyl)benzene.\textsuperscript{17}

It was presumed that the polar solvent system promotes the oxidative fission of C-S bonds and provides an appropriate environment for the generation of dipolar compounds such as \textit{o}-quinomethane. It is therefore envisioned that \textit{o}-quinodimethanes could be obtained by the electrochemical induction of C-S bond fission with the assistance of an effective polar ionic solvent system. Under the regulation of charge transfer, the generation and Diels-Alder reaction of \textit{o}-quinodimethane was successfully controlled to afford the desired cycloadducts in excellent yields, including those possessing natural aryltetralin lignan skeletons (Fig. 6).

As a precursor for the anodic generation of \textit{o}-quinodimethane, we focused on the synthesis of \textit{[2-(2,2-dibutyl-2-stanna-hexyl)phenyl]methyl-thio}benzene, which might generate corresponding \textit{o}-quinomethanes via electrooxidative 1,4-elimination. Electrooxidation of these sulfides was performed in the presence of dimethyl fumarate in both 1.0 mol dm\textsuperscript{-3} LPC/NM and 0.1 mol dm\textsuperscript{-3} ArOH systems, using glassy carbon as an anode and Pt as a cathode. It was found that only the LPC/NM system assisted the desired anodic generation of \textit{o}-quinomethanes followed by intermolecular Diels-Alder reaction. The electrochemical reaction provided varied cycloadducts including lignin skeletons.

Although anodic initiation of C-S bond fission in dithioacetal has been applied for efficient partial fluorination reactions,\textsuperscript{18} oxidative C-S bond fission followed by a nucleophilic attack of the carbon nucleophiles is generally difficult under mild electrolytic conditions. We planned to introduce the dithioacetal moiety as a promising electrolytic substrate for the generation of carbocations. It was expected that the first C-S bond fission would take place with the assistance of another R-sulfur atom. Moreover, the electrochemical method was expected to

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Anodic synthesis of an euglobal skeleton via intermolecular cycloaddition between electrogenerated \textit{o}-quinomethane and \textit{p}-phellandrene.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Anodic synthesis polycyclic compounds via intermolecular cycloaddition between electrogenerated \textit{o}-quinodimethanes and alkenes.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Synthesis polycyclic compounds via intermolecular cycloaddition between alkenes and \textit{o}-quinomethanes generated by the electrochemical oxidation of benzylic dithioacetics.}
\end{figure}
have powerful potential to realize stepwise oxidation, leaving the sulfur atoms under precisely controlled oxidation potential to yield double substituted products. An attempt was made to achieve novel anodic intermolecular C-C bond formation using benzyl dithioacetal as an electrolytic substrate. This reaction has been accomplished, yielding various aromatic compounds by intermolecular reaction between electro-generated benzyl cations and nucleophilic alkenes, including unactivated aliphatic carbon nucleophiles (Fig. 7). On the other hand, selective anodic oxidation of corresponding dithioacetals gave monoallylated products in good yield (Fig. 8). It was further found that additional allylation of the isolated products by a second-step anodic oxidation at higher potential (1.1 V vs. Ag/AgCl) resulted in di-substituted products (Fig. 9). These results clearly showed that various combinations of nucleophiles could be introduced by the potential-regulated stepwise electrolysis of dithioacetals, provided that the aryl ring was electron-rich. Furthermore, even unactivated alkenes such as aliphatic olefins provided cyclized products with electro-generated intermediates. For example, electrooxidation of dithioacetals having o-hydroxy groups yielded corresponding chromans by cyclization with various unactivated alkenes. The reaction was accomplished via a formal hetero-Diels-Alder reaction between anodically generated corresponding o-quinomethanes and alkenes.

4 Application for Paired Electrosynthesis

Paired electrolysis is one of the most effective means of synthesis using the varied redox system (Fig. 10). However, it is difficult to construct the paired electrolytic system, because finely tuned and divided cells are generally required. As in the LPC/NM system, NM could be activated on a cathode by direct reduction or by cathodically generated bases. An attempt was made to apply the system for paired electrolysis to produce intermolecular reactions between anodically generated benzyl cations and cathodically activated NM. Electrolysis was performed in an undivided cell using a glassy carbon anode and a Pt plate cathode in a 3 mol dm$^{-3}$ LPC/NM electrolyte solution. Although electrolysis of sulfides in a divided cell scarcely produced the nitromethylated product, paired electrolysis in 3 mol dm$^{-3}$ LPC/NM at the first oxidation potential (1.10 V vs. Ag/AgCl, 1.2 F mol$^{-1}$) afforded the desired product in excellent yield (Fig. 11). No desired product was obtained in the presence of such standard electrolytes, such as tetra-$n$-butylammonium tosylate or tetra-$n$-butylammonium perchlorate. The results indicated that the desired nitroalkylation took place only in the presence of highly concentrated LPC in solution, and LPC was presumed to assist the oxidative fission of the C-S bond to form corresponding $p$-quinomethanes. Electrogenerated $p$-quinomethane, which is an equivalent of the corre-
5 Anodic Modification of Proline Derivatives

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 the common amino acids, proline plays a particular role in the secondary structure formation of peptides. 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. From a synthetic standpoint, electrochemical means are among 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 that trapping of the iminium cation with a methoxy group leads to a product that is functionalized on the carbon α to nitrogen. However, it is 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 coworkers 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 reaction with carbon nucleophiles having lower oxidation potential than those of the amide or carbamate groups. Moeller and co-workers developed new routes to construct functionalized and/or conformationally constrained peptidomimetics by introducing silyl groups as electron auxiliaries to lower the oxidation potential and enable anodic substitution of the silyl group with a methoxy group, which functioned as a trigger for the following Lewis-acid-catalyzed cyclization reactions via N-acyliminium cations for the construction of peptidomimetics. 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, followed by reaction with nucleophiles in the absence of an electrolytic current. In anodic oxidation systems, a divided cell is often introduced to avoid cathodic re-reduction of electrogenerated products or their undesired reaction with cathodic products; however, the application of higher electrolytic potentials is generally required and there is an accumulation of electrogenerated acid accompanied by the generation of products. This motivated the development of an extended, simple electrochemical method that would enable the anodic generation and accumulation of unstable N-acyliminium cations of prolines in an undivided system that would be available for diverse functionalization. In this case, an electrolytic medium would play an important role to avoid re-reduction and decomposition of the reactive intermediates. Furthermore, if an electron auxiliary that converts to the corresponding N-acyliminium cation under neutral, lower oxidation potential conditions could also be introduced, it would further open the door for the introduction of varied functional groups in the proline residues of the resultant peptides. Herein, we report a new method for the introduction of nucleophiles on the carbon α to nitrogen of proline derivatives, including phenylsulfanylated derivatives, as precursors of iminium cations.

Initially, introduction of the phenylsulfanyl group in the α-position of MOC-pyrrrolidine was investigated (Fig. 13). Electrolysis of MOC-pyrrrolidine was performed in a 1 mol dm$^{-3}$ LPC/NM electrolyte solution in the presence of 50 mmol dm$^{-3}$ AcOH using an undivided cell. Electrooxodization of MOC-pyrrrolidine in the presence of thiophenols did not yield the desired product, due to the higher oxidation potential of MOC-pyrrrolidine (E$_{pa}$ 1.9 V vs. Ag/AgCl) compared with that of the thiols. On the other hand, electrolysis of MOC-pyrrrolidine conducted under constant current conditions (2 mA, 22 F mol$^{-1}$) at 0°C, followed by the addition of thiophenol (3 equiv), successfully afforded the desired product in 91% yield.
Fig. 13  Step-wise modification of pyrroliidine and pralines by using anodic oxidation in LPC/NM electrolyte system.

Fig. 14  Electro catalytic intermolecular olefin cross-coupling by anodically induced formal [2+2] cycloaddition between enol ethers and alkenes in the LPC/NM electrolyte solution.

The product was scarcely obtained under other typical electrolytic conditions, such as tetraalkylammonium tosylate in acetonitrile or in NM. Anodic generation of the iminium cation was confirmed by \(^{1}H\) and \(^{13}C\) NMR spectra in CDCl\(_3\)/NM (1:1) in the presence of LPC (0.5 mol dm\(^{-3}\)) and acetic acid at 25°C. This result suggested that the intermediate generated by anodic oxidation of MOC-pyrroliidine was highly stabilized in the reaction media, which also assisted the progress of the following C-S bond-forming reaction. The application of direct C-C bond formation of iminium cations with allyltrimethylsilane was also investigated. After the completion of anodic oxidation of MOC- or BOC-proline methylesters in LPC/NM in the presence of acetic acid (2.2 F mol\(^{-1}\)) at 0°C followed by the addition of allyltrimethylsilane at ambient temperature, the desired products from both methylesters were produced in good yield.

6  Electro catalytic Intermolecular Olefin Cross-Coupling by Anodically Induced Formal [2+2] Cycloaddition between Enol Ethers and Alkenes

Electro catalytic intermolecular cycdimerization of olefins activated by carbazole,\(^{20}\) aryl sulfonyl,\(^{20}\) pyridyl, and quinolyl\(^{11}\) groups has been achieved for four-mem-bered-ring formations. On the other hand, it has unfortunately been difficult to achieve electrolytic intermolecular selective cross-coupling of two different olefins to provide the [2+2] cycloadduct. This provided the incentive to determine whether such an electrochemical approach might provide a unique pathway for selective intermolecular olefin cross-coupling to construct [2+2] cycloadducts between the in situ generated electron-deficient olefins and unactivated olefins under regulation of the oxidation potential and intra- and intermolecular electron transfers. In the course of our research on electrochemical cross-couplings, we discovered the novel electro catalytic intermolecular formal [2+2] cycloaddition of electron-rich olefins. For example, it was surprising that the anodic activation of the enol ether in the presence of a 3 mol equivalent of alkene led to selective intermolecular cross-coupling to form the corresponding [2+2] cycloadduct in 46-88% yield (Fig. 14).\(^{32}\) The reaction was completed after the passage of ca. 0.5 F mol\(^{-1}\) of charge, and the product was also obtained under even dark electrolytic conditions. However, no desired product was obtained from the reaction in 1.0 mol dm\(^{-3}\) LPC/NM left to stand for more than 4 h without application of a potential. The amount of product at each stage scarcely changed dur-
7 Introduction of Hydrophobic Fields into the Electrolyte Solution System

In conventional electrochemical systems, it is often difficult to selectively generate reactive carbocation intermediates by anodic oxidation of the target precursor substrates in the presence of other species, such as nucleophiles and reaction products, because they are also easily oxidized during the anodic C-C bond formation reaction. In order to prevent the over-oxidation of undesired electrolytic substrates, we previously introduced a PTFE (poly-tetrafluoroethylene) fiber coated electrode to construct a hydrophobic reaction field over the surface of the electrode (Fig. 16). In the fluorous field, hydrophobic nucleophiles and/or products can be kept by the hydrophobic interaction in a highly polar electrolyte solution. By using this unique electrode system, selective oxidation of hydroquinones was achieved, followed by cycloaddition reaction with dienes on the surface of the PTFE fibers (Figs. 17 and 18).

In the LPC/NM electrolyte solution, phenol derivatives were anodically converted to corresponding phenoxonium cations followed by intermolecular [3+2] cycloaddition with unactivated aliphatic alkenes. However, the oxi-

Fig. 15 Formation of the [2+2] cycloadduct via the anodically induced cross-coupling by the interval potential application.

Fig. 16 An electrochemical reaction system with the PTFE-fiber coated electrode.

Fig. 17 Results of Diels-Alder reaction between anodically generated quinines and dienes by using the PTFE-fiber coated electrode in the LPC/NM electrolyte solution.
Electrochemistry potentials of the products were generally lower than those of the starting phenols. Over-oxidized byproducts were often obtained during the macroelectrolysis (Fig. 19). In this case, the PTFE coated electrode functioned to prevent the undesired over-oxidation of the hydrophobic dihydrobenzofuran derivatives generated in situ by electrochemical cycloaddition (Fig. 20).

8 Concluding Remarks

Electro-organic reaction systems can be constructed by consideration of several key factors, such as electrodes, solvents, electrolytes, reagents, additives, and reaction cells. We believe that an electro-organic reaction system provides a wide variety of choice and flexibility in the selection of reaction conditions and the construction of electrochemical systems. Research with such systems has sometimes led to unanticipated discoveries, and also difficulties yet to be overcome. However, such difficulties do provide important opportunities to elucidate new approaches in electrochemical synthesis. For example, the LPC/NM medium has played a very important role in the electrochemical system and most of the anodic reactions described have been accomplished only in the selected unique reaction medium. This has provided further motivation to investigate the basic function of the medium and to continue exploring new electrochemical reactions. One of the next very important stages in research should be aimed at constructing efficient reaction systems for practical syntheses that could be applied to new ideas and technologies. We hope that concerted efforts in the field of electro-organic chemistry could open the door for new concepts in electrochemistry and organic synthesis.

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References


