Parallel Electrosynthesis of *N*-Acyliminium Ion Equivalents Using Silica Gel-supported Piperidine

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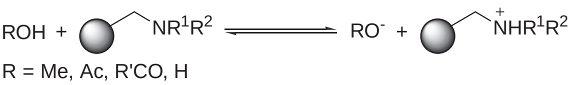
Parallel anodic methoxylation of carbamates was successfully carried out to provide the corresponding α-methoxylated products as *N*-acyliminium ion equivalents in high to excellent yields using silica gel-supported piperidine (Si–piperidine).

To achieve solution-phase parallel electrosynthesis, Yudin et al. have pioneered the design of a spatially addressable electrolysis platform, which consists of a rectangular array of electrochemical cells.[1] Speiser et al. have developed a computer-controlled automated instrument using the wells of microtiter plates.[2] On the other hand, Yoshida et al. have established cation pool and flow methods for carbon–carbon bond forming reactions in a combinatorial manner.[3] While these approaches have advanced the concept of solution-phase parallel electrosynthesis, a separation problem peculiar to organic electrosynthesis has still remained.

In organic electrosynthesis, large amounts of supporting electrolytes are necessary to provide sufficient ionic conductivity to the solvents for electrolysis. However, the use of supporting electrolytes requires laborious separation after the electrolysis. This practical disadvantage may restrict its application to solution-phase parallel electrosynthesis. We have recently developed a novel electrolytic system for organic electrosynthesis using solid-supported bases. The system is based on the acid–base reactions between protic solvents[4] or carboxylic acid substrates[5] and solid-supported bases (eq 1), and the conjugate acid–base pairs seem to act as supporting electrolytes. With the use of solid-supported bases, it is possible to do organic electrosynthesis without any additional supporting electrolytes. On the basis of the electrolytic system, we have successfully demonstrated anodic methoxylation of organic compounds using silica gel-supported piperidine (Si–piperidine), which involves the simple separation and purification processes after the electrolysis as shown in Figure 1. Therefore, it has the potential to be applied to solution-phase parallel electrosynthesis from the viewpoint of separation technology. In order to demonstrate parallel anodic methoxylation using Si–piperidine, we chose anodic methoxylation of carbamates as a model reaction in this work. Anodic methoxylation of amides is one of the most synthetically useful electroorganic reactions, because it can provide an oxidative alternative to the synthesis of *N*-acyliminium ion equivalents for carbon–carbon bond forming reactions as shown in Scheme 1.[6] With these facts in mind, we herein report parallel electrosynthesis of *N*-acyliminium ion equivalents using Si–piperidine.



(1)

R = Me, Ac, R'CO, H

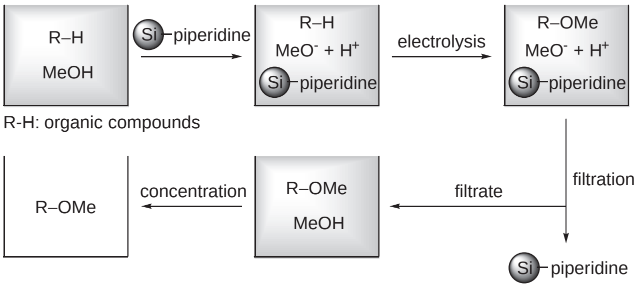
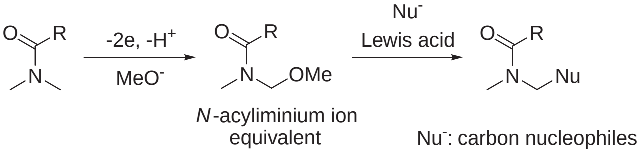
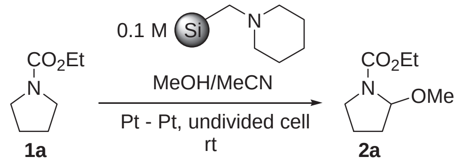


Figure 1. Experimental procedure for anodic methoxylation of organic compounds using Si–piperidine.



Scheme 1. Carbon–carbon bond forming reactions using anodic methoxylation of amides as a key step.

Table 1. Anodic methoxylation of **1a** using Si–piperidine



1a **2a**

Entry	MeOH/MeCN (v/v%)	Electricity /F mol^{-1}	Current density /mA cm^{-2}	Yield/%[a]
1	100/0	5	5	90
2	100/0	5	10	88 (35)[b]
3[c]	100/0	—	20	—
4[d]	50/50	3.5	10	92 (53)[b]

[a]Isolated yield. [b]Current efficiency in parentheses. [c]The cell voltage was too high to perform the electrolysis. [d]The cell voltage was ca. 20 V.

In order to optimize the best reaction conditions for parallel arrangement, we investigated anodic methoxylation of *N*-(ethoxycarbonyl)pyrrolidine (**1a**) using Si–piperidine as shown in Table 1. We first focused on the current density to control the reaction time. Anodic methoxylation of **1a** proceeded smoothly to provide the corresponding α-methoxylated product **2a** in high to excellent yields under relatively low current densities (Entries 1 and 2). In contrast, the cell voltage was too high to perform the electrolysis under higher current density (Entry 3). This is due to the high internal resistance and therefore, the Joule heat. On the other hand, the current efficiency increased by using MeCN as a cosolvent to reduce the reaction time (Entry 4). From these results, we selected Entry 4 as the best reaction conditions for parallel arrangement.

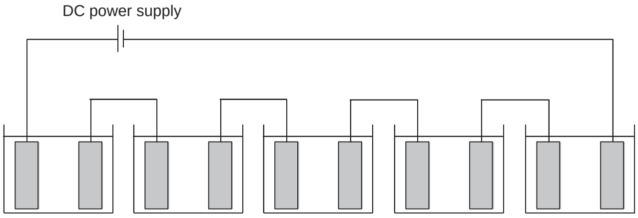
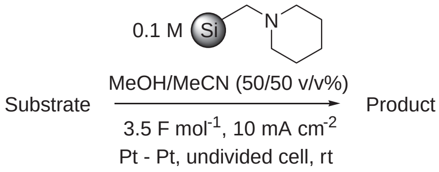
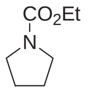
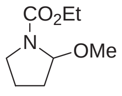
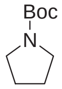
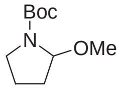
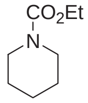
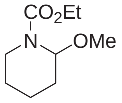
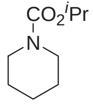
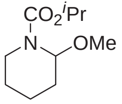
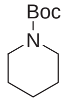
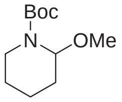


Figure 2. Experimental setup for parallel anodic methoxylation.

Table 2. Parallel anodic methoxylation of **1a**–**1e** using Si–piperidine



Substrate	E_p^{ox} /V vs. SCE[a]	Product	Yield/%[b]
 **1a**	2.09	 **2a**	91
 **1b**	2.04	 **2b**	93
 **1c**	2.11	 **2c**	94
 **1d**	2.13	 **2d**	89
 **1e**	2.04	 **2e**	93

[a]The oxidation potential was measured in 0.1 M Bu_4NBF_4/MeCN using a platinum disk electrode ($\phi = 0.8$ mm). The scan rate was 100 mV s^{-1}. [b]Isolated yield.

We next investigated the parallel arrangement of anodic methoxylation of carbamates **1a**–**1e** under the conditions of Entry 4 in Table 1.[7] The experimental setup is illustrated in Figure 2.[8] The five undivided cells were connected in series, because constant current electrolysis was applied to the parallel anodic methoxylation. As shown in Table 2, parallel anodic methoxylation of **1a**–**1e** using Si–piperidine was successfully carried out to provide the corresponding α-methoxylated products **2a**–**2e** as *N*-acyliminium ion equivalents in high to excellent yields. In the electrolysis, **1a**–**1e** were completely consumed with the fixed electricity (3.5 F mol^{-1}) owing to their similar oxidation potentials. Furthermore, Si–piperidine which was used with each cell was simultaneously separated by only filtration after the electrolysis, and the desired pure products were readily isolated simply by concentration of the filtrates as shown in Figure 1. These separation and purification processes can be automated to achieve high-throughput separation. In addition, application of the products to carbon–carbon bond forming reactions would be achieved by using the well-established method.[6]

In summary, we have successfully demonstrated the parallel arrangement of anodic methoxylation of carbamates using Si–piperidine. It is hoped that the separation and purification processes will make great advance in separation technology for solution-phase parallel electrosynthesis.

This work was supported by a Grant-in-Aid for Young Scientists (A) (No. 19685014) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT) and MEXT's program "Promotion of Environmental Improvement for Independence of Young Researchers" under the Special Coordination Funds for Promoting Science and Technology.

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7 General procedure for parallel anodic methoxylation of carbamates **1a**–**1e** using Si–piperidine: Parallel electrolysis experiments were carried out with a Hokuto Denko HA-105 potentiostat/galvanostat. Parallel anodic methoxylation of **1a**–**1e** (1 mmols) was carried out with platinum plate electrodes (2 × 2 cm^2) in MeOH/MeCN (50/50 v/v%, 10 mL) containing 0.1 M Si–piperidine (based on the concentration of piperidine) using 5 undivided cells connected in series. Constant current electrolysis (10 mA cm^{-2}, terminal voltage: ca. 100 V) was applied with magnetic stirring at room temperature. After the electricity was passed until the complete consumption of **1a**–**1e**, the electrolytic solutions were simultaneously passed through a glass filter (pore size: 5–10 µm) to remove Si–piperidine. The filtrates were respectively concentrated under reduced pressure to provide the corresponding α-methoxylated products **2a**–**2e**, which were identified by comparison with literature values[1a] using ^{1}H NMR and mass spectroscopy.

8 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.