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Development of a Novel Environmentally Friendly Electrolytic System by Using Recyclable Solid-Supported Bases for In Situ Generation of a Supporting Electrolyte from Methanol as a Solvent: Application for Anodic Methoxylation of Organic Compounds

Toshiki Tajima and Toshio Fuchigami*[a]

Abstract: We have successfully developed a novel environmentally friendly electrolytic system using recyclable solid-supported bases for in situ generation of a supporting electrolyte from methanol as a solvent. It was found that solid-supported bases are electrochemically inactive at an electrode surface. It was also found that solid-supported bases dissociate methanol into methoxide anions and protons. Therefore, in the presence of solid-supported bases, it was clarified that methanol serves as both a solvent and a supporting electrolyte generated in situ. Anodic methoxylation of various compounds with solid-supported bases was carried out to provide the corresponding methoxylated products in good to excellent yields with a few exceptions. The methoxylated products and the solid-supported bases were easily separated by only filtration, and the desired pure methoxylated products were readily isolated simply by concentration of the filtrates. The separated and recovered solid-supported bases were recyclable for several times.

Keywords: electrochemistry · electron transfer · electroorganic synthesis · green chemistry · solid-supported base

Introduction

Electroorganic synthesis is one of the most useful methods in organic synthesis and is even applied in large-scale industrial processes.[1] For example, the electrohydrodimerization of acrylonitrile to adiponitrile, an intermediate to nylon 66, originally developed by Monsanto Co. in early 1960s, is operating at several sites worldwide now. Furthermore, electroorganic synthesis has recently attracted much interest as an environmentally friendly method because electrons are inherently environmentally friendly reagents compared with conventional oxidizing and reducing reagents. However, large amounts of supporting electrolytes are necessary to provide sufficient electrical conductivity to the solvents for electrolyses. Therefore, after the electrolyses, separation of the supporting electrolytes is required, and the separated supporting electrolytes generally become industrial waste because they are mostly unrecyclable except for some industrialized cases.[2] Furthermore, the inefficient separation of the supporting electrolytes from the solvents requires a huge consumption of energy and causes large amounts of additional industrial waste.

In order to solve such separation and industrial waste problems, a capillary gap cell has been developed to minimize addition of supporting electrolytes.[3] On the other hand, a polymeric electron carrier system,[4] solid polymer electrolytes,[5] an aqueous silica gel disperse system,[6] and thermomorphic biphasic electroorganic synthesis[7] have been developed to eliminate the steps for the separation of supporting electrolytes. Furthermore, recently, electrochemical microreactors[8] and a thin-layer flow cell[9] have also been developed to conduct electroorganic synthesis without intentionally added supporting electrolytes. To our knowledge, an ideal electroorganic synthetic system from the viewpoint of green sustainable chemistry should be an electrolytic system not requiring the addition of any supporting electrolytes. Although electrochemical microreactors and a thin-layer flow cell realize such an ideal electroorganic synthetic system, they require special equipments.

On the other hand, it is well known that electron transfer between a solid and a solid is very difficult.[10] Therefore, it

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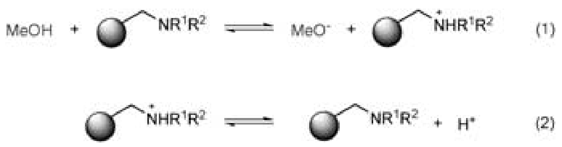
can be expected that solid-supported bases play the role of bases in bulk solutions as well as electrochemically inactive reagents at an electrode surface. In the presence of solid-supported bases such as amines, protic organic solvents such as methanol would be dissociated into anions and protons to some extent [Eqs. (1) and (2)]. This system would be suitable for electroorganic synthesis because the protons derived from protic organic solvents would act as the main carrier of an electronic charge via ammonium ions [Eq. (2)].[11] Therefore, in this system, protic organic solvents would serve as both a solvent and a supporting electrolyte generated in situ. Herein, we report a novel environmentally friendly electrolytic system using recyclable solid-supported bases for in situ generation of a supporting electrolyte from methanol as a solvent[12] and its application to anodic methoxylation of various organic compounds.



Results and Discussion

Electrochemical properties of solid-supported bases: At first, we examined the electrochemical properties of solid-supported bases. The cyclic voltammograms of *N*-methylpiperidine (**1**) and polystyrene-supported piperidine **2** were measured in 0.1 M $n\mathrm{Bu_4NBF_4}$/anhydrous acetonitrile. As shown in Figure 1a, **1** was easily oxidized at about 1.3 V versus SCE, while **2** was not oxidized at all even under stirring. This means that solid-supported bases are not oxidized at the electrode surface. Then, **2** was added into methanol (0.1 M based on the concentration of piperidine), and the cyclic voltammogram of this solution was measured. As shown in Figure 1b, the oxidation wave for $\mathrm{MeO^-}$ at about 1.0 V versus SCE and the reduction current for $\mathrm{H^+}$ were observed. Therefore, it is clear that solid-supported bases dissociate methanol into methoxide anions and protons, and the resulting protons seem to act as the main carrier of an electronic charge.

Anodic methoxylation of phenyl 2,2,2-trifluoroethyl sulfide using solid-supported bases: Next, we investigated anodic methoxylation using solid-supported bases. As a model reaction we chose the anodic methoxylation of phenyl 2,2,2-trifluoroethyl sulfide (**3**).[13] Anodic methoxylation processes such as 2,5-dimethoxylation of furans, anodic benzylic methoxylation of aromatic compounds, and α-methoxylation of organonitrogen compounds, are performed widely in organic synthesis and on an industrial scale.[14] The overall experimental procedure is illustrated in Figure 2. As shown in Figure 2, at first, solid-supported bases were added into methanol, and this solution was stirred for 1 h in order to dissociate methanol into methoxide anions and protons.

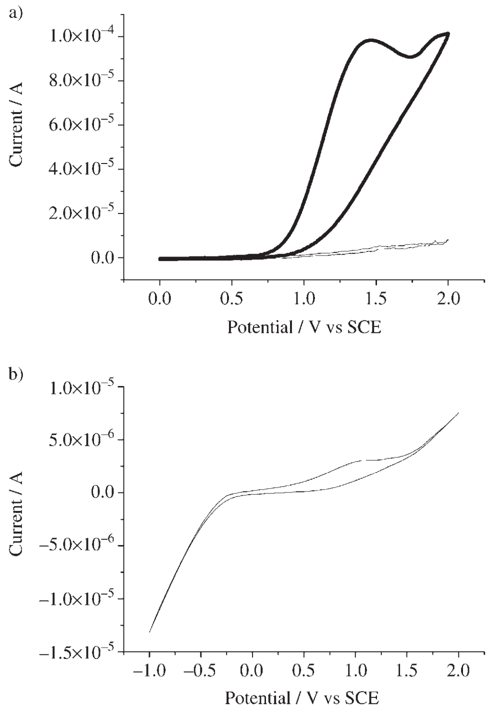


Figure 1. Cyclic voltammograms of a) *N*-methylpiperidine (0.1 M) and polystyrene-supported piperidine (0.1 M) in 0.1 M $n\mathrm{Bu_4NBF_4}$/MeCN (——: **1**, ——: **2**), and b) methanol in the presence of polystyrene-supported piperidine (0.1 M) recorded at a Pt disk anode ($\varphi = 0.8$ mm). The scan rate was 100 mV s^{-1}.

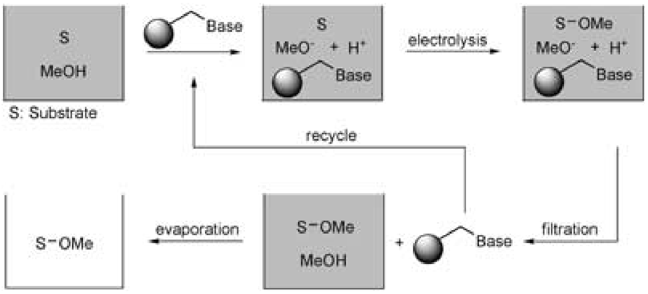
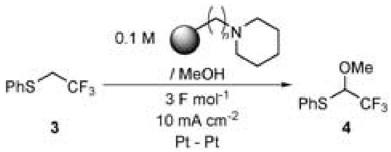


Figure 2. Experimental procedure.

Then, anodic methoxylation of a substrate was carried out. After the electrolysis, the corresponding methoxylated product and the solid-supported bases were easily separated by only filtration without neutralization. Finally, the desired pure methoxylated product was readily isolated simply by concentration of the filtrate.

At first, anodic methoxylation of **3** was carried out by using various solid-supported piperidines. As shown in Table 1, anodic methoxylation of **3** with polystyrene-supported piperidine provided the corresponding α-methoxylated product **4** in low yield (entry 1). In this case, the cell voltage was higher than 50 V since polystyrene-supported piperidine did not dissociate methanol into methoxide anions and protons efficiently. This means that the piperidine, which is inside in the polystyrene, does not interact with methanol

Table 1. Anodic methoxylation of **3** with various solid-supported piperidines.



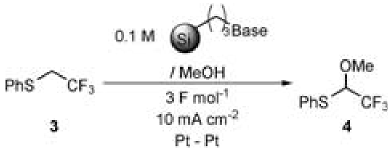
Entry	Solid	n	Yield[a] [%]
1	PS[b]	1	39
2	PS[c]	2	92 (87)[e]
3	SiO$_2$[d]	3	76 (73)

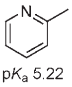
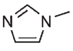
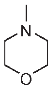
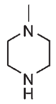
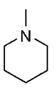
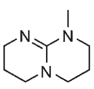
[a] ^{19}F NMR yield based on the CF$_3$ group using monofluorobenzene as an internal standard. [b] Polystyrene. [c] Porous polystyrene. [d] Silica gel. [e] Isolated yield in parentheses.

because polystyrene is not swelled in methanol. On the other hand, anodic methoxylation of **3** proceeded efficiently to provide **4** in good to excellent yields with porous polystyrene-supported and silica gel-supported piperidine (entries 2, 3). These results indicate that the solvent compatibility of solids is highly significant.

Next, anodic methoxylation of **3** was carried out with various silica gel-supported bases. As shown in Table 2, the methoxylated product **4** was obtained in moderate yields by using silica gel-supported pyridine and imidazole; their basicities are much lower compared with that of piperidine (entries 1, 2). In these cases, the cell voltage was higher than 50 V since silica gel-supported pyridine and imidazole did not dissociate methanol into methoxide anions and protons efficiently. On the other hand, the methoxylated product **4** was formed in good to high yields using relatively strong silica gel-supported bases (entries 3–6). However, the cell voltage in entry 6 was higher than those in entries 3–5. This can be explained as follows. Silica gel-supported **B** in entry 6 can dissociate methanol into methoxide anions and protons efficiently; however, silica gel-supported **B** strongly captures the protons because **B** has a high basicity. Therefore, the equilibrium (2) shifts to the left, and the resulting proton mobility is much lower compared with those of the other bases.[15] Thus, it was found that relatively strong bases, which have conjugated acid acidities close to that of methanol (pK_a 15.5), are suitable for the dissociation of methanol and anodic methoxylation. It is notable that the current efficiency for the anodic methoxylation of **3** was greatly increased about three times compared with our previous work using a conventional supporting electrolyte, Et$_4$NOTs.[13]

Table 2. Anodic methoxylation of **3** with various silica gel-supported bases.



Entry	Base	Yield[a] [%]
1	 pK_a 5.22	52
2	 pK_a 6.95	51
3	 pK_a 8.33	65
4	 pK_{a2} 9.80	89 (84)[b]
5	 pK_a 11.1	76 (73)
6	 **B** pK_a 24.3	70

[a] ^{19}F NMR yield based on the CF$_3$ group using monofluorobenzene as an internal standard. [b] Isolated yield in parentheses.

Recyclability of solid-supported bases: The recyclability of solid-supported bases was also examined. Anodic methoxylation of **3** was carried out 10 times by the recycling of silica gel-supported piperidine. In the recycling process, the silica gel-supported piperidine was easily separated and recovered by only filtration, and reused (Figure 2). As shown in Figure 3, the yield of **4** was always more than 70 % and did not decrease at all upon the reuse of silica gel-supported piperidine. In addition, the appearance of silica gel-supported piperidine did not change at all before and after electrolysis. This clearly suggests that solid-supported bases are recyclable for many times because solid-supported bases are not subject to oxidative decomposition at the electrode surface.

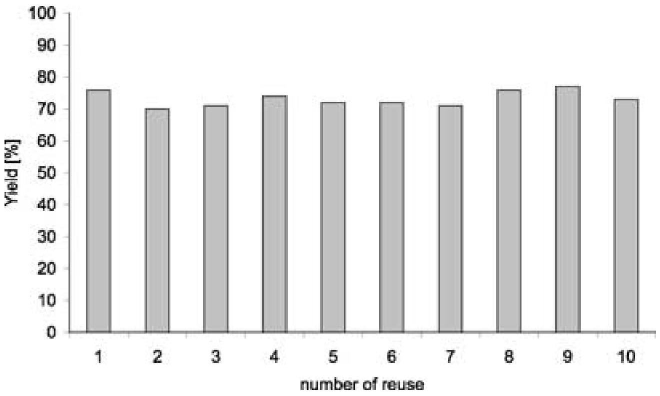
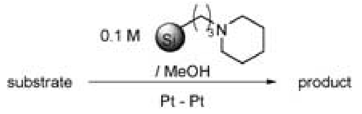


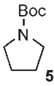
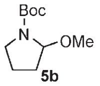
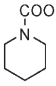
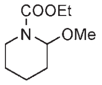
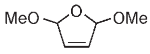
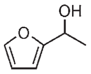
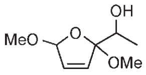
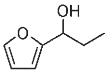
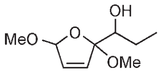
Figure 3. Yield of methoxylated product **4** in the reuse of silica gel-supported piperidine.

Generality of the electrolytic system using solid-supported bases: The generality of the new electrolytic system was demonstrated. As shown in Table 3, anodic methoxylation of carbamates **5a** and **6a** was carried out to provide the corresponding α-methoxylated products **5b** and **6b** in excellent yields (entries 1, 2 in Table 3). Anodic 2,5-dimethoxylation of furan (**7a**) proceeded to provide **7b** in 78% yield as a stereoisomeric mixture (entry 3 in Table 3). In this case, although **7a** was completely consumed, no by-product was formed. Then, anodic 2,5-dimethoxylation of furans **8a** and **9a** was also attempted to provide **8b** and **9b** in excellent yields (entries 4, 5 in Table 3). Anodic methoxylation of furans generally requires a Br$^-$/Br$^+$ mediator.[16] On the other hand, surprisingly, anodic methoxylation of furans proceeded smoothly without a Br$^-$/Br$^+$ mediator in this electrolytic system (entries 3–5 in Table 3).

Next, as shown in Table 4, anodic methoxylation of phenols **10a** and **11a** was carried out to provide the corresponding ring methoxylated products **10b** and **11b** in excellent yields (entries 1, 2 in Table 4). Anodic methoxylation of 1,4-dimethoxybenzene (**12a**) also proceeded to provide the corresponding ring dimethoxylated product **12b** in high yield (entry 3 in Table 4). Furthermore, anodic benzylic methoxylation of *p*-methoxytoluene (**13a**) took place to provide the benzylic mono- and dimethoxylated products **13b** and **13c** in 58 and 31% yields, respectively (entry 4 in Table 4). However, anodic benzylic methoxylation of **14a** and **15a** did not proceed smoothly and **14a** and **15a** were mostly recovered after the electrolyses, because the oxidation potentials of **14a** and **15a** are higher than that of methanol (entries 5, 6 in Table 4). Therefore, methanol seems to be mainly oxidized at the anode. From these results, it was demonstrated that the new electrolytic system by using solid-supported bases is effective for the wide range of anodic methoxylation except for some substrates whose oxidation potentials are higher than that of methanol.

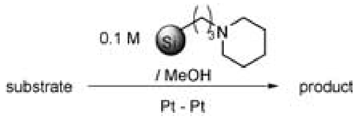
Table 3. Anodic methoxylation of carbamates and furans with silica gel-supported piperidine.

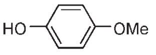
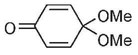
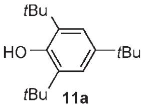
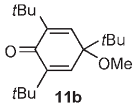
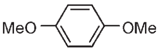
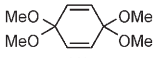
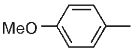
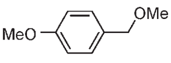
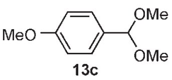
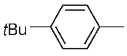
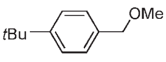
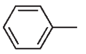
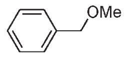


Entry	Substrate	Current density [mA cm^{-2}]	Electricity [F mol^{-1}]	Product	Yield[a] [%]
1	 5a	5	5	 5b	94
2	 6a	10	5	 6b	98
3	 7a	10	7	 7b	78[b] (*cis/trans* 1:1)
4	 8a	10	7	 8b	96[b]
5	 9a	10	7	 9b	94[b]

[a] Isolated yield. [b] Stereoisomeric mixture.

Table 4. Anodic methoxylation of substituted benzenes with silica gel-supported piperidine.



Entry	Substrate	Current density [mA cm^{-2}]	Electricity [F mol^{-1}]	Product	Yield[a] [%]
1	 10a	10	3	 10b	94
2	 11a	5	7	 11b	91
3	 12a	5	4	 12b	88
4	 13a[b, e]	5	6	 13b	58[f]
				 13c	31[f]
5	 14a[c, e]	10	10	 14b	18[g]
6	 15a[d, e]	10	10	 15b	0[h]

[a] Isolated yield. [b] Oxidation peak potential $(E_p^{ox})=1.72$ V vs SCE. [c] $E_p^{ox}=2.14$ V vs SCE. [d] $E_p^{ox}=2.36$ V vs SCE. [e] Oxidation peak potentials (E_p^{ox}) of **13a**, **14a**, and **15a** (0.01 M) were measured in 0.1 M $n\mathrm{Bu_4NBF_4}$/MeCN. The scan rate was 100 mV s^{-1}. [f] ^{1}H NMR yield based on the benzylic proton using toluene as an internal standard. [g] 74% of **14a** were recovered. [h] 93% of **15a** were recovered.

Conclusion

We have successfully developed a novel environmentally friendly electrolytic system for anodic methoxylation using recyclable solid-supported bases. This system has many practical advantages and characteristics: a) an electrolytic system without intentionally added supporting electrolytes; b) a supporting electrolyte generated in situ from methanol as a solvent; c) easy and simple separation of methoxylated products and solid-supported bases by only filtration without neutralization; d) simple isolation of methoxylated products; e) electrochemical stability and recyclability of solid-supported bases. It is hoped that this new electrolytic system will make significant contributions to green sustainable chemistry and open a new aspect of electroorganic synthesis.

Experimental Section

General methods: ^{1}H and ^{19}F NMR spectra were recorded on JEOL JNM EX-270 (^{1}H: 270 MHz, ^{19}F: 254 MHz) spectrometer in $CDCl_3$. The chemical shifts for ^{1}H and ^{19}F NMR spectra were given in δ (ppm) from internal TMS and monofluorobenzene (−36.5 ppm), respectively. EI mass spectra were recorded on Shimadzu GCMS-QP5050A mass spectrometer.

Materials: Phenyl 2,2,2-trifluoroethyl sulfide (**3**) was synthesized according to the literature.[17] All reagents except for **3** were purchased from commercial suppliers and used without further purification. All solid-supported bases were purchased from Aldrich. As a typical example, the loading of silica gel-supported piperidine was 1.1 mmol g^{-1}. In addition, silica gel size was 40–63 μm.

Cyclic voltammetry: Cyclic voltammetry was performed by using a computer-controlled electrochemical system (ALS/CHI 600). Cyclic voltammetry was carried out with a three-electrode system using a platinum disk ($\varphi = 0.8$ mm) working electrode, a platinum wire counter electrode, and a saturated calomel electrode (SCE) as a reference electrode.

General procedure for anodic methoxylation: Preparative electrolysis experiments were carried out with a Metronnix Corp. Tokyo constant-current power supply. Solid-supported bases (0.1 M based on the concentration of a base) were added into methanol (10 mL), and this solution was stirred for 1 h before electrolyses. Anodic methoxylation of a substrate (1 mmol) was carried out with platinum plate electrodes (2×2 cm^{2}) in CH_3OH (10 mL) containing various solid-supported bases (0.1 M based on the concentration of a base) by using an undivided cell. Constant current electrolysis was applied. When silica gel-supported piperidine was used (a typical procedure), the cell voltage was 7–16 V. The conversion of a substrate was monitored by TLC. After the electrolysis, the electrolytic solution was passed through a glass filter (pore size: 10–16 μm) to remove the solid-supported bases. The filtrate was evaporated to provide a pure methoxylated product, which was identified by authentic samples (**7b**, **8b**, **10b**, **12b**, **13b**, **13c**, **14b**, and **15b**) and literatures (**4**,[13] **5b**,[18] **6b**,[18] **9b**,[19] and **11b**[20]) using ^{1}H, ^{19}F NMR and Mass spectroscopy. However, when the yield of a methoxylated product was low, the residue was purified by Shimadzu LC-6AD liquid chromatography eluting with CH_3CN to give a pure methoxylated product. The yield of **4** was determined by ^{19}F NMR spectroscopy using monofluorobenzene as an internal standard material. The yields of **13b** and **13c** were determined by ^{1}H NMR spectroscopy using toluene as an internal standard material.

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