Development of an anodic substitution reaction system using acoustic emulsification†

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The anodic substitution reaction proceeded smoothly without affecting the oxidation of the nucleophile in a one-step electrochemical operation using acoustic emulsification.

The presence of several substrates in a single reactor often causes interference with a desired reaction. To avoid this drawback, chemo-selective reactions (which represent an elegant approach to discriminate between substrates, allowing reaction of one in preference to others) have been developed and they are extensively used as an important tool in organic synthesis, catalysis, biological chemistry, *etc.*[1]

The nucleophilic substitution reaction using an anodically generated carbocation has continued to be effectively utilized for carbon–carbon bond formation.[2] Since the carbocation is generally unstable, organic substrates and carbon nucleophiles need to coexist in a reactor during the anodic oxidation so that the nucleophile can trap the carbocation immediately as it is generated. However, the oxidation potentials of the nucleophiles are usually lower than those of organic substrates. Therefore, there is a considerable difficulty in achieving oxidation of the organic substrate preferentially in the presence of the nucleophile. In this regard, introduction of the electro-auxiliary into substrates[3] and the "cation pool" method[4] have been developed, but these necessarily include laborious multi-step reactions.

Recently we have reported that direct electropolymerization of water-insoluble monomers proceeded successfully in aqueous electrolytes using acoustic emulsification.[5] Ultrasonication of the water-insoluble monomer–aqueous electrolyte mixtures allowed the formation of very stable emulsions without added surfactants, and smooth electropolymerization in the emulsions took place *via* direct electron transfer between the electrode and the water-insoluble monomer droplets. In this kind of biphasic electron-transfer system, the supporting electrolyte should be dissolved not only in the aqueous phase but also in the monomer droplets and should contribute to the formation of an electric bilayer inside the droplets. Hence, when the droplet did not contain any supporting electrolytes, direct electron transfer was suppressed.

These findings gave us the incentive to develop a novel electrochemical system that would realize the anodic substitution reaction without affecting the oxidation of the nucleophile in a one-step electrochemical operation. In this system, illustrated in Fig. 1, the nucleophile is insoluble in an electrolytic medium and is dispersed as submicrometre range droplets by ultrasonication. In this situation, if the nucleophile droplet does not contain any supporting electrolyte, it becomes electro-inactive, and therefore the substrate is oxidized chemoselectively at the anode. Consequently, the desired coupling-product would be formed if the carbocation generated can be rapidly trapped by the coexisting nucleophile droplet before its decomposition. Thus, this system would realize the anodic substitution reaction to overcome the restraints such as the oxidation potentials of nucleophiles and the stability of carbocations.

Herein we wish to report our results indicating that this concept works. We chose the anodic substitution reaction of *N*-(methoxycarbonyl)pyrrolidine **1** (oxidation potential E_{ox} = 1.91 V *vs.* Ag/AgCl) with allyltrimethylsilane **2** (E_{ox} = 1.75 V *vs.* Ag/AgCl) as a model reaction (Scheme 1).[4a]

At first, we explored suitable electrolytic media which possess solubilizing ability for a substrate, but should not exhibit solubilizing ability for a nucleophile such as allyltrimethylsilane. Among various electrolytic media, an ionic liquid like 1-ethyl-3-methylimidazorium tetrafluoroborate (EMIM BF_4) was found to show the desired functions.[6] Furthermore, the ionic liquid can be used as an electrolytic medium on its own.

Subsequently, we measured linear sweep voltammograms of compounds **1**, **2** and a mixture of them. Since both **1** and **2** can be dissolved in acetonitrile solution, **2** which has lower oxidation potential was oxidized preferentially in acetonitrile solution as shown in Fig. 2(a). In contrast, Fig. 2(b) indicates that the anodic oxidation of **2** was hardly observed in EMIM BF_4 because **2** was

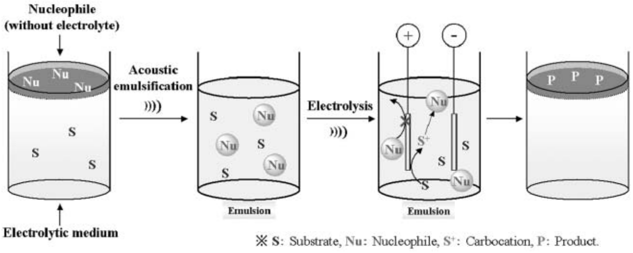
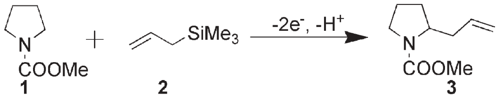


Fig. 1 Schematic illustration of the anodic substitution reaction system using acoustic emulsification.



Scheme 1 Anodic substitution reaction of *N*-(methoxycarbonyl)pyrrolidine **1** with allyltrimethylsilane **2**.

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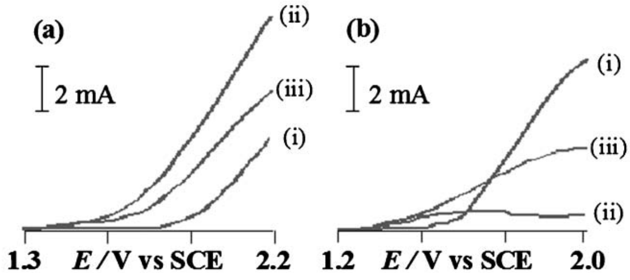


Fig. 2 Linear sweep voltammograms of (i) 0.1 M *N*-(methoxycarbonyl)pyrrolidine, (ii) 0.1 M allyltrimethylsilane and (iii) 0.1 M *N*-(methoxycarbonyl)pyrrolidine with 0.1 M allyltrimethylsilane in (a) 0.1 M *n*-Bu_4NBF_4–acetonitrile solution and (b) EMIM BF_4 under ultrasonication. Scan rate was 0.1 V s^{-1}.

phase-separated from the electrolytic medium and moreover the droplets of **2** did not contain EMIM BF_4 electrolyte.[7] Hence, the droplet of **2** should be electro-inactive as mentioned above, and **1** was oxidized preferentially even in the presence of **2** in the same reactor.

Next, we carried out the anodic substitution reaction on a preparative scale (Scheme 1).‡ 1 mmol of *N*-(methoxycarbonyl)-pyrrolidine **1** was galvanostatically electrolyzed at 5 mA in the presence of allyltrimethylsilane **2** by passing 2 F mol^{-1} of charge under ultrasonication with 150 W cm^{-2} intensity. As shown in entry 1 of Table 1, the desired carbon–carbon bond formation product **3** was obtained in only 11% yield and 76% of substrate was recovered in the acetonitrile solution. In this case, **2** was probably oxidized preferentially.

In sharp contrast, the use of the emulsion system resulted in an improvement of the conversion of **1** as shown in entry 2. However, the low yield problem still remained. Probably this is ascribed to the fact that the amount of **2** was insufficient to trap the carbocations generated. In fact, the addition of further amounts of **2** was effective for improving the yield and gave **3** in 70% yield when 10 equivalents of **2** were added (entry 4). It should be noted that the nucleophilic substitution reaction hardly proceeded under mechanical stirring conditions, although the substrate was oxidized smoothly as shown in entry 5. In this case, mechanical stirring could not form an emulsion because of the high viscosity of the EMIM BF_4.

The oxidation potential of product **3** (E_{ox} = 1.90 V *vs.* Ag/AgCl) was very close to that of substrate **1** implying that overoxidation of **3** would be a problem for this reaction.[4a] However, in our case, the overoxidized products were not detected at all. It can be considered that introduction of an allyl group into **1** greatly decreases its solubility in the electrolytic medium (EMIM BF_4), and consequently allylated product **3** would be extracted from EMIM BF_4 into the nucleophile phase. To confirm this conjecture, we measured the partition ratio of **1** and **3** between EMIM BF_4 and the nucleophile phase. As a result, it was found that about 75% of **3** was extracted into the nucleophile phase while only 16% of **1** was dissolved in this phase (see the ESI†). From these facts, it is likely that the allyl group serves as a "phase tag"[8] for extraction of the product from the electrolytic medium, and *in situ* extraction results in reducing the chance for overoxidation.

Table 1 Anodic substitution reaction of *N*-(methoxycarbonyl)pyrrolidine **1** with allyltrimethylsilane **2**

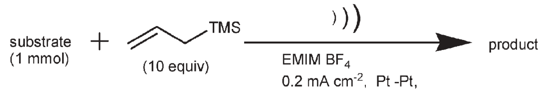
Entry	Electrolytic media	**2**/mmol	Yield of **3** (%)[a]	Conversion of **1** (%)[a]
1	0.1 M Bu_4NBF_4–CH_3CN	10	11	24
2	EMIM BF_4	2	16	88
3	EMIM BF_4	5	32	81
4	EMIM BF_4	10	70 (62)[b]	78
5[c]	EMIM BF_4	10	11	69

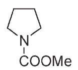
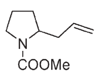
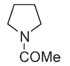
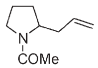
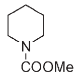
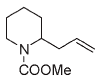
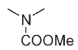
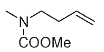
[a] Determined by GC. [b] Isolated yield in parenthesis. [c] Mechanical stirring (1500 rpm) was used instead of ultrasonication.

In order to demonstrate the generality of this new methodology, we also investigated the anodic substitution reactions of other compounds with allyltrimethylsilane. As shown in Table 2, the anodic substitution reactions of **6** and **8** were carried out to provide the corresponding allylated products **7** and **9**§ in reasonable yields, but the yield of **4** was not so good. Fully exploring the reason for this is beyond the scope of this short publication, but the stability of the anodically generated carbocation would be reflected in the yield of product.

In summary, we have developed a novel electrosynthetic system for an anodic substitution reaction using acoustic emulsification. This new methodology has many practical advantages and characteristics: (a) nucleophilic reaction by a one-step electrochemical operation in a single reactor; (b) the chemoselective oxidation of substrates even in the presence of nucleophile; (c) the smooth trapping of carbocations with submicrometre range nucleophile droplets formed by ultrasonication; (d) a reduction in the chance for overoxidation of products by the introduction of a "phase tag" into them. It is hoped that this facile and novel

Table 2 Anodic substitution reactions of various substrates with allyltrime thylsilane **2** using acoustic emulsification



Entry	Substrate	Electricity/F mol^{-1}	Product	Yield (%)[a]
1	 **1**	2	 **3**	70
2	 **4**	2	 **5**	43
3	 **6**	3	 **7**	50
4[b,c]	 **8**	4	 **9**	66

[a] Determined by GC. [b] After 2 F mol^{-1} of electricity was passed, 10 equivalents of nucleophile were further added. [c] Current density was 0.08 mA cm^{-2}.

electrolytic system will open a new aspect not only of synthetic electrochemistry but also of general synthetic chemistry. The scope, limitation and the further application of this new methodology are now under investigation.

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Notes and references

‡ General procedure for the anodic substitution reaction: a divided H-type glass cell with a glass frit diaphragm in a cooling bath was equipped with a Pt mesh anode (*ca.* 25 cm^2), a Pt mesh cathode (*ca.* 50 cm^2), and an ultrasonic stepped horn (3.2 mm diameter) connected with a 20 kHz oscillator (SONIFIER-250D, Branson Ultrasonics Co.). The top of the horn was positioned 3 cm apart from the cell bottom. *N*-(Methoxycarbonyl)pyrrolidine **1** and other compounds **4**, **6**, and **8** were galvanostatically electrolyzed at 5 mA in 0.1 M n-Bu$_4$NBF$_4$ acetonitrile solution and EMIM BF$_4$ (12 cm^3) in the presence of **2** by passing 2 F mol^{-1} of charge under ultrasonication with 150 W cm^{-2} intensity at a solution temperature of 25 ± 1 °C unless otherwise stated. Mechanical stirring at 1500 rpm (Magnestir, MGP-306 Sibata Scientific Technology Ltd.) was also used instead of ultrasonication. After electrolysis, products **3**, **5**, **7**, and **9** formed were extracted with diethyl ether (10 × 10 ml) and analyzed by gas chromatography (GC-2014 with Tween 80, 3m column, Shimadzu Co., Japan).

§ Synthesis of methyl (1-methyl-3-butenyl) ethylaminecarboxylate **9**: a divided H-type glass cell with a glass frit diaphragm in a cooling bath was equipped with a Pt mesh anode (*ca.* 125 cm^2), a Ag mesh cathode (*ca.* 200 cm^2), and an ultrasonic stepped horn (3.2 mm diameter) connected with a 20 kHz oscillator (SONIFIER-250D, Branson Ultrasonics Co.). The top of the horn was positioned 3 cm apart from the cell bottom. Compound **8** (0.10 g, 0.97 mmol) was galvanostatically electrolyzed at 10 mA in EMIM BF$_4$ (12 cm^3) in the presence of **2** (1.14 g, 9.98 mmol) under ultrasonication with 150 W cm^{-2} intensity at a solution temperature of 25 ± 1 °C. When 2 F mol^{-1} of electricity was passed, 10 mmol of **2** was further added. After 4 F mol^{-1} of electricity had been passed, the electrolysis was stopped, and then the product was extracted with diethyl ether (10 × 10 ml). Subsequently, the solvent was evaporated under reduced pressure and the residue was purified with reversed-phase high-performance liquid chromatography (HPLC) (SPD-10A with SUPERIOREX ODS, 25 cm column, SHISEIDO Co.) to obtain the title compound (0.08 g, 56%). ^{1}H NMR (270 MHz, CDCl$_3$): δ = 2.21–2.36 (m, 2H), 2.84–2.97 (m, 3H), 3.23–3.45 (m, 2H), 3.69 (s, 3H), 4.98–5.17 (m, 2H), 5.67–5.86 (m, 1H); ^{13}C NMR (68 MHz, CDCl$_3$) δ = 32.3, 34.4, 48.4, 52.5, 116.6, 135.1, 156.8; IR (KBr) v = 2926, 1705, 1485, 1396, 1217 cm^{-1}; LRMS (EI) *m/z* 143 (M$^+$), 102 (M$^+$ − CH$_2$=CHCH$_2$); HRMS (EI) calcd for C$_7$H$_{13}$NO$_2$ (M$^+$): 143.0946, found: 143.0946.

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