A Novel Synthetic Method for Penicillanic Acid Derivatives by Electroreduction

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Electroreductive dehalogenation of 6-halopenicillanic acid derivatives was conveniently carried out to give the corresponding penicillanic acid derivatives, key intermediates in syntheses of various β-lactamase inhibitors, in good yields.

Penicillanic acid (**6a**) and its esters (**6b, c, e**) are key intermediates in syntheses of β-lactamase inhibitors such as sulbactam (**1a**),[1] YTR-830,[2] *etc.* and their prodrugs, *e.g.*, **1b**.[3] Penicillanic acid (**6a**) and its simple ester were prepared by the reductive dehalogenation of 6,6-dibromo (**4a**) or 6-bromopenicillanic acid (**9a**) and their esters, respectively.[4] However, in our synthesis of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl penicillanate 1,1-dioxide (**1b**), a useful prodrug of sulbactam, the reduction of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 6,6-dibromopenicillanate (**4b**) by catalytic hydrogenation using palladium on calcium carbonate[4b] was found to be impractical.[3] Thus far, several reduction methods of 6-halopenicillanic acid 1,1-dioxide have been reported, including catalytic hydrogenation,[5] and zinc-,[6] magnesium-,[7] cadmium-promoted[8] reductions, but these methods gave unsatisfactory results in the reduction of **4b**. Thus, a new reduction method, widely applicable to 6-halopenicillanic acid derivatives, has been required.

Electroreduction is generally considered to be more attractive than metal-promoted reduction involving electron transfer because of the following features: 1) it is applicable to a variety of compounds by changing the electrode potential; 2) it can be done under various conditions (acidic, basic, neutral); 3) it is a clean reaction, without the use of any reducing reagent, thus being suitable for large-scale preparation. Although extensive studies on electroreduction of simple alkyl of aromatic halides have been reported,[9] there have been few

X = Cl, Br
Y = H, Br
n = 0, 1, 2

a: R = H   R = CH_2———R_1
b: R_1 = CH_3
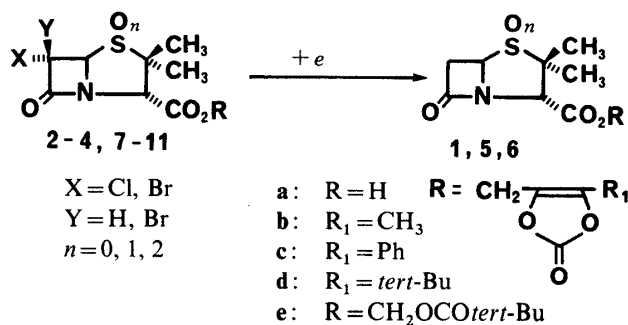c: R_1 = Ph
d: R_1 = *tert*-Bu
e: R = CH_2OCO*tert*-Bu

Chart 1

papers concerning electroreduction of β-lactam derivatives such as penicillin.[10] Therefore, we wish to report herein our results on electroreduction of 6-halopenicillanic acid derivatives.

The electrolysis was in principle performed in methanol (MeOH) containing tetraethyl-ammonium p-toluenesulfonate (Et$_4$NOTs) as a supporting electrolyte at 0—5 °C using a beaker-type divided cell equipped with a ceramic cylinder as a diaphragm under the constant-current conditions. At first, we tried the electroducion of 6,6-dibromopenicillanic acid (4a). Electricity (6—7 F/mol) was passed through the system until 4a was consumed. After usual work-up, penicillanic acid (6a), the dehalogenated product, was obtained as a sole product (Table I, entry 1). Using a carbon rod as an anode, we then studied the effect of cathode material to find a suitable cathode for the electroreduction of 4a. A lead cathode gave the best yield as shown in Table I.

Next, electroreduction of 4a in water was examined, because water (having high electroconductance) was considered to be superior in current efficiency, as well as being the cheapest solvent. Further, an expensive electrolyte such as Et$_4$NOTs was not always needed in electroreduction in water. The reduction of 4a was complete after passing 5 F/mol of electricity, and penicillanic acid (6a) was obtained in 74% yield. It is recognized[11] that electroreduction of halogeno compounds generally involves competitive reactions between simple dehalogenation (halogen atoms are substituted by protons) and dimerization, and the ratio of the products depends on reaction conditions such as electrode potential, character of the solvent, cathode material, etc. In the electroreduction of 4a, however, the simple reduction product, penicillanic acid (6a), was obtained in good yield, and the corresponding dimer was not detected.

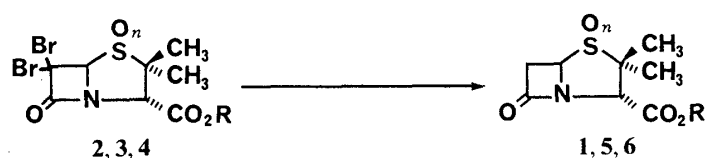In order to improve the total yield of penicillanic acid (6a) from 6-aminopenicillanic acid (6-APA), a one-pot-like electroreduction of 4a was carried out in water without isolation of 4a prepared by two-phase diazotization/bromination of 6-APA. In this direct method, the potassium salt of 6a was obtained from 6-APA in 66% yield (average of five runs). When 4a was isolated as an intermediate, the overall yield of 6a from 6-APA was 57% (average of five runs). In this manner, penicillanic acid (6a) could be obtained easily, and this direct method has afforded an efficient preparation of penicillanic acid.

Next we tried the electroreduction of 4b, which has a labile ester residue, the (5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl group. Electrolyses were performed in N,N-di-methylformamide (DMF) containing Et$_4$NOTs as a supporting electrolyte at 0—5 °C in a similar manner. At first a lead plate was used as the cathode, and a carbon rod as the anode. After 8.0 F/mol of electricity had been passed through the system, the reaction mixture was analyzed by thin layer chromatography (TLC). A small amount of penicillanic acid (6a) was found on TLC, but the desired penicillanate (6b) could not be obtained, and mostly the decomposition of 6,6-dibromopenicillanate (4b) took place. These facts suggested that the initially generated radical and/or carbanion intermediates[12] might decompose because of an insufficient amount of proton source and that formation of a small amount of 6a was due to base-catalyzed hydrolysis of 6b in the neighborhood of the cathode. Therefore, acetic acid (AcOH) was added to the solvent as a proton donor and a buffer agent in order to prevent cleavage of the ester bond. In the presence of AcOH the electroreduction of 4b under the same conditions was carried out successfully to give penicillanate (6b) in 40% yield without formation of penicillanic acid (6a) (Table I, entry 7). Furthermore, addition of methanol (MeOH) to the solvent raised the yield of the penicillanate (6b) to 55% (Table I, entry 8). From further investigations, optimum reaction conditions were revealed to be as follows; a copper plate as the cathode, and a mixture of DMF, AcOH and MeOH as the solvent (Table I, entries 10, 11).
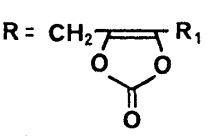
This electroreduction was also applied to the dehalogenation of other 6-halopenicillanic acid drivatives including sulfoxide and sulfone to find its scope and limitations. The results are

summarized in Tables I, II and III. It seems noteworthy that electroreduction of 6-halopenicillanic acid derivatives (2—4, 7—11) to the corresponding penicillanic acid derivatives (1, 5, 6) occurred easily in good yield irrespective of the oxidation level of the 1-sulfur atom. Both 6-chloropenicillanic acid (11a) and its ester (11b) were easily reduced to 6a and 6b, respectively, in good yields similarly to 6-chloropenicillanate 1,1-dioxide (10b), as shown in Table III. In addition it is interesting that sulfone and sulfoxide groups at the 1-position are inert under these electroreduction conditions. On the other hand, by the use of catalytic hydrogenation or zinc-promoted reduction, sulfone derivatives (2, 7 and 10) are reduced more easily than sulfoxide (3 and 8) and sulfide (4, 9 and 11) derivatives, and the reduction of sulfide

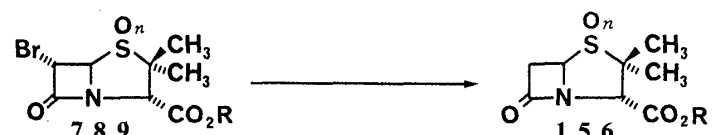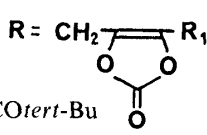TABLE I. Electroreduction of 6,6-Dibromopenicillanic Acid Derivatives

Entry	Starting material	n	Condition[a]	Cathode	Amount of current (F/mol)	Product	Yield (%)
1	4a	0	A	Pb	7	6a	75
2	4a	0	A	Cu	6.7	6a	71
3	4a	0	A	Zn	8	6a	61
4	4a	0	A	Pt	7	6a	73
5	4a	0	B	Pb	5	6a	74
6	4b	0	C	Pb	8	—	—
7	4b	0	D	Pb	10	6b	40
8	4b	0	E	Pb	8.5	6b	55
9	4b	0	E	Zn	8	6b	56
10	4b	0	E	Cu	8	6b	60
11	4c	0	E	Cu	7	6c	64
12	4d	0	E	Cu	7	6d	61
13	3b	1	E	Cu	7.7	5b	58
14	2a	2	B	Pb	5.2	1a	72
15	2b	2	E	Pb	5.7	1b	64

a) A, MeOH–Et$_4$NOTs; B, H$_2$O–K$_2$HPO$_4$; C, DMF–Et$_4$NOTs; D, DMF/AcOH–Et$_4$NOTs; E, DMF/AcOH/MeOH–Et$_4$NOTs.

TABLE II. Electroreduction of 6-Bromopenicillanic Acid Derivatives

Entry	Starting material	n	Condition[a]	Cathode	Amount of current (F/mol)	Product	Yield (%)
1	7a	2	B	Pb	4	1a	75
2	7b	2	E	Cu	5.7	1b	73
3	7e	2	E	Pb	4.7	1e	67
4	8b	1	E	Cu	7.7	5b	57
5	9a	0	B	Pb	2.1	6a	76
6	9b	0	E	Cu	6.5	6b	55

a) B, H$_2$O–K$_2$HPO$_4$; E, DMF/AcOH/MeOH–Et$_4$NOTs.

TABLE III.   Electroreduction of 6-Chloropenicillanic Acid Derivatives

Entry	Starting material	n	Condition[a]	Cathode	Amount of current (F/mol)	Product	Yield (%)
1	10b	2	E	Pb	4	1b	56
2	11a	0	B	Pb	4	6a	51
3	11b	0	E	Pb	7	6b	53

a) B, H_2O–K_2HPO_4; E, DMF/AcOH/MeOH–Et_4NOTs.

derivatives (4, 9 and 11) is most difficult.[13,14] In particular, 6-chloropenicillanic acid derivatives (11) could hardly be reduced to the corresponding penicillanic acid derivatives by catalytic hydrogenation.[4a] These facts clearly show that electroreduction is superior to catalytic hydrogenation or metal-promoted reduction in its applicability to a wide range of compounds.

Ease of electroreduction of alkyl halides decreases in the following order; dibromomethane > monobromomethane > monochloromethane.[9] This tendency is also observed in the electroreduction of 6-halopenicillanic acid derivatives, judging from the current efficiency.

As another application of this electrolysis, we investigated one-pot reduction/oxidation of 6,6-dibromopenicillanic acid (4a) without a diaphragm to obtain penicillanic acid 1-oxide (5a) or 1,1-dioxide (1a). Neither 5a nor 1a could be formed without complex decomposition of the starting 4a. Hence, a diaphragm was required for electroreduction of 6-halopenicillanic acid derivatives.

From the viewpoints of good yield, wide range of application, simple procedure and low cost, the present electroreduction seems to possess high potential for the synthesis of β-lactam derivatives by a reduction method. Further work is in progress.

Experimental

Melting points were determined on a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. Proton nuclear magnetic resonance (¹H-NMR) spectra were measured on a Nihon Denshi PS-100 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded with a Shimadzu IR-440 spectrometer.

Materials——6-Halopenicillanic acids, 2a,[5] 4a,[5] 7a,[13] 7e,[13] 9a[15] and 11a[15] were prepared by the reported procedures. Syntheses of the esters 2b, 4b, 8b and 9b were reported in our previous paper,[3] and 4c and 4d were obtained in the same way. The other esters, 10b and 11b, were prepared by the esterification of 6-halopenicillanic acid, and the sulfoxide 3b was obtained by the oxidation of 4b with 30% H_2O_2. The physical properties of new compounds were as follows.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl   6,6-Dibromopenicillanate   1-Oxide   (3b)——mp   116—118 °C.   IR ν_{max}^{KBr} cm^{-1}: 1820, 1815, 1805, 1755 (C=O). ¹H-NMR (CDCl₃): 1.42 (3H, s, 2-CH₃), 1.59 (3H, s, 2-CH₃), 2.23 (3H, s, C=CCH₃), 4.64 (1H, s, 3-H), 4.98 (2H, s, C=CCH₂), 5.31 (1H, s, 5-H). Anal. Calcd for $C_{13}H_{13}Br_2NO_7S$: C, 32.04; H, 2.69; N, 2.88. Found: C, 32.26; H, 2.75; N, 2.98.

(5-Phenyl-2-oxo-1,3-dioxol-4-yl)methyl   6,6-Dibromopenicillanate   (4c)——mp   95—97 °C.   IR ν_{max}^{KBr} cm^{-1}: 1825, 1790, 1745 (C=O). ¹H-NMR (CDCl₃): 1.50 (3H, s, 2-CH₃), 1.66 (3H, s, 2-CH₃), 4.63 (1H, s, 3-H), 5.22 (2H, s, C=CCH₂), 5.80 (1H, s, 5-H), 7.4—7.68 (5H, m, arom. H). Anal. Calcd for $C_{18}H_{15}Br_2NO_6S$: C, 40.55; H, 2.84; N, 2.63. Found: C, 40.48; H, 2.95; N, 2.56.

(5-tert-Buty-2-oxo-1,3-dioxol-4-yl)methyl   6,6-Dibromopenicillanate   (4d)——IR ν_{max}^{neat} cm^{-1}: 1830, 1780, 1760 (C=O). ¹H-NMR (CDCl₃): 1.35 (9H, s, C(CH₃)₃), 1.46 (3H, s, 2-CH₃), 1.61 (3H, s, 2-CH₃), 4.58 (1H, s, 3-H), 5.08

(2H, s, C=CCH$_2$), 5.77 (1H, s, 5-H).

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6α-Chloropenicillanate 1,1-Dioxide (10b)——mp 90—92 °C. IR ν_{max}^{KBr} cm^{-1}: 1825, 1807, 1762 (C=O). ^{1}H-NMR (CDCl$_3$): 1.40 (3H, s, 2-CH$_3$), 1.62 (3H, s, 2-CH$_3$), 2.22 (3H, s, C=CCH$_3$), 4.45 (1H, s, 3-H), 4.65 (1H, d, J=1.5 Hz, 6-H), 4.99 (2H, s, C=CCH$_2$), 5.17 (1H, d, J=1.5 Hz, 5-H). *Anal.* Calcd for C$_{13}$H$_{14}$ClNO$_8$S: C, 41.11; H, 3.72; N, 3.69. Found: C, 41.10; H, 3.76; N, 3.61.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6α-Chloropenicillanate (11b)——mp 92—95 °C. IR ν_{max}^{KBr} cm^{-1}: 1830, 1810, 1780, 1750, 1740 (C=O). ^{1}H-NMR (CDCl$_3$): 1.42 (3H, s, 2-CH$_3$), 1.60 (3H, s, 2-CH$_3$), 2.18 (3H, s, C=CCH$_3$), 4.57 (1H, s, 3-H), 4.77 (1H, d, J=1.5 Hz, 6-H), 4.95 (2H, s, C=CCH$_2$), 5.33 (1H, d, J=1.5 Hz, 5-H). *Anal.* Calcd for C$_{13}$H$_{14}$ClNO$_6$S: C, 44.90; H, 4.06; N, 4.03. Found: C, 45.08; H, 4.01; N, 4.15.

General Procedure for Electroreduction——Electroreduction was carried out at 0—10 °C in a beaker-type cell separated by a ceramic cylinder diaphragm (30 ml), which was fitted with a cathode (Pb or Cu plate) outside the cylinder and an anode (carbon rod, Pt or Pb) inside the cylinder. Constant current (current density; 2—20 mA/cm^2) was supplied by a Takasago PM-13R GP 050-2 device, until most of the starting materials had disappeared (checked by TLC or high performance liquid chromatography). The catholytes were worked up in the usual manner. The results are summarized in Tables I, II and III. A few examples of electroreduction are given below.

Electroreduction of 4a——A mixture of MeOH (40 ml) and Et$_4$NOTs (2.5 g) was added to both the cathodic and anodic compartments and **4a** (1.0 g) was added to the catholyte. Electrolysis was carried out at 13.3 mA/cm^2 using a Pb cathode (5 × 5 cm^2) and a carbon rod anode (8 mm diameter × 10 cm). After 7.0 F/mmol of electricity had been passed, the catholytes were poured into a stirred mixture of AcOEt (40 ml) and saturated aqueous NaCl (20 ml) at 5 °C. The pH of the mixture was adjusted to 1.5 with 6 N HCl. The organic layer was separated and the aqueous layer was extracted with AcOEt (20 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried over MgSO$_4$, and concentrated under reduced pressure to 1/3 volume. A solution of potassium acetate (0.3 g) in MeOH (10 ml) was added, and the mixture was concentrated again under reduced pressure to 1/2 volume and stored at 5 °C overnight. The solid was filtered off and washed with ether to give 0.5 g of **6a** potassium salt as colorless crystals in 75% yield. IR ν_{max}^{KBr} cm^{-1}: 1765, 1610 (C=O). ^{1}H-NMR (DMSO-d_6): 1.44 (3H, s, 2-CH$_3$), 1.54 (3H, s, 2-CH$_3$), 2.81 (1H, dd, J=2, 16 Hz, 6-H), 3.45 (1H, dd, J=4, 16 Hz, 6-H), 3.88 (1H, s, 3-H), 5.12 (1H, dd, J=2, 4 Hz, 5-H). *Anal.* Calcd for C$_8$H$_{10}$KNO$_3$S: C, 40.15; H, 4.21; N, 5.85. Found: C, 39.93; H, 4.20; N, 5.83.

Electroreduction of 4b——A mixture of DMF (100 ml), AcOH (25 ml), MeOH (20 ml) and Et$_4$NOTs (40 g) was added to the cathodic compartment, a mixture of MeOH (15 ml) and Et$_4$NOTs (3 g) was added to the anodic compartment, and **4b** (10 g) was added into the catholyte. Electrolysis was carried out at 2.3 mA/cm^2 using a Cu cathode (8.2 × 15.5 cm^2) and a carbon rod anode (8 mm diameter × 10 cm). After 8.0 F/mol of electricity had been passed, the catholyte was poured into a stirred mixture of AcOEt (200 ml) and water. The organic layer was separated and washed with 5% aqueous NaCl, dried over MgSO$_4$, and concentrated under reduced pressure to give a syrup. The syrup was purified by column chromatography on silica gel using chloroform as an eluent to afford **6b** (4.0 g, 60% yield) as a syrup, which crystallized from ether–hexane. The physical properties were in accord with the literature values.[3]

One-Pot-Like Synthesis of 6a from 6-APA——Bromine (4.8 ml), 2.5 N sulfuric acid (40 ml) and sodium nitrite (5.4 g) were added to dichloromethane (80 ml) with stirring at 0 °C. 6-APA (12 g) was added portionwise over a period of 20 min at 5—10 °C. The resultant solution was stirred at 5 °C for 30 min. Aqueous 5% sodium thiosulfate was added dropwise at 5—10 °C until the bromine color was discharged. The organic layer was separated and the aqueous layer was extracted with dichloromethane (20 ml). Water was added to the combined organic layer, and the mixture was stirred vigorously at 5 °C. The pH of the mixture was adjusted to 7.3 with saturated aqueous NaHCO$_3$. The aqueous layer was separated and the organic layer was extracted with water (40 ml). The pH of the combined aqueous layer was adjusted to 7.0 with 2 N HCl. This aqueous solution was added into the cathodic compartment and saturated aqueous NaHCO$_3$ (20 ml) was added into the anodic compartment. Electrolysis was carried out at 4.3 mA/cm^2 using a Pb cathode (14 × 10 cm^2) and a Pt anode (1.5 × 1.5 cm^2). After 3 F/mol of electricity had been passed, the catholyte was worked up in the same manner as for the electroreduction of **4a**. The potassium salt of **6a** was obtained as colorless crystals (8.8 g, 66%). The physical properties were in accordance with the assigned structure.

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