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Rapid Electrochemical Deprotection of the Isonicotinyloxycarbonyl Group from Carbonates and Thiocarbonates in a Microfluidic Reactor

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Supporting Information

ABSTRACT: Electroreductive deprotection of the isonicotinyloxycarbonyl (*i*Noc) group from hydroxy, thiol, and amino groups was carried out in an electrochemical microreactor. The small distance of the platinum electrodes in the microreactor enables a rapid electrochemical redox reaction without added electrolytes. As a result, the electrochemical deprotection of *O*- and *S*-*i*Noc aromatic substrates was achieved in short reaction times (<2 min), while *N*-*i*Noc and nonaromatic substrates did not react under the same reaction conditions. This method enables a rapid and site-selective deprotection of *O*- or *S*-*i*Noc groups without removal of *N*-*i*Noc moieties.

INTRODUCTION

The reductive removal of a protecting group from a functional moiety is traditionally carried out under reaction conditions using at least stoichiometric amounts of reagents and/or metal catalysis, which are undesirable from the viewpoint of green chemistry. On the other hand, clean and effective electrochemical deprotections without additional reagents have also been developed in several laboratories.[1]

Veber and co-workers developed the isonicotinyloxycarbonyl (*i*Noc) group (Figure 1), which has a high polarity and is useful

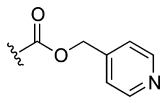

Figure 1. Isonicotinyloxycarbonyl group.

for the protection of the ε-amino group of lysine residues during peptide synthesis, and the *i*Noc group can be selectively deprotected using Zn(II) reagents.[2] They also showed that the *i*Noc group could be electroreductively removed using a mercury cathode. However, the reaction time was long (40−90 min) in the chemical and electrolytic deprotection of simple L-lysine. In addition, the electrochemical technique has not been applied to peptide molecules.

We have developed an electrochemical microreactor, which enables rapid and effective electrochemical reactions, and applied it to some practical procedures of organic syntheses.[3] Very recently, we demonstrated rapid difluoro- and trifluoromethylation of alkenes using the Kolbe electrolysis of difluoro- and trifluoroacetic acid in this electrochemical microreactor.[4] The electrochemical microreactor has a FEP (fluorinated ethylene propylene) flow channel sandwiched between platinum electrodes, as shown in Figure 2, where the thickness of the FEP foil defines the very short diffusion distances leading to high space−time yields. Different microreactor systems have already been well-established for synthetic studies and have been successfully used for electrochemical reactions.[5] In verity, some synthetic protocols and other examples for practical use of such reactors have been reported.[6] The flow technology developed for these reactions indicates that rapid and efficient electrolysis can be performed by using electrochemical microreactors.

RESULTS AND DISCUSSION

In this paper, we report the cathodic reduction of *i*Noc-protected hydroxyl groups (i.e., carbonates), thiol groups (i.e., thiocarbonates), and amino groups (i.e., carbamates) using platinum electrodes. We initially prepared *O*-*i*Noc phenols, **3a**, **3b**, and **3c** (Scheme 1).[7] These compounds were successfully synthesized in high yields (92−98%) by the reaction of the corresponding phenols **1** with isonicotinyl *p*-nitrophenyl carbonate **2** in the presence of a base in DMF. The reagent **2** for *i*Noc protection was prepared following the literature protocol.[2]

To achieve the electrochemical removal of the *i*Noc group, the electrolysis of *i*Noc-protected substrates **3** was performed by continuous flow of a water/DMF (1:5) solution containing 93 mM *i*Noc-protected substrate **3** and 50 mM tetrabutylammonium iodide (TBAI) as an electrolyte. The electrochemical microreactor has a flow channel of 23 μL volume (3 mm × 30 mm × 254 μm) with the electrolysis being performed at a constant current (16.7 mA cm^{-2}), at room temperature, and at a flow rate of 15 μL min^{-1} (residence time = 92 s) (Scheme 2). The reaction conditions were optimized in preliminary experiments. The analysis (TLC and ^1H NMR) of the crude products collected at the outlet of the electrochemical microreactor showed that the compounds **3** had completely disappeared and the deprotected phenols **1** with some byproducts had been formed. The byproducts were not identified but may include oxidized phenols. After extraction and purification by column chromatography, the deprotected phenols **1** were isolated in 40−60% yield (Scheme

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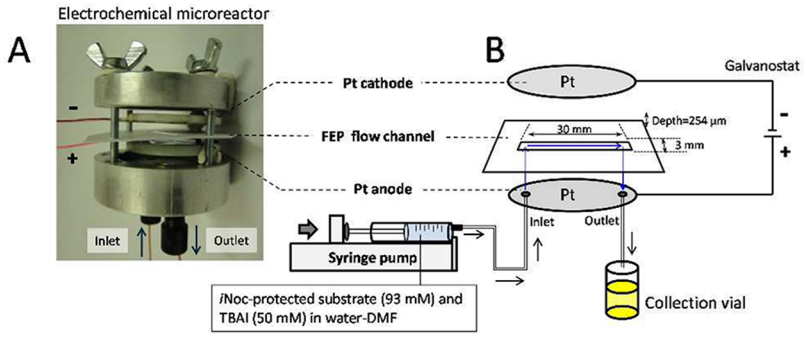
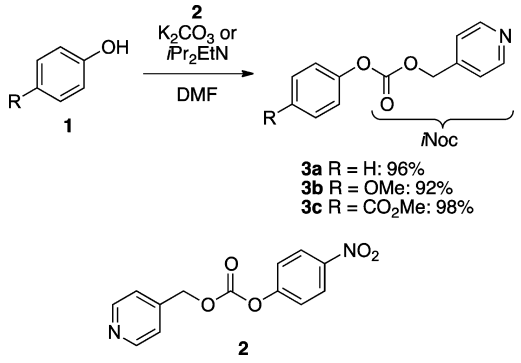
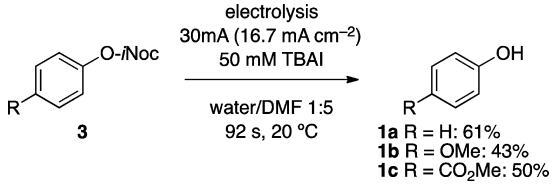


Figure 2. (A) Electrochemical microreactor device (opened). (B) Flow setup for the electrochemical deprotection of the *i*Noc group.

Scheme 1. Synthesis of *i*Noc-Protected Phenols 3



Scheme 2. Electrochemical Cleavage of the *i*Noc Protecting Group



2). The applicability of this technique for process chemistry could be regarded as being weak due to the low yields and productivity (11.5 mg/h for **1a**) under the conditions employed here. However, we only demonstrated the electrolysis with a typical reactor having a small channel volume to prove the usability for laboratory scale, and the productivity can be easily and largely improved by increasing the number of the reactor channels. This is one of the advantages of a microfluidic reactor.

In order to demonstrate the synthetic utility of the electrochemical microreactor for this type of reaction, the electrolysis of **3a** under batch conditions was carried out. A similar solution of **3a** in water/DMF (1:5) containing 50 mM TBAI was electrolyzed in an undivided cell fitted with two platinum foils as electrodes at a constant current (16.7 mA cm^{-2}). The progress of the reaction was monitored by TLC. The results clearly show that the starting material gradually decreased and completely disappeared after 6.5 h, while the concentration of **1a** increased. Finally, **1a** was obtained in 53% yield after purification by column chromatography. This result therefore clearly shows that the electrochemical microreactor is superior than batch electrolysis with regards to yield and reaction time.

Phenols are common moieties, for example, as side chains of tyrosine (Tyr) residues in peptides and protein. The deprotection of a natural protecting group such as a phosphate ester from Tyr is important as such a process can trigger biologic activities of proteins.[8] In addition, an aqueous solution of a short peptide including protected Tyr residues can be converted to an aqueous gel, which is useful as a biomaterial, by deprotection of Tyr and formation of hydrogen bond network between the hydroxyl groups.[9] The electrochemical deprotection of *i*Noc groups from phenols could be applied to electrochemically trigger such biochemical phenomena. In order to show the possibility for such applications, the electrolysis of a dipeptide including an *i*Noc-protected Tyr (Fmoc-Phe-Tyr(O*i*Noc)-OMe **4**) was performed. Compound **4** was prepared by protection of the Tyr-unprotected dipeptide. The reaction conditions for electrolysis were slightly modified so that **4** was converted completely (Figure 3). As a result, the

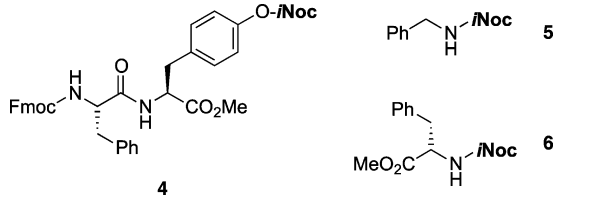


Figure 3. Peptide and carbamate substrates.

*i*Noc-deprotected dipetide Fmoc-Phe-Tyr-OMe was isolated in 12% yield. Although the yield decreased from simple phenols, we successfully demonstrated the electrochemical *i*Noc deprotection from a peptide molecule for the first time.

To investigate whether the electroreduction established for carbonates can be applied to carbamate substrates, *N*-*i*Noc-benzylamine **5** and *α*-*N*-*i*Noc-phenylalanine methyl ester **6** were electrolyzed. Initially, the reaction conditions for carbonates were employed. According to the analysis of the crude reaction mixture, these reactions did not progress at all and only starting material was observed. The current was increased to 140 mA cm^{-2}, and although the starting materials disappeared, only byproducts probably resulting from anodic oxidation of the aromatic moieties were observed. Carbamates are more stable under the electrolysis conditions than carbonates, which would allow a site-selective deprotection of *i*Noc groups in a molecule with multiple protection groups. While we did not achieve the electrochemical deprotection of carbamates, Veber et al. previously demonstrated that the *i*Noc moiety can be electrochemically removed from the *ε*-amine of lysine.[2] However, it should be noted that they employed a

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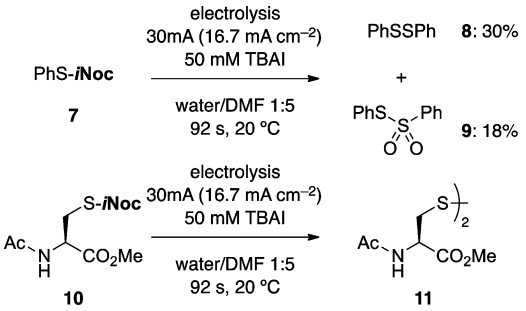
mercury cathode while we used platinum. The redox activities are clearly influenced by the electrode material.[10]

We then investigated the electrochemical reduction of *i*Noc-protected thiols, which is, for example, a functional group in L-cysteine. *i*Noc-protected benzenethiol **7** as a simple model substrate was prepared by the reaction of benzenethiol with **2** in DMF in good yield (93%). The electrochemical cleavage conditions for carbonates were applied (16.7 mA cm^{-2}), leading to diphenyl disulfide **8** and (*S*)-phenyl benzenesulfonothioate **9** as reaction products. As shown in Scheme 3, it seems

Scheme 3. Electrochemical Cleavage of Thiocarbonates



that **8** was electrochemically generated by sequential oxidation of deprotected **7** and was further oxidized to sulfonothioate **9**. It should be noted that deprotected **7** (benzenethiol) was not observed in the crude reaction mixture even when the solution exiting the microreactor was directly inserted into an aqueous solution of 0.3 M HCl to stop any spontaneous oxidation of thiols. This suggests that the disulfide and sulfonothioate formation occurs directly in the electrochemical microreactor. As electro-oxidation of thiols is a challenging task from both the viewpoint of clean peptide synthesis and the structural biology associated with protein folding,[11] this protocol might be useful to induce disulfide formation in other systems.

Therefore, the electrolysis of *i*Noc-protected L-cysteine derivative **10** was investigated to reveal whether the desired disulfide **11** can be obtained. *N*-Acetyl-L-cysteine methyl ester[12] was protected with an *i*Noc group, and **10** was electrolyzed. To achieve the full conversion of **10** during the electrolysis, the reaction conditions were optimized. As with the results of **7**, TLC and ^{1}H NMR analysis showed formation of disulfide cystine **11** and possibly also the corresponding sulfonothioate in the crude reaction mixture. However, these products are only formed in minor amounts. In light of the results that the electrolysis of **10** did not effectively progress while **7** was easily electrolyzed to the desired products, it seems that the benzene ring enhances the electroreductive deprotection of *i*Noc from the substrates.

CONCLUSIONS

In conclusion, we successfully accomplished the rapid electrochemical deprotection of an *i*Noc group from phenols and benzenethiol by using the electrochemical microreactor. It was also revealed that the *N*-*i*Noc group (carbamate) is enormously stable for the electrolysis in the conditions employed here, while the *O*-*i*Noc (carbonates) and *S*-*i*Noc (thiocarbonates) were easily cleaved, meaning that the reduction potentials of *O*-*i*Noc and *S*-*i*Noc compounds are more positive than that of *N*-*i*Noc compound under the reaction conditions employed. These results further indicate that the electrochemical method shown in this paper would enable a chemoselective deprotection of *i*Noc protection groups.

EXPERIMENTAL SECTION

General. Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on an AV-400 Bruker spectrometer in the indicated solvents at 400 MHz. Mass spectrometric data were obtained on a Varian 1200 quadrupole mass spectrometer and Micromass Quadro II spectrometer. ESI: Thermofisher LTQ Orbitrap XL. All reactions were monitored by thin-layer chromatography (TLC), which was performed on precoated sheets of silica gel 60 (Merck). The electrochemical microreactor, with a Pt foil (0.1 mm) as anode and cathode and fluorinated ethylene polymer (FEP) channel, as shown in Figure 1 and already described,[4] was used. The galvanostatic reactions were performed with a GWINSTEC GPR-30H100. Isonicotinyl *p*-nitrophenyl carbonate **2**,[2] 4-hydroxybenzoic acid methyl ester **1c**,[7] and *N*-acetyl-L-cysteine methyl ester[12] were prepared by following the previously reported procedures. Dipeptide Fmoc-Phe-Tyr-OMe was kindly provided by Dr. Robert Mart and Prof. Dr. Rudolf Allemann. All other chemicals were used as purchased without further purification.

General Procedure for Preparation of *i*Noc-Protected Compounds. To prepare **3a** and **3b**, phenol **1a** (1.20 mmol, 0.113 g) or 4-methoxyphenol **1b** (0.95 mmol, 0.235 g) as the starting material was dissolved in 2 mL of DMF and stirred for 3.5−16 h at 50 °C in the presence of *i*Noc reagent **2** (1.2 equiv) and K_2CO_3 (1.0 equiv). To prepare **3c**, **4**, **5**, **6**, **7**, and **10**, on the other hand, 4-hydroxybenzoic acid methyl ester **1c** (0.6 mmol, 91 mg), Fmoc-Phe-Tyr-OMe (0.30 mmol, 0.169 g), benzylamine (0.20 mmol, 22 μL), L-phenylalanine methyl ester hydrochloride (1.85 mmol, 0.400 g), benzenethiol (0.8 mmol, 82 μL), or *N*-acetyl-L-cysteine (0.60 mmol, 0.106 g) as the starting material was dissolved in 0.5−3.0 mL of DMF and stirred for 18 h at room temperature in the presence of the *i*Noc reagent **2** (1.2 equiv), diisopropylethylamine (1.0 equiv), and catalytic amounts of DMAP. After the reaction, 10 mL of EtOAc and 10 mL of water were added to the reaction solution and extracted with EtOAc (3 × 10 mL). The yellow organic layer was washed with 1 M aqueous $NaHCO_3$ (2 × 15 mL) and brine (20 mL) and dried with over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under reduced pressure to obtain a yellow oil of crude mixture. The crude product was then purified by column chromatography (silica gel). The collected fractions containing the *i*Noc-protected compound were combined and evaporated under reduced pressure.

Phenylpyridin-4-ylmethyl Carbonate 3a. The reaction was performed in 2.5 mL of DMF for 3.5 h. The colorless solid of **3a** was obtained by purification of the crude product by using column chromatography (Et_2O/EtOAc 3:2). Isolated yield: 0.263 g (96%).

4-Methoxyphenylpyridin-4-ylmethyl Carbonate 3b. The reaction was performed in 2.5 mL of DMF for 3.5 h. The colorless solid of **3b** was obtained by purification of the crude product by using column chromatography (Et_2O/EtOAc 9:1). Isolated yield: 0.227 g (92%).

Methyl 4-((Pyridin-4-ylmethoxy)carbonyloxy)-benzoate 3c. The reaction was performed in 1.0 mL of DMF. The colorless solid of **3c** was obtained by purification of the crude product by using column chromatography (Et_2O/EtOAc 3:2). Isolated yield: 0.169 g (98%).

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Fmoc-Phe-Tyr(O-*i*Noc)-OMe 4. The reaction was performed in 1.5 mL of DMF. The colorless solid of **4** was obtained by purification of the crude product by using column chromatography (Et_2O/EtOAc 1:4). Isolated yield: 0.125 g (59%).

Pyridin-4-ylmethyl Benzylcarbamate 5. The reaction was performed in 0.5 mL of DMF. The colorless solid of **5** was obtained by purification of the crude product by using column chromatography (Et_2O/EtOAc 3:5). Isolated yield: 52 mg (94%).

(*S*)-Methyl 3-Phenyl-2-((pyridin-4-ylmethoxy)-carbonylamino)propanoate 6. The reaction was performed in 3.0 mL of DMF. The yellow oil of **6** was obtained by purification of the crude product by using column chromatography (EtOAc/MeOH 7:1). Isolated yield: 0.46 g (79%).

(*S*)-Phenyl *O*-Pyridin-4-ylmethyl carbonothioate 7. The reaction was performed in 1.5 mL of DMF. The colorless solid of **7** was obtained by purification of the crude product by using column chromatography (Et_2O/EtOAc 3:2). Isolated yield: 0.188 g (93%).

(*R*)-Methyl 2-Acetamido-3-((pyridin-4-ylmethoxy)-carbonylthio)propanoate 10. The reaction was performed in 1.0 mL of DMF. The colorless solid of **10** was obtained by purification of the crude product by using column chromatography (EtOAc/MeOH 5:1). Isolated yield: 0.178 g (95%).

General Procedure for Electrochemical Deprotection in Flow. Compound **3a**, **3b**, **3c**, **4**, **7**, or **10** was dissolved in DMF/H_2O (5:1 v/v) containing 50 mM tetrabutylammonium iodide so that the final concentration was 93 mM. The mixture (2−4 mL) was introduced into the electrochemical microreactor equipped with a FEP channel (0.3 cm × 3.0 cm × 254 μm) through a syringe pump (flow rate = 12−15 μL min^{-1}, residence time = 92−115 s) with an applied current of 30−35 mA (current density = 16.7−19.4 mA cm^{-2}) and collected in a glass vial at the outlet. The solution was diluted with 10 mL of water and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with water (3 × 20 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated in vacuum. The residual black material was purified by column chromatography (silica gel). The fractions containing deprotected substrate were combined and evaporated. The products were identified by ^{1}H NMR and/or MS.

Electrolysis of 3a: 4 mL of a solution containing **3a** (0.37 mmol, 93 mg) and TBAI (0.2 mmol, 74 mg) was electrolyzed with constant current (16.7 mA cm^{-2}) at continuous flow (15 μL min^{-1}, residence time = 92 s). Following purification of the crude product using column chromatography (Et_2O/hexane 5:1), **1a** was obtained as a white solid. Isolated yield: 51 mg (61%).

Electrolysis of 3b: 4 mL of a solution containing **3b** (0.37 mmol, 96 mg) and TBAI (0.2 mmol, 74 mg) was electrolyzed with constant current (16.7 mA cm^{-2}) at continuous flow (15 μL min^{-1}, residence time = 92 s). Following purification of the crude product using column chromatography (Et_2O/hexane 5:1), **1b** was obtained as a colorless solid. Isolated yield: 20 mg (43%).

Electrolysis of 3c: 3.5 mL of a solution containing **3c** (0.33 mmol, 95 mg) and TBAI (0.17 mmol, 65 mg) was electrolyzed with constant current (16.7 mA cm^{-2}) at continuous flow (15 μL min^{-1}, residence time = 92 s). Following purification of the crude product using column chromatography (Et_2O/hexane 5:1), **1c** was obtained as a colorless solid. Isolated yield: 25 mg (50%).

Electrolysis of 4: 2.0 mL of a solution containing **4** (0.19 mmol, 0.13 g) and TBAI (0.1 mmol, 37 mg) was electrolyzed with constant current (19.4 mA cm^{-2}) at a continuous flow (12 μL min^{-1}, residence time = 115 s). Following purification of the crude product using column chromatography (Et_2O/hexane 5:1), the product (Fmoc-Phe-Tyr-OMe) was obtained as a colorless solid. Isolated yield: 13 mg (12%).

Electrolysis of 7: 3 mL of a solution containing **7** (0.28 mmol, 71 mg) and TBAI (0.15 mmol, 55 mg) was electrolyzed with constant current (16.7 mA cm^{-2}) at continuous flow (15 μL min^{-1}, residence time = 92 s). Following purification of the crude product using column chromatography (Et_2O/hexane 1:1), **8** and **9** were obtained as colorless solids. Isolated yield for **8**: 19 mg (30%). Isolated yield for **9**: 13 mg (18%).

Electrochemical Deprotection of 3a under Batch Conditions. A mixture of **3a** (0.95 mmol, 0.218 g) and TBAI (0.51 mmol, 0.188 g) dissolved in DMF/H_2O (5:1 v/v, 10.2 mL) was stirred and electrolyzed under aerobic conditions at room temperature in an undivided cell (7.4 cm tall and 2.5 cm in diameter) fitted with two platinum foils (1.2 × 0.7 cm^2) as the anode and cathode. A constant current density (16.7 mA cm^{-2}) was applied. After TLC analysis (silica gel, Et_2O/hexane 5:1) indicated that the starting material disappeared, the electrolysis was stopped and 35 mL of water was added to the black color of resulting solution. The solution was extracted with EtOAc (3 × 30 mL). The combined extracts was washed with water (3 × 30 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated in vacuum. The residual black material was purified by column chromatography (silica gel) equilibrated with a mixture of Et_2O/hexane (5:1 v/v) as eluent. The fractions containing deprotected phenol were combined and evaporated to give the colorless solid **1a** in a yield of 47 mg (53%).

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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