J|A|C|S
COMMUNICATIONS

Development of an Electrolytic System for Non-Kolbe Electrolysis Based on the Acid−Base Reaction between Carboxylic Acids as a Substrate and Solid-Supported Bases

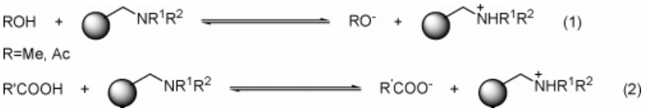
Toshiki Tajima,[*,†] Hitoshi Kurihara,[‡] and Toshio Fuchigami[‡]

Global Edge Institute, Tokyo Institute of Technology, Yokohama 226-8502, Japan, and Department of Electronic Chemistry, Tokyo Institute of Technology, Yokohama 226-8502, Japan

Received January 14, 2007; E-mail: tajima.t.ac@m.titech.ac.jp

Anodic oxidation of amides, lactams, carbamates, and N-acylated amino acids is one of the most synthetically useful electrochemical reactions and has proven to be a unique and powerful tool for the synthesis of biologically active compounds.[1] It can provide an oxidative alternative to the synthesis of *N*-acyliminium ion intermediates. Furthermore, it can serve as an excellent method for generating chiral building blocks for synthesis. However, the use of supporting electrolytes in electroorganic synthesis causes their separation and waste problems after the electrolysis to restrict the synthetic advantages.

We have recently developed a novel electrolytic system for anodic methoxylation[2] and acetoxylation[3] using easily separable and reusable solid-supported bases. The system is based on the acid−base reaction between protic solvents such as MeOH and solid-supported bases (eq 1). The ions derived from the acid−base reaction seem to play the role of supporting electrolytes. Therefore, no additional supporting electrolytes are necessary in the system. However, low acidity of MeOH ($pK_a = 15.5$) affords low concentration of the corresponding ions to cause high cell voltage ($V_{cell} = J\ C^{-1}$), which is a unit of energy to drive charge between the electrodes. On the other hand, carboxylic acids have much higher acidity compared to that of MeOH. Thus, carboxylic acids would serve as both a substrate and a supporting electrolyte based on the acid−base reaction between carboxylic acids and solid-supported bases in non-Kolbe electrolysis, and they would reduce the cell voltage in MeOH (eq 2). Non-Kolbe electrolysis, which is effective for anodic oxidation of amides, lactams, carbamates, and N-acylated amino acids, is defined as the two-electron oxidation of carboxylate ions with decarboxylation that leads to carbenium ions which are trapped by nucleophiles. Herein, we report a novel electrolytic system for non-Kolbe electrolysis based on the acid−base reaction between carboxylic acids as a substrate and solid-supported bases.



First, we measured the cyclic voltammogram of 0.1 M silica gel supported piperidine/MeOH (based on the concentration of piperidine). As shown in Figure 1a, the oxidation current for MeOH (over 1.5 V vs SCE) and the reduction current for H^+ were observed, respectively. Next, in order to confirm the acid−base reaction between carboxylic acids and solid-supported bases, the cyclic voltammogram of DL-pyroglutamic acid (**1a**, 0.1 M) in 0.1 M silica gel supported piperidine/MeOH was also measured. As shown in Figure 1b, the oxidation current for MeOH was decreased because of the adsorption of a carboxylate ion derived from **1a** on the anode surface,[4] while the reduction current for H^+ was remarkably increased. These indicate that the acid−base reaction between **1a** and silica gel supported piperidine preferentially takes place (eq 2), and the resulting ions seem to play the role of supporting electrolytes.

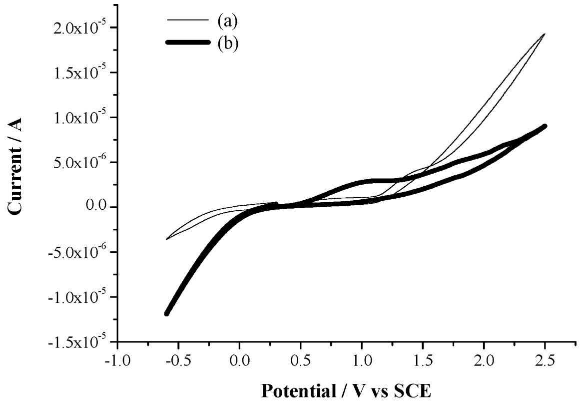


Figure 1. Cyclic voltammograms of (a) 0.1 M silica gel supported piperidine/MeOH and (b) **1a** (0.1 M) in 0.1 M silica gel supported piperidine/MeOH, recorded at a Pt disk electrode ($\phi = 0.8$ mm). The scan rate was 100 mV s^{-1}.

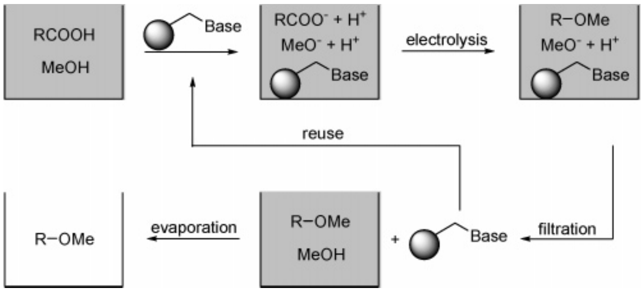


Figure 2. Experimental procedure for non-Kolbe electrolysis using solid-supported bases.

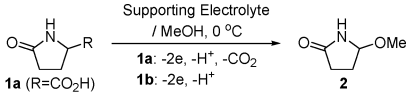
We, in contrast, investigated non-Kolbe electrolysis of **1a**[5] and anodic methoxylation of **1b** using silica gel supported piperidine. The overall experimental procedure for non-Kolbe electrolysis is illustrated in Figure 2. As shown in Table 1, non-Kolbe electrolysis of **1a** proceeded smoothly to provide **2** in quantitative yield (entry 1), while a large amount of **1b** was recovered because of the high oxidation potential of **1b** ($E_p^{ox} = 2.5$ V vs SCE; entry 2). The cell voltage in entry 1 (5−10 V) was much lower compared to that in entry 2 (20−25 V). In these cases, the cell voltages would depend mainly on the resistance of the solutions, which is closely related to the concentration of ions. Therefore, the acid−base reaction between **1a** and silica gel supported piperidine seems to preferen-

---

[†] Global Edge Institute.
[‡] Department of Electronic Chemistry.

10.1021/ja070283w CCC: $37.00

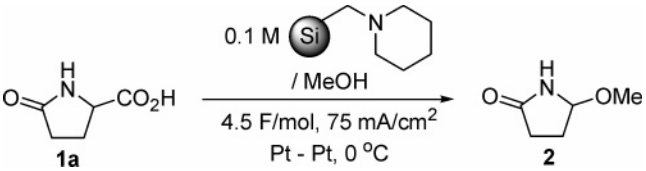
Table 1. Non-Kolbe Electrolysis of **1a** and Anodic Methoxylation of **1b** Using Silica Gel Supported Piperidine



entry	substrate	supporting electrolyte (0.1 M)	anode	current density (mA/cm^2)	electricity (F/mol)	yield[a] (%)
1[b]	**1a**	Si-piperidine[c]	Pt	10	7	quant (29)[d]
2[e]	**1b**	Si-piperidine	Pt	10	7	19[f] [81][g]
3	**1a**	Si-piperidine	graphite	10	7	97 (28)
4	**1b**	Si-piperidine	graphite	10	7	14[f] [84]
5	**1a**	$NaClO_4$	Pt	75	25	23[f]
6	**1a**	NaOMe	Pt	75	5	95 (38)
7	**1a**	Si-piperidine	Pt	75	4.5	quant (44)

[a] Isolated yield. [b] The cell voltage was 5−10 V. [c] Silica gel supported piperidine. [d] Current efficiency in parentheses. [e] The cell voltage was 20−25 V. [f] ^{1}H NMR yield based on the NH group using nitromethane as an internal standard. [g] Recovery of **1b** in brackets.

Table 2. Reusability of Silica Gel Supported Piperidine



cycle	1st	2nd	3rd	4th	5th
yield[a] (%) of **2**	quant	quant	92	quant	91

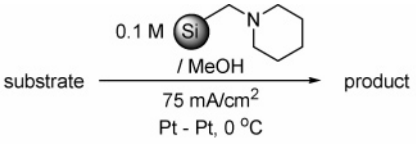
[a] Isolated yield.

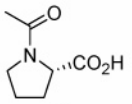
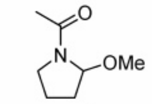
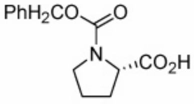
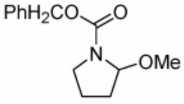
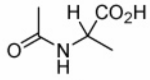
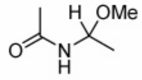
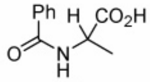
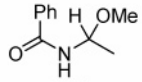
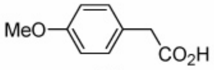
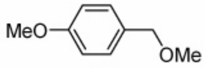
tially take place in entry 1 to realize the lower cell voltage compared to that in entry 2. The influence of the anode materials on the non-Kolbe electrolysis of **1a** was not observed at all because the generated carbenium ion is stabilized by the nitrogen atom to form the iminium ion (entries 1 and 3). From the comparisons of entries 1 and 2, and entries 3 and 4, non-Kolbe electrolysis of **1a** is superior to anodic methoxylation of **1b** from the viewpoints of not only cell voltage but also current efficiency. Entries 5 and 6 indicate that a base was effective for the promotion of the non-Kolbe electrolysis of **1a**. Then, silica gel supported piperidine also worked well as a base (entry 7). Therefore, silica gel supported piperidine seems to promote the dissociation of **1a** to enhance not only the adsorption of the corresponding carboxylate ion on the anode surface but also the oxidation of it. It is notable that **2** was easily isolated by only evaporation of the filtrate after the filtration of silica gel supported piperidine (Figure 2). Furthermore, as shown in Table 2, non-Kolbe electrolysis of **1a** was successfully carried out five times under the conditions of entry 7 in Table 1 by the reuse of silica gel supported piperidine.

On the basis of the electrolytic system based on the acid−base reaction between carboxylic acids and silica gel supported piperidine, we investigated non-Kolbe electrolysis of various carboxylic acids. As shown in Table 3, non-Kolbe electrolysis of a N-acylated proline **3**, a carbamate **5**, N-acylated alanines **7** and **9**, and *p*-methoxyphenylacetic acid (**11**) was carried out to provide the corresponding methoxylated products in excellent yields. From these results, it was demonstrated that the system based on the acid−base reaction between carboxylic acids and solid-supported bases is available for the wide range of non-Kolbe electrolysis.

In conclusion, we have successfully developed a novel electrolytic system for non-Kolbe electrolysis based on the acid−base reaction between carboxylic acids as a substrate and solid-supported bases. It was found that the acid−base reaction between carboxylic acids and solid-supported bases preferentially takes place to reduce the cell voltage in MeOH. It is hoped that this will make a significant contribution to green chemistry and open a new aspect of electroorganic synthesis.

Table 3. Non-Kolbe Electrolysis of Various Carboxylic Acids Using Silica Gel Supported Piperidine



entry	substrate	electricity (F/mol)	product	yield[a] (%)
1	 **3**	4	 **4**	92
2	 **5**	4	 **6**	98
3	 **7**	5	 **8**	quant.
4	 **9**	5	 **10**	quant.
5	 **11**	3	 **12**	96

[a] Isolated yield.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Young Scientists (B) (No. 17750144) from The Ministry of Education, Culture, Sports, Science and Technology, Japan. We also thank Nissan Motor Co., Mizuho Foundation for the Promotion of Sciences, The Foundation "Hattori-Hokokai", and Venture Business Laboratory of Tokyo Institute of Technology for their financial support.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Moeller, K. D. In *Organic Electrochemistry*; Schäfer, H. J., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 8, pp 277−312.
(2) (a) Tajima, T.; Fuchigami, T. *J. Am. Chem. Soc.* **2005**, *127*, 2848−2849. (b) Tajima, T.; Fuchigami, T. *Chem.*−*Eur. J.* **2005**, *11*, 6192−6196.
(3) Tajima, T.; Fuchigami, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4760−4763.
(4) (a) Vassiliev, Y. B.; Grinberg, V. A. *J. Electroanal. Chem.* **1990**, *283*, 359−378. (b) Vassiliev, Y. B.; Grinberg, V. A. *J. Electroanal. Chem.* **1992**, *336*, 281−307.
(5) (a) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 1552−1554. (b) Nishikawa, T.; Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Inoue, I.; Miyoshi, M. *J. Org. Chem.* **1982**, *47*, 1706−1712.

JA070283W