

[Chem. Pharm. Bull.]
36(6) 1976-1981(1988)

A Novel Synthetic Method for Penicillanic Acid Derivatives by Electroreduction

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(Received November 9, 1987)

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.

Keywords—penicillanic acid; sulbactam; β -lactamase inhibitor; 6-halopenicillanic acid; electroreduction; dehalogenation; prodrug

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-promoted⁸⁾ 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 or aromatic halides have been reported,⁹⁾ there have been few

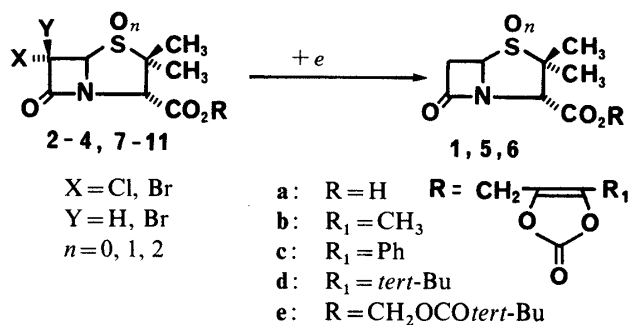


Chart 1

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 tetraethylammonium *p*-toluenesulfonate (Et₄NOTs) 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 electroreduction 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 Et₄NOTs 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 recognized¹¹⁾ 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*-dimethylformamide (DMF) containing Et₄NOTs 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 intermediates¹²⁾ 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 derivatives 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

2, 3, 4

→

1, 5, 6

a: R = H
b: R₁ = CH₃
c: R₁ = Ph
d: R₁ = *tert*-Bu

R =

Entry	Starting material	<i>n</i>	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-Et₄NOTs; B, H₂O-K₂HPO₄; C, DMF-Et₄NOTs; D, DMF/AcOH-Et₄NOTs; E, DMF/AcOH/MeOH-Et₄NOTs.

TABLE II. Electroreduction of 6-Bromopenicillanic Acid Derivatives

7, 8, 9

→

1, 5, 6

a: R = H
b: R₁ = CH₃
e: R = CH₂OCO*tert*-Bu

R =

Entry	Starting material	<i>n</i>	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, H₂O-K₂HPO₄; E, DMF/AcOH/MeOH-Et₄NOTs.

TABLE III. Electroreduction of 6-Chloropenicillanic Acid Derivatives

a: R = H R =

b: R₁ = CH₃

Entry	Starting material	<i>n</i>	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, H₂O-K₂HPO₄; E, DMF/AcOH/MeOH-Et₄NOTs.

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% H₂O₂. 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₃Br₂NO₇S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₈H₁₅Br₂NO₆S: C, 40.55; H, 2.84; N, 2.63. Found: C, 40.48; H, 2.95; N, 2.56.

(5-tert-Butyl-2-oxo-1,3-dioxol-4-yl)methyl 6,6-Dibromopenicillanate (4d)—IR $\nu_{\text{max}}^{\text{neat}}$ 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=CCH₂), 5.77 (1H, s, 5-H).

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6 α -Chloropenicillanate 1,1-Dioxide (10b)—mp 90–92°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1825, 1807, 1762 (C=O). ¹H-NMR (CDCl₃): 1.40 (3H, s, 2-CH₃), 1.62 (3H, s, 2-CH₃), 2.22 (3H, s, C=CCH₃), 4.45 (1H, s, 3-H), 4.65 (1H, d, *J*=1.5 Hz, 6-H), 4.99 (2H, s, C=CCH₂), 5.17 (1H, d, *J*=1.5 Hz, 5-H). *Anal.* Calcd for C₁₃H₁₄ClNO₈S: 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 6 α -Chloropenicillanate (11b)—mp 92–95°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1830, 1810, 1780, 1750, 1740 (C=O). ¹H-NMR (CDCl₃): 1.42 (3H, s, 2-CH₃), 1.60 (3H, s, 2-CH₃), 2.18 (3H, s, C=CCH₃), 4.57 (1H, s, 3-H), 4.77 (1H, d, *J*=1.5 Hz, 6-H), 4.95 (2H, s, C=CCH₂), 5.33 (1H, d, *J*=1.5 Hz, 5-H). *Anal.* Calcd for C₁₃H₁₄ClNO₆S: 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/cm²) 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 Et₄NOTs (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/cm² using a Pb cathode (5 × 5 cm²) 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 MgSO₄, 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 $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1765, 1610 (C=O). ¹H-NMR (DMSO-*d*₆): 1.44 (3H, s, 2-CH₃), 1.54 (3H, s, 2-CH₃), 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 C₈H₁₀KNO₃S: 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 Et₄NOTs (40 g) was added to the cathodic compartment, a mixture of MeOH (15 ml) and Et₄NOTs (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/cm² using a Cu cathode (8.2 × 15.5 cm²) 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 MgSO₄, 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 NaHCO₃. 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 NaHCO₃ (20 ml) was added into the anodic compartment. Electrolysis was carried out at 4.3 mA/cm² using a Pb cathode (14 × 10 cm²) and a Pt anode (1.5 × 1.5 cm²). 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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